(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2014 (12.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/137797 A2

(51) **International Patent Classification**:
A61K 9/14 (2006.01)

(21) **International Application Number**:
PCT/US2014/019349

(22) **International Filing Date**:
28 February 2014 (28.02.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/772,022 4 March 2013 (04.03.2013) US

(71) **Applicant**: **TRANSTECH PHARMA, LLC** [US/US]; 4170 Mendenhall Oaks Parkway, High Point, North Carolina 27265 (US).

(72) **Inventors**: **MO, Yun**; 27 Dillon Drive, Dix Hills, New York 11746 (US). **DEDHIYA, Mahendra G.**; 1 Lea Court, Pomona, New York 10970 (US). **CHHETTRY, Anil**; 11 Hickory Hill Drive, Holtsville, New York 11742 (US).

(74) **Agent**: **ROLLINS, Samuel B.**; 4170 Mendenhall Oaks Parkway, High Point, North Carolina 27265 (US).

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

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

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: STABLE GLUCOKINASE ACTIVATOR COMPOSITIONS

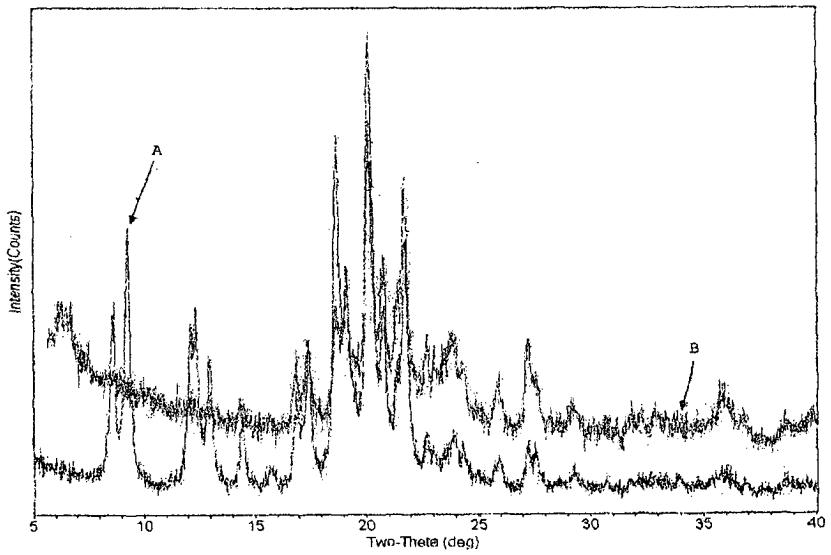


Figure 1

(57) **Abstract**: The invention relates to stable pharmaceutical compositions comprising a glucokinase (GK) activator suitable for oral administration. The invention also relates to methods of making and using such pharmaceutical compositions.

WO 2014/137797 A2

STABLE GLUCOKINASE ACTIVATOR COMPOSITIONS

FIELD OF THE INVENTION

The invention relates to stable pharmaceutical compositions comprising a glucokinase (GK) activator suitable for oral administration. The invention also relates to methods of making and using such pharmaceutical compositions.

BACKGROUND OF THE INVENTION

{2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (disclosed in, for example, U.S. Patent No. 7,851,636) is a GK activator that sensitizes the glucokinase (GK) sensor system. GK is an enzyme that belongs to the family of hexokinases, which catalyze the first step in the metabolism of glucose, *i.e.*, conversion of glucose to glucose-6-phosphate. GK may play a role in regulating carbohydrate metabolism by acting as a glucose sensor and causing shifts in metabolism or cell function in response to fluctuating blood-glucose levels. GK functions as a glucose sensor in the pancreas, liver, gut and brain. {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is a liver-selective GK activator that does not increase insulin secretion by the pancreas in the presence of glucose.

Ideal drugs for oral administration have moderate to high water solubility and membrane permeability, which quickly dissolve the drug in gastrointestinal fluids, as well as allow for quick absorption into the bloodstream. However, a significant amount of drug candidates are poorly soluble, and present a major hurdle for oral delivery. Poor solubility is often the reason for incomplete or erratic absorption, poor bioavailability, slow-onset of action, patient-to-patient PK variability, strong food effects and high dose requirements.

Formulation strategies have been explored to improve solubility of low solubility drugs, including forming solid dispersions of amorphous drugs, liquid filled capsules, and particle size reduction. Particle size reduction involves reducing larger drug particles to form smaller nanoparticles. However, forming drug nanoparticles has its challenges. For example, stabilizing nanoparticles from aggregation is difficult, particularly when formulating them into solid dosage forms. Conditions created during conversion of particle suspensions into solid forms can lead to particle aggregation, increases in particle size or induce crystallization of stabilizers, which present a great challenge in maintaining nanoparticle size and stability. Further, formation of

particle aggregates is typically irreversible where agglomerates cannot revert back to individually dispersed particles once they are reconstituted in dispersing medium.

Certain GK activators are poorly soluble, including {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid, leading to high dose requirements, high PK variability and strong food effects. Thus there is a need for stable formulations that improve solubility and stability of pharmaceutical compositions containing such agents. Applicants have now developed such soluble, stable and bioavailable formulations, which are disclosed herein.

SUMMARY OF THE INVENTION

The invention relates to stable pharmaceutical compositions comprising a glucokinase (GK) activator suitable for oral administration. The invention also relates to methods of making and using such pharmaceutical compositions.

In one aspect, the present invention relates to a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

In some embodiments, the present invention relates to a pharmaceutical composition comprising nanoparticles, one or more alkalizers and one or more redispersing agents, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm and comprise {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention relates to methods of treating various disorders by administering a GK activator. In some embodiments, the present invention relates to treating type II diabetes comprising administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

In other embodiments, the present invention relates to a method of improving glycemic control comprising administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. X-Ray Powder Diffraction (XRPD) pattern of nanosized {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid. "A" is the diffraction pattern for lyophilized drug suspension prior to nanosizing. "B" is the diffraction pattern for lyophilized drug suspension after nanosizing.

Figure 2. Differential scanning calorimetry (DSC) graph of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid obtained from lyophilizing the drug suspension prior to nanosizing and after nanosizing by microfluidization. "A" is the DSC graph for lyophilized drug suspension prior to nanosizing. "B" is the DSC graph for lyophilized drug suspension after nanosizing.

Figure 3. XPRD pattern of spray-dried nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid.

Figure 4. Dissolution of gelatin capsules of spray dried nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid and gelatin capsules of nanogranulated {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid.

Figure 5. *In vivo* exposure in beagle dogs of i) spray dried nanoparticle capsules containing {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid and ii) capsules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid nanogranules, in comparison with iii) {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid in aqueous solution and iv)

capsule containing granules formulated with micronized {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (reference capsule).

Figure 6. *In vivo* exposure (AUC) in humans of i) spray dried nanoparticle capsules containing {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid prepared in Example 39 and ii) capsules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid nanogranules prepared in Example 40, in comparison a capsule containing granules formulated with micronized {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (reference capsule).

Figure 7. *In vivo* exposure (Cmax) in humans of i) spray dried nanoparticle capsules containing {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid prepared in Example 39 and ii) capsules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid nanogranules prepared in Example 40, in comparison a capsule containing granules formulated with micronized {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (reference capsule).

DETAILED DESCRIPTION OF THE INVENTION

Novel stable pharmaceutical compositions of {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof, methods of treatment using these pharmaceutical compositions, and methods for preparing these pharmaceutical compositions are provided herein.

{2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is a Class IV drug under the Biopharmaceutics Classification System (BCS), having low solubility and low permeability. As a result, Class IV drugs have poor bioavailability and are usually not well-absorbed while having high variability. Preparing a stable, bioavailable composition containing {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof is, however, not straight forward. Such compositions may exhibit enhanced stability, are highly bioavailable and readily release the active ingredient in the stomach environment, *e.g.*, at pH 1-4, with a desirable dissolution profile.

In one aspect, the present invention provides a pharmaceutical composition comprising solid stabilized particles and a pharmaceutically acceptable excipient, wherein the solid stabilized particles comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or pharmaceutically acceptable salt thereof. In some embodiments, the solid stabilized particles further comprise one or more alkalizers. In other embodiments, the solid stabilized particles further comprise one or more redispersing agents. In yet other embodiments, the solid stabilized particles further comprise one or more redispersing agents and one or more alkalizers. In some embodiments, the present invention relates to a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the present invention relates to a pharmaceutical composition comprising nanoparticles, one or more alkalizers and one or more redispersing agents, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm and comprise {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.The solid stabilized particles comprise {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof in an amount from about 1 % to about 80 % w/w. In some embodiments, {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt is present in an amount from about 2.5 % to about 65 % w/w. In other embodiments, {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt is present in an amount from about 5 % to about 60 % w/w.

Suitable alkalizers include any basic compound that is suitable for oral administration, including, for example, meglumine, sodium carbonate, potassium carbonate, calcium carbonate, magnesium oxide, calcium hydroxide, sodium hydroxide, potassium hydroxide, diethanolamine, potassium bicarbonate, potassium citrate, sodium borate, sodium citrate, triethanolamine, or combinations thereof. Alkalizers can be present in amounts of about 0.1 % to about 90 % w/w.

In some embodiments, the ratio of alkalizer to active ingredient is between about 2:1 to about 1:50. In other embodiments, the ratio of alkalizer to active ingredient is between about 2:1

to about 1:2. In certain embodiments, the microenvironmental pH of the pharmaceutical composition is more than about 6, for example, more than about 8, more than about 9, more than about 10 or more than about 11. Without wishing to be bound by theory, Applicants believe that microenvironmental pH of the pharmaceutical composition enhances stability of the active agent toward degradation, as well as enhances the dissolution of the active ingredient.

Suitable redispersing agents are agents having good aqueous solubility, are non-hygroscopic and can easily form hydrogen bonds with drug particles. In some embodiments, the redispersing agent is a sugar alcohol. Redispersing agents include, for example, mannitol, trehalose, xylitol, lactose, sucrose, sorbitol, dextran, lactitol, maltitol, erythritol, threitol, arabitol, ribitol, galactitol, fucitol, iditol, inocitol, velomitol, isomalt, inulin or mixtures thereof. Without being bound to any theory, redispersing agents can stabilize microparticles and/or nanoparticles by a mechanism where during the drying process redispersing agent molecules (*e.g.*, sugar alcohols) replace water molecules surrounding the particles, forming hydrogen bonds between redispersing agent molecules and particles, thereby immobilizing particles and limiting particle-particle interaction that leads to aggregation.

Preparation of Solid Stable Particles

Stable pharmaceutical compositions of the invention comprise stable solid particles. Stable solid particles can be prepared starting with a particle suspension comprising {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof and a solvent, and then removing solvent from the suspension to form stable solid particles. Particle suspensions include microsuspensions, *i.e.*, suspensions comprising particles in the micrometer size range of about 1 μm to about 100 μm, or nanosuspensions, *i.e.*, suspensions comprising particles in the nanometer size range from about 0.5 nm to about 1000 nm, or mixtures thereof. In exemplary embodiments, particle suspensions comprise nanoparticles.

Suitable processes for removing solvent from particle suspensions include for example, granulation, lyophilization, vacuum drying, oven drying, desiccant drying and spray drying. Suitable solvents for particle suspensions include any solvent that is generally recognized as safe (GRAS) by a regulatory authority, *e.g.*, the U.S. Food & Drug Administration, and should be

compatible with the drug substance and provide minimal solubility to the drug product. Such solvents include aqueous and organic solvents, for example, water, methanol, heptane, propanol, isopropanol, acetic acid, acetone, ethyl acetate, ethanol, and mixtures thereof. Exemplary particle suspensions comprise water.

Particle suspensions can be prepared by various methods, which can be classified into two categories: top-down methods and bottom-up methods. The top-down method start with bulk materials and break them down to micro- or nano-sized particles by using mechanical, chemical or electrical energy. In certain embodiments, the size reduction method allows for particle size reduction with little or no impact on maintaining crystallinity/polymorphism and stability of a drug substance. Resulting particle suspensions allow for flexibility in formulation. In some embodiments, particle suspensions can be used directly for oral administration, or can be further processed into solid forms (for example by spray drying, granulation or lyphophilization), as well as manufactured into solid dosage forms, for example, tablets and capsules and the like. Oral administration of such formulations described herein can effectively improve drug solubility, reduce dosing amounts, increase dissolution velocity, improve bioavailability, reduce PK variability and alleviate food effects.

Particle suspensions described herein also exhibit chemical stability and show little or no degradation of the drug product into degradation products, even under accelerated conditions.

In top-down methods, larger particles are broken apart to form smaller microsized or nanosized particles. Top-down methods include, for example, microfluidization, wet milling, media milling, rotation-revolution, jet milling, ball milling, micronization or homogenization (*e.g.*, high shear homogenization). Milling methods can utilize various ceramic media, such as ceramic grinding beads (*e.g.*, zirconium milling beads having bead size of about 5 μm to about 500 μm).

Bottom-up methods, on the other hand, synthesize micro- or nano-particle from the atomic or molecular level through chemical reactions or physical processes under strictly selected conditions. Bottom-up methods include, for example, fast evaporation, desolvation, spray drying, lyophilization, precipitation, chemical methods or supercritical fluid processing.

Particle suspensions can comprise one or more stabilizers. In some embodiments, the stabilizers comprise at least one polymeric stabilizer, at least one surfactant stabilizer or a

combination thereof. Polymeric stabilizers include, for example, hydroxypropyl cellullose, microcrystalline cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl sulfate, poloxamer (*e.g.*, poloxamer-188, poloxamer-237, poloxamer-338, poloxamer-407 and other suitable grades of poloxamer can be used), polyethylene glycol, polyethylene glycol-polylactic acid (PEG-PLA), polyethylene oxide, polyoxyethylene alkyl ether, polyoxypropylene glycol alkyl ethers, glucoside alkyl ethers, polyoxyethylene glycol octylphenol ethers, polyoxyethylene glycol alkylphenol ethers, glycerol alkyl ethers, polyoxyethylene glycol sorbitan alkyl esters, sorbitan alkyl esters, cocamide monoethanolamine, cocamide diethanolamine, dodecyldimethylamine oxide, polyethoxylated tallow amine, gelatin, albumin, guar gum, agar or copolymers thereof. In some embodiments, particle suspensions comprise one or more polymeric stabilizers in an amount of about 0.01 % w/v to about 40 % w/v.

Surfactant stabilizers include, for example, sulfuric acid alkyl ester salts (*e.g.*, sodium lauryl sulfate), dioctyl sulfosuccinate salts (*e.g.*, sodium docusate), sodium deoxycholate, polyoxylene caster oils, polysorbates, polyoxylene stearates, polyoxylglycerides, phospholipids, tocopherol derivatives, bile acid salts, propylene glycol fatty acid mono- or diesters, polyethylene glycol fatty acid esters, polysorbates, polyoxyethylene derivatives of natural oils and waxes, and sorbitan fatty acid esters or mixtures thereof. In other embodiments, particle suspensions comprise from about 0.01 % w/v to about 80 % w/v surfactant stabilizer.

Particle suspensions described herein have well-controlled and relatively narrow/uniform mean particle size distribution, which can be characterized by measuring polydispersity index (PDI). Polydispersity index is a dimensionless parameter to define the particle size distribution of micro- or nanoparticles obtained from dynamic light scattering analysis. In general, lower PDI values indicate greater particle size uniformity. In some embodiments, particle suspensions comprise particles (*i.e.*, microparticles or nanoparticles) having a PDI of below 0.400. In other embodiments, particle suspensions comprise particles having a PDI of about 0.001 to about 0.400, about 0.001 to about 0.300, 0.001 to about 0.250, about 0.001 to about 0.200, about 0.001 to about 0.190, about 0.001 to about 0.180, about 0.001 to about 0.170, about 0.001 to about 0.160, and about 0.001 to about 0.150.

Particle suspensions can also be characterized by measuring zeta potentials. Zeta potentials reflect the difference in potential between a dispersion medium and stationary layer of fluid attached to the dispersed particle. Zeta potential further indicates the degree of repulsion between adjacent, similarly charged particles in dispersion and is a useful indicator of colloidal stability, *i.e.*, resistance to particle aggregation. In some embodiments, particle suspensions described herein have a zeta potential with an absolute value of greater than 30, for example greater than about 30 mV or less than about -30 mV. In other embodiments, the particle suspensions have a zeta potential of greater than about 50 mV or less than about -50 mV. In yet other embodiments, the particle suspensions have a zeta potential of greater than about 60 mV or less than about -60 mV. In other embodiments, the particle suspensions have a zeta potential of greater than about 80 mV or less than about -80 mV. In other embodiments, the particle suspensions have a zeta potential of greater than about 100 mV or less than about -100 mV. In yet other embodiments, the particle suspensions have a zeta potential of between about -30 mV and -100 mV or between about 30 mV to about 100 mV.

In some embodiments, particle suspensions described herein have a solid concentration of about 0.5 % to about 80 % w/v. In other embodiments, particle suspensions have a viscosity of about 0.5 cps to about 600 cps.

Top-down and bottom-up techniques can form drug microparticles and/or nanoparticles in suspension having uncompromised physical stability, *e.g.,* little or negligible particle size change over time, little or negligible degradation of the drug product, little or negligible change in crystallinity/polymorphism. However, challenges arise when converting particle suspensions into solid forms where it is difficult to maintain stability, such as avoiding particle aggregation while maintaining particle size, and avoiding interconversion among polymorph forms. Stable solid microparticles and/or nanoparticles are provided by admixing one or more redispersing agents with a particle suspension prior to converting the particle suspension into a solid form.

In some embodiments, particle suspensions comprise one or more redispersing agents in an amount of about 0.1 % to about 90 % w/w. In other embodiments, redispersing agents can be present from about 1 % to about 80 % w/w or about 5 % to about 70 % w/w. In some embodiments, redispersing agents can be present from about 2.5 % to about 10 % w/w. In other embodiments, redispersing agents can be present from about 25 % to about 40 % w/w.

Solid stabilized particles can be formed from the particle suspensions described herein using various known methods including, for example, spray drying, wet granulation, dry granulation, steam granulation techniques, melt granulation techniques, moisture-activated dry granulation techniques (MADG), moist granulation techniques (MGT), thermal adhesion granulation processes (TAGP), foam granulation techniques, lyophilization, vacuum drying, oven drying, desiccant drying and the like.

In some embodiments, the mean solid particle size is between about 1 μm to about 100 μm. In other embodiments, the mean solid particle size is between about 2 μm to about 90 μm. In yet other embodiments, the mean solid particle size is between about 5 μm to about 80 μm. In other embodiments, the mean solid particle size is between about 10 μm and about 70 μm.

In further embodiments, the mean solid particle size is between about 0.5 nm to about 1000 nm. In other embodiments, the mean solid nanoparticle size is less than about 900 nm. In other embodiments, the mean solid nanoparticle size is between about 0.5 nm to about 800 nm. In yet other embodiments, the mean solid nanoparticle size is between about 200 nm to about 400 nm.

Solid stabilized particles formed from the particle suspensions described herein also have well-controlled and relatively narrow mean particle size distribution. Without being bound to any theory, narrow mean particle size distribution can provide highly bioavailable pharmaceutical compositions having consistent drug delivery with less PK variability. In some embodiments, solid stabilized particles formed from the particle suspensions described herein have a polydispersity index (PDI) of below 0.400. In other embodiments, solid stabilized particles formed from the particle suspensions described herein have a PDI of about 0.001 to about 0.400, 0.001 to about 0.300, 0.001 to about 0.250, about 0.001 to about 0.200, about 0.001 to about 0.190, about 0.001 to about 0.180, about 0.001 to about 0.170, about 0.001 to about 0.160, and about 0.001 to about 0.150.

In some embodiments, spray drying is used to make solid stabilized particles comprising {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, spray dried solid stabilized particles can be used directly as a solid dosage form or further formulated into a solid dosage form, such as a tablet and the like.

In other embodiments, wet granulation is used to make solid stabilized particles comprising {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. Wet granulation methods include, for example, standard wet granulation techniques and specialized wet granulation techniques, such as high-shear mixture granulation, fluid-bed granulation, extrusion, spheronization lyophilization, spray dry granulation and the like. In certain embodiments, fluid-bed granulation or spray dry granulation is used to make solid stabilized particles comprising {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. Dry granulation methods include standard dry granulation and specialized dry granulation techniques, such as slugging, roller compaction, and the like. Melt granulation methods include thermoplastic melt granulation and the like.

Wet granulation methods involve the use of a liquid binder solution comprising one or more binders. Liquid binder solutions can be mixed with a powder to cause the powder to agglomerate lightly, thereby forming granules. In some embodiments, one or more redispersing agents are added to the liquid binder solution, which is then added to a particle suspension of the present invention prior to granulation. Following granule formation, the granules are typically dried and sized (using, *e.g.*, mesh screens). In some embodiments, the granules can be milled to achieve a desired particle size. Both low-shear and high-shear mixing equipment can be utilized.

Suitable binders include cellulose derivatives (*e.g.*, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose acetate, hydroxypropylmethyl cellulose phthalate, hydroxypropyl cellulose, methylcellulose, hydroxyethyl cellulose, hydroxethyl cellulose acetate, and the like), monosaccharides (*e.g.*, dextrose and the like), polysaccharides/oligosaccharides (*e.g.*, dextrin, maltodextrin, pectin, maltose, polydextrose, starch and the like), polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl caprolactam, carbomer, povidone, copovidone, gelatin, natural gums (*e.g.*, guar gum, acacia, carrageenan, agar, alginic acid, gum arabic, and the like), poloxamer, polycarbophil or mixtures thereof. Binders can be present in amounts from about 0.01 % to about 20 % w/w dry weight.

Binder solutions can also include one or more fillers, diluents, disintegrants or mixtures thereof. Suitable filler/diluents include, for example, microcrystalline cellulose, dicalcium phosphate, lactose, starch, calcium carbonate, calcium lactate, calcium phosphate, calcium

silicate, calcium sulfate, hypromellose, pregelatinzed starch, dextrin, magnesium carbonate, magnesium oxide, maltodextrin, maltose, polydextrose, polymethacrylate, simethicone, sodium alginate, sodium carbonate, mannitol, trehalose, xylitol, lactose, sucrose, sorbitol, lactitol, maltitol, erythritol, threitol, arabitol, ribitol, galactitol, fucitol, iditol, inocitol, velomitol, isomalt or mixtures thereof. Fillers/diluents can be present in amounts from about 0.1 % to about 99 % w/w dry weight.

Suitable disintegrants include, for example, croscarmellose sodium, sodium starch glycolate, microcrystal cellulose, crospovidone, pregelatinized starch, sodium alginate, chitosan, magnesium aluminum silicate; methyl cellulose, guar gum or mixtures thereof. Disintegrants can be present in amounts from about 0.01 % to about 30 % w/w dry weight.

Dosage Forms

The invention further provides pharmaceutical compositions in forms for oral administration. Such pharmaceutical compositions exhibit chemical stability and show little or no degradation of the drug product into degradation products. Pharmaceutical compositions can be in solid or liquid form. In one embodiment, the pharmaceutical composition is a solid composition. Pharmaceutical compositions comprise solid stabilized particles described herein.

