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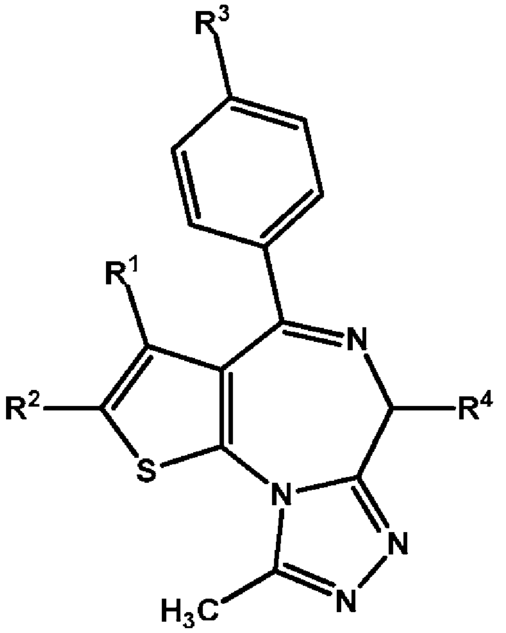


(1)

(57) Abstract: A solid dispersion comprising an amorphous thienotriazolodiazepine compound of the Formula (I), wherein X is a halogen, R^1 is C_1-C_4 alkyl, R2 is C_1-C_4 alkyl, a is an integer of 1-4, R^3 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, phenyl optionally having substituent(s), or heteroaryl optionally having substituent(s), a pharmaceutically acceptable salt thereof or a hydrate thereof; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is HPMCAS. The solid dispersion may be made by spray drying.

WO 2014/068402 A2

TITLE OF THE INVENTION

PHARMACEUTICAL FORMULATION CONTAINING THIENOTRIAZOLODIAZEPINE COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 61/707,465, filed September 28, 2012, U.S. Provisional Application Serial No. 61/782,882, filed March 14, 2013 and U.S. Provisional Application Serial No. 61/831,811, filed June 6, 2013, all of which are incorporated herein by reference in their entirety.

FIELD OF INVENTION

[0002] The present disclosure describes solid dispersions of thienotriazolodiazepine compounds which have improved solubility and bioavailability.

BACKGROUND OF THE INVENTION

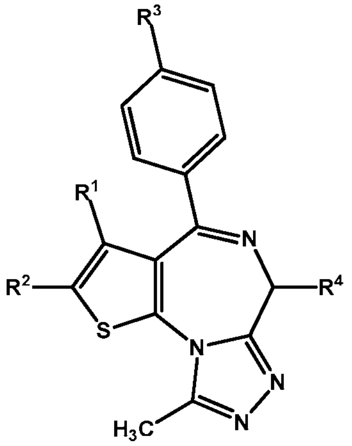
[0003] The compound of Formula (1), described herein below, has been shown to inhibit the binding of acetylated histone H4 to the tandem bromodomain (BRD)-containing family of transcriptional regulators known as the BET (bromodomains and extraterminal) proteins, which include BRD2, BRD3, and BRD4. *See* U.S. Patent Application Publication No. 2010/0286127 A1, which is incorporated herein by reference in its entirety. The BET proteins have emerged as major epigenetic regulators of proliferation and differentiation and also have been associated with predisposition to dyslipidemia or improper regulation of adipogenesis, elevated inflammatory profile and risk for cardiovascular disease and type 2 diabetes, and increased susceptibility to autoimmine diseases such as rheumatoid arthritis and systemic lupus erythematosus as reported by Denis, G.V. "Bromodomain coactivators in cancer, obesity, type 2 diabetes, and inflammation," *Discov Med* 2010; 10:489-499, which is incorporated herein by reference in its entirety. Accordingly, the compound of formula (II) may be useful for treatment of various cancers, cardiovascular disease, type 2 diabetes, and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus.

[0004] The thienotriazolodiazepine compound of Formula (1), described herein below, presents highly specific difficulties in relation to administration generally and the preparation of galenic compositions in particular, including the particular problems of drug bioavailability and variability in inter- and intra-patient dose response, necessitating development of a non-conventional dosage form with respect to the practically water-insoluble properties of the thienotriazolodiazepine.

[0005] Previously, it had been found that thienotriazolodiazepine compound of Formula (1) could be formulated with the carrier ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer (Eudragit RS, manufactured by Rohm) to provide an oral formulation that preferentially released the pharmaceutical ingredient in the lower intestine for treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease as reported in U.S. Patent Application Publication No. 20090012064 A1, which is incorporated herein by reference in its entirety. Through various experiments including animal tests, it was found that that for inflammatory bowel diseases, the thienotriazolodiazepine compound of Formula (1) release in a lesion and a direct action thereof on the inflammatory lesion were more important than the absorption of thienotriazolodiazepine compound of Formula (1) into circulation from the gastrointestinal tract. However, for many other disease conditions high absorption of thienotriazolodiazepine compound of Formula (1) into the circulation from gastrointestinal tract is required. Accordingly, a need exists for formulations of thienotriazolodiazepine compound of Formula (1) that can provide high absorption of thienotriazolodiazepine compound of Formula (1) into the circulation from gastrointestinal tract.

BRIEF SUMMARY OF THE INVENTION

[0006] In one embodiment, the present disclosure provides for a solid dispersion comprising an amorphous thienotriazolodiazepine compound of the Formula (1)



wherein X is a halogen, R^1 is C_1-C_4 alkyl, R^2 is C_1-C_4 alkyl, a is an integer of 1-4, R^3 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, phenyl optionally having substituent(s), or heteroaryl optionally having substituent(s), a pharmaceutically acceptable salt thereof or a hydrate thereof; and a pharmaceutically acceptable polymer.

In one embodiment, Formula (1) is selected from the group consisting of: (i) (S)-2-[4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo- [4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide or a dihydrate thereof, (ii) methyl (S)-{4-(3'-cyanobiphenyl-4-yl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]tri- azolo[4,3-a][1,4]diazepin-6-yl}acetate, (iii) methyl (S)-{2,3,9-trimethyl-4-(4-phenylaminophenyl)-6H-thieno[3,2-f][1,2,4]triaz- olo[4,3-a][1,4]diazepin-6-yl}acetate; and (iv) methyl (S)-{2,3,9-trimethyl-4-[4-(3-phenylpropionylamino)phenyl]-6H-thieno[3,2-f-][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate. In one such embodiment, Formula (1) is (S)-2-[4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,- 4]triazolo[4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide.

[0007] In some embodiments, the pharmaceutically acceptable polymer is hydroxypropylmethylcellulose acetate succinate. In some such embodiments, the solid dispersion has a thienotriazolodiazepine compound to hydroxypropylmethylcellulose acetate succinate (HPMCAS), weight ratio of 1:3 to 1:1. In some such embodiments, the solid dispersion exhibits a single glass transition temperature (Tg) inflection point ranging from about 130 °C to about 140 °C. In some such embodiments, a concentration of the thienotriazolodiazepine compound after exposure to the relative humidity of 75 % at 40 °C for at least one month is at least 90 % of the concentration the amorphous thienotriazolodiazepine compound prior to such exposure.

[0008] In other embodiments, the pharmaceutically acceptable polymer is PVP. In some such embodiments, the solid dispersion has a thienotriazolodiazepine compound to PVP weight ratio of 1:3 to 1:1. In some such embodiments, the solid dispersion exhibits a single glass transition temperature (Tg) inflection point ranging from about 175 °C to about 185 °C. In some such embodiments, a concentration of the thienotriazolodiazepine compound after exposure to the relative humidity of 75 % at 40 °C for at least one month is at least 90 % of the concentration the amorphous thienotriazolodiazepine compound prior to such exposure.

[0009] In another embodiment, the solid dispersion is obtained by spray drying.

[0010] In another embodiment, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1).

[0011] In yet another embodiment, the solid dispersion provides an area under the curve (AUC) value that is at least 0.5 times that of a corresponding AUC value provided by a control composition administered intravenously, wherein the control composition comprises an equivalent quantity of a crystalline thienotriazolodiazepine compound of Formula (1).

[0012] In still yet another embodiment, the solid dispersion provides a concentration, of the amorphous thienotriazolodiazepine compound, in an aqueous in vitro test medium at pH between 5.0 to 7.0, of at least 5-fold greater than a concentration of a crystalline thienotriazolodiazepine compound of Formula (1) without polymer, in a control in vitro test medium at pH between 5.0 to 7.0 test medium.

[0013] In yet another embodiment, a concentration of the amorphous thienotriazolodiazepine compound, from the solid dispersion, in an aqueous in vitro test medium having a pH of 1.0 to 2.0, is at least 50% higher than a concentration of a crystalline thienotriazolodiazepine compound of Formula (1) without polymer in an in vitro test medium having a pH between 5.0 and 7.0.

[0014] In one embodiment, the concentration of the amorphous thienotriazolodiazepine compound, is at least 50% higher compared to a concentration of thienotriazolodiazepine compound of Formula (1), from a solid dispersion of thienotriazolodiazepine compound of the Formula (1) and a pharmaceutically acceptable polymer selected from the group consisting of: hypromellose phthalate and ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer, wherein each solid dispersion was placed in an aqueous in vitro test medium having a pH of 1.0 to 2.0.

[0015] In one embodiment, the concentration of the amorphous thienotriazolodiazepine compound of Formula (1), is at least 50% higher compared to a concentration of thienotriazolodiazepine compound of Formula (1), from a solid dispersion of thienotriazolodiazepine compound of the Formula (1) and a pharmaceutically acceptable polymer selected from the group consisting of: hypromellose phthalate and ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer, wherein each solid dispersion was placed in an aqueous in vitro test medium having a pH of 1.0 to 2.0.

[0016] The present disclosure further provides for a pharmaceutical formulation comprising a spray dried solid dispersion, as described herein, and one or more pharmaceutically acceptable excipients selected from the group consisting of: lactose monohydrate; microcrystalline cellulose; croscarmellose sodium; colloidal silicon dioxide; magnesium stearate; and combinations thereof. In some embodiments, the pharmaceutical formulation has a bulk density ranging from 0.55 g/cc to 0.60 g/cc. In some embodiments, the pharmaceutical formation may be a pharmaceutical capsule. In some embodiments, the pharmaceutical formation may be a pharmaceutical tablet.

[0017] The present disclosure further provides for a pharmaceutical formulation comprising 10-15 wt. % of a spray dried solid dispersion, as described herein, and hydroxypropylmethylcellulose acetate succinate (HPMCAS), wherein the thienotriazolodiazepine compound is amorphous in the dispersion and has a thienotriazolodiazepine compound to hydroxypropylmethylcellulose acetate succinate (HPMCAS), weight ratio of 1:3 to 1:1; 45 -50 wt. % of lactose monohydrate; 35-40 wt. % of microcrystalline cellulose; 4-6 wt. % of croscarmellose sodium; 0.8-1.5 wt. % of colloidal silicon dioxide; and 0.8-1.5 wt. % of magnesium stearate.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The foregoing summary, as well as the following detailed description of embodiments of the pharmaceutical compositions including thienotriazolodiazepine formulations and methods of the present invention, will be better understood when read in conjunction with the appended drawings of exemplary embodiments. It should be understood, however, that the invention is not limited to the precise arrangements and instrumentalities shown.