In one aspect, pharmaceutical compositions of the present invention may be prepared by controlling microenvironmental pH of the composition. Thus, in one embodiment, the present invention relates to pharmaceutical compositions (*e.g.*, solid oral dosage forms) comprising solid stabilized particles and a compound that modulates the pH environment of the composition (*e.g.*, an alkalizer), wherein the solid stabilized particles comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

In some embodiments, pharmaceutical compositions comprise about 0.5 mg to about 1200 mg of {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, pharmaceutical compositions comprise about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950

mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg or about 1200 mg of {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

Solid oral compositions of the present invention can be formulated to have an immediate release profile as referenced by FDA guidelines ("Dissolution Testing of Immediate Release Solid Oral Dosage Forms", issued 8/1997, Section IV-A). In the dissolution testing guideline for immediate release profiles, materials which dissolve at least 80 % in the first 30 to 60 minutes in solution qualify as immediate release profiles. Therefore, in one embodiment, solid oral compositions release of most or all the active ingredient over a short period of time, such as 60 minutes or less, and make rapid absorption of the drug possible. In other embodiments, solid oral compositions release about 80 % of the drug over about 15 minutes.

In some embodiments of the invention, the solid composition further comprises at least one additional pharmaceutical ingredient. Additional pharmaceutical ingredients include any component or excipient other than powdered pharmaceutically acceptable carriers, so long as the material is not generally deleterious to a human subject when the solid composition is administered at dosing quantities. Non-limiting examples of additional ingredients include: glidants and lubricants, such as colloidal silica, talc, magnesium stearate, calcium stearate, stearic acid, solid polyethylene glycol, sodium oleate, sodium stearate, sodium benzoate, sodium acetate, sodium chloride, sodium stearyl furamate, and sodium lauryl sulfate; solubilizing agents, such as agar-agar, calcium carbonate, sodium carbonate, croscarmellose sodium, starches, pregelatinized starches, sodium starch glycolate, crospovidone, methyl cellulose, agar, bentonite, xanthan gum, alginic acid, and certain silicates; solution retarding agents, such as polymers, for example biodegradable polymers such as polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogelsparaffin, and wax, for example, paraffin; resorption accelerating agents, such as quaternary ammonium compounds; absorption agents, such as quaternary ammonium compounds, bentonite, kaolin, or dicalcium phosphate.

The pharmaceutical compositions of the invention can be prepared by various means. Such compositions comprise solid stabilized particles. In some embodiments, the solid stabilized particles are provided as powder.

In some embodiments, capsules may be prepared by, for example, obtaining solid stabilized particles described herein containing {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof and encapsulating the solid stabilized particles with gelatin or another suitable shell material. In some embodiments, the solid stabilized particles are provided as a powder. Additional ingredients, such as those described herein, including alkalizers, binders, fillers, diluents, glidants, lubricants, disintegrating agents, solubilizing agents, or mixtures thereof may be combined with the solid stabilized particles prior to encapsulation.

In other embodiments, tablets may be prepared by, for example, obtaining solid stabilized particles described herein containing {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof and pressing the solid stabilized particles into tablets using conventional methods. In some embodiments, the solid stabilized particles are provided as a powder. Additional ingredients, such as those described herein, including binders, fillers, diluents, glidants, lubricants, disintegrating agents, solubilizing agents, solution retardants, absorption agents, or mixtures thereof, may be added to the solid stabilized particles before pressing into tablets.

The tablets described herein may be either uncoated or coated. In various embodiments, tablets are coated with a clear or opaque protective coating, which may for example, comprise a sealing coat of shellac, a coating of sugar or polymeric material, and/or a polish coating of wax. In various embodiments, tablets are coated to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Such coatings may comprise glyceryl monostearate or glyceryl distearate. Additionally, dyestuffs can be added to these coatings to distinguish different unit dosages.

The dosage of the pharmaceutical composition of the present invention will vary depending on the symptoms, the treatment desired, age and body weight of the subject, the nature and severity of the disorder to be treated, the route of administration and pharmacokinetics of the active ingredients. The frequency of the dose indicated will also vary with the treatment desired and the disorder indicated.

In one embodiment, {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt is administered in an amount

sufficient to achieve a therapeutic effect. The dosage range for {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt can be from about 0.5 mg to about 2400 mg per day in one or more administrations. In other embodiments, {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt can be administered in amounts from about 5 mg to about 1200 mg per day, or about 10 mg to about 800 mg per day in one or more administrations. In some embodiments, {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt can be administered in one or more administrations for a total daily amount of about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2300 mg or about 2400 mg.

In some embodiments, the dosage of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt can be in an amount from about 0.001 mg/kg of body weight per day to about 100 mg/kg of body weight per day. In other embodiments, the dosage of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt can be in an amount from about 0.003 mg/kg of body weight per day to about 60 mg/kg of body weight per day. In yet other embodiments, the dosage of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt can be in an amount of about 0.5 mg/kg of body weight per day, about 1 mg/kg of body weight per day, about 2 mg/kg of body weight per day, about 5 mg/kg of body weight per day, about 10 mg/kg of body weight per day, about 20 mg/kg of body weight per day, about 40 mg/kg of body weight per day or about 60 mg/kg of body weight per day. One skilled in the art will appreciate that the administered doses can be converted to suitable human equivalent doses.

Pharmaceutical compositions described herein may exhibit improved biovailability of {2-[3-cyclohexyl-3-(*trans*-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a

pharmaceutically acceptable salt thereof upon administration to a subject relative to reference compositions that do not include a solid stabilized particle described herein.

Methods of use:

The present invention also provides methods for treating a disease, disorder or condition that can be managed by activating glucokinase in a subject (*e.g.*, a mammal, such as a human) by administering to a patient in need thereof a stable pharmaceutical composition described herein. Such methods including, for example, treating type I diabetes and/or type II diabetes; normalizing or lowering blood glucose levels; improving glucose tolerance; improving glycemic control; reducing fasting plasma glucose; reducing postprandial plasma glucose; reducing glycosylated hemoglobin HbA1c; slowing progression of, delaying or treating complications of diabetes, *e.g.*, diabetic nephropathy, retinopathy, neuropathy or cardiovascular disease; reducing weight or preventing an increase of weight or facilitating a reduction of weight; treating the degeneration of pancreatic beta cells; improving and/or restoring functionality of pancreatic beta cells; stimulating and/or restoring functionality of pancreatic insulin secretion; enhancing phosphorylation of glucose; or maintaining and/or improving insulin sensitivity; and/or treating or preventing hyperinsulinemia and/or insulin resistance.

In one embodiment, the present invention relates to treating type II diabetes comprising administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In another embodiment, the present invention provides for normalizing blood glucose levels and improving glucose tolerance by administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective

amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In another embodiment, the present invention provides for improving glycemic control; and/or for reducing fasting plasma glucose, reducing postprandial plasma glucose and/or reducing glycosylated hemoglobin HbA1c by administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In some embodiments, the administration of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof may reduce the levels of HbA1C in a subject in need thereof. In other embodiments, the administration of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof may reduce the amount of HbA1C in a subject in need thereof by at least 0.1 of a percentage point, or 0.2 of a percentage point, or 0.3 of a percentage point, or 0.4 of a percentage point, or 0.5 of a percentage point, or 0.6 of a percentage point, or 0.7 of a percentage point, or 0.8 of a percentage point, or 0.9 of a percentage point, or one percentage point. In still other embodiments, the administration of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof may reduce the level of HbA1C in a subject in need thereof to less than 7%. In other embodiments, the level of HbA1C may be reduced to a level between 5 and 6.5%.

In another embodiment, the present invention provides for slowing progression of, delaying or treating complications (*e.g.*, diabetic nephropathy, retinopathy, neuropathy or cardiovascular disease) by administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of

about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In yet another embodiment, the present invention provides for reducing weight or preventing an increase of weight or facilitating a reduction of weight by administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In another embodiment, the present invention provides for treating the degeneration of pancreatic beta cells; and/or improving and/or restoring functionality of pancreatic beta cells; and/or stimulating and/or restoring functionality of pancreatic insulin secretion by administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In another embodiment, the present invention provides for maintaining and/or improving insulin sensitivity; and/or treating or preventing hyperinsulinemia and/or insulin resistance by administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In yet another embodiment, the present invention provides for decreasing the daily dose of insulin by administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In yet another embodiment, the present invention provides for treating a condition in a subject comprising administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof, wherein the condition is selected from metabolic disorders (including metabolic syndrome), glucose intolerance, prediabetic state, insulin resistance, blood glucose lowering, hyperglycemia, impaired glucose tolerance (IGT), Syndrome X, impaired fasting glucose (IFG), type II diabetes, type I diabetes, delaying IGT to type II diabetes, delaying the progression of non-insulin-requiring type II diabetes to insulin-requiring type II diabetes, dyslipidemia, hyperlipidemia, hyperlipoproteinemia, hypertension, osteoporosis, non-alcoholic fatty liver disease (NAFLD), complications resulting from or associated with diabetes, (including nephropathy, retinopathy, neuropathy, impaired wound healing)) cardiovascular disease (including arteriosclerosis, atherosclerosis), lowering of food intake, appetite regulation, obesity, regulating feeding behavior, and enhancing secretion of enteroincretins. In other embodiments, the nanoparticles further comprise one or more redispersing agents.

In other embodiments, the present invention provides for methods of treatment described herein as an adjunct to diet and exercise in subjects with type II diabetes or type I diabetes.

Definitions

The term "pharmaceutically acceptable" means biologically or pharmacologically compatible for *in vivo* use in animals or humans, and preferably means approved by a regulatory

agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term "treating," "treatment," and "treat" refer to managing or controlling a disease, condition or disorder. This includes relieving, alleviating, ameliorating, delaying, reducing, reversing, improving a disease, disorder or condition or at least one symptom thereof, depending on the nature of the disease, disorder, or condition and its characteristic symptoms.

The term "subject" means animals. The subject can be any animal in the context of a trial or screening or activity experiment. Thus, as can be readily appreciated by one of ordinary skill in the art, the methods, compounds, and formulations of the present invention are particularly suited to administration to any animal, particularly a mammal, and including, but not limited to, humans, domestic animals, such as feline or canine subjects, farm animals, such as bovine, equine, caprine, ovine and porcine subjects, wild animals, research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, cats etc., avian species for veterinary medical use.

The terms "effective amount" and "therapeutically effective" refer to an amount or quantity of a compound or pharmaceutical formulation that is sufficient to result in a desired biological or therapeutic response in a tissue, system, or subject in need thereof. For example, the terms "effective amount" and "therapeutically effective amount" refer to an amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof that is sufficient to produce an effective response upon administration to a subject. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the subject to be treated.

The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviation, per practice in the art. Alternatively, "about" with respect to the formulations can mean plus or minus a range of up to 30 %, up to 20 %, up to 10 % and even up to 5 %.

The pharmacokinetic parameters described herein include area under the plasma concentration-time curve (AUC_{0-t} and $AUC_{0-\infty}$), maximum plasma concentration (C_{max}) and time of maximum plasma concentration (T_{max}). The time of maximum concentration, T_{max}, is

determined as the time corresponding to C_{max}. Area under the plasma concentration-time curve up to the time corresponding to the last measurable concentration (AUC_{0-t}) is calculated by numerical integration using the linear trapezoidal rule as follows:

$$AUC_{0-t} = \sum_{i-2} 0.5 \cdot (C_i = C_{i-1}) \cdot (t_i - t_{i-1}) \qquad \text{Eq. 1}$$

where C_i is the plasma concentrations of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid at the corresponding sampling time point t_i and n is the number of time points up to and including the last quantifiable concentration.

The area under the plasma concentration-time curve from time zero to infinity is calculated according to the following equation :

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_{last}}{\lambda_z} \qquad \text{Eq. 2}$$

where C_{last} is the last measurable concentration.

The following examples are merely illustrative of the present invention and should not be construed as limiting the scope of the invention in any way. Many variations and equivalents that are encompassed by the present invention will become readily apparent to those skilled in the art upon reading the present disclosure.

EXAMPLES

A. Preparation of Particle Suspensions

General Experimental Procedure to Prepare Microsuspensions or Nanosuspensions of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (drug ingredient)

A polymeric stabilizer (10 g, 1 % w/v) was added to 1 L purified water with mixing until a clear solution was obtained. A surfactant stabilizer (5 g, 0.5 % w/v) was added to the solution with mixing until a clear solution was obtained. {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (100 g, 10 % w/v) was then added stepwise with mixing until a uniform suspension was obtained. The suspension was microfluidized using a Microfluidizer M-110EH equipped with a mixing chamber of 200 microns and interaction of

80 microns at a mill pressure of between about 20,000 to about 30,000 psi until there was no further particle size reduction. The resulting particle suspension was collected.

Example 1

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was prepared using the method above, where the polymeric stabilizer was hydroxypropyl methylcellulose (HPMC) and the surfactant stabilizer was sodium lauryl sulfate (SLS). The resulting nanosuspension had a 10 % solid content, a mean particle size of 225.6 nm, a polydispersity index of 0.145 and a zeta potential of -57.6 mV.

The physical stability of the nanosuspension is shown in the Table 1 below, where no agglomeration was observed after storage at room temperature for 6-48 hours and at 5 °C for 1.5 months.

Table 1: Physical stability of nanoparticle suspension

Time/Temp	Mean particle size (nm)
0	225.6
6 h, RT	223.1
24 h, RT	230.9
48 h, RT	229.4
1.5 month, 5°C	226.0

Figure 1 shows X-ray powder diffraction (XRPD) patterns of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid obtained from lyophilizing the drug suspension prior to nanosizing ("A") and after nanosizing ("B") by microfluidization. The crystal structure of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was not changed during nanosizing.

Figure 2 shows a differential scanning calorimetry graph of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid obtained from lyophilizing the drug suspension prior to nanosizing ("A") and after nanosizing ("B") by microfluidization. Chemical stability of the drug suspension before and after nanosizing (via monitoring drug degradation induced by the nanosizing process) is shown in Table 2 below.

Table 2: Degradation profile of active ingredient suspension before and after nanosizing

Sample	Degradant profile									
	A	B	C	D	E	F	G	H	I	Drug Ingredient % Assay
Suspension before nanosizing 100µg/mL	0.04	0.02	0.04	0.2	0.05	0.04	0.02	0.02	0.02	99.49
Nanosuspension 100µg/mL	0.04	0.02	0.04	0.19	0.05	0.04	0.04	0.02	0.02	99.47

Chemical stability of the nanosuspension stored under refrigerated conditions is shown in Table 3 below.

Table 3 Degradation profile of drug ingredient nanosuspension stored at 5 °C

Sample	Degradation profile									
	A	B	C	D	E	F	G	H	I	Drug Ingredient %Assay
3 wks T-1	0.09	0.03	0.03	0.2	0.04	0.03	0.02	0.01	0.02	99.53
3 wks T-2	0.07	0	0.03	0.19	0.04	0.04	0.03	0.01	0.02	99.57
2 month T-1	0.07	0	0.04	0.19	0.04	0.03	0.03	0.02	0.02	99.56
2 month T-2	0.07	0	0.04	0.19	0.04	0.03	0.02	0.02	0.02	99.59

Example 2

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was prepared using the method above, where the polymeric stabilizer was hydroxypropyl cellulose (HPC) and the surfactant stabilizer was sodium lauryl sulfate (SLS). The resulting nanosuspension had a 10 % solid content, a mean particle size of 252.2 nm, a polydispersity index of 0.171 and a zeta potential of -55.6 mV.

Example 3

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was prepared using the method above, where the polymeric stabilizer was poloxamer 188 and the surfactant stabilizer was sodium lauryl sulfate (SLS). The resulting nanosuspension had a 10 % solid content, a mean particle size of 260.4 nm, a polydispersity index of 0.183 and a zeta potential of -54.4 mV.

Example 4

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was prepared using the method above, where the polymeric stabilizer was polyvinyl alcohol and the surfactant stabilizer was sodium lauryl sulfate (SLS). The resulting nanosuspension had a 10 % solid content, a mean particle size of 261.4 nm, a polydispersity index of 0.166 and a zeta potential of -57.3 mV.

Example 5

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was prepared using the method above, where the polymeric stabilizer was hydroxypropyl cellulose and the surfactant stabilizer was sodium lauryl sulfate (SLS). The resulting nanosuspension had a 10 % solid content, a mean particle size of 252.2 nm, a polydispersity index of 0.171 and a zeta potential of -55.6 mV.

Example 6

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was prepared using the method above, where the polymeric stabilizer was polyvinyl pyrrolidone and the surfactant stabilizer was sodium lauryl sulfate (SLS). The resulting nanosuspension had a 10 % solid content, a mean particle size of 258.7 nm, a polydispersity index of 0.154 and a zeta potential of -58.3 mV.

Example 7

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is polyvinyl sulfate and the surfactant stabilizer is sodium lauryl sulfate (SLS).

Example 8

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is polyethylene glycol-polylactic acid (PEG-PLA) and the surfactant stabilizer is sodium lauryl sulfate (SLS).

Example 9

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is gelatin and the surfactant stabilizer is sodium lauryl sulfate (SLS).

Example 10

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is agar and the surfactant stabilizer is sodium lauryl sulfate (SLS).

Example 11

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is hydroxypropylmethyl cellulose and the surfactant stabilizer is polysorbate 80.

Example 12

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is hydroxypropylmethyl cellulose and the surfactant stabilizer is sodium docusate.

Example 13

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is hydroxypropylmethyl cellulose and the surfactant stabilizer is sodium deoxycholate.

Example 14

A nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid is prepared using the method above, where the polymeric stabilizer is hydroxypropylmethyl cellulose and the surfactant stabilizer is vitamin E polyethylene glycol succinate.

B. Preparation of Nanogranules

General Experimental Procedure to Prepare Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (drug ingredient):

Solvent was removed from a nanosuspension obtained from Example 1 until the nanosuspension had a total weight of 1000 g with 10 % w/w solid content. A redispersing agent (50 g, 5 % w/w) was added to the nanosuspension and the mixture was stirred until redispersing agent was completely dissolved. A fluid bed was warmed to about 60 °C and a binder (800 g, 80 % w/w) and filler (5 g, 5 % w/w) were added to the fluid bed. The excipients were fluidized in the fluid bed to mix. The nanosuspension was top sprayed in the fluid bed while maintaining a product temperature of about 40 °C. After top spraying is complete, the resulting granules were dried at 40 °C until less than 3 % loss on drying (LOD) of the granules is obtained.

Example 15

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid were prepared using the general method above, where the redispersing agent was mannitol, the binder was hydroxypropylmethyl cellulose and the filler was microcrystalline cellulose.

The nanoparticle size after granulation is shown in Table 4 below, with a comparison of particle size with and without redispersing agent.

Table 4: Particle size of reconstituted {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid

	Nanoparticle size (nm)	PDI
Before granulation	252.1	0.172
Reconstituted nanogranule without redispersing agent	479.3	0.385
Reconstituted nanogranule with redispersing agent	399.6	0.322

Example 16

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is trehalose, the binder is hydroxypropylmethyl cellulose and the filler is microcrystalline cellulose.

Example 17

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is sorbitol, the binder is hydroxypropylmethyl cellulose and the filler is microcrystalline cellulose.

Example 18

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is lactose, the binder is hydroxypropylmethyl cellulose and the filler is microcrystalline cellulose.

Example 19

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing

agent is sucrose, the binder is hydroxypropylmethyl cellulose and the filler is microcrystalline cellulose.

Example 20

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is isomalt, the binder is hydroxypropylmethyl cellulose and the filler is microcrystalline cellulose.

Example 21

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is innulin, the binder is hydroxypropylmethyl cellulose and the filler is microcrystalline cellulose.

Example 22

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is dextran, the binder is hydroxypropylmethyl cellulose and the filler is microcrystalline cellulose.

Example 23

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is dicalcium phosphate.

Example 24

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is isomalt.

Example 25

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is lactose.

Example 26

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is mannitol.

Example 27

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is starch.

Example 28

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is trehalose.

Example 29

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is sodium carbonate.

Example 30

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is glucose.

Example 31

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropylmethyl cellulose and the filler is hydroxypropylmethyl cellulose.

Example 32

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is hydroxypropyl cellulose and the filler is microcrystalline cellulose.

Example 33

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is polyvinyl pyrrolidone and the filler is microcrystalline cellulose.

Example 34

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is polyvinyl alcohol and the filler is microcrystalline cellulose.

Example 35

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is polyvinyl caprolactam and the filler is microcrystalline cellulose.

Example 36

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is gelatin and the filler is microcrystalline cellulose.

Example 37

Nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid are prepared using the general method above, where the redispersing agent is mannitol, the binder is pregelatinized starch and the filler is microcrystalline cellulose.

C. Preparation of Spray-Dried Nanoparticles

General Experimental Procedure to Prepare Spray-Dried Nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (drug ingredient):

Solvent was removed from a nanosuspension obtained from Example 1 until the nanosuspension had a total weight of 1000 g with 10 % w/w solid content. A redispersing agent (50 g, 5 % w/w) was added to the nanosuspension and the mixture was stirred until the redispersing agent was completely dissolved. The nanosuspension was spray dried using a spray dryer with an inlet temperature of 90 ± 10°C and outlet temperature of 50 ± 10°C. After all of the nanosuspension was spray dried, the dried nanoparticles were collected from cyclone of the spray drier (Buchi Mini Spray Dryer B-290, Buchi Labortechnik AG, Flawil, Switzerland). TGA analysis of the resulting spray dried nanoparticles gave a moisture content of about 0.1 %. The particle size of the spray-dried nanoparticles was characterized using a Melvern Zetasizer ZS (Model Zen3600, by Malvern Instruments, Ltd., Worcestershire, United Kingdom).

Example 38

Spray-dried nanoparticles were prepared using the general procedure above, where the redispersing agent was mannitol. Table 5 shows the particle size of nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid before and after spray drying.

Table 5: Particle size of spray-dried nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid

	Nanoparticle size (nm)	PDI
Before spray drying	222	0.112

(nanosuspension)		
spray dried nanoparticle	258	0.219

Figure 3 shows X-ray powder diffraction (XRPD) patterns of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid and spray-dried nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid. The crystal structure of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid was not changed during spray drying.

Stability of the active ingredient after being subjected to spray drying is shown in Table 6 below. Spray drying did not result in significant degradation of the active ingredient.

Table 6. Degradation profile of spray dried nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid

Sample	Degradant Profile											Drug Ingredient % Assay
	a	b	c	d	e	f	g	h	i	j	k	
%	0.17	0	0	0.02	0.09	0.01	0.04	0.01	0.03	0.04	0.02	99.53

D. Solid dosage forms of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid

Example 39

Preparation of Capsules Containing Spray Dried Nanoparticles:

Spray dried nanoparticles prepared in Example 38 (424 mg, containing {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid 0.47 g/g) was blended with meglumine (100 mg) in a V-blender for 15 minutes, and then tested for blend uniformity. The blend was then charged into a powder station of a capsule filling machine. After adjusting the capsule fill weight based on the composition, the blend was filled into gelatin capsules.

Example 40

Preparation of Capsules Containing Nanogranules:

A mixture of isomalt (106 mg, Galen IQ 800), polyvinyl pyrrolidone (20 mg, PVP K30) and meglumine (150 mg) was screened through a 20 mesh hand screen. The screened mixture was added to a fluid bed granulator heated to 50 °C, and the nanosuspension of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid obtained in Example 1 (about 2224 g) was top-sprayed onto the substrate. The product temperature was maintained at 40 °C during granulation. After granulation was completed, the nanogranules were dried until the moisture content was less than 3%. The nanogranules were discharged and then stored in a refrigerator for at least 12 hours, and then brought to room temperature. The nanogranules (500 mg) were then charged into a powder station of a capsule filling machine. After adjusting the capsule fill weight based on the composition, the nanogranules were filled into gelatin capsules (size AA EL, Grey Opaque).

Figure 4 shows the dissolution of: a capsule containing only micronized {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (API Cap); a capsule containing granules formulated with micronized {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (reference capsule)
a capsule containing spray-dried nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid obtained from Example 39, and a capsule containing nanogranules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid obtained from Example 40.

The dissolutions were conducted in an aqueous medium of 0.3 % w/v sodium laurel sulfate in 0.01 N HCl, pH 2, pedal method, 50 rpm. The dissolution was performed at 37 °C for up to 60 minutes, and dissolution sampling was performed at 15, 30, 45 and 60 minutes. Drug release was analyzed using HPLC.

Example 41

Preparation of Tablets Containing Nanogranules

A mixture of isomalt (106 mg, Galen IQ 800), polyvinyl pyrrolidone (20 mg, PVP K30) and meglumine (150 mg) was screened through a 20 mesh hand screen. The screened mixture was added to a fluid bed granulator heated to 50 °C, and the nanosuspension of {2-[3-

cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid obtained in Example 1 (about 2224 g) was top-sprayed onto the substrate. The product temperature was maintained at 40 °C during granulation. After granulation was completed, the nanogranules were dried until the moisture content was less than 3%. The nanogranules were discharged and then stored in a refrigerator.

The nanogranules were brought to room temperature and then milled to obtain uniform particle size. The milled granules (500 mg) were screened through a 20 mesh hand screen then added to a V-blender. A mixture of croscarmellose sodium (18 mg), isomalt (74 mg) was screened through a 20 mesh hand screen and added to the V-blender. The mixture was blended for about 15 minutes. Talc (5 mg) was screened through a 20 mesh hand screen and then added to the V-blender. The mixture was blended for about 5 minutes. Magnesium stearate (3 mg) was screened through a 20 mesh hand screen and added to the V-blender. The mixture was blended for 5 minutes. The blended mixture was then discharged. The blended mixture was added into the hopper of a tablet press, and was compressed to form a tablet with a weight of 600 mg and hardness of 8 to 12 kiloponds (kp).

Example 42

A Single Dose Study Conducted in Male Beagle Dogs

Various 100 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid oral formulations were administered in single doses to male beagle dogs on Day 1 and Day 11. Measurable plasma samples were obtained and analyzed at 0.5 hours to 24 hours for concentrations of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid by a validated LC-MS/MS assay (Internal Standards: deuterated compounds; Sample Preparation: liquid extraction; Sample Volume: 1 mL; Calibration Range: 1.00 - 1.000 ng/mL; Ionization: Turbo IonSpray).

The subjects in the study were administered the following formulations:

A. 10 mL aqueous solution of 10 mg/mL {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid and 1% meglumine

B. Capsules containing nanogranules having 100 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid,

C. Spray-dried nanoparticle capsules containing 100 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid, and

D. Capsules containing granules formulated with 100 mg micronized {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (reference capsule).

The mean pharmacokinetic parameters observed after administration of a single dose of the above formulations are shown below in Table 7.

Table 7. Pharmacokinetic Parameters on Day 1 and Day 11 Following Oral Administration of 100 mg active ingredient in Various Formulations to Male Dogs

Formulation	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng*hr/mL)
A	8870	0.667	13686
B	6730	1.17	14196
C	6657	0.833	11532
D	2680	2.33	7488

Figure 5 shows the *in vivo* exposure ($AUC_{0-\infty}$) of these various formulations in beagle dogs.

Example 43

Single-Dose Study Conducted in Healthy Subjects

Healthy subjects were randomized into different groups (A, B and C) in a single-center, randomized, open-label, 4-way cross-over study with 7-day washout period. Measurable plasma samples were obtained and analyzed at 1 hour to 24 hours for concentrations of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid by a validated assay.

The subjects were administered the following formulations under fasted conditions with water:

A. 4 x 200 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid capsule (reference)

B. 4 x 200 mg capsules of spray-dried nanoparticles of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid

C. 4 x 200 mg capsules of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid nanogranules.

Formulation A (Reference):

Microgranules of Formulation A was prepared with the following ingredients:

Ingredient	**% w/w**	**Theor. wt (mg/g)**
Active Ingredient	65.60	657.0
Microcrystalline Cellulose, NF (Ph.Eur. (Avicel PH101)	11.50	115.0
Lactose Monohydrate	12.29	122.9
Croscarmellose sodium, NF (Ac-Di-Sol)	7.56	75.6
Polysorbate 80, NF	2.37	23.7
Hydropropyl Methylcellulose E3 LV premium	0.59	5.9
Sterile Water for irrigation	N/A	N/A
Granule Total, 200 mg active ingred./304.4 mg	**100**	**1000**

A master blend having the following ingredients was then prepared from the microgranules:

Ingredient	**% w/w**	**Theor. wt (mg/g)**
Granule Total, 200 mg active ingred./304.4 mg	84.56	845.6
Microcrystalline Cellulose, NF (Ph.Eur. (Avicel PH101)	4.94	49.4
Croscarmellose sodium, NF (Ac-Di-Sol)	5.00	50.0
Pregelatinized Starch, NF (Starch 1500)	5.00	50.0
Magnesium Stearate, NF (Hyqual 2257)	0.50	5.0
Active Ingred. Master Blend, 200 mg/360 mg	**100**	**1000**

Capsules (gelatin capsules, size 0, gray opaque, 96 mg) were then filled with 180 mg of the active ingredient master blend, 200 mg/360 mg.

Formulation B (capsules with spray dried nanoparticles):

A nanoparticle suspension composition with 10 % solids was prepared as described in Example 2, except using the following modified amounts for each ingredient:

Ingredient	% w/w	Theor. wt (mg/g)
Active Ingredient	10.0	9.0
Hydropropyl Cellulose	0.2	0.2
Sodium Lauryl Sulfate	1	0.9
Purified Water, USP	N/A	89.9
Nanoparticle Suspension, 10 % solids	**N/A**	**100**

Using the procedure of Example 38, the nanoparticle suspension was spray-dried to form spray-dried nanoparticles, where the redispersing agent was mannitol in a modified amount of 90 g (9 % w/w). The resulting spray dried nanoparticles contained 0.47 g of active ingredient per gram of total dry weight. A master blend was then formed by combining the spray dried nanoparticles (80.9 %) with meglumine (19.1 %), to form a master blend having 200 mg of active ingredient per 524 mg total dry weight. Capsules (gelatin capsules, size AA EL, gray opaque, 168 mg) were then filled with 524 mg of the active ingredient master blend, 200 mg/524 mg.

Formulation C (Capsules with nanogranules)

Nanoparticle granules were prepared using the general procedure in Example 40, except the nanoparticle suspension was obtained in Formulation B above, and each ingredient amount was modified as follows:

Ingredient	% w/w	Theor. wt (mg/g)
Nanoparticle Suspension, 10% solids	44.8	448
Isomalt (GalenIQ 800)	21.2	212
Meglumine	30	300
Polyvinyl Pyrrolidone (PVP K30)	4	40
Nanoparticle Granules, 200 mg/500 mg	**100**	**1000**

Capsules (gelatin capsules, size AA EL, gray opaque, 168 mg) were then filled with 500 mg of the nanoparticle granules, 200 mg/500 mg.

The mean pharmacokinetic parameters observed after administration of a single dose of the above formulations are shown below in Table 8.

Table 8. Summary Pharmacokinetic Parameters Following Oral Administration in Healthy Subjects

Formulation	Cmax (ng/mL)	Tmax (hr)	$AUC_{0-\infty}$ (ng*hr/mL)
A	1382	1.5	4705
B	5802	1.5	10347
C	5606	1.0	10231

Figures 6 and 7 show the *in vivo* exposure (AUC and Cmax respectively) in the three groups.

Example 44

Multiple Dose Study in Patients with Type 2 Diabetes Mellitus

Patients with Type 2 diabetes mellitus were randomized into different groups (A, B and C) in a multi-center, randomized, double-blind, parallel-group, multiple-dose study. The patients were administered the following formulations:

A. Single oral dose of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (1x 200 mg capsule) on Day 1 followed by multiple oral doses of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (1x 200 mg capsule) twice daily (BID) (reference).

B. Single oral dose of 800 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (4 x 200 mg capsule) on Day 1 followed by multiple oral doses of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid 800 mg (4x 200 mg capsule) once daily (QD).

C. Single oral dose of 800 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid (4 x 200 mg capsule) on Day 1 followed by multiple oral doses of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid 800 mg (4x 200 mg capsule) twice daily (BID).

The mean pharmacokinetic parameters observed after administration of a single dose of the above formulations are shown below in Table 9.

Table 9. Summary Pharmacokinetic Parameters After 42 days Following Oral Administration in Patients with Type 2 Diabetes Mellitus

Formulation	Cmax (ng/mL)	Tmax (hr)	AUC_{0-24} (ng*hr/mL)
A	1047	1	3825
B	10802	1	16218
C	9794	1	29407

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition of claim 1, wherein the nanoparticles further comprise one or more redispersing agents.

3. The pharmaceutical composition of claim 1, wherein the nanoparticles have a mean diameter between about 200 nm to about 400 nm.

4. The pharmaceutical composition of claim 3, wherein the nanoparticles have a polydispersity index of about 0.001 to about 0.300.

5. The pharmaceutical composition of claim 1, wherein the one or more alkalizers are selected from the group consisting of meglumine, sodium carbonate, potassium carbonate, calcium carbonate, magnesium oxide, calcium hydroxide, sodium hydroxide, potassium hydroxide, diethanolamine, potassium bicarbonate, potassium citrate, sodium borate, sodium citrate, triethanolamine and a mixture thereof.

6. The pharmaceutical composition of claim 5, wherein the one or more alkalizer is meglumine.

7. The pharmaceutical composition of claim 2, wherein the one or more redispersing agents are selected from the group consisting of mannitol, trehalose, xylitol, lactose, sucrose, sorbitol, dextran, lactitol, maltitol, erythritol, threitol, arabitol, ribitol, galactitol, fucitol, iditol, inocitol, velomitol, isomalt, inulin and a mixture thereof.

8. The pharmaceutical composition of claim 1, wherein the nanoparticles are formed by removing solvent from a nanoparticle suspension comprising:
(a) {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof,
(b) one or more stabilizers,
(c) one or more redispersing agents, and
(d) one or more solvents.

9. The pharmaceutical composition of claim 8, wherein the one or more solvents are selected from the group consisting of water, methanol, heptane, propanol, isopropanol, acetic acid, acetone, ethyl acetate, ethanol and a mixture thereof.

10. The pharmaceutical composition of claim 8, wherein the one or more stabilizers are selected from the group consisting of a polymeric stabilizer, a surfactant stabilizer and a mixture thereof.

11. The pharmaceutical composition of claim 8, wherein the nanoparticle suspension has a zeta potential of greater than about 30 mV or less than about -30 mV.

12. The pharmaceutical composition of claim 1, further comprising one or more of a binder, a filler, a diluent, a disintegrant or a mixture thereof.

13. The pharmaceutical composition of claim 1, wherein the composition comprises about 800 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid, or a pharmaceutically acceptable salt thereof, and provides an *in vivo* plasma profile comprising:
(i) a mean C_{max} of less than about 6000 ng/mL
(ii) a mean $AUC_{0-\infty}$ of more than about 5000 ng·hr/mL, and
(iii) a mean T_{max} of about 1 or more hours.

14. The pharmaceutical composition of claim 13, wherein the mean $AUC_{0-\infty}$ is more than about 7500 ng·hr/mL.

15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition releases {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid, or a pharmaceutically acceptable salt thereof at a rate of more than about 80 % of the drug within the first 15 minutes following administration of the formulation to a patient in need thereof.

16. A pharmaceutical composition comprising nanoparticles, one or more alkalizers and one or more redispersing agents, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm and comprise {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

17. A method of treating type II diabetes comprising administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

18. The method of claim 17, wherein the composition comprises about 800 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid, or a pharmaceutically acceptable salt thereof, and provides an *in vivo* plasma profile comprising:

(i) a mean C_{max} of less than about 6000 ng/mL

(ii) a mean $AUC_{0-\infty}$ of more than about 5000 ng·hr/mL, and

(iii) a mean T_{max} of about 1 or more hours.

19. The method of claim 18, wherein the mean $AUC_{0-\infty}$ is more than about 7500 ng·hr/mL.

20. A method of improving glycemic control comprising administering to a patient in need thereof a pharmaceutical composition comprising nanoparticles and one or more alkalizers, wherein the nanoparticles have a mean diameter between about 0.5 nm to about 1000 nm, have a polydispersity index of about 0.001 to about 0.400 and comprise a therapeutically effective amount of {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid or a pharmaceutically acceptable salt thereof.

21. The method of claim 20, wherein the composition comprises about 800 mg {2-[3-cyclohexyl-3-(trans-4-propoxy-cyclohexyl)-ureido]-thiazol-5-ylsulfanyl}-acetic acid, or a pharmaceutically acceptable salt thereof, and provides an *in vivo* plasma profile comprising:

(i) a mean C_{max} of less than about 6000 ng/mL

(ii) a mean $AUC_{0-\infty}$ of more than about 5000 ng·hr/mL, and

(iii) a mean T_{max} of about 1 or more hours.

22. The method of claim 21, wherein the mean $AUC_{0-\infty}$ is more than about 7500 ng·hr/mL.

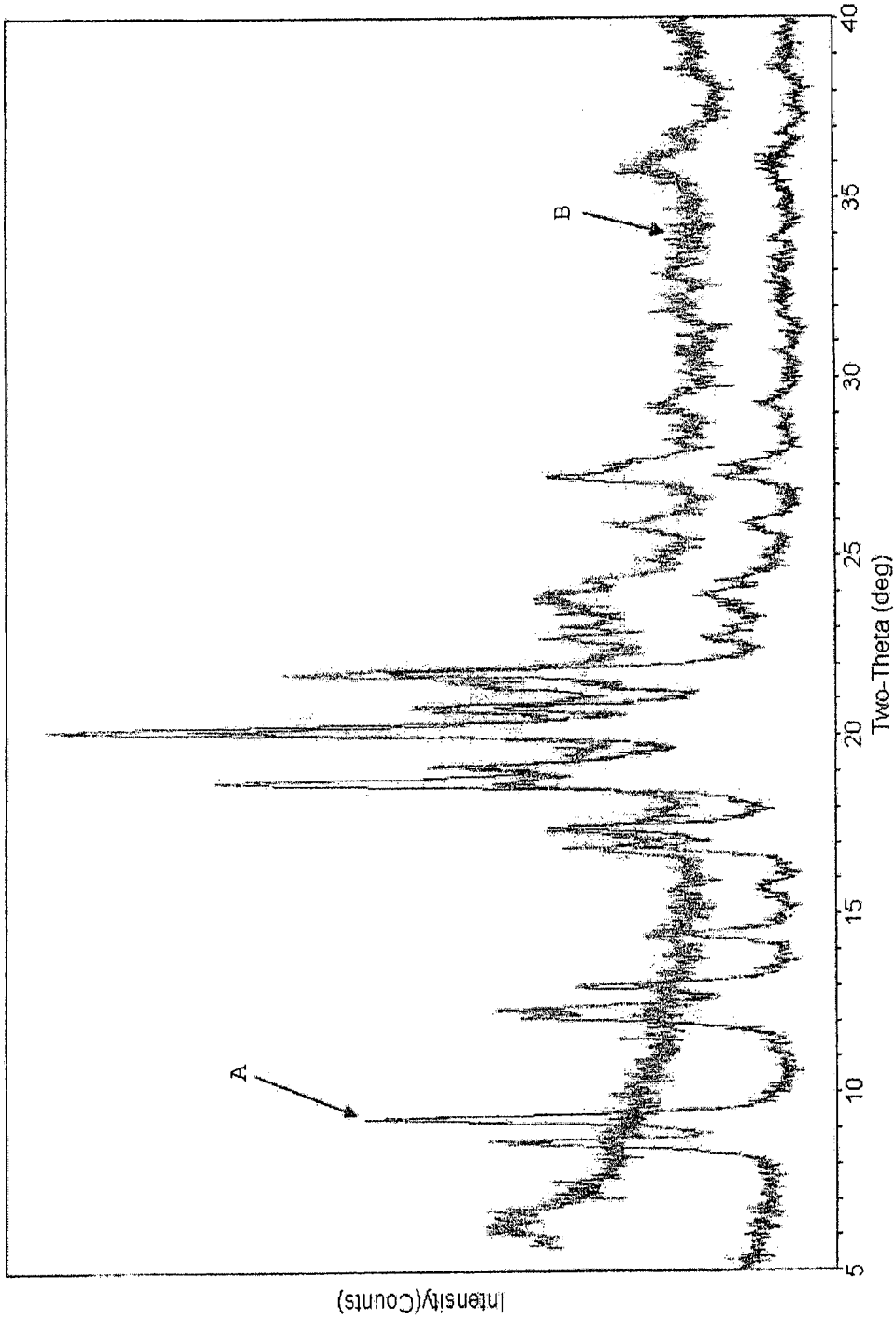


Figure 1

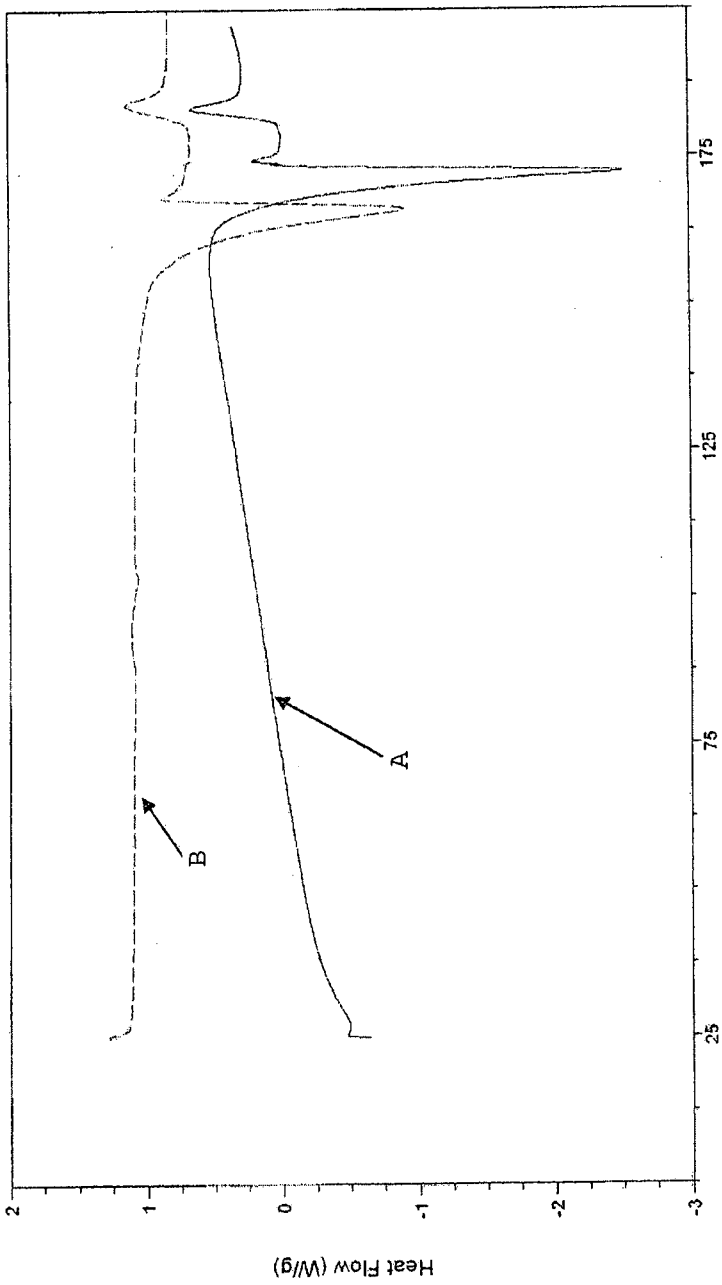


Figure 2

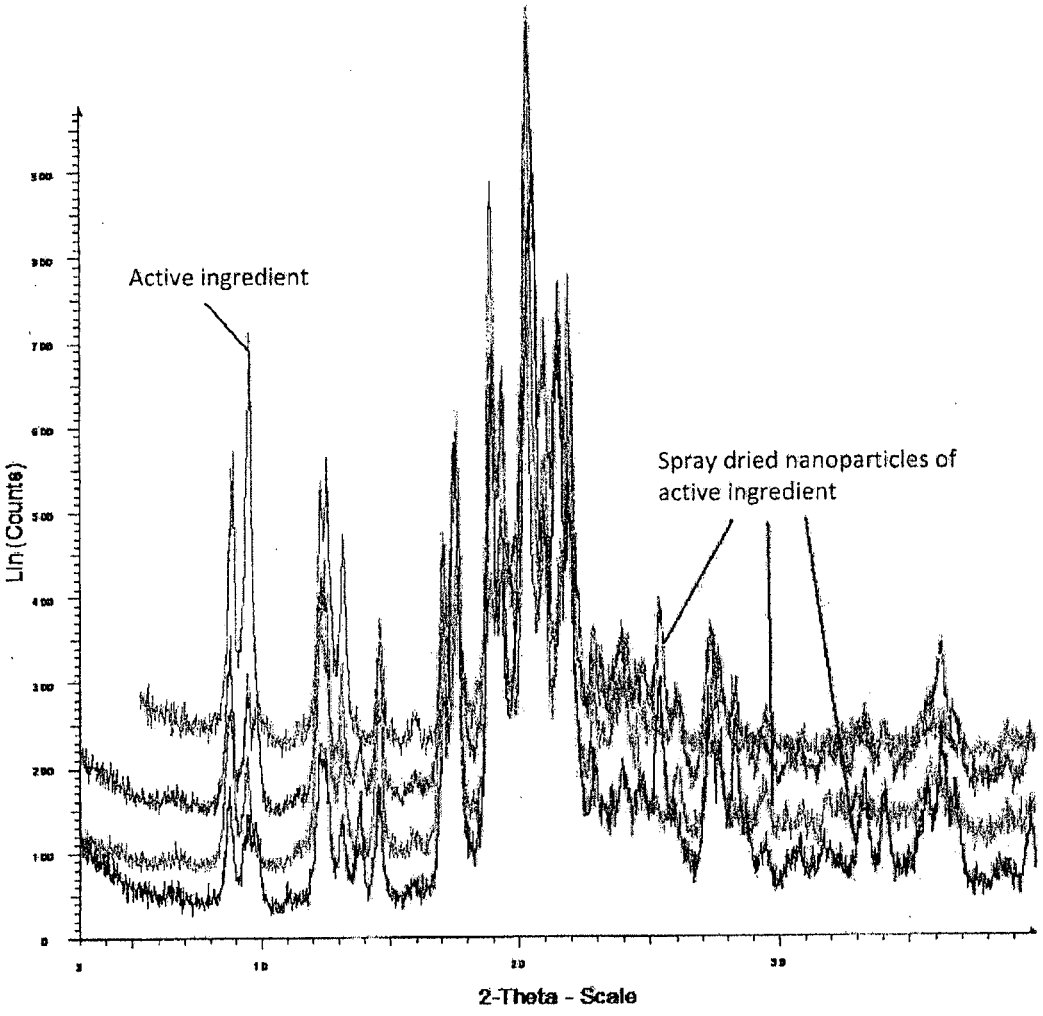

Active ingredient
Spray dried nanoparticles of active ingredient
Lin (Counts)
2-Theta - Scale