[0019] In the drawings:

[0020] Figure 1A illustrates dissolution profile of a comparator formulation comprising a solid dispersion comprising 25% compound (1-1) and Eudragit L100-55;

[0021] Figure 1B illustrates dissolution profile of a comparator formulation comprising a solid dispersion comprising 50% compound (1-1) and Eudragit L100-55;

[0022] Figure 1C illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 25% compound (1-1) and polyvinylpyrrolidone (PVP);

[0023] Figure 1D illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 50% compound (1-1) and PVP;

[0024] Figure 1E illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 25% compound (1-1) and PVP-vinyl acetate (PVP-VA);

[0025] Figure 1F illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 50% compound (1-1) and PVP-VA;

[0026] Figure 1G illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 25% compound (1-1) and hypromellose acetate succinate (HPMCAS-M);

[0027] Figure 1H illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 50% compound (1-1) and HPMCAS-M;

[0028] Figure 1I illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 25% compound (1-1) and hypromellose phthalate (HPMCP-HP55);

[0029] Figure 1J illustrates dissolution profile of an exemplary formulation comprising a solid dispersion comprising 50% compound (1-1) and HMCP-HP55;

[0030] Figure 2A illustrates results of *in vivo* screening of an exemplary formulation comprising a solid dispersion of 25% compound (1-1) and PVP;

[0031] Figure 2B illustrates results of an *in vivo* screening of an exemplary formulation comprising a solid dispersion of 25% compound (1-1) and HPMCAS-M;

[0032] Figure 2C illustrates results of an *in vivo* screening of an exemplary formulation comprising a solid dispersion of 50% compound (1-1) and HPMCAS-M;

[0033] Figure 3 illustrates powder X-ray diffraction profiles of solid dispersions of compound (1-1);

[0034] Figure 4A illustrates modified differential scanning calorimetry trace for a solid dispersion of 25% compound (1-1) and PVP equilibrated under ambient conditions;

[0035] Figure 4B illustrates modified differential scanning calorimetry trace for a solid dispersion of 25% compound (1-1) and HPMCAS-M equilibrated under ambient conditions;

[0036] Figure 4C illustrates modified differential scanning calorimetry trace for a solid dispersion of 50% compound (1-1) and HPMCAS-M equilibrated under ambient conditions;

[0037] Figure 5 illustrates plot of glass transition temperature (Tg) versus relative hunidity (RH) for solid dispersions of 25% compound (1-1) and PVP or HMPCAS-M and 50% compound (1-1) and HPMCAS-MG;

[0038] Figure 6 illustrates modified differential scanning calorimetry trace for a solid dispersion of 25% compound (1-1) and PVP equilibrated under 75% relative humidity;

[0039] Figure 7 illustrates plasma concentration versus time curves for Compound (1-1) after 1 mg/kg intravenous dosing (solid rectangles) and 3 mg/kg oral dosing as 25% Compound (1-1):PVP (open circles), 25% Compound (1-1):HPMCAS-MG (open triangles), and 50% Compound (1-1):HPMCAS-MG (open inverted triangles). The inset depicts the same data plotted on a semilogarithmic scale;

[0040] Figure 8 illustrates plasma concentration versus time curves for Compound (1-1) after 3 mg/kg oral dosing as 25% Compound (1-1):PVP (open circles), 25% Compound (1-1):HPMCAS-MG (open triangles), and 50% Compound (1-1):HPMCAS-MG (open inverted triangles). The inset depicts the same data plotted on a semi-logarithmic scale;

[0041] Figure 9 illustrates a powder X-ray diffraction profile of solid dispersions of compound (1-1) in HPMCAS-MG at time zero of a stability test;

[0042] Figure 10 illustrates a powder X-ray diffraction profile of solid dispersions of compound (1-1) in HPMCAS-MG after 1 month at 40 °C and 75 % relative humidity;

[0043] Figure 11 illustrates a powder X-ray diffraction profile of solid dispersions of compound (1-1) in HPMCAS-MG after 2 months at 40 °C and 75 % relative humidity; and

[0044] Figure 12 illustrates a powder X-ray diffraction profile of solid dispersions of compound (1-1) in HPMCAS-MG after 3 month at 40 °C and 75 % relative humidity.

DETAILED DESCRIPTION OF THE INVENTION

[0045] The present subject matter will now be described more fully hereinafter with reference to the accompanying Figures and Examples, in which representative embodiments are shown. The present subject matter can, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided to describe and enable one of skill in the art. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the subject matter pertains. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entireties.

I. Definitions:

[0046] The term “alkyl group” as used herein refers to a saturated straight or branched hydrocarbon.

[0047] The term “substituted alkyl group” refers to an alkyl moiety having one or more substituents replacing a hydrogen or one or more carbons of the hydrocarbon backbone.

[0048] The term “alkenyl group” whether used alone or as part of a substituent group, for example, “C_{1-4}alkenyl(aryl),” refers to a partially unsaturated branched or straight chain monovalent hydrocarbon radical having at least one carbon—carbon double bond, whereby the double bond is derived by the removal of one hydrogen atom from each of two adjacent carbon atoms of a parent alkyl molecule and the radical is derived by the removal of one hydrogen atom from a single carbon atom. Atoms may be oriented about the double bond in either the cis (Z) or trans (E) conformation. Typical alkenyl radicals include, but are not limited to, ethenyl, propenyl, allyl(2-propenyl), butenyl and the like. Examples include C_{2-8}alkenyl or C_{2-4}alkenyl groups.

[0049] The term “$C_{(j-k)}$” (where *j* and *k* are integers referring to a designated number of carbon atoms) refers to an alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl radical or to the alkyl portion of a radical in which alkyl appears as the prefix root containing from j to k carbon atoms inclusive. For example, $C_{(1-4)}$ denotes a radical containing 1, 2, 3 or 4 carbon atoms.

[0050] The terms “halo” or “halogen” as used herein refer to F, Cl, Br, or I.

[0051] The term “pharmaceutically acceptable salts” is art-recognized and refers to the relatively non-toxic, inorganic and organic acid addition salts, or inorganic or organic base addition salts of compounds, including, for example, those contained in compositions of the present invention.

[0052] The term “solid dispersion” as used herein refers to a group of solid products consisting of at least two different components, generally a hydrophilic carrier and a hydrophobic drug (active ingredient).

[0053] The term “chiral” is art-recognized and refers to molecules That have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner. A “prochiral molecule” is a molecule that has the potential to be converted to a chiral molecule in a particular process.

[0054] The symbol “$\overline{\text{------}}$” is used to denote a bond that may be a single, a double or a triple bond.

[0055] The term “enantiomer” as it used herein, and structural formulas depicting an enantiomer are meant to include the “pure” enantiomer free from its optical isomer as well as mixtures of the enantiomer and its optical isomer in which the enantiomer is present in an enantiomeric excess, e.g., at least 10%, 25%, 50%, 75%, 90%, 95%, 98%, or 99% enantiomeric excess.

[0056] The term “stereoisomers” when used herein consist of all geometric isomers, enantiomers or diastereomers. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Conformational isomers and rotamers of disclosed compounds are also contemplated.

[0057] The term “stereoselective synthesis” as it is used herein denotes a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, and are well known in the art. Stereoselective syntheses encompass both enantioselective and diastereoselective transformations. For examples, see Carreira, E. M. and Kvaerno, L., *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[0058] The term “spray drying” refers to processes which involve the atomization of the feed suspension or solution into small droplets and rapidly removing solvent from the mixture in a processor chamber where there is a strong driving force for the evaporation (e.g., hot dry gas or partial vacuum or combinations thereof).

[0059] The term “therapeutically effective amount” as used herein refers to any amount of a thienotriazolodiazepine of the present invention or any other pharmaceutically active agent which, as compared to a corresponding a patient who has not received such an amount of the thienotriazolodiazepine or the other pharmaceutically active agent, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder.

[0060] The term “about” means +/- 10%.

[0061] Throughout this application and in the claims that follow, unless the context requires otherwise, the word “comprise”, or variations such as “comprises” or “comprising”, should be understood to imply the inclusion of a stated integer step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0062] It has now been found that thienotriazolodiazepine compound of Formula (1), described herein below, can be formulated as a solid dispersion with pharmaceutically acceptable polymers, to provide an oral formulation that provides high absorption of the pharmaceutical ingredient into the circulation from the gastrointestinal tract. In one embodiment, the pharmaceutically acceptable polymer is hypromellose acetate succinate (also called hydroxypropylmethylcellulose acetate succinate or HPMCAS). In one embodiment, the pharmaceutically acceptable polymer is polyvinylpyrrolidone (PVP).

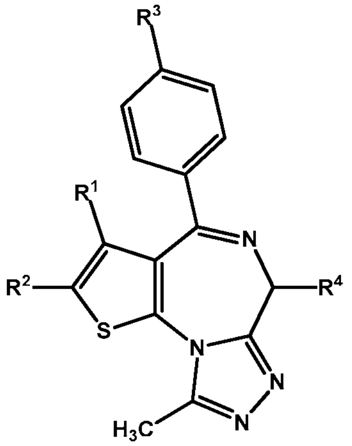
[0063] In some embodiments, the hydroxypropylmethyl cellulose acetate succinates (HPMCAS), may include M grade having 9% acetyl/11% succinoyl (e.g., HPMCAS having a mean particle size of 5 μm (i.e., HPMCAS-MF, fine powder grade) or having a mean particle size of 1 mm (i.e., HPMCAS-MG, granular grade)), H grade having 12% acetyl/6% succinoyl (e.g., HPMCAS having a mean particle size of 5 μm (i.e., HPMCAS-HF, fine powder grade) or having a mean particle size of 1 mm (i.e., HPMCAS-HG, granular grade)), and L grade having 8% acetyl/15% succinoyl (e.g., HPMCAS having a mean particle size of 5 μm (i.e., HPMCAS-LF, fine powder grade) or having a mean particle size of 1 mm (i.e., HPMCAS-LG, granular grade).

[0064] In some embodiments, the polyvinyl pyrrolidones may have molecular weights of about 2,500 (Kollidon ®12 PF, weight-average molecular weight between 2,000 to 3,000), about 9,000

(Kollidon® 17 PF, weight-average molecular weight between 7,000 to 11,000), about 25,000 (Kollidon® 25, weight-average molecular weight between 28,000 to 34,000), about 50,000 (Kollidon® 30, weight-average molecular weight between 44,000 to 54,000), and about 1,250,000 (Kollidon® 90 or Kollidon® 90F, weight-average molecular weight between 1,000,000 to 1,500,000).

II. Thienotriazolodiazepine Compounds:

[0065] In one embodiment, the thienotriazolodiazepine compounds, used in the formulations of the present invention, are represented by Formula (1):



(1)

[0066] wherein

R^1 is alkyl having a carbon number of 1-4, R^2 is a hydrogen atom; a halogen atom; or alkyl having a carbon number of 1-4 optionally substituted by a halogen atom or a hydroxyl group, R^3 is a halogen atom; phenyl optionally substituted by a halogen atom, alkyl having a carbon number of 1-4, alkoxy having a carbon number of 1-4 or cyano; $—NR^5—(CH_2)_m—R^6$ wherein R^5 is a hydrogen atom or alkyl having a carbon number of 1-4, m is an integer of 0-4, and R^6 is phenyl or pyridyl optionally substituted by a halogen atom; or $–NR^7—CO—(CH_2)_n—R^8$ wherein R^7 is a hydrogen atom or alkyl having a carbon number of 1-4, n is an integer of 0-2, and R^8 is phenyl or pyridyl optionally substituted by a halogen atom, and R^4 is $—(CH_2)_a—CO—NH—R^9$ wherein a is an integer of 1-4, and R^9 is alkyl having a carbon number of 1-4; hydroxyalkyl having a carbon number of 1-4; alkoxy having a carbon number of 1-4; or phenyl or pyridyl optionally substituted by alkyl having a carbon number of 1-4, alkoxy having a carbon number of 1-4, amino or a hydroxyl group or $—(CH_2)_b—COOR^{10}$ wherein b is an integer of 1-4, and R^{10} is alkyl having a carbon number of 1-4, including any salts, isomers, enantiomers, racemates, hydrates, solvates, metabolites, and polymorphs thereof.

[0067] In one embodiment, a suitable alkyl group includes linear or branched akyl radicals including from 1 carbon atom up to 4 carbon atoms. In one embodiment, a suitable alkyl group includes linear or branched akyl radicals including from 1 carbon atom up to 3 carbon atoms. In one embodiment, a suitable alkyl group includes linear or branched akyl radicals include from 1 carbon atom up to 2 carbon atoms. In one embodiment, exemplary alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl. In one embodiment, exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, and 2-methyl-2-propyl.

[0068] In some embodiments, the present invention provides pharmaceutically acceptable salts, solvates, including hydrates, and isotopically-labeled forms of the thienotriazolodiazepine compounds described herein. In one embodiment, pharmaceutically acceptable salts of the thienotriazolodiazepine compounds include acid addition salts formed with inorganic acids. In one embodiment, pharmaceutically acceptable inorganic acid addition salts of the thienotriazolodiazepine include salts of hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric and sulfuric acids. In one embodiment, pharmaceutically acceptable salts of the thienotriazolodiazepine compounds include acid addition salts formed with organic acids. In one embodiment, pharmaceutically acceptable organic acid addition salts of the thienotriazolodiazepine include salts of tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, formic, propionic, glycolic, gluconic, maleic, succinic, camphorsulfuric, isothionic, mucic, gentisic, isonicotinic, saccharic, glucuronic, furoic, glutamic, ascorbic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, stearic, sulfinilic, alginic, galacturonic and arylsulfonic, for example benzenesulfonic and 4-methyl benzenesulfonic acids.

[0069] The present invention provides pharmaceutically acceptable isotopically-labeled forms of the thienotriazolodiazepine compounds, described herein, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the thienotriazolodiazepine compounds include isotopes of hydrogen, e.g., ^{2}H and ^{3}H, carbon, e.g., ^{11}C, ^{13}C and ^{14}C, chlorine, e.g., ^{36}Cl, fluorine, e..g., ^{18}F, iodine, e.g., ^{123}I and ^{125}I, nitrogen, e.g., ^{13}N and ^{15}N, oxygen, e.g., ^{15}O, ^{17}O and ^{18}O, and sulfur, e.g., ^{35}S. Isotopically-labeled forms of the thienotriazolodiazepine compounds generally can be prepared by conventional techniques known to those skilled in the art.

[0070] Certain isotopically-labeled forms of the compound of Formula (1), for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^3H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium (^2H) may afford certain therapeutic advantages that result from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O, and ^{13}N can be used in Positron Emission Tomography (PET) studies for examining substrate receptor occupancy.

[0071] In some embodiments, the thienotriazolodiazepine compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents. It will be understood by those skilled-in the art that a solvate is a complex of variable stoichiometry formed by a solute (in this case, the thienotriazolodiazepine compounds described herein) and a solvent. It is preferred that such solvents not interfere with the biological activity of the solute (the thienotriazolodiazepine compounds). Examples of suitable solvents for solvate formation include, but are not limited to, water, methanol, dimethyl sulfoxide, ethanol and acetic acid. Suitably the solvent used is a pharmaceutically acceptable solvent. Suitably the solvent used is water. In one embodiment, pharmaceutically acceptable solvates of the thienotriazolodiazepine compounds, described herein, include ethanol solvate, a isopropanol solvate, a dioxolane solvate, a tetrahydrofuran solvate, a dimethyl sulfoxide solvate, tert-butanol solvate, 2-butanol solvate, dioxolane solvate, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (“DMPU”) solvate, 1,3-dimethylimidazolidinone (“DMI”) solvate, and 1,3-dimethylimidazolidinone (“DMP”) solvate, or mixtures thereof.

[0072] In some embodiments, the thienotriazolodiazepine compounds, described herein, may contain one or more chiral centers and/or double bonds and, therefore, may exist as geometric isomers, enantiomers or diastereomers. The enantiomer and diastereomers of the thienotriazolodiazepine compounds may be designated in accordance with the Cahn–Ingold–Prelog convention, which assigns an *“R”* or *“S”* descriptor to each stereocenter (also sometimes referred to as a chiral center) and an *E* or *Z* descriptor to each carbon-carbon double bond (to designate geometric isomers) so that the configuration of the entire molecule can be specified uniquely by including the descriptors in its systematic name.

[0073] In some embodiments, the thienotriazolodiazepine compounds, described herein, may exist as a racemic mixture, or racemate, which includes equal amounts of left- and right-handed enantiomers of a chiral molecule. Such a racemic mixture may be denoted by the prefix (±)- or dl-, indicating an equal (1:1) mixture of dextro and levo isomers. Also, the prefix *rac*- (or *racem*-) or the symbols *RS* and *SR* may be used to designate the racemic mixture.

[0074] Geometric isomers, resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a cycloalkyl or heterocyclic ring, can also exist in the compounds of the present invention. In some embodiments, the symbol ⎓ may be used to denote a bond that may be a single, double or triple bond. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "*E*" and "*Z*" isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as "*cis*" or "*trans*," where "*cis*" represents substituents on the same side of the double bond and "*trans*" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "*cis*" or "*trans*." The term "*cis*" represents substituents on the same side of the plane of the ring and the term "*trans*" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of a plane of a ring are designated "*cis/trans*" or "*Z/E*."

[0075] In some embodiments, thienotriazolodiazepine compounds disclosed herein may exist in single or multiple crystalline forms or polymorphs. In one embodiment, a thienotriazolodiazepine compound disclosed herein comprises an amorphous form thereof. In one embodiment, a thienotriazolodiazepine compound disclosed herein comprises a single polymorph thereof. In another embodiment, a thienotriazolodiazepine compound disclosed herein comprises a mixture of polymorphs thereof. In another embodiment, the compound is in a crystalline form.

[0076] In some embodiments, thienotriazolodiazepine compounds disclosed herein may exist as a single enantiomers or in enatiomerically enriched forms. In one embodiment, a thienotriazolodiazepine compound disclosed herein exists in an entiomeric excess of more than 80%. In one embodiment, a thienotriazolodiazepine compound disclosed herein exists in an entiomeric excess of more than 90%. In one embodiment, a thienotriazolodiazepine compound disclosed herein exists in an entiomeric excess of more than 98%. In one embodiment, a thienotriazolodiazepine compound disclosed herein exists in an entiomeric excess of more than 99%. In some embodiments, a thienotriazolodiazepine compound disclosed herein exists in an entiomeric excess selected from the group consisting of at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, at least 95%, at least 98%, at least and at least 99% enantiomeric excess.

[0077] For a pair of enantiomers, enantiomeric excess (ee) of enantiomer *E1* in relation to enantiomer *E2* can be calculated using the following equation eq. (1):

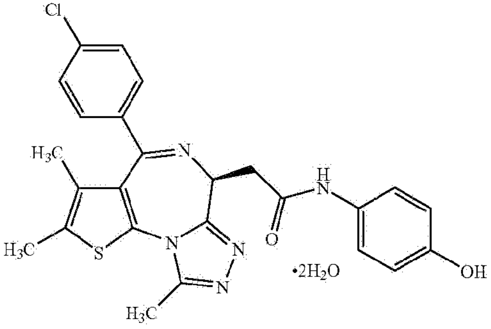
$$\%\ \text{enantiomeric excess of}\ E1 = \frac{(E1 - E2)\text{x}100\%}{(E1 + E2)} \qquad \text{eq. (1)}$$

Relative amounts of *E1* and *E2* can be determined by chiral high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR) or any other suitable methods. In some embodiments, purity of an entiormeric compound may refer to the amount of the enantiomers *E1* and *E2*, relative to the amount of other materials, which may notably include by-products and/or unreacted reactants or reagents.

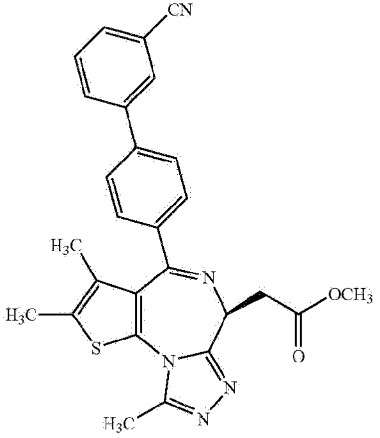
[0078] In some embodiments, thienotriazolodiazepine compounds of Formula (1) include, but are not limited to, the thienotriazolodiazepine compounds (1-1) to (1-18), which are listed in the following Table A.

[0079] Table A: Exemplary compounds which may be used in the formulations described herein:

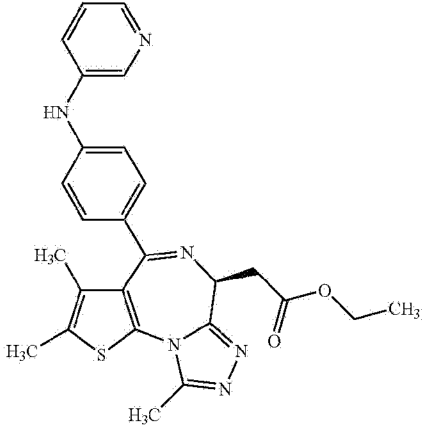
(1-1)



(1-2)



(1-3)



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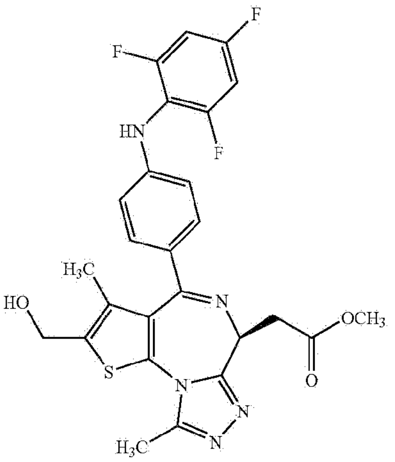

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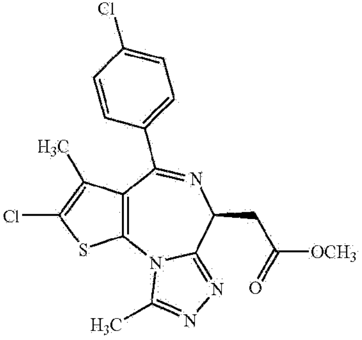
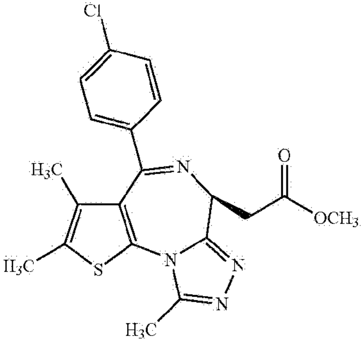
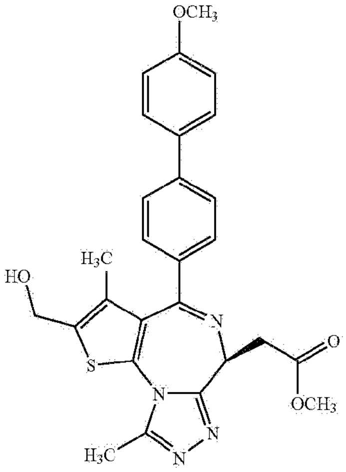


(1-6)

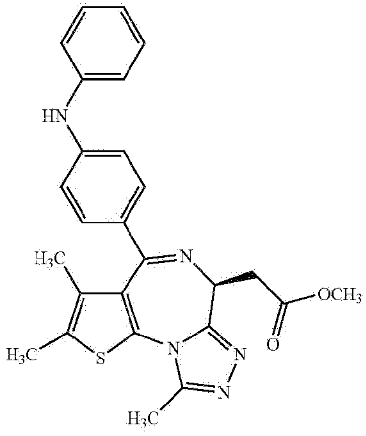


[0080] Table A (continued):

(1-7)