Figure 3

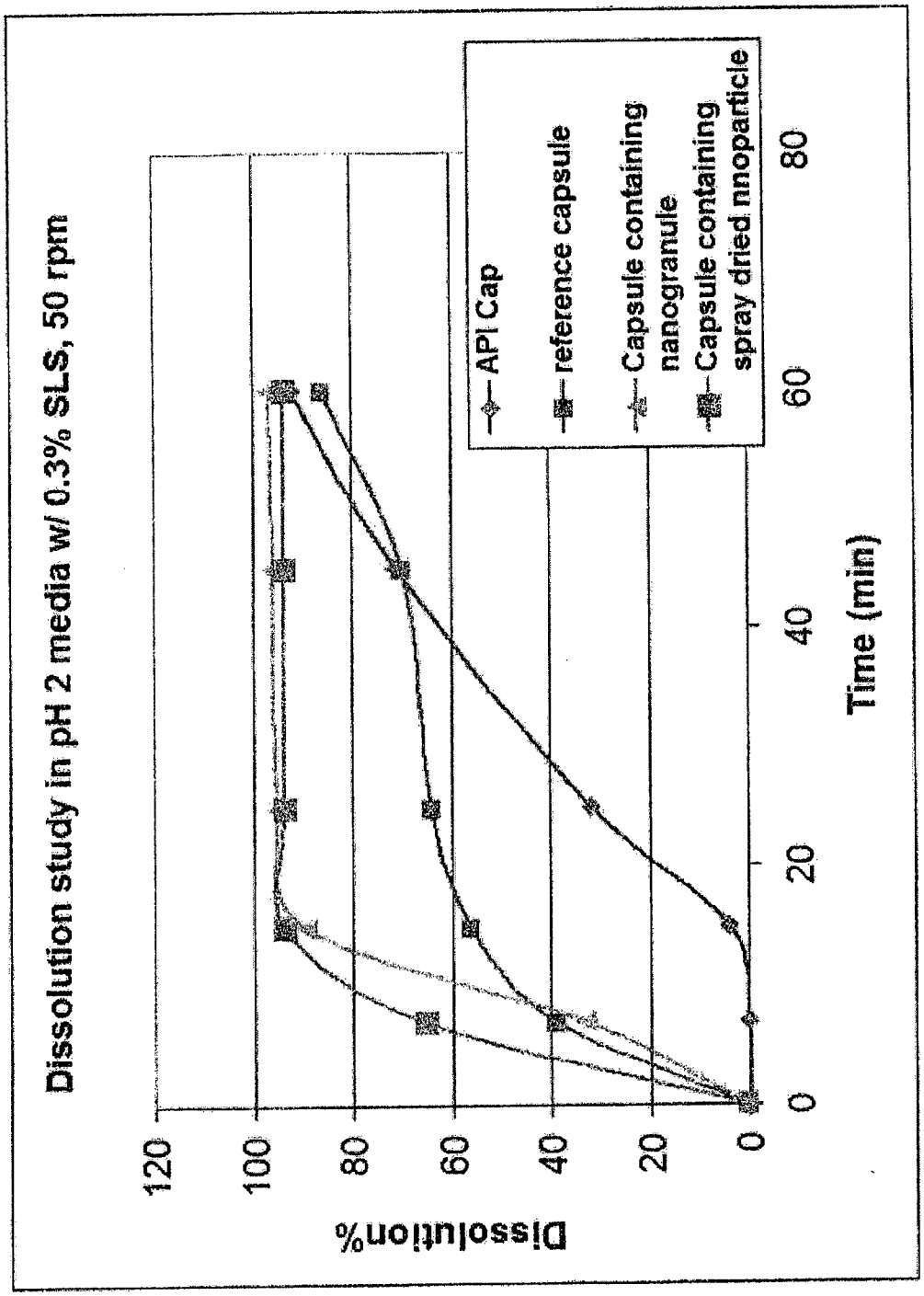

Dissolution study in pH 2 media w/ 0.3% SLS, 50 rpm
Dissolution%
120
100
80
60
40
20
0
0
20
40
60
80
Time (min)
API Cap
reference capsule
Capsule containing nanogranule
Capsule containing spray dried nnoparticle

Figure 4

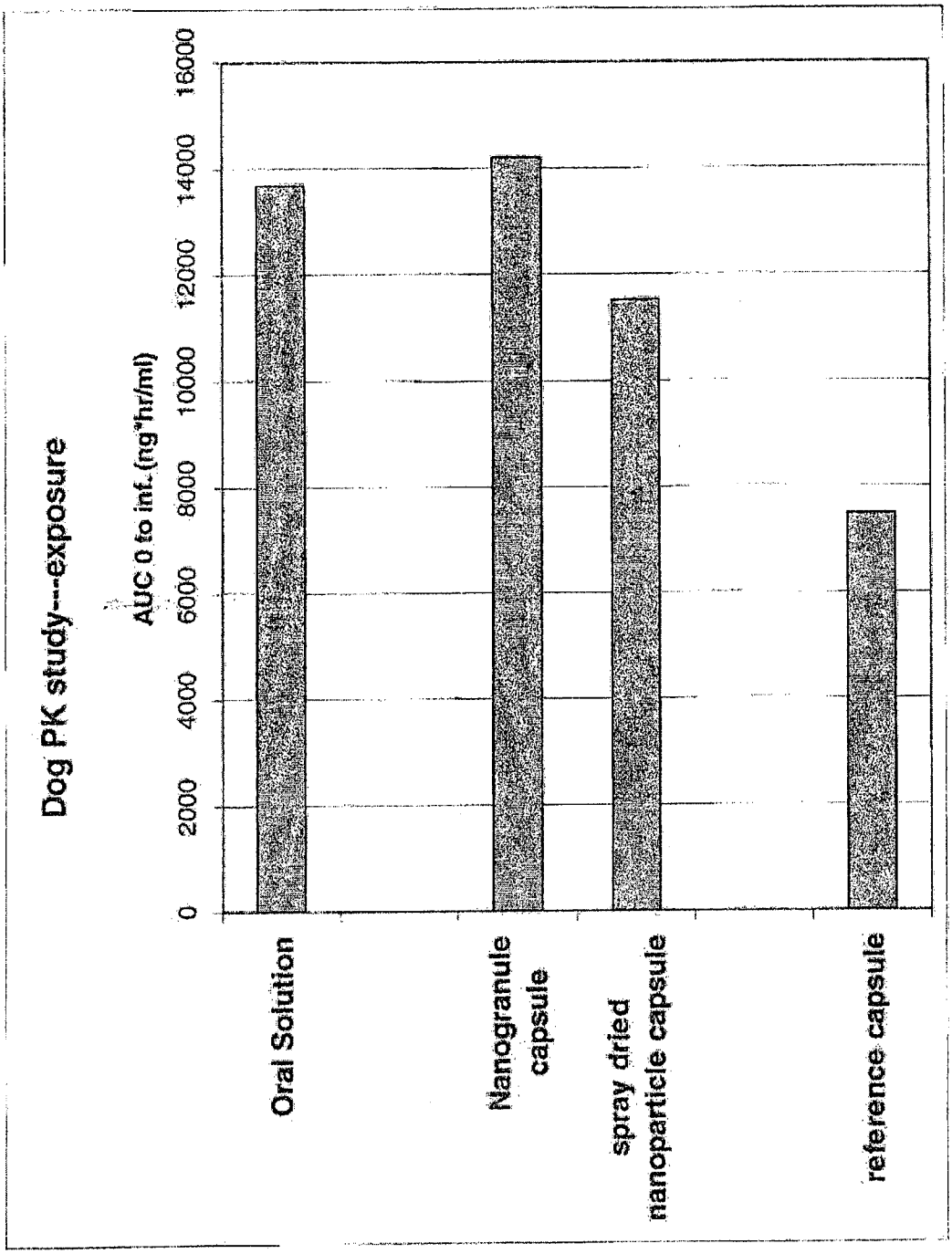

Dog PK study--exposure
AUC 0 to inf.(ng*hr/ml)
0
2000
4000
6000
8000
10000
12000
14000
16000
Oral Solution
Nanogranule capsule
spray dried nanoparticle capsule
reference capsule

Figure 5

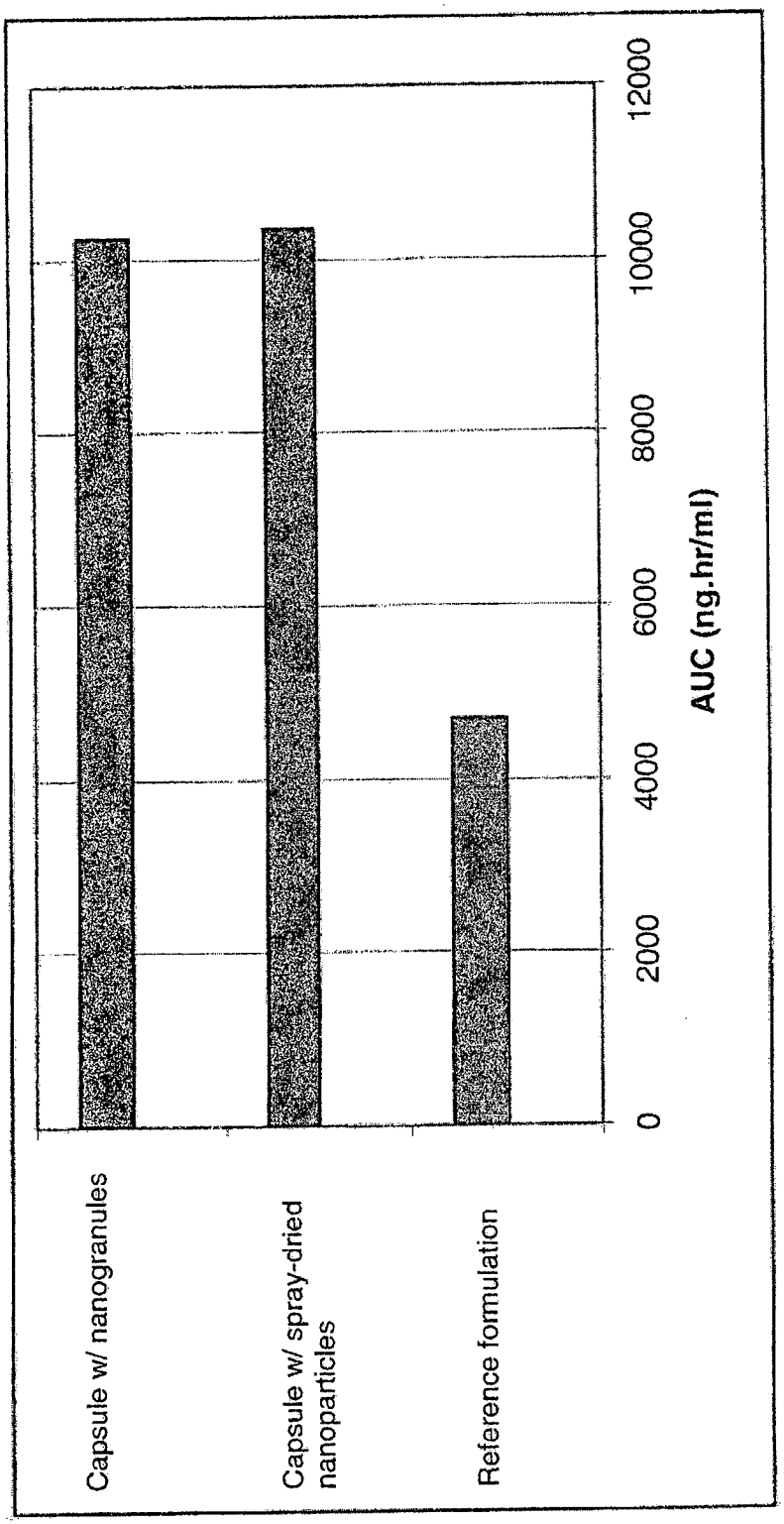

Capsule w/ nanogranules
Capsule w/ spray-dried nanoparticles
Reference formulation
0
2000
4000
6000
8000
10000
12000
AUC (ng.hr/ml)

FIGURE 6

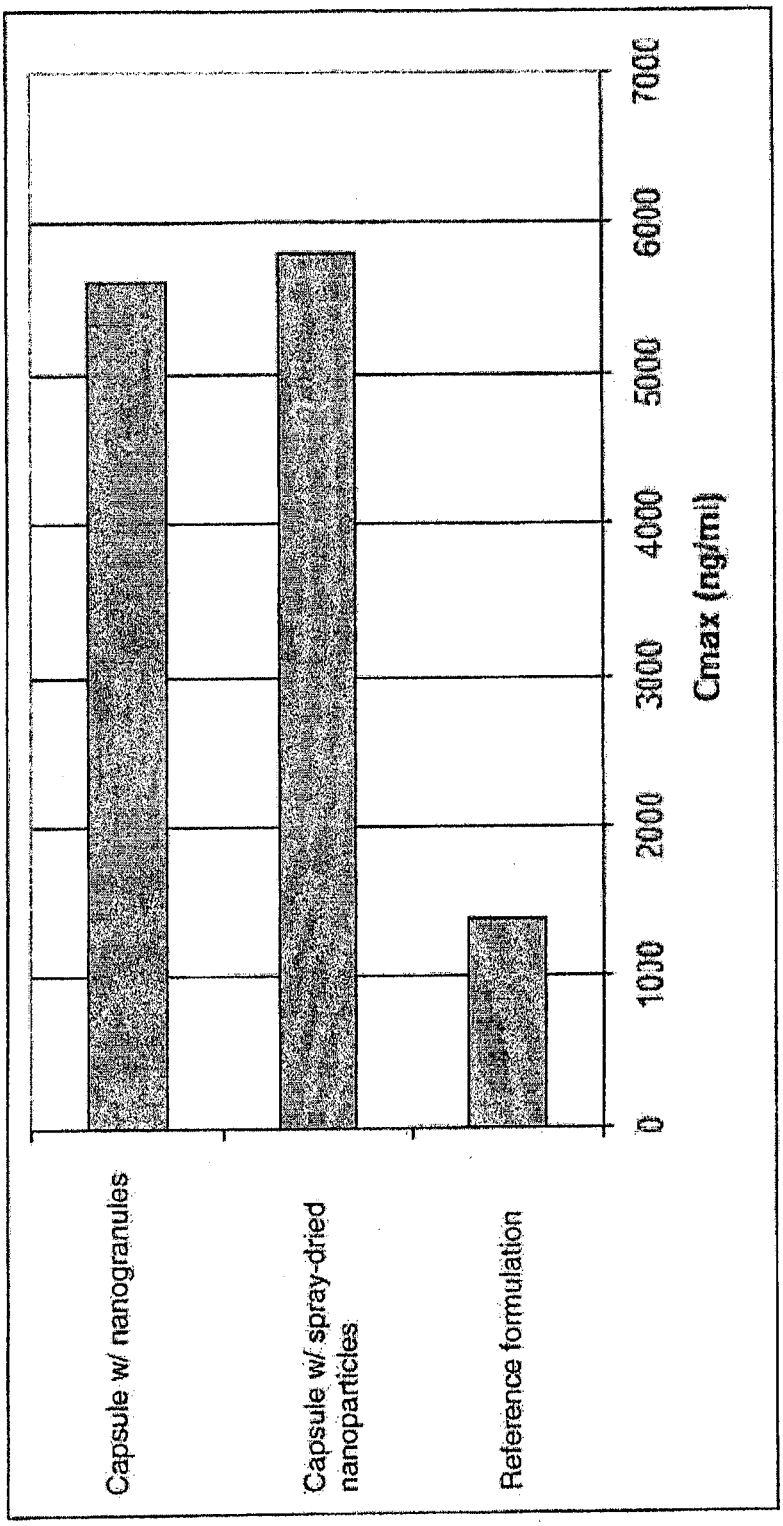

Capsule w/ nanogranules
Capsule w/ spray-dried nanoparticles
Reference formulation
0
1000
2000
3000
4000
5000
6000
7000
Cmax (ng/ml)

Figure 7

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2014 (12.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/137797 A3

(51) International Patent Classification:
A61K 9/14 (2006.01) *A61K 31/425* (2006.01)

(21) International Application Number:
PCT/US2014/019349

(22) International Filing Date:
28 February 2014 (28.02.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/772,022 4 March 2013 (04.03.2013) US

(71) Applicant: **TRANSTECH PHARMA, LLC** [US/US]; 4170 Mendenhall Oaks Parkway, High Point, North Carolina 27265 (US).

(72) Inventors: **MO, Yun**; 27 Dillon Drive, Dix Hills, New York 11746 (US). **DEDHIYA, Mahendra G.**; 1 Lea Court, Pomona, New York 10970 (US). **CHHETTRY, Anil**; 11 Hickory Hill Drive, Holtsville, New York 11742 (US).

(74) Agent: **ROLLINS, Samuel B.**; 4170 Mendenhall Oaks Parkway, High Point, North Carolina 27265 (US).

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

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

Published:

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

(88) Date of publication of the international search report:
30 October 2014

(54) Title: STABLE GLUCOKINASE ACTIVATOR COMPOSITIONS

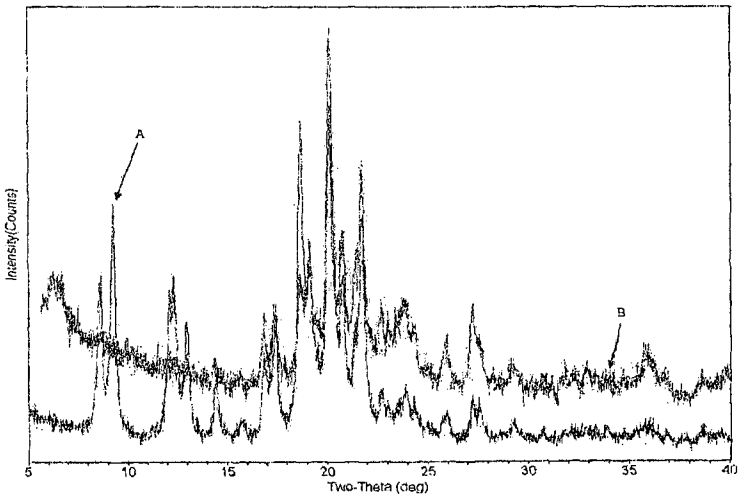


Figure 1

(57) Abstract: The invention relates to stable pharmaceutical compositions comprising a glucokinase (GK) activator suitable for oral administration. The invention also relates to methods of making and using such pharmaceutical compositions.

WO 2014/137797 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/019349

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K31/425
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/066145 A1 (NOVO NORDISK AS [DK]; MURRAY ANTHONY [DK]; LAU JESPER [DK]; JEPPESEN L) 21 July 2005 (2005-07-21) example 365 abstract	1-22
Y	WO 2008/079787 A2 (TAKEDA SAN DIEGO INC [US]; CHERUVALLATH ZACHARIA [US]; FENG JUN [US];) 3 July 2008 (2008-07-03) paragraphs [0250], [0251], [0255] abstract	1-22
Y	EP 0 499 299 A2 (STERLING WINTHROP INC [US] NANOSYSTEMS LLC [US]) 19 August 1992 (1992-08-19) page 2, line 46 - page 3, line 41 page 4, lines 32-36, 50-52 claims 1-4	1-22

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2014	21/05/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Vázquez Lantes, M

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/019349

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005066145 A1	21-07-2005	AU 2005203930 A1	21-07-2005
		BR PI0506662 A	15-05-2007
		CA 2551324 A1	21-07-2005
		CN 102516240 A	27-06-2012
		DK 1723128 T3	18-02-2013
		EP 1723128 A1	22-11-2006
		EP 2444397 A1	25-04-2012
		ES 2399052 T3	25-03-2013
		HK 1103074 A1	17-08-2012
		IL 176257 A	30-04-2012
		JP 4834840 B2	14-12-2011
		JP 5415477 B2	12-02-2014
		JP 2007517812 A	05-07-2007
		JP 2011201892 A	13-10-2011
		KR 20060124671 A	05-12-2006
		KR 20120007090 A	19-01-2012
		MX PA06007667 A	01-09-2006
		PT 1723128 E	27-02-2013
		SI 1723128 T1	30-04-2013
		US 2007054897 A1	08-03-2007
		US 2009216013 A1	27-08-2009
		US 2010204288 A1	12-08-2010
		US 2011060019 A1	10-03-2011
		WO 2005066145 A1	21-07-2005
WO 2008079787 A2	03-07-2008	EP 2091947 A2	26-08-2009
		JP 5419706 B2	19-02-2014
		JP 2010514677 A	06-05-2010
		US 2009105255 A1	23-04-2009
		US 2012252814 A1	04-10-2012
		WO 2008079787 A2	03-07-2008
EP 0499299 A2	19-08-1992	AT 195416 T	15-09-2000
		AU 654836 B2	24-11-1994
		CA 2059432 A1	26-07-1992
		DE 69231345 D1	21-09-2000
		DE 69231345 T2	26-04-2001
		DK 0499299 T3	02-01-2001
		EP 0499299 A2	19-08-1992
		ES 2149164 T3	01-11-2000
		FI 920321 A	26-07-1992
		GR 3034759 T3	28-02-2001
		HU 221586 B	28-11-2002
		IE 920217 A1	29-07-1992
		IL 100754 A	16-10-1996
		JP 3602546 B2	15-12-2004
		JP H04295420 A	20-10-1992
		NO 920334 A	27-07-1992
		NZ 241362 A	25-06-1993
		PT 499299 E	31-01-2001
		RU 2066553 C1	20-09-1996
		SG 55104 A1	21-12-1998
		US 5145684 A	08-09-1992

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 105050585 A
(43)申请公布日 2015.11.11

(21)申请号 201480011647.2
(22)申请日 2014.02.28
(30)优先权数据
61/772,022 2013.03.04 US
(85)PCT国际申请进入国家阶段日
2015.09.01
(86)PCT国际申请的申请数据
PCT/US2014/019349 2014.02.28
(87)PCT国际申请的公布数据
WO2014/137797 EN 2014.09.12
(71)申请人 VTV治疗有限责任公司
地址 美国北卡罗来纳
(72)发明人 Y·莫 M·G·戴德希亚 A·切特里
(74)专利代理机构 中国国际贸易促进委员会专利商标事务所 11038
代理人 邵华一
(51)Int.Cl.
A61K 9/14(2006.01)
A61K 31/425(2006.01)