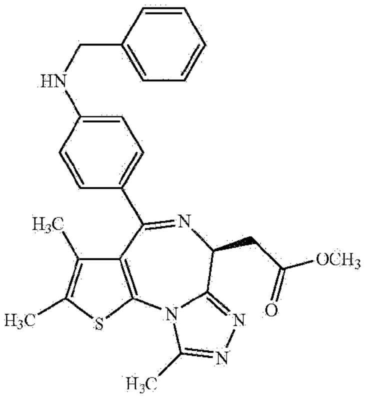


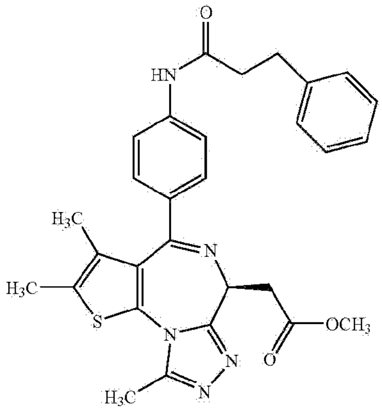
(1-8)



(1-9)

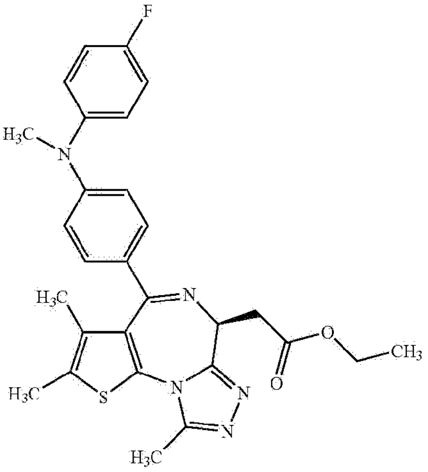
(1-10)

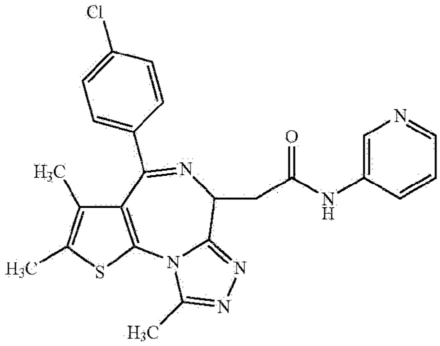




(1-11)

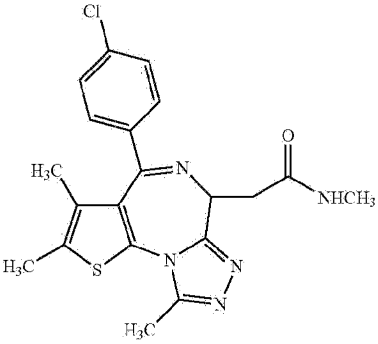
(1-12)



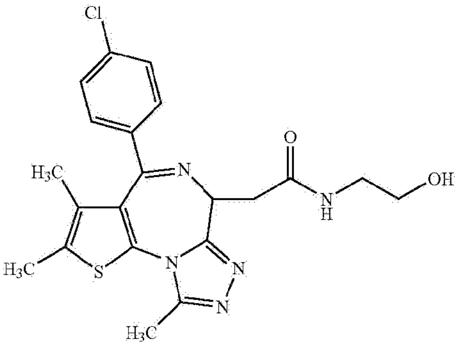


[0081] Table A (continued):

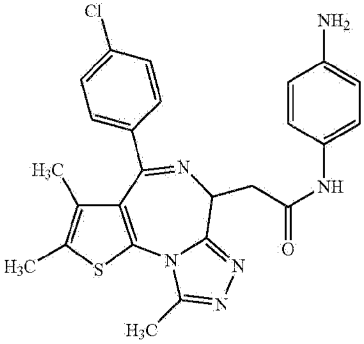
(1-13)



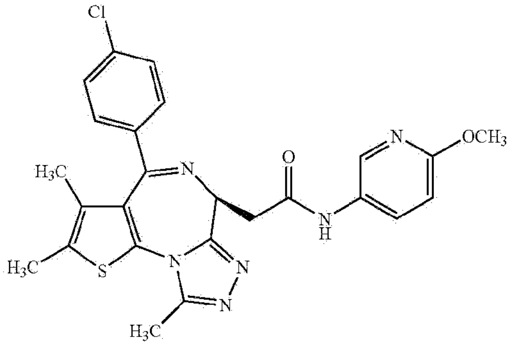
(1-15



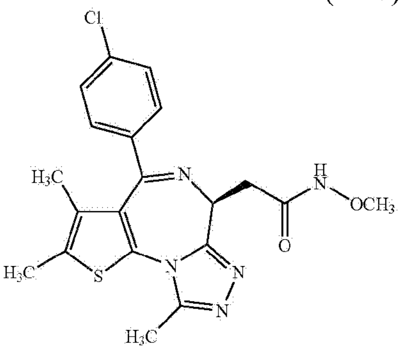
(1-15)



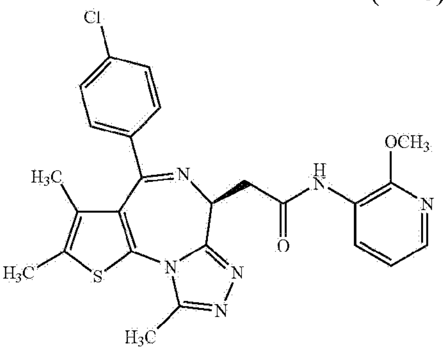
(1-16)



(1-17)



(1-18)



[0082] In some embodiments, thienotriazolodiazepine compounds of Formula (1) include (i) (S)-2-[4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo- [4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide or a dihydrate thereof, (ii) methyl (S)-{4-(3'-cyanobiphenyl-4-yl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]tri- azolo[4,3-a][1,4]diazepin-6-yl}acetate, (iii) methyl (S)-{2,3,9-trimethyl-4-(4-phenylaminophenyl)-6H-thieno[3,2-f][1,2,4]triaz- olo[4,3-a][1,4]diazepin-6-yl}acetate; and (iv) methyl (S)-{2,3,9-trimethyl-4-[4-(3-phenylpropionylamino)phenyl]-6H-thieno[3,2-f-][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate.

[0083] In some embodiments, thienotriazolodiazepine compounds of Formula (1) include (S)-2-[4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,- 4]triazolo[4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide.

III. Formulations:

[0084] The compound of Formula (1) presents highly specific difficulties in relation to administration generally and the preparation of galenic compositions in particular, including the particular problems of drug bioavailability and variability in inter- and intra-patient dose response, necessitating development of a non-conventional dosage form with respect to the practically water-insoluble properties of the compound.

[0085] Previously, it had been found that the compound of Formula (1) could be formulated as a solid dispersion with the carrier ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer (Eudragit RS, manufactured by Rohm) to provide an oral formulation that preferentially released the pharmaceutical ingredient in the lower intestine for treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease (US Patent Application 20090012064 A1, published Jan 8, 2009). It was found, through various experiments, including animal tests, that in inflammatory bowel diseases drug release in a lesion and a direct action thereof on the inflammatory lesion were more important than the absorption of the drug into circulation from the gastrointestinal tract.

[0086] It has now been unexpectedly found that thienotriazolodiazepine compounds, according to Formula (1), pharmaceutically acceptable salts, solvates, including hydrates, racemates, enantiomers isomers, and isotopically-labeled forms thereof, can be formulated as a solid dispersion with pharmaceutically acceptable polymers to provide an oral formulation that provides high absorption of the pharmaceutical ingredient into the circulation from the gastrointestinal tract for treatment of diseases other than inflammatory bowel diseases. Studies in both dogs and humans have confirmed high oral bioavailability of these solid dispersions compared with the Eudragit solid dispersion formulation previously developed for the treatment of inflammatory bowel disease.

[0087] Solid dispersions are a strategy to improve the oral bioavailability of poorly water soluble drugs.

[0088] The term “solid dispersion” as used herein refers to a group of solid products including at least two different components, generally a hydrophilic carrier and a hydrophobic drug, the thienotriazolodiazepine compounds, according to Formula (1). Based on the drug’s molecular arrangement within the dispersion, six different types of solid dispersions can be distinguished. Commonly, solid dispersions are classified as simple eutectic mixtures, solid solutions, glass solution and suspension, and amorphous precipitations in a crystalline carrier. Moreover, certain combinations can be encountered, for example, in the same sample some molecules may be present in clusters while some are molecularly dispersed.

[0089] In one embodiment, the thienotriazolodiazepine compounds, according to Formula (1) can be dispersed molecularly, in amorphous particles (clusters). In another embodiment, the thienotriazolodiazepine compounds, according to Formula (1) can be dispersed as crystalline particles. In one embodiment, the carrier can be crystalline. In another embodiment, the carrier can be amorphous.

[0090] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of a thienotriazolodiazepine compound, in accordance with Formula (1), or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is hypromellose acetate succinate (also called hydroxypropylmethylcellulose acetate succinate or HPMCAS). In one embodiment, the dispersion has a thienotriazolodiazepine compound to hydroxypropylmethylcellulose acetate succinate (HPMCAS) weight ratio of 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 130 °C to 140 °C. In other such embodiments, the single Tg occurs at about 135 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application "substantially free" shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

[0091] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof in a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is polyvinylpyrrolidone (also called povidone or PVP). In one embodiment, the dispersion has a thienotriazolodiazepine compound to PVP weight ratio of 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 175 °C to about 185 °C. In other such embodiments, the single Tg occurs at about 179 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application "substantially free" shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

[0092] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of an amorphous form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is hypromellose acetate succinate. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to hypromellose acetate succinate ranges from 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 130 °C to 140 °C. In other such embodiments, the single Tg occurs at about 135 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application "substantially free" shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

[0093] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of an amorphous form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is polyvinylpyrrolidone. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to polyvinylpyrrolidone ranges from 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 175 °C to about 185 °C. In other such embodiments, the single Tg occurs at about 179 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application "substantially free" shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

[0094] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of a crystalline form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is hypromellose acetate succinate. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to hypromellose acetate succinate ranges from 1:3 to 1:1.

[0095] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of a crystalline form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is polyvinylpyrrolidone. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to polyvinylpyrrolidone ranges from 1:3 to 1:1.

[0096] In some embodiments, a pharmaceutical composition comprising a solid dispersion is prepared by spray drying.

[0097] In one embodiment, a pharmaceutical composition of the present invention comprises a spray dried solid dispersion of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is hypromellose acetate succinate. In one embodiment, the weight ratio of compound (1) to hypromellose acetate succinate ranges from 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 130 °C to 140 °C. In other such embodiments, the single Tg occurs at about 135 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application “substantially free” shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

[0098] In one embodiment, a pharmaceutical composition of the present invention comprises a spray dried solid dispersion of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is polyvinylpyrrolidone. In one embodiment, the weight ratio of compound (1) to polyvinylpyrrolidone ranges from 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 175 °C to 185 °C. In other such embodiments, the single Tg occurs at about 179 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application "substantially free" shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

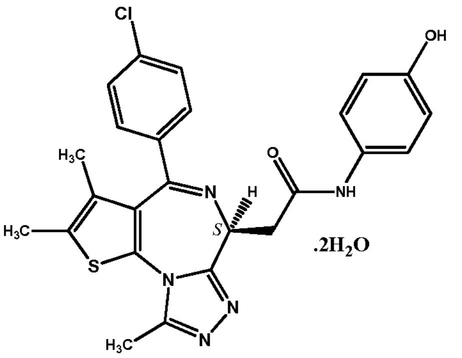
[0099] In one embodiment, a pharmaceutical composition of the present invention comprises a spray dried solid dispersion of an amorphous form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is hypromellose acetate succinate. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to hypromellose acetate succinate ranges from 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 130 °C to 140 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In other such embodiments, the single Tg occurs at about 135 °C. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application "substantially free" shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

[00100] In one embodiment, a pharmaceutical composition of the present invention comprises a spray dried solid dispersion of an amorphous form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is polyvinylpyrrolidone. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to polyvinylpyrrolidone ranges from 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 175 °C to 185 °C. In other such embodiments, the single Tg occurs at about 179 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1). For the purpose of this application “substantially free” shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound of Formula (1).

[00101] In one embodiment, a pharmaceutical composition of the present invention comprises a spray dried solid dispersion of a crystalline form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is hypromellose acetate succinate. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to hypromellose acetate succinate ranges from 1:3 to 1:1.

[00102] In one embodiment, a pharmaceutical composition of the present invention comprises a spray dried solid dispersion of a crystalline form of a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is polyvinylpyrrolidone. In one embodiment, the weight ratio of thienotriazolodiazepine compound of Formula (1) to polyvinylpyrrolidone ranges from 1:3 to 1:1.

[00103] In one preferred embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of 2-[(6S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thienol[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide dihydrate, compound (1-1):



(1-1)

or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is HPMCAS. In one embodiment, the dispersion has compound (1-1) and HPMCAS in a weight ratio of 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In one embodiment, the solid dispersion is spray dried. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 130 °C to 140 °C. In other such embodiments, the single Tg occurs at about 135 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound (1-1). For the purpose of this application “substantially free” shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound (1-1).

[00104] In another embodiment, the pharmaceutical composition comprises a solid dispersion compound (1-1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is PVP. In one embodiment, the dispersion has compound (1-1) and PVP in weight ratio 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In one embodiment, the solid dispersion is spray dried. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 175 °C to 185 °C. In other such embodiments, the single Tg occurs at about 179 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound (1-1). For the purpose of this application “substantially free” shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound (1-1).

[00105] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of an amorphous form of a thienotriazolodiazepine compound (1-1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is HPMCAS. In one embodiment, the dispersion has compound (1-1) and HPMCAS in a weight ratio of 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In one embodiment, the solid dispersion is spray dried. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 130 °C to 140 °C. In other such embodiments, the single Tg occurs at about 135 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound (1-1). For the purpose of this application “substantially free” shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound (1-1).

[00106] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of an amorphous form of a thienotriazolodiazepine compound (1-1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is PVP. In one embodiment, the dispersion has compound (1-1) and PVP in weight ratio 1:3 to 1:1. In one embodiment, at least some portion of the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In another embodiment, the thienotriazolodiazepine compound is homogeneously dispersed throughout the solid dispersion. In one embodiment, the solid dispersion is spray dried. In some embodiments, the solid dispersion exhibits a single inflection for the glass transition temperature (Tg). In some embodiments, the single Tg occurs between 175 °C to 185 °C. In other such embodiments, the single Tg occurs at about 189 °C. In some such embodiments, the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month. In some embodiments, the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound (1-1). For the purpose of this application "substantially free" shall mean the absence of a diffraction line, above the amorphous halo, at about 21° 2-theta associated with crystalline thienotriazolodiazepine compound (1-1).

[00107] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of a crystalline form of a thienotriazolodiazepine compound (1-1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is HPMCAS. In one embodiment, the dispersion has compound (1-1) and HPMCAS in a weight ratio of 1:3 to 1:1. In one embodiment, the solid dispersion is spray dried.

[00108] In one embodiment, a pharmaceutical composition of the present invention comprises a solid dispersion of a crystalline form of a thienotriazolodiazepine compound (1-1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is PVP. In one embodiment, the dispersion has compound (1-1) and PVP in weight ratio 1:3 to 1:1. In one embodiment, the solid dispersion is spray dried.

[00109] The solid dispersions of the invention, described herein, exhibit especially advantageous properties when administered orally. Examples of advantageous properties of the solid dispersions include, but are not limited to, consistent and high level of bioavailability when administered in standard bioavailability trials in animals or humans. The solid dispersions of the invention can include a solid dispersion comprising thienotriazolodiazepine compound of Formula (1) and a polymer and additives. In some embodiments, the solid dispersions can achieve absorption of the thienotriazolodiazepine compound of Formula (1) into the bloodstream that cannot be obtained by merely admixing the thienotriazolodiazepine compound of Formula (1) with additives since the thienotriazolodiazepine compound of Formula (1) drug has negligible solubility in water and most aqueous media. The bioavailability, of thienotriazolodiazepine compound of Formula (1) or of thienotriazolodiazepine compound (1-1) may be measured using a variety of in vitro and/or in vivo studies. The in vivo studies may be performed, for example, using rats, dogs or humans.

[00110] The bioavailability may be measured by the area under the curve (AUC) value obtained by plotting a serum or plasma concentration, of the thienotriazolodiazepine compound of Formula (1) or thienotriazolodiazepine compound (1-1), along the ordinate (Y-axis) against time along the abscissa (X-axis). The AUC value of the thienotriazolodiazepine compound of Formula (1) or thienotriazolodiazepine compound (1-1) from the solid dispersion, is then compared to the AUC value of an equivalent concentration of crystalline thienotriazolodiazepine compound of Formula (1) or crystalline thienotriazolodiazepine compound (1-1) without polymer. In some embodiments, the solid dispersion provides an area under the curve (AUC) value, when administered orally to a dog, that is selected from: at least 0.4 times, 0.5 times, 0.6 time, 0.8 time, 1.0 times, a corresponding AUC value provided by a control composition administered intravenously to a dog, wherein the control composition comprises an equivalent quantity of a crystalline thienotriazolodiazepine compound of Formula (1).

[00111] The bioavailability may be measured by in vitro tests simulating the pH values of a gastric environment and an intestine environment. The measurements may be made by suspending a solid dispersion of the thienotriazolodiazepine compound of Formula (1) or thienotriazolodiazepine compound (1-1), in an aqueous in vitro test medium having a pH between 1.0 to 2.0, and the pH is then adjusted to a pH between 5.0 and 7.0, in a control in vitro test medium. The concentration of the amorphous thienotriazolodiazepine compound of Formula (1) or amorphous thienotriazolodiazepine compound (1-1) may be measured at any time during the first two hours following the pH adjustment. In some embodiments, the solid dispersion provides a concentration, of the amorphous thienotriazolodiazepine compound of Formula (1) or amorphous thienotriazolodiazepine compound (1-1), in an aqueous in vitro test medium at pH between 5.0 to 7.0 that is selected from: at least 5-fold greater, at least 6 fold greater, at least 7 fold greater, at least 8 fold greater, at least 9 fold greater or at least 10 fold greater, compared to a concentration of a crystalline thienotriazolodiazepine compound of Formula (1) or crystalline thienotriazolodiazepine compound (1-1), without polymer.

[00112] In other embodiments, the concentration of the amorphous thienotriazolodiazepine compound of Formula (1) or amorphous thienotriazolodiazepine compound (1-1), from the solid dispersion placed in an aqueous in vitro test medium having a pH of 1.0 to 2.0, is: at least 40%, at least 50% higher, at least 60 %, at least 70 %; at least 80 %, than a concentration of a crystalline thienotriazolodiazepine compound of Formula (1) without polymer. In some such embodiments, the polymer of the solid dispersion is HPMCAS. In some such embodiments, the polymer of the solid dispersion is PVP.

[00113] In other embodiments, a concentration of the amorphous thienotriazolodiazepine compound of Formula (1) or amorphous thienotriazolodiazepine compound (1-1), from the solid dispersion, is: at least 40%, at least 50% higher, at least 60 %, at least 70 %; at least 80 %, compared to a concentration of thienotriazolodiazepine compound of Formula (1), from a solid dispersion of thienotriazolodiazepine compound of the Formula (1) and a pharmaceutically acceptable polymer selected from the group consisting of: hypromellose phthalate and ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer, wherein each solid dispersion was placed in an aqueous in vitro test medium having a pH of 1.0 to 2.0. In some such embodiments, the polymer of the solid dispersion is HPMCAS. In some such embodiments, the polymer of the solid dispersion is PVP.

[00114] In some embodiments, the solid dispersions, described herein, exhibit stability against recrystallization of the thienotriazolodiazepine compound of the Formula (1) or the thienotriazolodiazepine compound (1-1) when exposed to humidity and temperature over time. In one embodiment, the concentration of the amorphous thienotriazolodiazepine compound of the Formula (1) or the thienotriazolodiazepine compound (1-1) which remains amorphous is selected from: at least 90 %, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% and at least 99%.

IV. Dosage Forms:

[00115] Suitable dosage forms that can be used with the solid dispersions of the present invention include, but are not limited to, capsules, tablets, mini-tablets, beads, beadlets, pellets, granules, granulates, and powder. Suitable dosage forms may be coated, for example using an enteric coating. Suitable coatings may comprise but are not limited to cellulose acetate phthalate, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, a polymethylacrylic acid copolymer, or hydroxylpropylmethylcellulose acetate succinate (HPMCAS). In some embodiments, certain combinations can be encountered, for example, in the same sample some molecules of the thienotriazolodiazepine of the present invention may be present in clusters while some are molecularly dispersed with a carrier.

[00116] In some embodiments, the solid dispersions of the invention may be formulated as tablets, caplets, or capsules. In one some embodiments, the solid dispersions of the invention may be formulated as mini-tablets or pour-into-mouth granules, or oral powders for constitution. In some embodiments, the solid dispersions of the invention are dispersed in a suitable diluent in combination with other excipients (e.g., re-crystallization/precipitation inhibiting polymers, taste-masking components, etc.) to give a ready-to-use suspension formulation. In some embodiments, the solid dispersions of the invention may be formulated for pediatric treatment.

[00117] In one embodiment, the pharmaceutical composition of the present invention is formulated for oral administration. In one embodiment, the pharmaceutical composition comprises a solid dispersion, according to the various embodiments described herein, comprising a thienotriazolodiazepine compound of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof; and a polymer carrier. In one embodiment, the pharmaceutical composition further includes one or more additives such as disintegrants, lubricants, glidants, binders, and fillers.

[00118] Examples of suitable pharmaceutically acceptable lubricants and pharmaceutically acceptable glidants for use with the pharmaceutical composition include, but are not limited to, colloidal silica, magnesium trisilicate, starches, talc, tribasic calcium phosphate, magnesium stearate, aluminum stearate, calcium stearate, magnesium carbonate, magnesium oxide, polyethylene glycol, powdered cellulose, glyceryl behenate, stearic acid, hydrogenated castor oil, glyceryl monostearate, and sodium stearyl fumarate.

[00119] Examples of suitable pharmaceutically acceptable binders for use with the pharmaceutical composition include, but are not limited to starches; celluloses and derivatives thereof, e.g., microcrystalline cellulose (e.g., AVICEL PH from FMC), hydroxypropyl cellulose, hydroxyethyl cellulose, and hydroxylpropylmethylcellulose (HPMC, e.g., METHOCEL from Dow Chemical); sucrose, dextrose, corn syrup; polysaccharides; and gelatin.

[00120] Examples of suitable pharmaceutically acceptable fillers and pharmaceutically acceptable diluents for use with the pharmaceutical composition include, but are not limited to, confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol, microcrystalline cellulose (MCC), powdered cellulose, sorbitol, sucrose, and talc.

[00121] In some embodiments, excipients may serve more than one function in the pharmaceutical composition. For example, fillers or binders may also be disintegrants, glidants, anti-adherents, lubricants, sweeteners and the like.

[00122] In some embodiments, the pharmaceutical compositions of the present invention may further include additives or ingredients, such as antioxidants (e.g., ascorbyl palmitate, butylated hydroxylanisole (BHA), butylated hydroxytoluene (BHT), α-tocopherols, propyl gallate, and fumaric acid), antimicrobial agents, enzyme inhibitors, stabilizers (e.g., malonic acid), and/or preserving agents.

[00123] Generally, the pharmaceutical compositions of the present invention may be formulated into any suitable solid dosage form. In some embodiments, the solid dispersions of the invention are compounded in unit dosage form, e.g., as a capsule, or tablet, or a multi-particulate system such as granules or granulates or a powder, for administration.

[00124] In one embodiment, a pharmaceutical compositions includes a solid dispersion of a thienotriazolodiazepine compound of Formula (1), according to the various embodiments of solid dispersions described herein, and hydroxypropylmethylcellulose acetate succinate (HPMCAS), wherein the thienotriazolodiazepine compound is amorphous in the solid dispersion and has a thienotriazolodiazepine compound to hydroxypropylmethylcellulose acetate succinate (HPMCAS), weight ratio of 1:3 to 1:1; 45 -50 wt. % of lactose monohydrate; 35-40 wt. % of microcrystalline cellulose; 4-6 wt. % of croscarmellose sodium; 0.8-1.5 wt. % of colloidal silicon dioxide; and 0.8-1.5 wt. % of magnesium stearate.