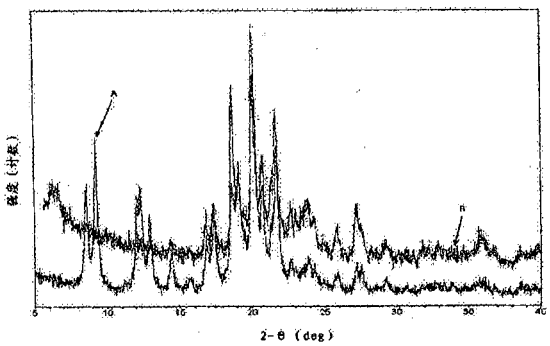
权利要求书2页 说明书24页 附图7页

(54)发明名称

稳定的葡萄糖激酶活化剂组合物

(57)摘要

本发明涉及包括葡糖激酶(GK)活化剂的适用于口服给药的稳定药物组合物。本发明还涉及制备和使用这样的药物组合物的方法。



CN 105050585 A

1. 一种药物组合物，其包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 的平均直径，具有大约 0.001 至约 0.400 的多分散性指数，并且包括 {2-[3- 环己基 -3--(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。

2. 权利要求 1 的药物组合物，其中所述纳米粒子进一步包含一种或多种再分散剂。

3. 权利要求 1 的药物组合物，其中所述纳米粒子具有约 200nm 至约 400nm 的平均直径。

4. 权利要求 3 的药物组合物，其中所述纳米粒子具有约 0.001 至约 0.300 的多分散性指数。

5. 如权利要求 1 的药物组合物，其中一种或多种碱化剂选自葡甲胺，碳酸钠，碳酸钾，碳酸钙，氧化镁，氢氧化钙，氢氧化钠，氢氧化钾，二乙醇胺，碳酸氢钾，柠檬酸钾，硼酸钠，柠檬酸钠，三乙醇胺和它们的混合物。

6. 权利要求 5 的药物组合物，其中所述一种或多种碱化剂是葡甲胺。

7. 权利要求 2 的药物组合物，其中所述的一种或多种再分散剂选自甘露醇，海藻糖，木糖醇，乳糖，蔗糖，山梨糖醇，葡聚糖，乳糖醇，麦芽糖醇，赤藓醇，苏糖醇，阿糖醇，核糖醇，半乳糖醇，岩藻糖醇，艾杜糖醇，肌醇，velomitol，异麦芽糖，菊粉或它们的混合物。

8. 权利要求 1 的药物组合物，其中通过从纳米粒子悬浮液除去溶剂形成所述纳米粒子，包括：

(a) {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐，

(b) 一种或多种稳定剂，

(c) 一种或多种再分散剂，以及

(d) 一种或多种溶剂。

9. 权利要求 8 的药物组合物，其中所述一种或多种溶剂选自水，甲醇，庚烷，丙醇，异丙醇，乙酸，丙酮，乙酸乙酯，乙醇和它们的混合物。

10. 权利要求 8 的药物组合物，其中所述一种或多种稳定剂选自聚合物稳定剂，表面活性剂稳定剂和它们的混合物。

11. 权利要求 8 的药物组合物，其中所述纳米粒子悬浮液具有大于约 30mV 或小于约 -30mV 的 ζ 电势。

12. 权利要求 1 的药物组合物，还包含一种或多种粘合剂，填充剂，稀释剂，崩解剂或其混合物。

13. 权利要求 1 的药物组合物，其中组合物包含约 800mg {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸，或药学上可接受的盐，其提供的体内血浆性质包括：

(i) 小于约 6000ng/mL 的平均 C_{max}

(ii) 大于约 5000ng. hr/mL 的平均 $AUC_{0-\infty}$，和

(iii) 约 1 小时或更多小时的平均 T_{max}。

14. 权利要求 13 的药物组合物，其中平均 $AUC_{0-\infty}$ 大于约 7500ng. hr/mL。

15. 权利要求 1 的药物组合物，其中药物组合物在将制剂给药至有需要的患者后第一个 15 分钟内以大于约 80％的药物的速度释放 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己

基)-脲基]-噻唑-5-基硫烷基}-乙酸,或者其药学上可接受的盐。

16. 药物组合物,其包括纳米粒子,一种或多种碱化剂和一种或多种再分散剂,其中所述纳米粒子具有约 0.5nm 至约 1000nm 的平均直径,并包括 {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。

17. 治疗 II 型糖尿病的方法,包括给予有需要的患者药物组合物,其包括纳米粒子和一种或多种碱化剂,其中所述纳米粒子具有约 0.5nm 至约 1000nm 的平均直径,具有大约 0.001 至约 0.400 的多分散性指数,并且包括治疗有效量的 {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。

18. 权利要求 17 的方法,其中组合物包含约 800mg {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸,或药学上可接受的盐,其提供的体内血浆性质包括:

(i) 小于约 6000ng/mL 的平均 C_{max}

(ii) 大于约 5000ng.hr/mL 的平均 $AUC_{0-\infty}$,和

(iii) 约 1 小时或更多小时的平均 T_{max}。

19. 权利要求 18 的方法,其中平均 $AUC_{0-\infty}$ 大于约 7500ng.hr/mL。

20. 改善血糖控制的方法,包括给予有需要的患者药物组合物,其包括纳米粒子和一种或多种碱化剂,其中所述纳米粒子具有约 0.5nm 至约 1000nm 的平均直径,具有大约 0.001 至约 0.400 的多分散性指数,并且包括治疗有效量的 {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。

21. 权利要求 20 的方法,其中组合物包含约 800mg {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸,或药学上可接受的盐,其提供的体内血浆性质包括:

(i) 小于约 6000ng/mL 的平均 C_{max}

(ii) 大于约 5000ng.hr/mL 的平均 $AUC_{0-\infty}$,和

(iii) 约 1 小时或更多小时的平均 T_{max}。

22. 权利要求 21 的方法,其中平均 $AUC_{0-\infty}$ 大于约 7500ng.hr/mL。

稳定的葡萄糖激酶活化剂组合物

发明领域

[0001] 本发明涉及包括葡糖激酶（GK）活化剂的适用于口服给药的稳定药物组合物。本发明还涉及制备和使用这样的药物组合物的方法。

[0002] 发明背景

[0003] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸（公开在，例如，美国专利号7851636中）是作为GK活化剂，其敏化葡糖激酶（GK）传感器系统。GK是属于己糖激酶家族的酶，其催化葡萄糖代谢的第一步，即葡萄糖转化为葡萄糖-6-磷酸。GK可以通过作为葡萄糖传感器，并造成在响应血糖水平波动的代谢或细胞功能中的变化而调节碳水化合物的代谢。GK用作在胰腺，肝脏，肠和大脑的葡萄糖传感器。{2-[3-环己基3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸是一种肝选择性的GK活化剂，在葡萄糖的存在下不通过胰腺增加胰岛素的分泌。

[0004] 用于口服给药的理想的药物具有中度到高水溶性和膜渗透性，从而迅速溶解该药物在胃肠液中，以及允许快速吸收到血流中。然而，显著量的药物候选物是难溶的，并呈现用于口服递送的主要障碍。不良溶解度通常是不完整的或不稳定的吸收，生物利用度差，缓慢发生作用，患者到患者的PK变异性，强的食物效应，高剂量的要求的原因。

[0005] 制剂策略已被探索以改善低溶解度的药物的溶解度，包括形成无定形的药物的固体分散体，液体填充的胶囊，和粒度减小。粒度减少包括减少更大的药物颗粒以形成更小的纳米粒子。然而，形成药物纳米粒子有其挑战。例如，稳定来自聚集的纳米粒子是困难的，配制成固体剂型时尤为如此。转换粒子悬浮液成固体形式过程中创建的条件可导致粒子聚集，增加粒度或诱导稳定剂的结晶，其在维持纳米粒子的大小和稳定性中呈现出很大的挑战。此外，形成颗粒聚集体通常是不可逆的，其中结块一旦在分散媒介物中被重构，不能恢复成单独分散的粒子。

[0006] 一定的GK活化剂是难溶的，包括{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸，这导致高剂量的要求，高的PK变异性和强的食物的影响。因此，需要一种稳定的制剂，其可提高含有这类试剂的药物组合物的溶解性和稳定性。申请人现已开发了这样可溶性的，稳定的和生物可利用的制剂，其在本文中公开。

发明内容

[0007] 本发明涉及包括葡糖激酶（GK）活化剂的适用于口服给药的稳定药物组合物。本发明还涉及制备和使用这样的药物组合物的方法。

[0008] 在一个方面，本发明涉及药物组合物，其包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约0.5nm至约1000nm之间的平均直径，具有大约0.001至约0.400的多分散性指数并且包括{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。

[0009] 在一些实施方案中，本发明涉及药物组合物，其包括纳米粒子，一种或多种碱化剂和一种或多种再分散剂，其中所述纳米粒子具有约0.5nm至约1000nm之间的平均直径，并

包括 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。

[0010] 在另一个方面，本发明涉及通过施用 GK 活化剂治疗各种病症的方法。在一些实施方案中，本发明涉及治疗 11 型糖尿病，包括给予有需要的患者药物组合物，其包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 之间的平均直径，具有大约 0.001 至约 0.400 的多分散性指数，并且包括治疗有效量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。

[0011] 在其他实施方案中，本发明涉及改善血糖控制的方法，包括给予有需要的患者药物组合物，其包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 之间的平均直径，具有约 0.001 至约 0.400 的多分散性指数，并且包括将治疗有效量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或药学上可接受的盐。

[0012] 附图的简单说明

[0013] 图 1. 纳米化的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的 X 射线粉末衍射 (XRPD) 图案。“A”为纳米化之前的冻干药物悬浮液衍射图案。“B”为纳米化后冻干药物悬浮液的衍射图案。

[0014] 图 2. 在纳米化前和通过微流化纳米化后从冷冻干燥的药物悬浮液得到 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的差示扫描量热 (DSC) 曲线图。“A”是在纳米化之前冻干的药物悬浮液 DSC 曲线图。“B”是在纳米化后冻干药物悬浮液 DSC 曲线图。

[0015] 图 3. {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的喷雾干燥的纳米粒子的 XPRD 图案。

[0016] 图 4. {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的喷雾干燥的纳米粒子的明胶胶囊和纳米粒子化的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的明胶胶囊的溶出。

[0017] 图 5. 将以下在体内暴露于比格犬：i) 喷雾干燥的包含 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子胶囊和 ii) {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸纳米粒子的胶囊，与其相比的是，iii) 在水溶液中的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸和 iv) 含有与微粉化的 {2-[3- 环己基 -3-(反式 4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸一同配制的颗粒的胶囊 (参考胶囊)。

[0018] 图 6. 以下在人类中的体内暴露 (AUC) :i) 实施例 39 中制备的含 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的喷雾干燥的纳米胶囊和 ii) 实施例 40 中制备的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 } 乙酸纳米粒子胶囊，与之比较的含有与微粉化的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸一同配制的颗粒的胶囊 (参考胶囊)。

[0019] 图 7. 以下在人类在的体内暴露 (C_{max}) :i) 实施例 39 中制备的含 {2-[3- 环己

基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的喷雾干燥的纳米粒子胶囊和 ii) 实施例 40 中制备的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸纳米粒子胶囊，在之比较的含有与微粉化的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸一同配制的颗粒的胶囊 (参考胶囊)。

[0020] 发明详述

[0021] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐的新稳定的组合物，使用这些药物组合物的治疗方法，以及用于制备这些药物组合物的方法在本文被提供。

[0022] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸是生物药剂学分类系统 (BCS) 下的第 IV 类药物，具有低的溶解度和低的渗透性。其结果是，IV 类药物具有差生物利用度，并且通常不能很好地吸收，而具有高的变异性。然而，制备含一种稳定的，生物可利用的含有 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐的组合物是不显而易见的。这样的组合物可以显示出增强的稳定性，这是高度生物可利用的和在胃的环境中，例如，在 pH 1-4 容易释放活性成分，具有所需溶出性质。

[0023] 在一个方面，本发明提供了一种药物组合物，其包括固体稳定化的粒子和药学上可接受的赋形剂，其中所述固体稳定化的粒子包含治疗有效量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。在一些实施方案中，固体稳定化的粒子还包含一种或多种碱化剂。在其它的实施方案中，固体稳定化的粒子还包含一种或多种再分散剂。在又其他实施方案中，该固体稳定化的粒子还包含一种或多种再分散剂和一种或多种碱化剂。在一些实施方案中，本发明涉及药物组合物，其包括纳米粒子和一种或多种碱化剂，其中该纳米粒子具有约 0.5nm 至约 1000nm 的平均直径，约 0.001 至约 0.400 的多分散性指数，并且包括 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。在其他实施方案中，本发明涉及药物组合物，其包括纳米粒子，一种或多种碱化剂和一种或多种再分散剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 的平均直径和包括 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。所述固体稳定化的粒子包含 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐，其量为约 1％至约 80％ w/w。在一些实施方案中，{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐的存在量为约 2.5％至约 65％ w/w。在其它的实施方案中，{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐存在量为约 5％至约 60％ w/w。

[0024] 合适的碱化剂包括适合于口服给药的任何碱性化合物，包括，例如，葡甲胺，碳酸钠，碳酸钾，碳酸钙，氧化镁，氢氧化钙，氢氧化钠，氢氧化钾，二乙醇胺，碳酸氢钾，柠檬酸钾，钠硼酸盐，柠檬酸钠，三乙醇胺，或它们的组合。碱化剂可以以约 0.1％至约 90％ w/w 的量存在。

[0025] 在一些实施方案中，碱化剂与活性成分的比率为约 2 :1 至约 1:50。在其它实施方

案中，碱化剂与活性成分的比率为约 2 :1 至约 1 :2。在某些实施方案中，该药物组合物的微环境 pH 大于约 6。例如，大于约 8，大于约 9，大于约 10 或大于约 11。不希望受理论的束缚，申请人认为，该药物组合物的微环境 pH 值增强了活性剂针对降解的稳定性，以及提高活性成分的溶出。

[0026] 合适的再分散剂是具有良好的水中溶解性的试剂，是不吸湿的，可以容易形成与药物颗粒的氢键。在一些实施方案中，再分散剂是糖醇。再分散剂包括，例如，甘露糖醇，海藻糖，木糖醇，乳糖，蔗糖，山梨糖醇，葡聚糖，乳糖醇，麦芽糖醇，赤藓醇，苏糖醇，阿糖醇，核糖醇，半乳糖醇，岩藻糖醇，艾杜糖醇，肌醇 (inocitol)，velomitol，异麦芽糖，菊粉或它们的混合物。不束缚于任何理论，再分散剂可通过一种机制稳定微粒和 / 或纳米粒子，其中在干燥过程中再分散剂分子（例如，糖醇）代替水分子包围粒子，形成再分散剂分子和粒子之间的氢键，由此固定化粒子和限制粒子 - 粒子相互作用，其导致聚合。

[0027] 固体稳定粒子的制备

[0028] 本发明的稳定药物组合物包含固体稳定化的粒子。稳定固体粒子可如下制备 :开始于包含 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐和溶剂的粒子悬浮液，然后从悬浮液中除去溶剂，以形成固体稳定化的粒子。粒子悬浮液包括微悬浮液，即，包括微米尺寸范围在约 1 μm 至约 100 μm 内的粒子的悬浮液，或纳米悬浮液，即，包括纳米尺寸范围在约 0.5nm 至约 1000nm 的粒子的悬浮液，或它们的混合物。在示例性的实施方案中，粒子悬浮液包括纳米粒子。

[0029] 从粒子悬浮液除去溶剂的合适方法包括，例如，制粒，冻干，真空干燥，烘炉干燥，干燥剂干燥和喷雾干燥。对粒子悬浮液的合适的溶剂包括由一个管理机构，例如，美国食品与药物管理局公认安全 (GRAS) 的任何溶剂，并且应该与药物物质兼容，并对药物产品提供最小的溶解度。这样的溶剂包括水性和有机溶剂，例如，水，甲醇，庚烷，丙醇，异丙醇，乙酸，丙酮，乙酸乙酯，乙醇，以及它们的混合物。示例性的粒子悬浮液包括水。

[0030] 粒子悬浮液可通过各种方法制备，这些方法可分为两类 :自上而下方法和自下而上的方法。自上而下的方法开始于块状物质和通过使用机械，化学或电能将它们破坏为微或纳米大小的颗粒。在某些实施方案中，尺寸减小方法允许减小粒度很少或对维持药物物质的结晶度 / 多态性与稳定性没有影响。所得粒子悬浮液允许在制剂的灵活性。在一些实施方案中，粒子悬浮液可直接使用于口服给药，或者可以进一步加工成固体形式（例如通过喷雾干燥，制粒或冷冻干燥），以及制备成固体剂型，例如，片剂和胶囊等。在本文描述的这种制剂的口服给药（给予）可以有效地提高药物的溶解度，减少给药量，增加溶出速度，提高生物利用度，降低 PK 变异性，减轻食品效果。

[0031] 在本文中描述的粒子悬浮液也表现出化学稳定性，并显示药物产品很少降解到降解产物或没有，甚至在加速条件也是如此。

[0032] 在自上而下方法中，较大的颗粒被分解开以形成较小微米化的或纳米化的粒子。自上而下的方法包括，例如，微流化，湿磨，媒介物研磨，转动旋转，喷射研磨，球磨，微粉化或均质化（例如，高剪切均化）。研磨方法可以利用各种陶瓷媒介物，如陶瓷研磨珠（例如，具有约 5 μm 至约 500 μm 的的珠粒度锆磨珠）。

[0033] 自下而上的方法，在另一方面，从通过在严格选择的条件下的化学反应或物理过程从原子或分子水平合成微米或纳米粒子。自下而上的方法包括，例如，快速蒸发，去溶剂

化，喷雾干燥，冻干，沉淀，化学方法或超临界流体处理。

[0034] 粒子悬浮液可包括一种或多种稳定剂。在一些实施方案中，稳定剂包括至少一种聚合物稳定剂，至少一种表面活性剂稳定剂或它们的组合。聚合的稳定剂包括，例如，羟丙基纤维素，微晶纤维素，羟丙基甲基纤维素，聚乙烯吡咯烷酮，聚乙烯醇，聚乙烯硫酸酯，泊洛沙姆（例如，泊洛沙姆188，泊洛沙姆237，泊洛沙姆338，泊洛沙姆407和其他合适的等级的泊洛沙姆可以使用），聚乙二醇，聚乙二醇-聚乳酸（PEG-PLA），，聚环氧乙烷，聚氧乙烯烷基醚，聚氧化亚丙基二醇烷基醚，葡糖苷烷基醚，聚氧化亚乙基二醇辛基酚醚，聚氧化亚乙基二醇烷基苯酚醚，甘油烷基醚，聚氧化亚乙基二醇脱水山梨糖醇烷基酯，脱水山梨糖醇烷基酯，椰油酰胺单乙醇胺，椰油酰胺二乙醇胺，十二烷基二甲基胺氧化物，聚乙氧基牛脂胺（tallow amine），明胶，白蛋白，瓜尔胶，琼脂或它们的共聚物。在一些实施方案中，粒子悬浮液包含约0.01% w/v至约40% w/v之间的量的一种或多种聚合物稳定剂。

[0035] 表面活性剂稳定剂包括，例如，硫酸烷基酯盐（例如，月桂基硫酸钠），二辛基磺基琥珀酸盐（例如，多库酯钠），脱氧胆酸钠，聚氧烯烃蓖麻油（polyoxylene caster oils），聚山梨酸酯，聚氧烯烃硬脂酸酯（polyoxylene stearates），聚氧基甘油酯，磷脂，生育酚衍生物，胆汁酸盐，丙二醇脂肪酸单酯或二酯，聚乙二醇脂肪酸酯，聚山梨醇酯，天然油和蜡的聚氧乙烯衍生物，和脱水山梨糖醇脂肪酸酯或它们的混合物。在其它的实施方案中，粒子悬浮液包括约0.01% w/v至约80% w/v的表面活性剂稳定剂。

[0036] 本文所述的粒子悬浮液都具有良好控制的和相对窄的/均匀的平均粒度分布，其可以通过测量多分散性指数（PDI）而被表征。多分散性指数是一个无量纲参数，其用于定义从动态光散射分析获得的微-或纳米粒子的粒度分布。通常，较低的PDI值表示更大的粒度的均匀性。在一些实施方案中，粒子悬浮液包括具有低于0.400的PDI的粒子（例如，微粒或纳米粒子）。，在其他实施方案中，粒子悬浮液包括具有约0.001至约0.400，约0.001至约0.300，0.001至约0.250，约0.001至约0.200，约0.001至约0.190，约0.001至约0.180，约0.001至约0.170，约0.001至约0.160，约0.001至大约0.150的PDI的粒子。

[0037] 粒子悬浮液也可通过测量ζ电势而被表征。ζ电势反映在分散媒介物和附着到分散的颗粒的流体静止层之间的电势差。ζ电势进一步表明在分散体中相邻、同样带电的粒子之间排斥的程度，是胶体稳定性，即，对粒子聚集的抵抗的有用的指标。在一些实施方案中，本文描述的粒子悬浮液的ζ电势为大于30的绝对值，例如大于约30mV或低于约-30mV。在其它实施方案中，粒子悬浮液具有大于约50mV或小于约-50mV的ζ电势。在另外的其它实施方案中，粒子悬浮液具有大于约60mV或小于约-60mV的ζ电势。在其他实施方案中，粒子悬浮液具有大于约80mV或小于约-80mV的ζ电势。在其他实施方案中，粒子悬浮液具有大于约100mV或小于约-100mV的ζ电势。在其它实施方案中，粒子悬浮液具有约-30mV至-100mV，或大约30mV至约100mV的ζ电势。

[0038] 在一些实施方案中，本文描述的粒子悬浮液具有约0.5%至约80% w/v的固体浓度。在其他实施方案中，粒子悬浮液具有约0.5厘泊（cps）至约600厘泊的粘度。

[0039] 自上而下和自下而上的技术可以形成在悬浮液中的药物的微粒和/或纳米粒子，其具有无可比拟的物理稳定性，例如，几乎没有或可忽略的粒度随着时间的改变，该药物产品的小的或可忽略的降解，在结晶度/同质多晶型现象很小或可忽略的变化。然而，在难以保持稳定，如避免粒子聚集同时保持粒度，以及避免其中多晶型物形式相互转化的情况下，

将粒子悬浮液转换成固体形式时，出现挑战。在转换颗粒悬浮成固体形式之前，通过混合一种或多种再分散剂与粒子悬浮液，提供稳定的固体微粒和 / 或纳米粒子。

[0040] 在一些实施方案中，粒子悬浮液包含约 0.1％至约 90％ w/w 的量的一种或多种再分散剂。在其他实施方案中，再分散剂可以以约 1％至约 80％ w/w 或约 5％至约 70％ w/w 存在。在一些实施方案中，再分散剂可以以约 2.5％至约 10％ w/w 存在。在其它的实施方案中，再分散剂可以以约 25％至约 40％ w/w 存在。

[0041] 固体稳定化的粒子可以从本文所述的粒子悬浮液使用多种已知方法来形成，所述已知方法包括例如，喷雾干燥，湿法制粒，干法制粒，蒸汽制粒技术，熔融制粒技术，水分活化的干法制粒技术 (MADG)，湿润制粒技术 (MGT)，热粘合制粒方法 (TAGP)，泡沫制粒技术，冷冻干燥，真空干燥，烘炉干燥，干燥剂干燥等。

[0042] 在一些实施方案中，平均固体粒度为约 1 μm 至约 100 μm。在其他实施方案中，平均固体粒度为约 2 μm 至约 90 μm。在其它实施方案中，平均固体粒度为约 5 μm 至约 80 μm。在其他实施方案中，平均固体粒度为约 10 μm 至约 70 μm。

[0043] 在进一步的实施方案中，平均固体粒度为约 0.5nm 至约 1000nm。在其他实施方案中，平均固体纳米粒度（纳米粒子尺寸）小于约 900nm。在其他实施方案中，平均固体纳米粒度是约 0.5nm 至约 800nm。在其它实施方案中，平均固体纳米粒度为约 200nm 至约 400nm。

[0044] 从本文描述粒子悬浮液形成的固体稳定化的粒子也具有良好控制的，相对窄的平均粒度分布。不束缚于任何理论，窄平均粒度分布可以提供高度生物可利用的药物组合物，其具有较少的 PK 变异性的一致的药物递送。在一些实施方案中，从本文所述的粒子悬浮液而形成的固体稳定化的粒子具有低于 0.400 的多分散性指数 (PDI)。在其他实施方案中，从本文所述的粒子悬浮液形成的固体稳定的颗粒具有约 0.001 至约 0.400，0.001 至约 0.300，0.001 至约 0.250，约 0.001 至约 0.200，约 0.001 至约 0.190，约 0.001 至约 0.180，约 0.001 至约 0.170，约 0.001 至约 0.160，和约 0.001 至约 0.150 的 PDI。

[0045] 在一些实施方案中，喷雾干燥是用来制备固体稳定化的粒子，其包含 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。在其他的实施方案中，喷雾干燥的固体稳定化的粒子可以直接用作固体剂型或进一步配制成固体剂型，例如片剂等。

[0046] 在其他实施方案中，湿法制粒是用来制备固体稳定化的粒子，其包含 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。湿法制粒的方法包括，例如，标准的湿法制粒技术和专门的湿法制粒技术，如高剪切混合制粒，流化床制粒，挤出，滚圆冻干，喷雾干燥制粒等。在某些实施方案，流化床制粒或喷雾干法制粒是用来制备包括 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐的固体稳定化的粒子。干法制粒的方法包括标准干法制粒和专门干法制粒技术，如预压片法（击块制颗粒法），碾压，和类似物。熔体制粒法包括热塑性熔融制粒等。

[0047] 湿法制粒方法包括使用液体粘合剂溶液，其包含一种或多种粘合剂。液体粘合剂溶液可以与粉末混合，以使粉末轻微结块，由此形成颗粒。在一些实施方案中，一种或多种再分散剂加入液体粘合剂溶液，然后在制粒之前将其加入到本发明的粒子悬浮液。颗粒形成之后，颗粒剂通常被干燥和筛分（使用，例如，网筛）。在一些实施方案中，可以将颗粒研

磨以获得所需的粒度。两种低剪切和高剪切混合设备可以被利用。

[0048] 合适的粘合剂包括纤维素衍生物（例如，羟丙基甲基纤维素，羟丙基甲基纤维素乙酸酯，羟丙基甲基纤维素邻苯二甲酸酯，羟丙基纤维素，甲基纤维素，羟乙基纤维素，羟乙基纤维素乙酸酯，等），单糖（如，葡萄糖等），多糖／寡糖（例如糊精，麦芽糖糊精，果胶，麦芽糖，聚葡萄糖，淀粉等），聚乙烯吡咯烷酮，聚乙烯醇，聚乙烯己内酰胺，卡波姆，聚维酮，共聚维酮（聚乙烯吡咯烷酮），明胶，天然树胶（例如瓜尔胶，阿拉伯胶，角叉菜胶，琼脂，藻酸，阿拉伯树胶，等），泊洛沙姆，聚卡波非或其混合物。粘合剂可以存在的量为约 0.01％至约 20％ w/w 干重。

[0049] 粘合剂溶液也可以包括一种或多种填充剂，稀释剂，崩解剂或它们的混合物。适合的填充剂／稀释剂包括，例如，微晶纤维素，磷酸二钙，乳糖，淀粉，碳酸钙，乳酸钙，磷酸钙，硅酸钙，硫酸钙，羟丙甲纤维素，预胶化淀粉，糊精，碳酸镁，氧化镁，麦芽糊精，麦芽糖，聚葡萄糖，聚甲基丙烯酸酯，二甲基硅油，藻酸钠，碳酸钠，甘露糖醇，海藻糖，木糖醇，乳糖，蔗糖，山梨糖醇，乳糖醇，麦芽糖醇，赤藓醇，苏糖醇，阿糖醇，核糖醇，半乳糖醇，岩藻糖醇，艾杜糖醇，肌醇，velomitol，异麦芽糖醇或它们的混合物。填充剂／稀释剂可以存在的量为约 0.1％至约 99％ w/w 干重。

[0050] 合适的崩解剂包括例如，交联羧甲基钠，淀粉羟乙酸钠，微晶纤维素，交聚维酮，预胶化淀粉，藻酸钠，脱乙酰壳多糖，硅酸镁铝 ;. 甲基纤维素，瓜尔豆胶或其混合物。崩解剂可以存在的量为约 0.01％至约 30％ w/w 干重。

[0051] 剂型

[0052] 本发明进一步提供了用于口服给药的形式的药物组合物。这样的药物组合物显示化学稳定性，并显示药物产品的很少或没有降解成降解产物。药物组合物可以是固体或液体形式。在一个实施方案中，药物组合物是固体组合物。药物组合物包含本文所述的固体稳定化的粒子。

[0053] 在一个方面，本发明的药物组合物可以通过控制组合物的微环境 pH 来制备。因此，在一个实施方案中，本发明涉及药物组合物（例如固体口服剂型），其包含固体稳定化的粒子和调节组合物的 pH 环境的化合物（例如，碱化剂），其中固体稳定化的粒子包括治疗有效量的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。

[0054] 在一些实施方案中，药物组合物包含约 0.5mg 至约 1200mg 的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。在其他的实施方案中，药物组合物包含约 50mg，约 100mg，约 200mg，约 250mg，约 300mg，约 350mg，约 400mg，约 450mg，约 500mg，约 550mg，约 600mg，约 650mg，约 700mg，约 750mg，约 800mg，约 850mg，约 900mg，约 950mg，约 1000mg，约 1050mg，约 1100mg，约 1150mg 或约 1200mg 的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。

[0055] 本发明的固体口服组合物可被配制成具有如下立即释放特性，如 FDA 指南所述（“立即释放固体口服剂型的溶出测试”，公布于 8/1997，第 IV-A），在立即释放性质的溶出试验指南中，在溶解的前 30 至 60 分钟溶出至少 80％的物质被认为是具有立即释放性质。因此，在一个实施方案中，固体口服组合物在一段短时间内如 60 分钟或更少时间释放大部分

或所有的活性成分，并且使药物可能快速吸收。在其它的实施方案中，固体口服组合物在约15分钟内释放约80％的药物。

[0056] 在本发明的一些实施方案中，固体组合物还包含至少一种另外的药物成分。另外的药物成分包括任何成分或赋形剂，其不是粉末状的药学上可接受的载体，只要该物质在固体组合物以给药量给药至人受试者时一般不是有害的即可。另外的成分的非限制性的实例包括：助流剂和润滑剂如胶态二氧化硅，滑石，硬脂酸镁，硬脂酸钙，硬脂酸，固体聚乙二醇，油酸钠，硬脂酸钠，苯甲酸钠，乙酸钠，氯化钠，硬脂酰富马酸钠，和月桂基硫酸钠；增溶剂，如琼脂，碳酸钙，碳酸钠，交联羧甲基钠，淀粉，预胶化淀粉，淀粉羟乙酸钠，交聚维酮，甲基纤维素，琼脂，膨润土，黄原胶，藻酸，和某些硅酸盐；溶解阻滞剂，如聚合物，例如生物可降解聚合物如聚乳酸，聚 ε 己内酯，聚羟基丁酸，聚原酸酯，聚缩醛，聚二氢吡喃，聚氰基丙烯酸酯，和水凝胶石蜡（hydrogelsparaffin）的交联的或两亲性嵌段共聚物，和蜡，例如石蜡；吸收加速剂，如季铵化合物；吸收剂，如季铵化合物，膨润土，高岭土，或磷酸二钙。

[0057] 本发明的药物组合物可以通过各种方式来制备。这样的组合物包括固体稳定化的粒子。在一些实施方案中，固体稳定化的粒子被提供为粉末。

[0058] 在一些实施方案中，胶囊可以通过以下制备，例如，获得本文所述的固体稳定化的粒子，其含有{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐，和用明胶或其他合适的壳物质以胶囊化固体稳定化的粒子。在一些实施方案中，固体稳定化的粒子提供为粉末。另外的成分，例如本文所述的那些，包括碱化剂，粘合剂，填充剂，稀释剂，助流剂，润滑剂，崩解剂，增溶剂，或它们的混合物可以在胶囊化前与固体稳定化的粒子合并。

[0059] 在其他实施方案中，片剂可以通过以下制备，例如，获得本文所述的固体稳定化的粒子，其含有{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐，和使用常规的方法将固体稳定化的粒子压制成片剂。在一些实施方案中，固体稳定化的粒子提供为粉末。另外的成分，例如本文所述的那些，包括粘合剂，填充剂，稀释剂，助流剂，润滑剂，崩解剂，增溶剂，溶液剂，吸收剂，或它们的混合物在压制成片剂之前可被添加到固体稳定化的粒子。

[0060] 本发明的片剂可以是未包衣或包衣的。在各种不同的实施方案中，片剂包有透明或不透明的保护性包衣，其可以例如包括虫胶密封包衣，糖或聚合物质的包衣，和/或蜡的抛光包衣。在各种不同的实施方案中，片剂被包衣以延迟在胃肠道中崩解和吸收，从而提供较长时期的持续作用。这样的包衣可以包括单硬脂酸甘油酯或二硬脂酸甘油酯。另外，染料可以加入到这些包衣以区分不同的单元剂量。

[0061] 本发明的药物组合物的剂量将根据以下而变化：症状，所需的治疗，受试者的年龄和体重，待治疗疾病的性质和严重程度，给药的途径和活性成分的药物动力学。所示给药量的频率也将随所希望的治疗和所指示的疾病而变化。

[0062] 在一个实施方案中，{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐的给药量足以达到治疗效果。{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐的剂量范围可以是约0.5mg至约2400mg，每天一次或多次给药。在其他实施方案，{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或药学上

可接受的盐可以被施用的量是，每天约 5mg 至约 1200mg，或每天约 10mg 至约 800mg，一次或多次给药。在一些实施方案中，{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐可以通过一次或多次施用来施用的每日总用量是约 100mg，约 150mg，约 200mg，大约 250mg，大约 300mg，大约 350mg，大约 400mg，大约 450mg，大约 500mg，大约 550mg，大约 600mg，大约 650mg，大约 700mg，大约 750mg，大约 800mg，约 850mg，约 900mg，约 950mg，约 1000mg，约 1100mg，约 1200mg，约 1300mg，约 1400mg，约 1500mg，约 1600mg，约 1700mg，约 1800mg，约 1900mg，约 2000mg，约 2100mg，约 2200mg，约 2300mg 或约 2400mg。

[0063] 在一些实施方案中，{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐的所述剂量可以是以下量：每天约 0.001mg/kg 体重至每天约 100mg/kg 的体重。在其他实施方案中，{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐的所述剂量可以是以下量：每天约 0.003mg/kg 体重至每天约 60mg/kg 的体重。在另外的其它实施方案中，{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐的剂量可以是以下量：大约 0.5mg/kg 的量体重每天，约 1mg/kg 的体重每天，约 2mg/kg 的体重每天，约 5mg/kg 的体重每天约 10mg/kg 的体重每天，约 20mg/kg 的体重每天，约 40mg/kg 的体重每天或约 60mg/kg 的体重每天。本领域技术人员的将理解，所施用的剂量可转化为合适的人类当量剂量。

[0064] 本文所述的药物组合物在给药于受试者后相对于不包括本文中所描述的固体稳定化的粒子的参考组合物可表现出 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐改善的生物利用度。

[0065] 使用方法：

[0066] 本发明还提供了用于治疗疾病，障碍或病症的方法，疾病，障碍或病症可以经由给予有需要的患者本文所述的稳定的药物组合物通过在受试者（例如，哺乳动物，如人）中激活葡糖激酶来管理。这样的方法包括，例如，治疗 I 型糖尿病和 / 或 II 型糖尿病；正常化或降低血糖水平；改善葡萄糖耐受性（抵抗）；改善血糖控制；减少空腹血浆葡萄糖；降低餐后血浆葡萄糖；减少糖化血红蛋白 HbA1c；减缓糖尿病的进展，延迟或治疗糖尿病的并发症，例如，糖尿病性肾病，视网膜病变，神经病变或心血管疾病；减少重量或防止增加重量或促进重量减少；治疗胰腺 β 细胞变性；改善和 / 或恢复胰腺 β 细胞的功能；刺激和 / 或恢复胰腺胰岛素分泌功能；提高葡萄糖磷酸化；或维持和 / 或改善胰岛素敏感性；和 / 或治疗或预防高胰岛素血症和 / 或胰岛素抵抗。

[0067] 在一个实施方案中，本发明涉及治疗 II 型糖尿病，包括给予有需要的患者药物组合物，其包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 的平均直径，有约 0.001 至约 0.400 和多分散性指数，包括治疗有效量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上的可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0068] 在另一个实施方案中，本发明提供了通过向需要其的患者施用药物组合物而正常化血糖水平和改善葡萄糖耐受性，所述组合物包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 的平均直径，具有约 0.001 至约 0.400 的多分散性

指数，并且包括治疗有效量的{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0069] 在另一个实施方案中，本发明提供了通过给予有需要的患者药物组合物改善血糖控制和/或用于降低空腹血浆葡萄糖，降低餐后血浆葡萄糖和/或减少糖化血红蛋白HbA1c，所述组合物包括纳米粒子和一种或多种的碱化剂，其中所述纳米粒子具有约0.5nm至约1000nm之间的平均直径，具有大约0.001至约0.400的多分散性指数，并且包括治疗有效量的{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0070] 在一些实施方案中，施用{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐可以在需要其的受试者中降低糖化血红蛋白水平。在其他实施方案中，{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐的施用可以在有需要的受试者中减少HbA1C的量，至少0.1个百分点，或0.2个百分点，或0.3个百分点，或0.4个百分点，或0.5个百分点，或0.6个百分点，或0.7个百分点，或0.8个百分点，或0.9个百分点，或一个百分点。在另一些实施方案中，{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐的施用可以在有需要的受试者中降低HbA1C的水平至小于7%，在其他实施方案中，HbA1C的水平可以降低到5至6.5%的水平。

[0071] 在另一个实施方案中，本发明提供了通过给予有需要的患者药物组合物用于减缓并发症进展，延迟或治疗并发症(例如，糖尿病性肾病，视网膜病变，神经病变或心血管疾病)，所述组合物包括纳米粒子和一种或多种碱化剂，其中纳米粒子具有约0.5nm至约1000nm之间的平均直径，具有大约0.001至约0.400的多分散性指数，并且包括治疗有效量的{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0072] 在又一个实施方案中，本发明提供了通过给予有需要的患者药物组合物用于减少重量或防止增加重量或促进重量减少的方法，所述组合物包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约0.5nm至约1000nm之间的平均直径，具有约0.001至约0.400的多分散性指数，并且包括治疗有效量的{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0073] 在另一个实施方案中，本发明提供了通过给予需要其的患者药物组合物而用于治疗胰腺β细胞变性和/或改善和/或恢复胰腺β细胞功能和/或刺激和/或恢复胰腺胰岛素分泌功能，所述组合物包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约0.5nm至约1000nm之间的平均直径，具有大约0.001至约0.400的多分散性指数，并且包括治疗有效量的{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸或其药学上可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0074] 在另一个实施方案中，本发明提供了通过给予有需要的患者药物组合物用于保持和/或改善胰岛素敏感性和/或治疗或预防高胰岛素血症和/或胰岛素抵抗，所述组合物

包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5 纳米至约 1000nm 之间的平均直径，具有大约 0.001 至约 0.400 的多分散性指数，并且包括治疗有效量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基) 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0075] 在又一个实施方案中，本发明提供了通过向需要其的患者施用药物组合物而降低胰岛素的日剂量，所述组合物包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 之间的平均直径，具有约 0.001 至约 0.400 的多分散性指数，并且包括治疗有效量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0076] 在又一个实施方案中，本发明提供了在受试者中治疗病症，包括给予有需要的患者药物组合物，其包括纳米粒子和一种或多种碱化剂，其中所述纳米粒子具有约 0.5nm 至约 1000nm 之间的平均直径，具有约 0.001 至约 0.400 的多分散性指数，并且包括将治疗有效量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸或其药学上可接受的盐，其中的病症选自代谢紊乱 (包括代谢综合征)，葡萄糖耐受不良，糖尿病前期，胰岛素抵抗，血糖降低，高血糖症，葡萄糖耐量减低 (IGT)，X 综合征，空腹血糖受损 (IFG)，II 型糖尿病，I 型糖尿病，延缓 IGT 到 II 型糖尿病，延迟非胰岛素需要 II 型糖尿病至需要胰岛素 II 型糖尿病，血脂异常，高脂血症，高脂蛋白血症，高血压，骨质疏松症，非酒精性脂肪肝病 (NAFLD)，糖尿病造成的或与糖尿病相关联的并发症，(包括肾病，视网膜病，神经病，受损伤口愈合)) 心血管疾病 (包括动脉粥样硬化，动脉粥样硬化)，降低食物摄取，食欲调节，肥胖症，调节摄食行为，并提高肠肠促胰岛素类的分泌。在其他实施方案中，纳米粒子还包含一种或多种再分散剂。

[0077] 在其他实施方案中，本发明提供了用于本文中所描述的治疗方法，其作为 II 型糖尿病或 I 型糖尿病受试者饮食和运动中的的辅助。

[0078] 定义

[0079] 术语“药学上可接受的”是指在动物或人体内在生物学上或药理学上相容的，并优选指经联邦管理机构或州政府批准的或在美国药典或其它一般公认的药典在列出的用于动物，并且更特别是人的。

[0080] 术语“治疗”，“治疗”和“治疗”指的是管理或控制的疾病，病症或障碍。这包括减轻，缓解，改善，延迟，减少，逆转，改善疾病，障碍或病症，或至少它们的一种症状，这取决于不同的疾病，病症或病况的性质和它的特征性症状。

[0081] 术语“个体”是指动物。受试者可以是在一个试验或筛选或活性实验中的环境中的任何动物。因此，如可通过本领域的技术人员容易地理解的，所述方法，化合物和制剂本发明特别适合于施用于任何动物，特别是哺乳动物，并且包括，但不限于，人类，家畜，例如猫或犬受试者，农场动物，如牛，马，山羊，绵羊和猪受试者，野生动物，研究动物，例如小鼠，大鼠，兔，山羊，绵羊，猪，狗，猫等，禽类，其用于兽医医疗用途。

[0082] 术语“有效量”和“治疗有效的”指的是足以导致在组织，系统，或在需要其受试者中期望的生物或治疗应答的化合物或药物制剂的量或数量。例如，术语“有效量”和“治疗有效量”是指一定量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基

硫烷基}-乙酸或其药学上可接受的盐，所述一定量是在对受试者给药后足以产生有效应答。“治疗有效量”取决于化合物，疾病和其严重性和待治疗受试者的年龄，体重，身体状况和反应性而变化。

[0083] 术语“约”或“近似”是指在如通过本领域的普通技术人员确定的特定值的可接受误差范围内，其将部分取决于所述值如何被测量或确定，即，测量系统的限制。例如，“约”可以在1个超过1个标准差内，如在本领域实践中。或者，“约”相对于该制剂可以意味着加或减最多30%，最多20%，最多10%，甚至最多5%的范围。

[0084] 本文所描述的药物动力学参数包括血浆浓度-时间曲线（AUC_{0-t}和$AUC_{0-\infty}$），最大血浆浓度（C_{max}）和最大血浆浓度（T_{max}）。最大浓度时间，T_{max}，是对应C_{max}的时间而确定。至多对应于最后可测量浓度的时间的血浆浓度-时间曲线下面积（AUC 0-t）是使用如下线性梯形规则通过数值积分而计算：

[0085] $$AUC_{0-t} = \sum_{i=2} 0.5*(C_i + C_{i-1})*(t_i - t_{i-1}) \qquad \text{Eq. 1}$$

[0086] 这里C_i是{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸在相应的采样时刻t_i的血浆浓度，和n是直到并包括最后可定量的浓度的时间点数量。

[0087] 血浆浓度-时间曲线下从零时间到无限大的面积是根据下列公式计算：

[0088] $$AUC_{0-\infty} = AUC_{0-t} + \frac{C_{最后}}{\lambda_z} \qquad \text{Eq. 2}$$

[0089] 其中$C_{最后}$是最后可测量的浓度。

[0090] 以下实施例仅是说明本发明的，不应被解释为以任何方式限制本发明的范围。在本领域技术人员阅读了本公开后本发明所包括的许多变化和等同物变得显而易见。

实施例

[0091] A. 粒子悬浮液的制备

[0092] 制备{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸（药物成分）微悬浮液或纳米悬浮液的一般实验方法

[0093] 聚合物稳定剂（10克，1% w/v）加入到1升纯化水中，混合，直到得到澄清的溶液。将表面活性剂稳定剂（5克，0.5% w/v）加入到该溶液中并混合直至获得澄清溶液。然后逐步加入{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸（100克，10% w/v），混合直至获得均匀的悬浮液。用装有200μm的混合室的M-110EH微流化机和采用约20,000至约30,000psi的粉碎机压力的80μm相互作用将该悬浮液微流化，直到没有进一步减少粒度。收集得到的粒子的悬浮液。

[0094] 实施例1

[0095] 使用上述方法制备{2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米悬浮液，其中聚合物稳定剂是羟丙基甲基纤维素（HPMC）和表面活性剂稳定剂是月桂基硫酸钠（SLS），得到的纳米悬浮液有10%的固体含量，225.6纳米的平均粒度，0.145的多分散性指数和-57.6mV的ζ电势。

[0096] 纳米悬浮液的物理稳定性被示于下表 1 中，在室温下储存 6-48 小时和在 5℃储存 1.5 个月后，没有观察到凝聚。

[0097] 表 1 :纳米粒子悬浮液的物理稳定性

[0098]