V. Dosage:

[00125] In one embodiment, the present invention provides a pharmaceutical composition that maybe formulated into any suitable solid dosage form. In one embodiment, a pharmaceutical composition in accordance with the present invention comprises one or more of the various embodiments of the thienotriazolodiazepine of Formula (1) as described herein in a dosage amount ranging from about 10 mg to about 100 mg. In one embodiment, the pharmaceutical composition of the present invention includes one or more of the various embodiments of the thienotriazolodiazepine of Formula (1) as described herein in a dosage amount selected from the group consisting of from about 10 mg to about 100 mg, about 10 mg to about 90 mg, about 10 mg to about 80 mg, about 10 mg to about 70 mg, about 10 mg to about 60 mg, about 10 mg to about 50 mg, about 10 mg to about 40 mg, about 10 mg to about 30 mg, and about 10 mg to about 20 mg. In one embodiment, the pharmaceutical composition of the present invention includes one or more of the various embodiments of the thienotriazolodiazepine of Formula (1) as described herein in a dosage amount selected from the group consisting of about 10 mg, about 50 mg, about 75 mg, about 100 mg.

[00126] Such unit dosage forms are suitable for administration 1 to 5 times daily depending on the particular purpose of therapy, the phase of therapy, and the like. In one embodiment, the dosage form may be administered to a subject in need thereof at least once daily for at least two successive days. In one embodiment, the dosage form may be administered to a subject in need thereof at least once daily on alternative days. In one embodiment, the dosage form may be administered to a subject in need thereof at least weekly and divided into equal and/or unequal doses. In one embodiment, the dosage form may be administered to a subject in need thereof weekly, given either on three alternate days and/or 6 times per week. In one embodiment, the dosage form may be administered to a subject in need thereof in divided doses on alternate days, every third day, every fourth day, every fifth day, every sixth day and/or weekly. In one embodiment, the dosage form may be administered to a subject in need thereof two or more equally or unequally divided doses per month.

[00127] The dosage form used, e.g., in a capsule, tablet, mini-tablet, beads, beadlets, pellets, granules, granulates, or powder may be coated, for example using an enteric coating. Suitable coatings may comprise but are not limited to cellulose acetate phthalate, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, a polymethylacrylic acid copolymer, or hydroxylpropylmethylcellulose acetate succinate (HPMCAS).

VI. Process:

[00128] The thienotriazolodiazepine compounds disclosed herein can exist as free base or as acid addition salt can be obtained according to the procedures described in US Patent Application Publication No. 2010/0286127, incorporated by reference in its entirety herein, or in the present application. Individual enantiomers and diastereomers of the thienotriazolodiazepine compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well-known methods, such as chiral-phase gas chromatography or crystallizing the compound in a chiral solvent.

[00129] If desired, a particular enantiomer of the thienotriazolodiazepine compounds disclosed herein may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers, thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers. Various methods well known in the art may be used to to prepare the thienotriazolodiazepine compounds of Formula (1) with an enantiomeric excess of generally more than about 80%. Advantageously, preferred enantiomeric excess is of more than 80%, preferably of more than 90%, more preferably of more than 95%, and most preferably of 99% and more.

[00130] The solid dispersions of the present invention can be prepared by a number of methods, including by melting and solvent evaporation. The solid dispersions of the present invention can also be prepared according to the procedures described in: Chiou WL, Riegelman S: "Pharmaceutical applications of solid dispersion systems", *J. Pharm. Sci.* 1971; 60:1281-1302; Serajuddin ATM: "Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recentbreakthroughs", *J. Pharm. Sci.* 1999; 88:1058-1066; Leuner C, Dressman J: "Improving drug solubility for oral delivery using solid dispersions", *Eur. J. Pharm. Biopharm.* 2000; 50:47-60; and Vasconcelos T, Sarmento B, Costa P: "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs", *Drug Discovery Today* 2007; 12:1068-1075, all of which are incorporated herein by reference in their entireties.

[00131] In one embodiment, solid dispersions of the present invention are prepared by a melting process. In one embodiment, the melting process comprises melting one or more of the various embodiments of the thienotriazolodiazepine of Formula (1) within a carrier. In one embodiment, the melting process includes cooling a melted compound of the present invention and a carrier. In one embodiment, the melting process comprises pulverization of the melted compound and the carrier.

In one embodiment, a melted compound of the present invention and a carrier are pulverized following the cooling step.

[00132] In some embodiments in which the thienotriazolodiazepine of Formula (1) or a pharmaceutically acceptable salt, a solvate, including a hydrate, a racemate, an enantiomer, an isomer, or an isotopically-labeled form thereof and the carrier are incompatible, a surfactant may be added during the melting step to prevent formation of two liquid phases or a suspension in the heated mixture. In some embodiments, one or more of the various embodiments of the thienotriazolodiazepine of Formula (1) is suspended in a previously melted carrier, instead of using both drug and carrier in the melted state, thereby reducing the process temperature. In one embodiment, melted drug and carrier mixture is cooled an ice bath agitation. In one embodiment, melted drug and carrier mixture is cooled and solidified by spray cooling (alternatively spray congealing).

[00133] In one embodiment, melted drug and carrier mixture is cooled and solidified by forming the melt into particles by spraying the melt into a cooling chamber through which ambient or cooled, low temperature air is passing. In one embodiment, melted drug and carrier mixture is cooled and solidified by atomization and re-solidification of the molten dispersion in a suitable fluid bed processor. In one embodiment, melted drug and carrier mixture is cooled and solidified by melt-granulation in a heatable high-shear mixer.

[00134] In some embodiments, hot-stage extrusion or melt agglomeration may be used to avoid melting limitations of the drug. Hot-stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a short period of time; the resulting product is collected after cooling at room temperature and milled.

[00135] In one embodiment, one or more of the various embodiments of the thienotriazolodiazepine of Formula (1) is processed at a reduced processing temperature to avoid degradation of any thermally labile compound. In one embodiment, the reduced processing temperature is achieved by associating a hot-stage extrusion with a temporary plasticizer such as carbon dioxide. In one embodiment, melt agglomeration is used in the preparation of solid dispersions in accordance with the present invention in conventional high shear mixers or in a rotary processors. In one embodiment, the solid dispersion in accordance with the present invention is prepared by adding a molten carrier containing a thienotriazolodiazepine compound in accordance with the present invention to a heated excipient. In one embodiment, the solid dispersion in accordance with the present invention is prepared by adding by adding a molten carrier to a heated mixture of the thienotriazolodiazepine in accordance with the present invention and one or more excipients. In one embodiment, the solid dispersion in accordance with the present invention is prepared by heating a mixture of a thienotriazolodiazepine compound in accordance with the present invention, a carrier and one or more excipients to a temperature within or above the melting range of the carrier.

[00136] In some embodiments, a one or more of the various embodiments for the formulation of the thienotriazolodiazepine, according to Formula (1), is prepared by a solvent evaporation method. In one embodiment, the solvent evaporation method comprises solubilization of a thienotriazolodiazepine compound, according to Formula (1), carrier in a volatile solvent that is subsequently evaporated. In one embodiment, the volatile solvent may one or more excipients. In one embodiment, the one or more excipients include, but are not limited to anti-sticking agents, inert fillers, surfactants wetting agents, pH modifiers and additives. In one embodiment, the excipients may dissolved or in suspended or swollen state in the volatile solvent.

[00137] In one embodiment, preparation of solid dispersions in accordance with the present invention includes drying one or more excipients suspended in a volatile solvent. In one embodiment, the drying includes vacuum drying, slow evaporation of the volatile solvent at low temperature, use of a rotary evaporator, spray-drying, spray granulation, freeze-drying, or use of supercritical fluids.

[00138] In one embodiment, spray drying preparation of a formulation for the thienotriazolodiazepine composition, according to Formula (1), is used which involves atomization of a suspension or a solution of the composition into small droplets, followed by rapid removal solvent from the formulation. In one embodiment, preparation of a formulation in accordance with the present invention involves spray granulation in which a solution or a suspension of the composition in a solvent is sprayed onto a suitable chemically and/or physically inert filler, such as lactose or mannitol. In one embodiment, spray granulation of the solution or the suspension of the composition is achieved via two-way or three-way nozzles.

[00139] In some embodiments, preparation of solid dispersions in accordance with the present invention includes use of supercritical fluids. The term “supercritical fluids” refers to substances existing as a single fluid phase above their critical temperature and critical pressure. In one embodiment, preparation of a formulation, in accordance with the present invention, includes use a supercritical carbon dioxide fluid. In one embodiment, preparation of a formulation, in accordance with the present invention, using the supercritical fluid technique comprises dissolving a thienotriazolodiazepine compound, according to Formula (1), and carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with carbon dioxide; and spraying the solution to allow the solvent be rapidly extracted by the supercritical fluid, thereby resulting in the precipitation of solid dispersion particles on the walls of the vessel.

[00140] In some embodiments, preparation of solid dispersions in accordance with the present invention includes use of a co-precipitation method. In one embodiment, a non-solvent is added dropwise to a thienotriazolodiazepine composition, according to Formula (1), and a carrier solution, under constant stirring. In one embodiment, the thienotriazolodiazepine composition, according to Formula (1), and the carrier are co-precipitated to form microparticles during the addition of the non-solvent. In one embodiment, the resulting microparticles are filtered and dried to provide the desired solid dispersion.

[00141] The proportion of compound of Formula (1) and polymeric carrier(s) to be mixed is not particularly limited, as long as it can improve the bioavailability of the compound of Formula (1) and varies depending on the kind of polymer.

[00142] The invention is illustrated in the following non-limiting examples.

VII. Examples:

[00143] The invention is illustrated in the following non-limiting examples.

Example 1: *in vitro* screening of solid dispersions of compound (1-1)

[00144] Ten solid dispersions were prepared using compound (1-1) and one of five polymers, including hypromellose acetate succinate (HPMCAS-M), hypromellose phthalate (HPMCP-HP55), polyvinylpyrrolidone (PVP), PVP-vinyl acetate (PVP-VA), and Euragit L100-55, at both 25% and 50% of compound (1-1) loading, for each polymer. Solid dispersions were prepared by a solvent evaporation method, using spray-drying followed by secondary drying in a low-temperature convection oven. The performance of each solid dispersion was assessed via a non-sink dissolution performance test which measured both the total amount of drug and the amount of free drug present in solution over time. Non-sink dissolution was chosen because it best represents the in vivo situation for low soluble compounds. This test included a “gastric transfer” of dispersion from gastric pH (0.1N NaCl, pH 1.0) to intestinal pH (FaFSSIF, pH 6.5) approximately 30 to 40 minutes after the introduction of dispersion to the test medium, simulating *in vivo* conditions. [FaFSSIF is Fasted State Simulated Intestinal Fluid, comprised of 3 mM sodium taurocholate, 0.75 mM lechithin, 0.174 g NaOH pellets, 1.977 g $NaH_2PO_4 \cdot H_2O$, 3.093 g NaCl, and purified water qs 500 mL.] The amount of dissolved drug was quantified using a high-performance liquid chromatrography (HPLC) method and an Agilent 1100 series HPLC. The dissolution profiles of the formulations (Figures 1A-1J) showed large increases in drug solubility in all dispersion candidates relative to the unformulated compound in the same media. Of the solid dispersions, the 25% compound (1-1) in PVP, 25% compound (1-1) in HPMCAS-M, and 50% compound (1-1) in HPMCAS-M dispersions provided enhanced oral absorption as compared to the unformulated compound, based on finding higher levels of free drug released at intestinal pH.