时间 / 温度	平均粒度 (nm)
0	225.6
6h, RT	223.1
24h, RT	230.9
48h, RT	229.4
1.5 个月，5℃	226.0

[0099] 图 1 示出，在纳米化之前（“A”）和通过微流化纳米化后（“B”）通过冻干药物悬浮液得到的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的 X 射线粉末衍射 (XRPD) 图案。{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5-- 基硫烷基 }- 乙酸的晶体的结构在纳米化期间未发生变化。

[0100] 图 2 示出，在纳米化之前（“A”）和由微流体化纳米化后（“B”）通过冻干药物悬浮液获得的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸差示扫描量热曲线。纳米化前和后药悬浮液的化学稳定性（通过监测纳米化过程诱导的药物降解）示于下表 2。

[0101] 表 2 :纳米化之前和之后活性成分悬浮液降解性质

[0102]

样品	降解性质									
	A	B	C	D	E	F	G	H	I	药物成分含量%
纳米化前悬浮液为 100μg/mL 的	0.04	0.02	0.04	0.2	0.05	0.04	0.02	0.02	0.02	99.49
纳米悬浮液 100μg/mL 的	0.04	0.02	0.04	0.19	0.05	0.04	0.04	0.02	0.02	99.47

[0103] 冷藏条件下储存的纳米悬浮液的化学稳定性列于下表 3 中。

[0104] 表 3 储存在 5℃的药物成分纳米悬浮液降解性质

[0105]

样品	降解性质									
	A	B	C	D	E	F	G	H	I	药物成分%含量
3 周（wks） T-1	0.09	0.03	0.03	0.2	0.04	0.03	0.02	0.01	0.02	99.53
3 wks T-2	0.07	0	0.03	0.19	0.04	0.04	0.03	0.01	0.02	99.57
2 个月 T-1	0.07	0	0.04	0.19	0.04	0.03	0.03	0.02	0.02	99.56
2 个月 T-2	0.07	0	0.04	0.19	0.04	0.03	0.02	0.02	0.02	99.59

[0106] 实施例 2

[0107] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是羟丙基纤维素（HPC）和表面活性剂稳定剂是月桂基硫酸钠（SLS）。所得纳米悬浮液有 10％的固体含量，252.2 纳米的平均粒度，0.171 的多分散性指数和 -55.6mV 的 ζ 电势。

[0108] 实施例 3

[0109] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是泊洛沙姆 188 和表面活性剂稳定剂是月桂基硫酸钠（SLS）。所得纳米悬浮液有 10％的固体含量，260.4 纳米的平均粒度，0.183 的多分散性指数和 -54.4mV 的 ζ 电势。

[0110] 实施例 4

[0111] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是聚乙烯醇和表面活性剂稳定剂是月桂基硫酸钠（SLS）。所得纳米悬浮液有 10％的固体含量，261.4 纳米的平均粒度，0.166 的多分散性指数和 -57.3mV 的 ζ 电势。

[0112] 实施例 5

[0113] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是羟丙基纤维素和表面活性剂稳定剂是月桂基硫酸钠（SLS）。所得纳米悬浮液有 10％的固体含量，252.2 纳米的平均粒度，0.171 的多分散性指数和 -55.6mV 的 ζ 电势。

[0114] 实施例 6

[0115] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂为聚乙烯基吡咯烷酮和表面活性剂稳定剂是月桂基硫酸钠（SLS）。所得纳米悬浮液有 10％的固体含量，258.7 纳米的平均粒度，0.154 的多分散性指数和 -58.3mV 的 ζ 电势。

[0116] 实施例 7

[0117] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙

酸的纳米悬浮液采用上面的方法制备，其中聚合物稳定剂为聚乙烯硫酸酯和所述表面活性剂稳定剂是月桂基硫酸钠 (SLS)。

[0118] 实施例 8

[0119] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米悬浮液采用上面的方法制备，其中聚合物稳定剂为聚乙二醇 - 聚乳酸 (PEG-PLA) 和表面活性剂稳定剂是月桂基硫酸钠 (SLS)。

[0120] 实施例 9

[0121] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米悬浮液采用上面的方法制备，其中聚合物稳定剂是明胶和表面活性剂稳定剂是月桂基硫酸钠 (SLS)。

[0122] 实施例 10

[0123] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸纳米悬浮液使用上述方法制备，其中聚合物稳定剂是琼脂和表面活性剂稳定剂是月桂基硫酸钠 (SLS)。

[0124] 实施例 11

[0125] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是羟丙基甲基纤维素和表面活性剂稳定剂是聚山梨醇酯 80。

[0126] 实施例 12

[0127] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是羟丙基甲基纤维素和表面活性剂稳定剂是多库酯钠。

[0128] 实施例 13

[0129] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是羟丙基甲基纤维素和表面活性剂稳定剂为脱氧胆酸钠。

[0130] 实施例 14

[0131] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米悬浮液使用上述方法制备，其中聚合物稳定剂是羟丙基甲基纤维素和表面活性剂稳定剂是维生素 E 聚乙二醇琥珀酸酯。

[0132] B. 纳米粒子的制备

[0133] 制备 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 (药物成分) 的纳米颗粒的一般实验方法 :

[0134] 从由实施例 1 得到的纳米悬浮液除去溶剂直到纳米悬浮液具有 1000 克总重量，具有 10% w/w 的固体含量。再分散剂 (50 克，5% w/w) 加入到该纳米悬浮液和搅拌该混合物直到再分散剂完全溶解。流化床温热至约 60℃和粘合剂 (800 克，80% w/w) 和填充剂 (5 克，5% w/w) 加入到流化床。所述赋形剂在流化床被流化以混合。纳米悬浮液在流化床被顶喷 (top spray)，同时保持约 40 摄氏度的产物温度。顶喷完成后，将得到的颗粒在 40 摄氏度干燥，直到得到该颗粒的低于 3% 的干燥损失 (LOD)。

[0135] 实施例 15

[0136] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米颗粒用上述的一般方法制备，其中再分散剂为甘露糖醇，所述粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0137] 制粒后的纳米粒度示于下面的表 4 中，比较采用和不采用再分散剂的粒度。

[0138] 表 4 :重构的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸粒度

[0139]

	纳米粒子的大小 (纳米粒度) (nm)	PDI
制粒前	252.1	0.172
不采用再分散剂重构的纳米粒子	479.3	0.385
采用再分散剂重构的纳米粒子	399.6	0.322

[0140] 实施例 16

[0141] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用一般方法制备，其中再分散剂是海藻糖，粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0142] 实施例 17

[0143] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是山梨糖醇，粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0144] 实施例 18

[0145] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是乳糖，粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0146] 实施例 19

[0147] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是蔗糖，粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0148] 实施例 20

[0149] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是异麦芽糖，所述粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0150] 实施例 21

[0151] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙

酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是 innulin，所述粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0152] 实施例 22

[0153] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是葡聚糖，粘合剂是羟丙基甲基纤维素和填充剂是微晶纤维素。

[0154] 实施例 23

[0155] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是磷酸二钙。

[0156] 实施例 24

[0157] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是异麦芽糖。

[0158] 实施例 25

[0159] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是乳糖。

[0160] 实施例 26

[0161] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是甘露糖醇。

[0162] 实施例 27

[0163] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是淀粉。

[0164] 实施例 28

[0165] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是海藻糖。

[0166] 实施例 29

[0167] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是碳酸钠。

[0168] 实施例 30

[0169] {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是葡萄糖。

[0170] 实施例 31

[0171] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基甲基纤维素和填充剂是羟丙基甲基纤维素。

[0172] 实施例 32

[0173] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是羟丙基纤维素和填充剂是微晶纤维素。

[0174] 实施例 33

[0175] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是聚乙烯基吡咯烷酮和填充剂是微晶纤维素。

[0176] 实施例 34

[0177] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是聚乙烯醇和填充剂是微晶纤维素。

[0178] 实施例 35

[0179] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是聚乙烯基己内酰胺和填充剂是微晶纤维素。

[0180] 实施例 36

[0181] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂是明胶和填充剂是微晶纤维素。

[0182] 实施例 37

[0183] {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸的纳米颗粒使用上文所述的一般方法制备，其中再分散剂是甘露醇，粘合剂预胶化淀粉和填充剂是微晶纤维素。

[0184] C. 喷雾干燥的纳米粒子的制备

[0185] 制备 {2-[3-环己基-3-(反式-4-丙氧基-环己基)-脲基]-噻唑-5-基硫烷基}-乙酸（药物成分）的喷雾干燥纳米粒子的一般实验方法：

[0186] 从由实施例 1 得到的纳米悬浮液除去溶剂直到纳米悬浮液具有 1000 克总重量，10% w/w 的固体含量。再分散剂 (50 克，5% w/w) 加入到该纳米悬浮液，将混合物搅拌直至再分散剂完全溶解。使用入口温度为 90±10℃的和 50±10℃的出口温度的喷雾干燥器对纳米悬浮液进行喷雾干燥。对所有的纳米悬浮液的进行喷雾干燥后，将干燥的纳米粒子从喷雾干燥器的旋流器收集（步琪小型喷雾干燥仪 B-290，步琪琪公司，弗拉维尔，瑞士）(Buchi Mini Spray Dryer B-290, Buchi Labortechnik AG, Flawil, Switzerland)。所得喷雾干燥纳米粒子的 TGA 分析给出约 0.1%的含水量。使用 Melvern 的 Zetasizer ZS（型号 Zen3600，通过马尔文仪器有限公司，伍斯特郡，英国）(Model Zen3600, by Malvern Instruments, Ltd., Worcestershire, United Kingdom) 对喷雾干燥纳米粒子的粒度进行了表征。

[0187] 实施例 38

[0188] 喷雾干燥纳米粒子用上文所述的一般方法制备，其中再分散剂为甘露醇。表 5 示出 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米粒子在喷雾干燥前和后的粒度。

[0189] 表 5 :{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸喷雾干燥纳米粒子的粒度

[0190]

	纳米粒子尺寸（纳米粒度）(nm)	PDI
在喷雾干燥之前（纳米悬浮液）	222	0.112
喷雾干燥的纳米粒子	258	0.219

[0191] 图 3 示出了，{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸和 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的喷雾干燥的纳米粒子的 X 射线粉末衍射 (XRPD) 图案。在喷雾干燥过程中 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的晶体的结构不改变。

[0192] 被进行喷雾干燥后的活性成分的稳定性列于下表 6 中。喷雾干燥不导致活性成分的显著降解。

[0193] 表 6. {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的干燥纳米粒子的降解喷雾性质

[0194]

样品	降解性质											药物成分 % 含量
	a	b	c	d	e	f	g	h	i	j	k	
%	0.17	0	0	0.02	0.09	0.01	0.04	0.01	0.03	0.04	0.02	99.53

[0195] D. {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸固体剂型

[0196] 实施例 39

[0197] 含有喷雾干燥纳米粒子的胶囊的制备 :

[0198] 实施例 38 中制备的喷雾干燥的纳米粒子 (424mg，含有 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 0. 47 克 / 克) 在 V 型混合器中与葡甲胺 (100mg) 混合 15 分钟，然后测试共混物的均匀性。然后将共混物装入胶囊填充机的粉末站。调整基于所述组合物的胶囊填充重量后，将共混物填入明胶胶囊中。

[0199] 实施例 40

[0200] 含有纳米粒子的胶囊的制备：

[0201] 异麦芽酮糖的混合物（106 毫克，盖伦 (Galen) IQ 800），聚乙烯吡咯烷酮（20mg，PVP K30）和葡甲胺（150mg）通过 20 目手筛过筛。将过筛的混合物加入到加热至 50℃的流化床制粒机，和实施例 1 中得到的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的纳米悬浮液（约 2224 克）被顶喷到基板上。在制粒期间产品温度保持在 40℃。制粒完成后，将纳米粒子物干燥至水分含量小于 3%。所述纳米粒子被排出，然后在冰箱中贮存至少 12 小时，然后恢复至室温。然后所述纳米粒子（500mg）被装入胶囊填充机的粉末站。调整基于所述组合物的胶囊填充重量后，将纳米粒子填充到明胶胶囊（AA EL 的尺寸，灰色不透明）。

[0202] 图 4 示出以下的溶出：仅含有微粉化的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的胶囊（API 胶囊（API Cap））；

[0203] 含有采用微粉化的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸配制的颗粒的胶囊（参考胶囊）

[0204] 含有从实施例 39 得到的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 } 乙酸的喷雾干燥的纳米粒子的胶囊，和

[0205] 含有从实施例 40 得到的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸纳米粒子的胶囊。

[0206] 如下进行溶出：在 0.3w/v% 月桂基硫酸钠在 0.01N HCl 的水性媒介物中，pH 为 2，踏板法 (pedal method)，50rpm。在 37℃下进行长达 60 分钟的溶出，并在 15，30，45 和 60 分钟进行溶出采样。使用 HPLC 对药物释放进行了分析。

[0207] 实施例 41

[0208] 含有纳米粒子的片剂的制备

[0209] 异麦芽酮糖（106 毫克，盖伦 IQ 800），聚乙烯吡咯烷酮（20mg，PVP K30）和葡甲胺（150mg）的混合物通过 20 目手筛过筛。将过筛的混合物加入到加热至 50℃的流化床制粒机，和实施例 1 中得到的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸（约 2224 克）的纳米悬浮液被顶喷到基板上。在制粒期间产品温度保持在 40℃。制粒完成后，将纳米粒子物干燥至水分含量小于 3%。所述纳米粒子被排出，然后贮存在冰箱中。

[0210] 所述纳米粒子被带到室温，然后进行粉碎，得到均匀的粒度。磨碎的颗粒（500mg）通过 20 目的手筛进行了筛选，然后加入到 V- 混合器。交联羧甲基纤维素钠（18 毫克），异麦芽糖醇（74mg）的混合物通过 20 目手筛筛分并加入到 V- 混合器。将混合物混合约 15 分钟。滑石（5mg）通过 20 目手筛过筛，然后加入到 V- 混合器。将混合物混合约 5 分钟。硬脂酸镁（3 毫克）通过 20 目手筛过筛并加入到 V- 混合器。将混合物混合 5 分钟。该共混的混合物然后被排出。该共混的混合物加入到压片机的料斗中，并被压制，形成重量 600mg 和硬度 8 至 12 千磅 (kilopound)(kp) 的片剂。

[0211] 实施例 42

[0212] 雄性比格犬中进行的单剂量研究

[0213] 各种 100mg 的 {2-[3- 环己基 -3-（反式 -4- 丙氧基 - 环己基）- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的口服制剂在第 1 天，和第 11 天被以单一剂量施用至雄性比格犬。可测量

血浆样品在 0.5 小时至 24 小时被获取，并分析，其针对 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸浓度，是由 LC-MS/MS 法验证的 (内部标准 ：氘代化合物样品的制备 ：液体萃取 ；样品体积 ：1 毫升 ；校准范围 ：1.00-1.000ng/mL ；电离 ：涡轮离子喷雾)。

[0214] 在研究中向受试者施用下述制剂 ：

[0215] A. 10mg/mL{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸和 1％葡甲胺的 10 毫升水溶液

[0216] B. 含有 100mg{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸纳米粒子的胶囊，

[0217] C. 含有 100mg{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的喷雾干燥的纳米粒子胶囊和

[0218] D. 含有与 100mg 微粉化的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸配制颗粒的的胶囊 (参考胶囊)。

[0219] 施用单剂量的上述制剂之后观察的平均药代动力学参数示于下表 7 中。

[0220] 表 7. 口服给药各种制剂中 100mg 的活性成分后在雄性犬中在第 1 天和第 11 天的药代动力学参数

[0221]

制剂	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (ng*hr/mL)
A	8870	0.667	13686
B	6730	1.17	14196
C	6657	0.833	11532
D	2680	2.33	7488

[0222] 图 5 示出了这些各种制剂在比格犬中体内暴露 ($AUC_{0-\infty}$)。

[0223] 实施例 43

[0224] 在健康受试者中实施的单剂量研究

[0225] 健康受试者被随机分为在具有 7 天洗脱期的单中心，随机，开放标记，4 向交叉的研究中不同组中 (A，B 和 C)。可测量血浆样品在 1 小时至 24 小时获取并分析，其针对 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸浓度，这由试验验证。

[0226] 在伴有水的禁食条件下受试者被给予下列制剂 ：

[0227] A. 4×200mg{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸胶囊 (参考)

[0228] B. {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸的喷雾干燥纳米粒子的 4×200mg 胶囊

[0229] C. {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸纳米颗粒的 4×200mg 胶囊。

[0230] 制剂 A(参考) ：

[0231] 制剂 A 的微粒采用下列成分制备：

[0232]

成分	% w/w	Theor. wt (mg/g)
有效成分	65.60	657.0
微晶纤维素，NF（欧洲药典（微晶纤维素 PH101）（(Ph.Eur. (Avicel PH101)）	11.50	115.0
一水合乳糖	12.29	122.9
交联羧甲纤维素钠，NF（AC-Di-SOL）	7.56	75.6
聚山梨醇酯 80，NF	2.37	23.7
羟丙基甲基纤维素 E3 LV 溢价（premium）	0.59	5.9
用于灌溉的无菌水	N/A	N/A
颗粒总共，200mg 活性成分/304.4 mg	100	1000

[0233] 然后从微粒制备具有以下成分的原始混合物：

[0234]

成分	% w/w	Theor. wt (mg/g)
颗粒总共，200mg 活性成分/304.4 mg	84.56	845.6

[0235]

微晶纤维素，NF（欧洲药典（微晶纤维素 PH101）	4.94	49.4
交联羧甲基纤维素钠，NF（AC-Di-SOL）	5.00	50.0
预胶化淀粉，NF（淀粉 1500）	5.00	50.0
硬脂酸镁，NF（Hyqual2257）	0.50	5.0
活性成分，原始混合物，200mg/360mg	100	1000

[0236] 然后胶囊（明胶胶囊，大小为 0，灰色不透明的，96 毫克）被充满 180mg 活性成分的原始混合物，200mg/360mg。

[0237] 制剂 B（喷雾干燥纳米粒子的胶囊）：

[0238] 具有 10％的固体的纳米粒子悬浮液组合物的制备如实施例 2 中描述的，不同的是使用下面的针对每种成分的改变量：

[0239]

成分	% w/w	Theor. wt (mg/g)
有效成分	10.0	9.0
羟丙基纤维素	0.2	0.2
十二烷基硫酸钠	1	0.9
纯净水，USP	N/A	89.9
纳米粒子悬浮液，10％固体	N/A	100

[0240] 使用实施例 38 的方法，对所述纳米粒子悬浮液进行喷雾干燥以形成喷雾干燥的纳米粒子，其中再分散剂为甘露醇，其改变的量是 90 克（9％ w/w）。所得喷雾干燥的纳米粒子包含 0.47 克的活性成分每克总干重。然后通过与混合喷雾干燥纳米粒子（80.9％）与葡甲胺（19.1％）形成原始混合物，以形成具有 200mg 的活性成分每 524mg 总干重的原始混合物。然后胶囊（明胶胶囊，尺寸 AA EL，灰色不透明的，168 毫克）被填充 524mg 的活性成分的原始混合物，200mg/524mg。

[0241] 制剂 C（具有纳米粒子的胶囊）

[0242] 纳米粒子的颗粒用实施例 40 中的一般方法制备，不同之处在于纳米粒子悬浮液在上述制剂 B 中获得，并且各成分的量修改如下：

[0243]

成分	% w/w	Theor. wt (mg/g)
纳米粒子悬浮液，10％的固体	44.8	448
异麦芽糖（Isomalt）（GalenIQ800）	21.2	212
葡甲胺	30	300
聚乙烯吡咯烷酮（PVP K30）	4	40
纳米粒子，200mg/ 500mg	100	1000

[0244] 胶然后囊（胶囊，大小 AA EL，灰色不透明，168 毫克）被填充 500mg 的纳米粒子颗粒，200mg/500mg。

[0245] 施用单剂量的上述制剂后观察的平均药代动力学参数示于下表 8。

[0246] 表 8. 健康受试者中口服给药后总结的药代动力学参数

[0247]

制剂	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (ng*hr/mL)
A	1382	1.5	4705
B	5802	1.5	10347
C	5606	1.0	10231

[0248] 图 6 和 7 示出了三组的体内暴露（分别 AUC 和 C_{max}）。

[0249] 实施例 44

[0250] 2 型糖尿病患者中多剂量研究

[0251] 2 型糖尿病患者随机分成不同的组 (A, B 和 C),所述组在一个多中心,随机,双盲,平行组,多剂量研究中。患者被施用以下的制剂 :

[0252] A. 在第 1 天单一剂量的口服 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 (1×200mg 胶囊),接着是多个口服剂量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 (1×200mg 胶囊),每天两次 (BID)(参考)。

[0253] B. 在第 1 天的口服单剂量的 800mg{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 (4×200mg 胶囊),随后是多次口服剂量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 800mg(4×200mg 的胶囊),每天一次 (QD)。

[0254] C. 在第 1 天的口服单剂量的 800mg{2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 (4×200mg 胶囊),随后是多次口服剂量的 {2-[3- 环己基 -3-(反式 -4- 丙氧基 - 环己基)- 脲基]- 噻唑 -5- 基硫烷基 }- 乙酸 800mg(4×200mg 的胶囊),每天两次 (BID)。

[0255] 施用单剂量的上述制剂之后观察的平均药代动力学参数示于下表 9。

[0256] 表 9. 2 型糖尿病患者中口服给药后 42 天后总结的药代动力学参数

[0257]

制剂	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng*hr/mL)
A	1047	1	3825
B	10802	1	16218
C	9794	1	29407

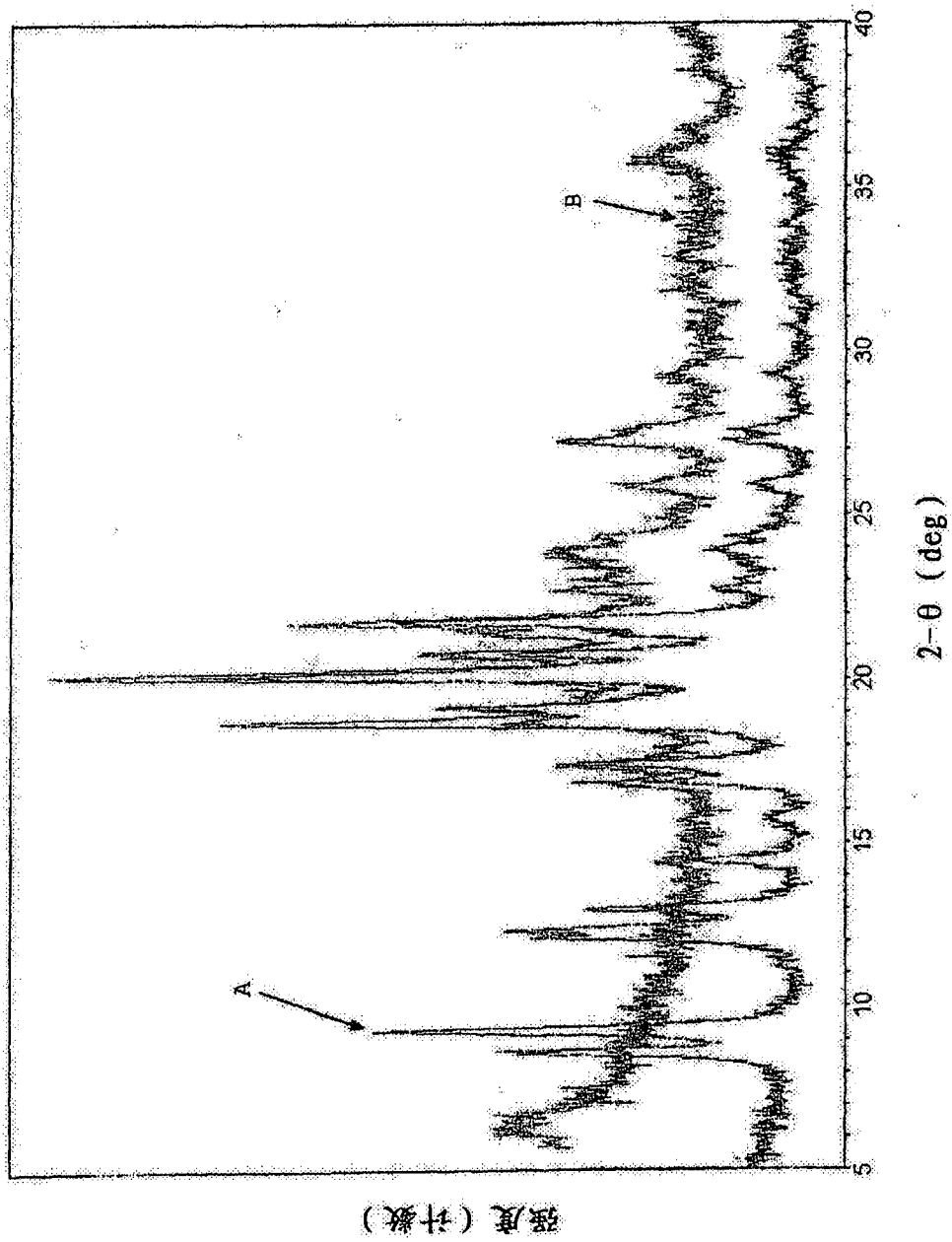


图 1

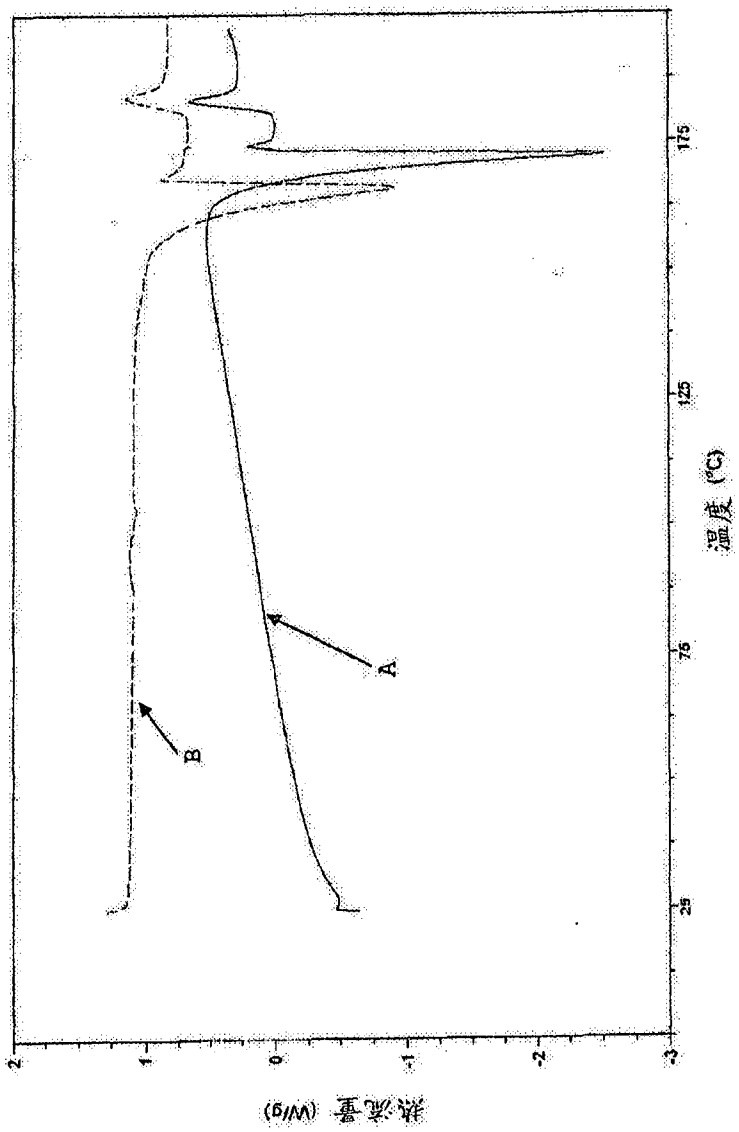


图 2

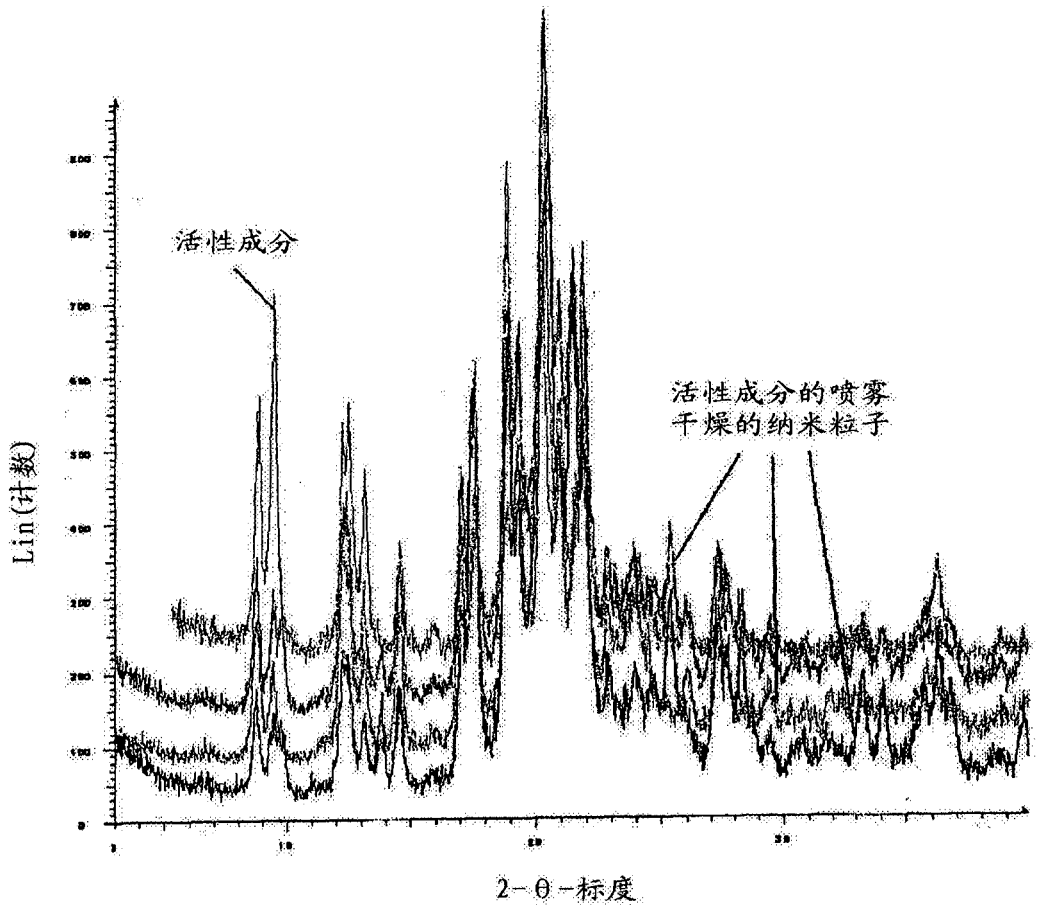


图 3

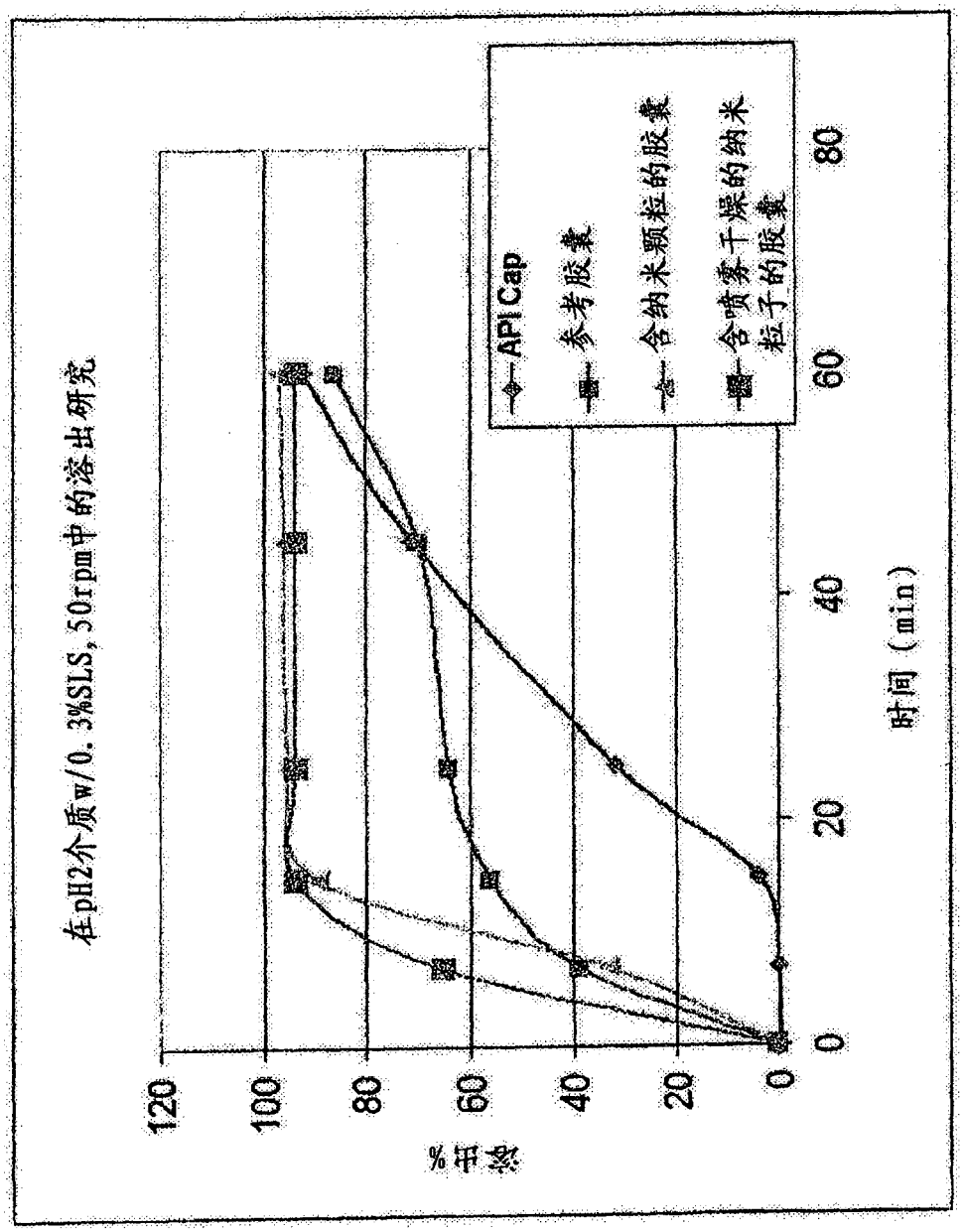

在pH2介质w/0.3%SLS，50rpm中的溶出研究
溶出%
时间（min）
0
20
40
60
80
100
120
0
20
40
60
80
API Cap
参考胶囊
含纳米颗粒的胶囊
含喷雾干燥的纳米粒子的胶囊

图 4

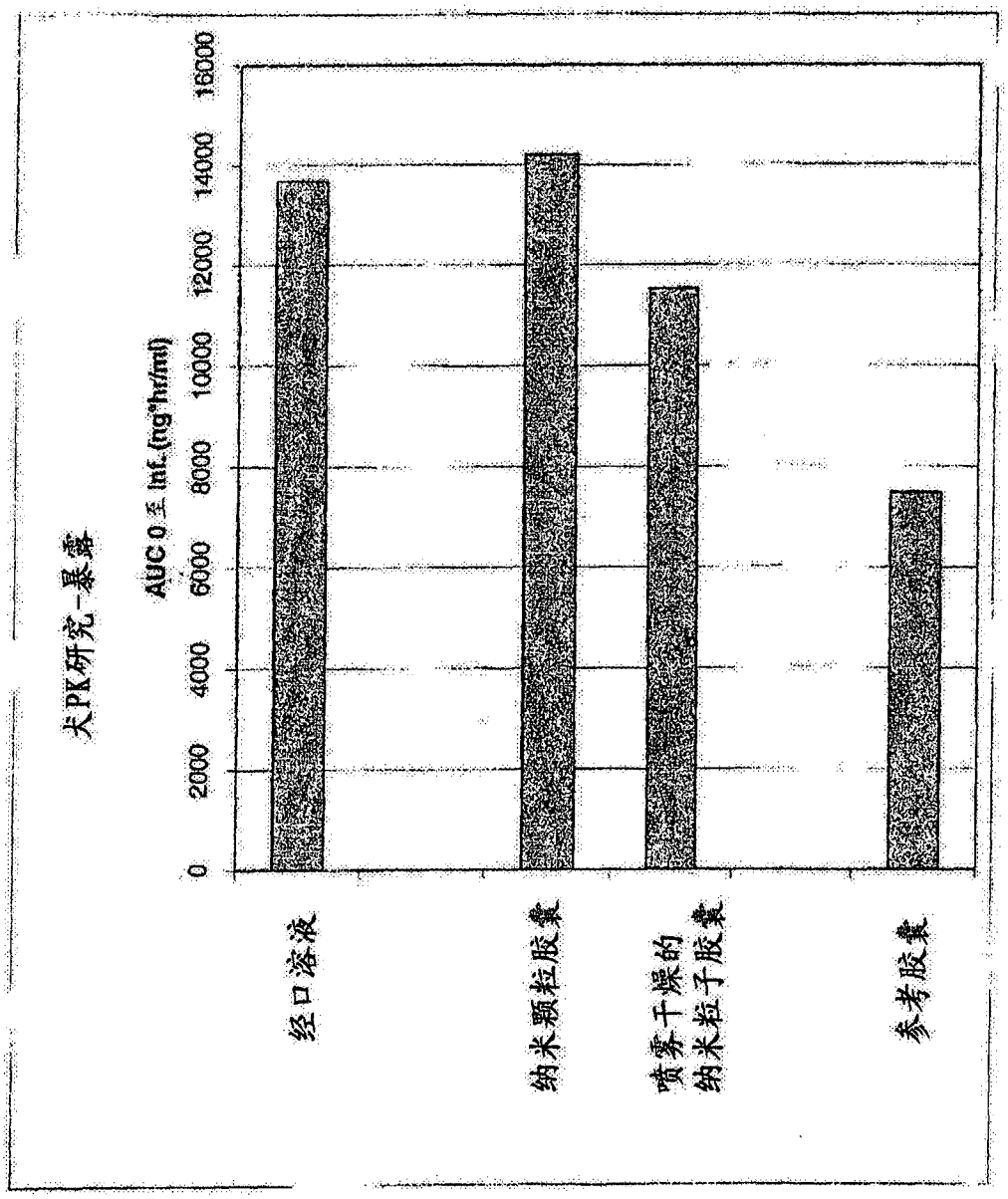

犬PK研究-暴露
AUC 0至Inf.(ng*hr/ml)
0
2000
4000
6000
8000
10000
12000
14000
16000
经口溶液
纳米颗粒胶囊
喷雾干燥的
纳米粒子胶囊
参考胶囊

图 5

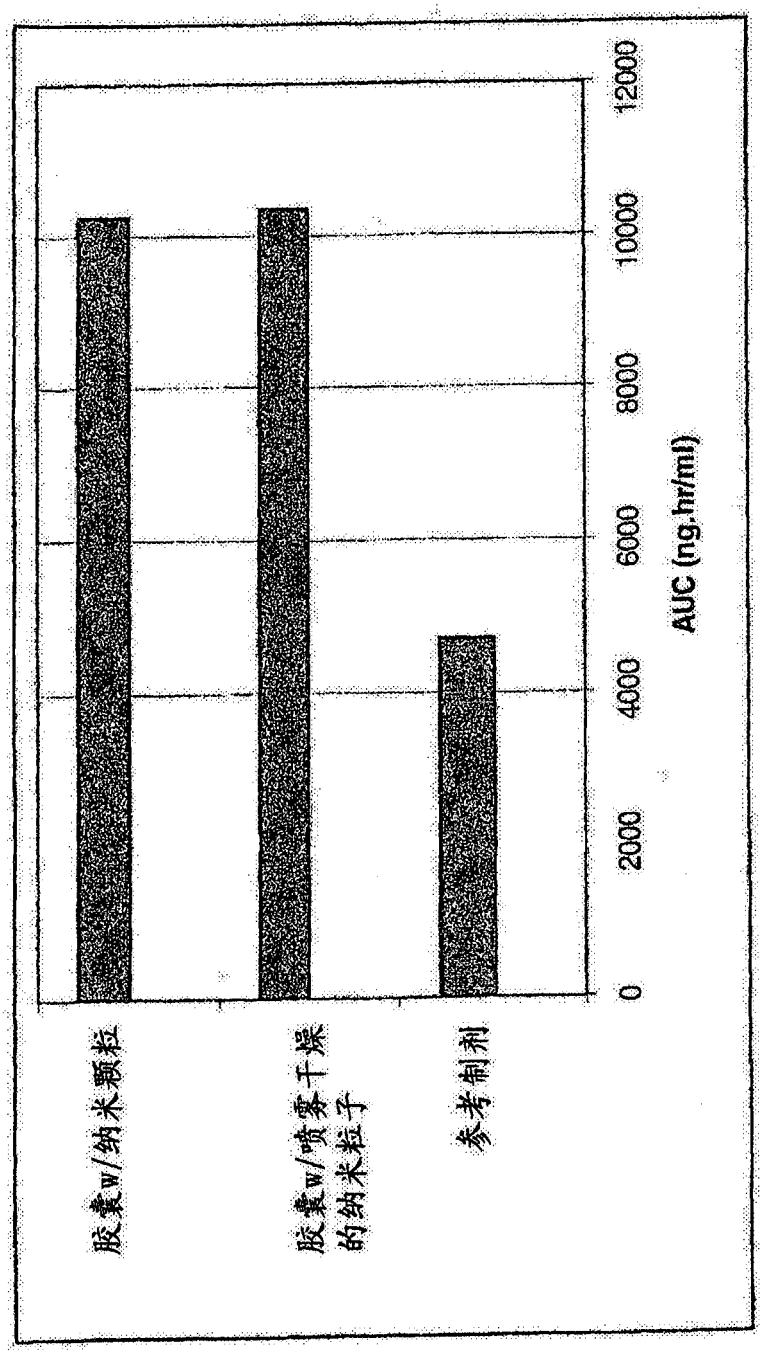

AUC (ng.hr/ml)
0
2000
4000
6000
8000
10000
12000
胶囊w/纳米颗粒
胶囊w/喷雾干燥的纳米粒子
参考制剂

图 6

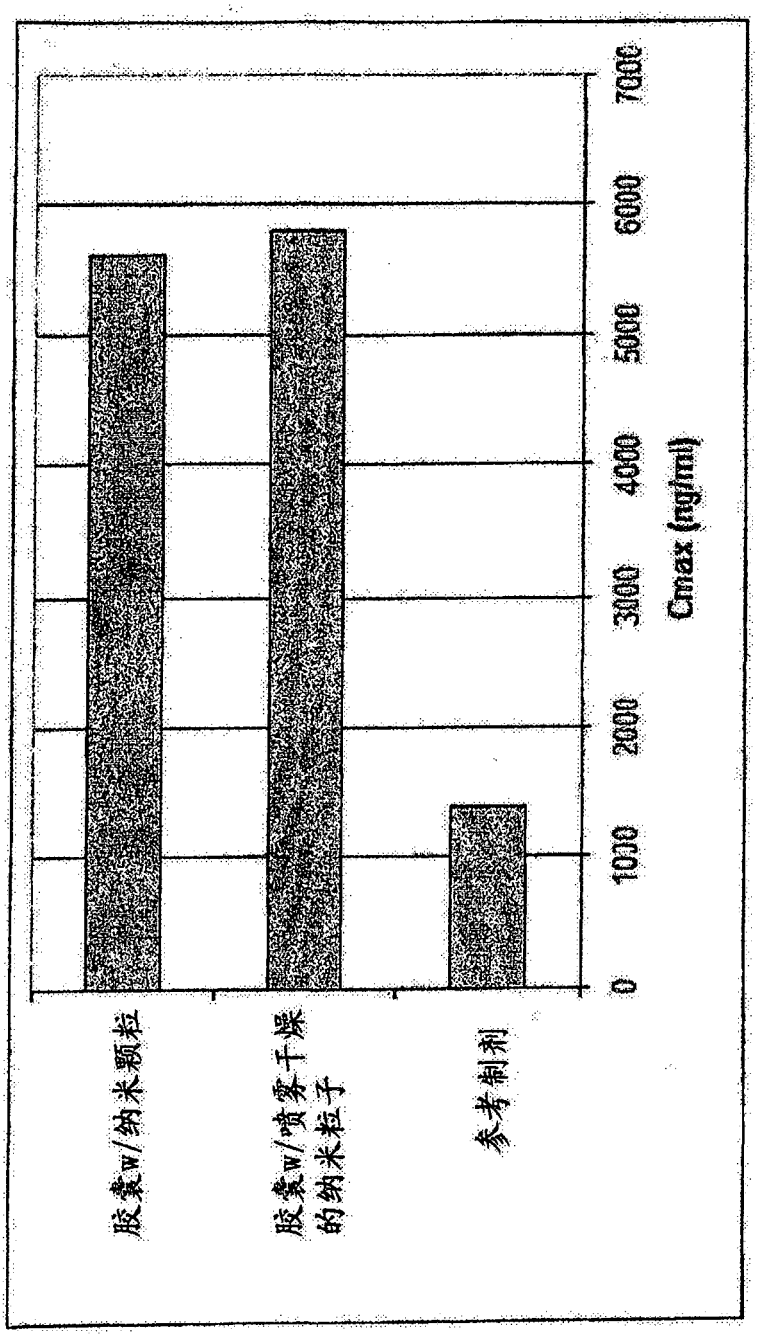

0
1000
2000
3000
4000
5000
6000
7000
Cmax (ng/ml)
胶囊w/纳米颗粒
胶囊w/喷雾干燥的纳米粒子
参考制剂

图 7