Example 2: *in vivo* screening of solid dispersions of compound (1-1)

[00145] The solid dispersions of compound (1-1), namely the 25% compound (1-1) in PVP, 25% compound (1-1) in HPMCAS-MG, and 50% compound (1-1) in HPMCAS-M dispersions, were prepared at larger scale for *in vivo* studies. Each formulation was assessed in the in vitro dissolution test described in Example 1. To ensure that these dispersions were both amorphous and homogeneous, each dispersion was assessed by powder x-ray diffraction (PXRD) and modulated differential scanning calorimetry (mDSC). The x-ray diffractomer was a Bruker D-2 Phaser. Additionally, to understand the effect of water on the glass transition temperature (Tg) for each dispersion, mDSC was performed on samples first equilibrated at a set relative humidity (i.e., 25%, 50%, and 75% RH) for at least 18 hours. [Water can act as a plasticizer for solid dispersions and the hygroscopicity of the system due to the active compound or polymer can affect the amount of water uptake by these systems.]

[00146] The non-sink dissolution results (Figures 2A-2C) were comparable to those found for the dispersions in Example 1. PXRD results (Figure 3) showed no evidence of crystalline compound in any of the dispersions and mDSC results (Figures 4A-4C) showed a single glass transition temperature (Tg) for each dispersion, indicating that each dispersion was homogeneous. An inverse relationship between Tg and relative humidity was observed for each (Figure 5). Notably, for the 25% compound (1-1) in PVP solid dispersion equilibrated at 75% RH, there appeared to be two Tgs, indicating that phase separation was occurring, and this dispersion also showed a melt event at 75% RH, suggesting that crystallization occurred during the RH equilibration (Figure 6). This finding suggests that the 25% compound (1-1) in PVP dispersion may be less stable than the HPMCAS-M dispersions.

[00147] To assess the bioavailability of the three dispersions, groups of male beagle dogs (three per group) were given a 3 mg/kg dose of an aqueous suspension of solid dispersion of compound (1-1) administered by oral gavage or a 1 mg/kg dose of compound (1-1) dissolved in water:ethanol:polyethylene glycol (PEG) 400 (60:20:20) and administered as an intravenous bolus into the cephalic vein. Blood samples were collected from the jugular vein of each animal at 0 (pre-dose), 5, 15, and 30 minutes and 1, 2, 4, 8, 12, and 24 hours following intravenous administration and at 0 (pre-dose), 15 and 30 minutes and 1, 2, 4, 8, 12, and 24 hours following oral gavage administration. The amount of compound (1-1) present in each sample was detected using a qualified LC-MS/MS method with a lower limit of quantification of 0.5 ng/mL. The area under the plasma concentration-time curve (AUC) was determined by use of the linear trapezoidal rule up to the last measurable concentration without extrapolation of the terminal elimination phase to infinity. The elimination half-life ($t_{1/2}$) was calculated by least-squares regression analysis of the terminal linear part of the log concentration-ime curve. The maximum plasma concentration (C_{max}) and the time to C_{max} (t_{max}) were derived directly from the plasma concentration data. The oral bioavailability (F) was calculated by dividing the dose normalized AUC after oral administration by the dose normalized AUC after intravenous administration and reported as percentages (%). Results, summarized in Table 1 below, gave mean oral bioavailabilities of the 25% compound (1-1) in PVP, 25% compound (1-1) in HPMCAS-M, and 50% compound (1-1) in HPMCAS-M solid dispersions of 58%, 49%, and 74%, respectively.

Table 1: pharmacokinetic parameters of compound (1-1) after oral (po) and intravenous (iv) administrations to dogs (the values are averages from three dogs)

Compound (1-1) formulation	Dose & Route	C_{max} (ng/L)	t_{max} (hr)	AUC (ng•min/mL)	$t_{1/2}$ (hr)	F (%)
Solution in water:ethanol: PEG400 (60:20:20)	1 mg/kg IV	769	0.083	53,312	1.5	----
Aqueous suspension of 25% compound (1-1)/PVP solid dispersion	3 mg/kg PO	487	1.0	93,271	1.6	58
Aqueous suspension of 25% compound (1-1)/HPMCAS-M solid dispersion	3 mg/kg PO	228	0.5	78,595	2.0	49
Aqueous suspension of 50% compound (1-1)/HPMCAS-M solid dispersion	3 mg/kg PO	371	1.0	118,174	1.5	74

AUC: area under the plasma concentration-time curve; C_{max}: maximum plasma concentration; F: bioavailability; HPMCAS: hypromellose acetate sodium; IV: intravenous; PEG: polyethylene glycon; PO; *per os*, oral; PVP: polyvinylpyrrolidone; t_{max}: time of C_{max}; $t_{1/2}$: plasma elimination half-life

Example 3: preparation and clincial use of capsules containing a solid dispersion of compound (1-1)

[00148] A gelatin capsule of 10 mg strength was prepared for initial clinical studies in patients with hematologic malignancies. Based on results of *in vitro* and *in vivo* testing of solid dispersions of compound (1-1), as described in Examples 1 and 2, a 50% compound (1-1) in HPMCAS-M solid dispersion was selected for capsule development. Capsule development was initiated targeting a fill weight of 190 mg in a size 3 hard gelatin capsule, as this configuration would potentially allow increasing the capsule strength by filling a larger size capsule while maintaining the pharmaceutical composition. Based on experience, four capsule formulations were designed with different amounts of disintegrant and with and without wetting agent. Since all four formulations showed similar disintegration test and dissolution test results, the simplest formulation (without wetting agent and minimum disintegrant) was selected for manufacturing. Manufacturing process development and scale-up studies were performed to confirm the spray drying process and post-drying times for the solid dispersion; blending parameters; roller compaction and milling of the blend to achieve target bulk density of approximately 0.60 g/cc; and capsule filling conditions.

[00149] Crystalline compound (1-1) and the polymer hypromellose actate succinate (HPMCAS-M) were dissolved in acetone and spray-dried to produce solid dispersion intermediate (SDI) granules containing a 50% compound (1-1) loading. The SDI was shown by PXRD analysis to be amorphous and by mDSC analysis to be homogeneous (i.e., single Tg under ambient conditions). The 50% compound (1-1) in HPMCAS-M solid dispersion (1000 g) and excipients, including microcrystalline cellulose filler-binder (4428 g), croscarmellose sodium disintegrant (636 g), colloidal silicon dioxide dispersant/lubricant 156 g), magnesium stearate dispersant/lubricant (156 g), and lactose monohydrate filler (5364 g) were blended in stages in a V-blender. The blend was them compacted and granulated to obtain a bulk density of approximately 0.6 g/mL. The blend was dispensed into size 3 hard gelatin capsules (target fill weight: 190 mg) using an automated filling machine and finished capsules were polished using a capsule polisher machine.

[00150] Pharmacokinetic assessments were performed following oral dosing of 10 mg capsules containing the 50% compound (1-1) in HPMCAS solid dispersion and results were compared with pharmacokinetic assessments performed following oral dosing of administration of 4 x 10 mg capsules containing the Eudragit solid dispersion of compound (1-1) to healthy volunteers

[00151] A comparison of the two pharmaceutical compositions is provided in Tables 2A and 2B below. The Eudragit formulation previously was described in Example 5 in US Patent Application 2009/0012064 A1, published January 8, 2009. That application noted that the Eudragit solid dispersion formulation was made by dissolving and/or dispersing the thienotriazolodiazepine of formula (A) and coating excipients, including ammonio methacrylate copolymer type B (Eudragit RS), methacrylic acid copolymer type C (Eudragit L100-55), talc, and magnesium aluminosilicate, in a mixture of water and ethanol. This heterogeneous mixture then was applied to microcrystalline cellulose spheres (Nonpareil 101, Freund) using a centrifugal fluidizing bed granulator to produce granules that were dispensed into size 2 hydroxypropyl methylcellulose capsules.

[00152] In both clinical studies, blood levels of compound (1-1) were determined using validated LC-MS/MS methods and pharmacokinetic analyses were performed based on plasma concentrations of compound (1-1) measured at various time points over 24 hours after capsule administration. Results, summarized in Table 3 below, showed that the HPMCAS-M solid dispersion formulation had over 3-fold higher bioavailability in humans than the Eudragit solid dispersion formulation based on AUCs (924*4 / 1140, adjusting for difference in doses administered). Additionally, based on the observed T_{max}, the HPMCAS formulation is more rapidly absorbed than the Eudragit formulation (T_{max} of 1 h vs 4-6 h). The marked improvement in systemic exposure with the HPMCAS-M solid dispersion formulation is unexpected.

Table 2A: solid dispersion capsules of compound (1-1) for clinical use

pharmaceutical composition containing 50% HPMCAS solid dispersion of compound (1-1): 10 mg strength, size 3 hard gelatin capsule

Ingredient	Function	Capsule Content	
		mg	Wt %
Compound of formula (II)	active agent	10.0*	5.56
Hypromellose acetate succinate (HPMCAS-M)	carrier for solid dispersion	10.0	5.56
Lactose monohydrate	filler	85.0	47.22
Microcrystalline cellulose	filler-binder	70.0	38.89
Croscarmellose sodium	disintegrant	10.0	5.56
Collidal silicon dioxide	dispersant/lubricant	2.5	1.39
Magnesium stearate	dispersant/lubricant		
	Total	190.0	100.0

Table 2B: pharmaceutical composition containing Eudragit L100-55solid dispersion of compound (1-1): 10 mg strength, size 2 hard gelatin capsule

Ingredient	Function	Capsule Content	
		mg	Wt %
Compound (1-1)	active agent	10.0*	3.8

Core:			
Microcrystalline cellulose spheres (Nonpareil 101, Freund, Inc)	vehicle	100.0	38.5
Compound/polymer layer:			
Ammonio methacrylate copolymer, type B (NF. PhEur) (Edragit RS, Evonik)	coating agent	10.8	4.2
Methacrylic acid copolymer, type C (NF)/ Methacrylic acid-ethyl acrylate copolymer (1:1) type A (PhEur) (Eudragit L100-55, Evonik)	coating agent	25.2	9.7
Talc	coating agent	88.2	33.9
Magnesium aluminometasilicate (Neuslin, Fuji Chemical)	coating agent	20.0	7.7
Triethyl citrate	plasticizer	5.0	1.9
Silicon dioxide	fluidizing agent	0.8	0.3
		260.0	100.0

* as anhydrate

Table 3: pharmacokinetic parameters following oral administration of solid dispersions of compound (1-1) to humans

Compound (1-1) formulation	# Patients	Dose and Route	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24h} (ng•h/mL)
Eudragit solid dispersion formulation	7	40 mg PO	83	4 to 6	1140
50% HMPCAS-M solid dispersion formulation	7	10 mg PO	286	1	925

AUC_{0-24h}: area under the OTX015 plasma concentration vs. time curve over 24 hours
C_{max}: maximum concentration in plasma
hr: hour
HPMCAS: hypromellose acetate succinate
mL: milliliter
ng: nanogram
PO: *per os*, oral
T_{max}: time of C_{max}

[00153] Example 4. Oral exposure in the rat

[00154] The oral bioavailability of three formulations of solid dispersions of compound (1-1) was determined in rats. The three dispersions chosen were the 25% dispersion of compound (1-1) in PVP, the 25% dispersion of compound (1-1) in HPMCAS-MG, and the 50% dispersion of compound (1-1) in HPMCAS-MG. The animals used in the study were Specific Pathogen Free (SPF) Hsd:Sprague Dawley rats obtained from the Central Animal Laboratory at the University of Turku, Finland. The rats were originally purchased from Harlan, The Netherlands. The rats were female and were ten weeks of age, and 12 rats were used in the study. The animals were housed in polycarbonate Makrolon II cages (three animals per cage), the animal room temperature was 21 +/-

3 °C, the animal room relative humidity was 55 +/- 15%, and the animal room lighting was artificial and was cycled for 12 hour light and dark periods (with the dark period between 18:00 and 06:00 hours). Aspen chips (Tapvei Oy, Estonia) were used for bedding, and bedding was changed at least once per week. Food and water was provided prior to dosing the animals but was removed during the first two hours after dosing.

[00155] The oral dosing solutions containing the 25% dispersion of compound (1-1) in PVP, the 25% dispersion of compound (1-1) in HPMCAS-MG, and the 50% dispersion of compound (1-1) in HPMCAS-MG were prepared by adding a pre-calculated amount of sterile water for injection to containers holding the dispersion using appropriate quantities to obtain a concentration of 0.75 mg/mL of compound (1-1). The oral dosing solutions were subjected to vortex mixing for 20 seconds prior to each dose. The dosing solution for intravenous administration contained 0.25 mg/mL of compound (1-1) and was prepared by dissolving 5 mg of compound (1-1) in a mixture containing 4 mL of polyethylene glycol with an average molecular weight of 400 Da (PEG400), 4 mL of ethanol (96% purity), and 12 mL of sterile water for injection. The dosing solution containing the 25% dispersion of compound (1-1) in PVP was used within 30 minutes after the addition of water. The dosing solutions containing the 25% dispersion of compound (1-1) in HPMCAS-MG and the 50% dispersion of compound (1-1) in HPMCAS-MG were used within 60 minutes of after the addition of water. A dosing volume of 4 mL/kg was used to give dose levels of compound (1-1) of 1 mg/kg for intravenous administration and 3 mg/kg for oral administration. The dosing scheme is given in Table 4.

[00156] Table 4. Dosing scheme for rat oral exposure study.

Rat	**Weight**	**Dose (mL)**	**Test Item**	**Route**
1	236.5	0.95	Compound (1-1)	intravenous
2	221	0.88	Compound (1-1)	intravenous
3	237.5	0.95	Compound (1-1)	intravenous
4	255.5	1.02	25% dispersion of compound (1-1) in PVP	oral
5	224.2	0.90	25% dispersion of compound (1-1) in PVP	oral
6	219.2	0.88	25% dispersion of compound (1-1) in PVP	oral

7	251.6	1.01	25% dispersion of compound (1-1) in HPMCAS-MG	oral
8	240.4	0.96	25% dispersion of compound (1-1) in HPMCAS-MG	oral
9	238	0.95	25% dispersion of compound (1-1) in HPMCAS-MG	oral
10	226.6	0.91	50% dispersion of compound (1-1) in HPMCAS-MG	oral
11	228.4	0.91	50% dispersion of compound (1-1) in HPMCAS-MG	oral
12	228.5	0.91	50% dispersion of compound (1-1) in HPMCAS-MG	oral

[00157] Blood samples of approximately 50 µL were collected into Eppendorf tubes containing 5 µL of ethylenediaminetetraacetic acid (EDTA) solution at time points of 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours after dosing, with each sample collected within a window of 5 minutes from the prescribed time point. From each sample, 20 µL of plasma was obtained and stored at dry ice temperatures for analysis. Analysis of each sample for the concentration of compound (1-1) was performed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantitation of 0.5 ng/mL.

[00158] Pharmacokinetic parameters were calculated with the Phoenix WinNonlin software package (version 6.2.1, Pharsight Corp., CA, USA) with standard noncompartmental methods. The elimination phase half-life ($t_{1/2}$) was calculated by least-squares regression analysis of the terminal linear part of the log concentration-time curve. The area under the plasma concentration-time curve (AUC) was determined by use of the linear trapezoidal rule up to the last measurable concentration and thereafter by extrapolation of the terminal elimination phase to infinity. The mean residence time (MRT), representing the average amount of time a compound remains in a compartment or system, was calculated by extrapolating the drug concentration profile to infinity. The maximum plasma concentration (C_{max}) and the time to C_{max} (t_{max}) were derived directly from the plasma concentration data. The tentative oral bioavailability (F) was calculated by dividing the dose normalised AUC after oral administration by the dose normalised AUC after intravenous administration, i.e. F = (AUC(oral)/Dose(oral))/(AUC(intravenous) / Dose(intravenous))] and is reported as percentage (%).

[00159] The pharmacokinetic parameters are given in Table 5, and the plasma concentration versus time plots are shown in Figures 7 and 8.

Table 5. Pharmacokinetic parameters of compound (1-1) after oral and intravenous administrations. The values are an average from three animals.

Compound	Parameter	1 mg/kg intravenous	3 mg/kg oral	F(%)
Compound (1-1) water:ethanol:PEG 400 (60:20:20)	AUC (min*ng/ml) C_{max} (ng/ml) T_{max} (hr) $t_{1/2}$ (hr) 8.5 CI/F (ml/min/kg) MRT (hr)	74698 730 0.25 8.5 13.4 7.4		
25% dispersion of compound (1-1) in PVP	AUC (min*ng/ml) C_{max} (ng/ml) T_{max} (hr) $t_{1/2}$ (hr) 8.5 CI/F (ml/min/kg) MRT (hr)		39920 77.9 1 13.8 75.2 18.0	18
25% dispersion of compound (1-1) in HPMCAS-MG	AUC (min*ng/ml) C_{max} (ng/ml) T_{max} (hr) $t_{1/2}$ (hr) 8.5 CI/F (ml/min/kg) MRT (hr)		35306 48.3 0.5 11.0 85.0 17.1	16
50% dispersion of compound (1-1) in HPMCAS-MG	AUC (min*ng/ml) C_{max} (ng/ml) T_{max} (hr) $t_{1/2}$ (hr) 8.5 CI/F (ml/min/kg) MRT (hr)		40238 67.0 2 9.5 74.6 12.8	18

[00160] Example 5. Preparation of spray dried dispersions.

[00161] Spray dried dispersions of compound (1-1) were prepared using five selected polymers: HPMCAS-MG (Shin Etsu Chemical Co., Ltd.), HPMCP-HP55 (Shin Etsu Chemical Co., Ltd.), PVP (ISP, a division of Ashland, Inc.), PVP-VA (BASF Corp.), and Eudragit L100-55 (Evonik Industries AG). All spray dried solutions were prepared at 25% and 50% by weight with each polymer. All solutions were prepared in acetone, with the exception of the PVP solutions, which were prepared in ethanol. For each solution, 1.0 g of solids (polymer and compound (1-1)) were prepared in 10 g of solvent. The solutions were spray dried using a Büchi B-290, PE-024 spray dryer with a 1.5 mm nozzle and a Büchi B-295, P-002 condenser. The spray dryer nozzle pressure was set to 80 psi, the target outlet temperature was set to 40 °C, the chiller temperature was set to -20 °C, the pump speed was set to 100%, and the aspirator setting was 100%. After spray drying, the solid dispersions were collected and dried overnight in a low temperature convection oven to remove residual solvents.

[00163] Example 6: Stability with humidity and temperature.

[00164] Table 6

<table>
<tr><th>Test</th><th>Procedure</th><th>Acceptance Criteria</th><th colspan="2">T=0 (Initial)</th><th colspan="2">T=1 month (storage at 40°C/75%RH)</th><th colspan="2">T=2 month (storage at 40°C/75%RH)</th><th colspan="2">T= 3 month (storage at 40°C/75%RH)</th></tr>
<tr><td rowspan="2">Appearance</td><td rowspan="2">AM-0002</td><td rowspan="2">White to off-white powder</td><td colspan="2">Test Date/Ref: 06Aug2012/02-41-2</td><td colspan="2">Test Date/Ref: 24Sep2012/02-41-59</td><td colspan="2">Test Date/Ref:24Oct2012/02-37-106</td><td colspan="2">Test Date/Ref:17Dec2012/02-37-119</td></tr>
<tr><td colspan="2">White Powder</td><td colspan="2">White Powder</td><td colspan="2">White Powder</td><td colspan="2">White Powder</td></tr>
<tr><td rowspan="2">Potency (HPLC)</td><td rowspan="2">AM-0028</td><td rowspan="2">45.0 • 55.0 wt%</td><td colspan="2">Test Date/Ref: 25Jul2012/02-37-21</td><td colspan="2">Test Date/Ref: 25Sep2012/02-4HI0</td><td colspan="2">Test Date/Ref:24Oct2012/02-37-105</td><td colspan="2">Test Date/Ref: 29Nov2012/02-34-107</td></tr>
<tr><td colspan="2">50.0</td><td colspan="2">49.4</td><td colspan="2">49.8</td><td colspan="2">49.2</td></tr>
<tr><td rowspan="4">Individual Related Substances (HPLC)</td><td rowspan="4">AM-0029</td><td rowspan="4">Report results</td><td colspan="2">Test Date/Ref: 25Jul2012/02-34-49</td><td colspan="2">Test Date/Ref: 26Sep2012/02-41-64</td><td colspan="2">Test Date/Ref: 24Oct2012/02-37-105</td><td colspan="2">Test Date/Ref: 29Nov2012/02-34-107</td></tr>
<tr><td>RRT</td><td>% Area</td><td>RRT</td><td>% Area</td><td>RRT</td><td>% Area</td><td>RRT</td><td>% Area</td></tr>
<tr><td colspan="2" rowspan="2">No reportable related substances</td><td colspan="2" rowspan="2">No reportable related substances</td><td>0.68</td><td>0.06</td><td>0.68</td><td>0.07</td></tr>
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<tr><td colspan="2">No reportable related substances</td><td colspan="2">No reportable related substances</td><td colspan="2">0.12%</td><td colspan="2">0.16%</td></tr>
<tr><td rowspan="2">Water Content (KF)</td><td rowspan="2">AM-0030
USP <921></td><td rowspan="2">Report results (wt%)</td><td colspan="2">Test Date/Ref: 02Aug2012/02-41-1</td><td colspan="2">Test Date/Ref: 27Sep2012/02-37-99</td><td colspan="2">Test Date/Ref: 25Oct2012102-37-110</td><td colspan="2">Test Date/Ref: 29Nov2012/02-37-116</td></tr>
<tr><td colspan="2">1.52</td><td colspan="2">2.53</td><td colspan="2">2.70</td><td colspan="2">3.43</td></tr>
<tr><td rowspan="2">X-Ray Powder Diffraction (XRPD)</td><td rowspan="2">USP <941></td><td rowspan="2">Consistent with an amorphous form</td><td colspan="2">Test Date/Ref: 24Jul2012/02-24-131</td><td colspan="2">Test Date/Ref: 01Oct2012/02-41-73</td><td colspan="2">Test Date/Ref: 24Oct2012/02-37-107</td><td colspan="2">Test Date/Ref: 17Dec2012/02-37-120</td></tr>
<tr><td colspan="2">Consistent with an amorphous form See Figure 9</td><td colspan="2">Consistent with an amorphous form See Figure 10</td><td colspan="2">Consistent with an amorphous form See Figure 11</td><td colspan="2">Consistent with an amorphous form See Figure 12</td></tr>
<tr><td rowspan="2">Modulated Differential Scanning Calorimetry (mDSC)</td><td rowspan="2">USP <891> (n = 2 replicates)</td><td rowspan="2">Report individual and average glass transition temperatures (T_g, °C)</td><td colspan="2">Test Date/Ref: 24Jul2012/02-24-130</td><td colspan="2">Test Date/Ref: 26Sep2012/02-37-98</td><td colspan="2">Test Date/Ref: 24Oct2012/02-37-108</td><td colspan="2">Test Date/Ref: 17Dec2012/02-37-121</td></tr>
<tr><td colspan="2">Replicate 1 = 134.30°C,Replicate 2 = 134.23°C,Replicate 3 = 135.28°C, Average = 134.60°C</td><td colspan="2">Replicate 1 = 134.65°C, Replicate 2 = 134.43°C, Average=134.54°C</td><td colspan="2">Replicate 1 = 135.35°C, Replicate 2 = 134.93°C, Average = 135.14°C</td><td colspan="2">Replicate 1 = 134.36°C. Replicate 2 = 137.16°C. Average= 135.76°C</td></tr>
</table>

[00165] Spray dried dispersions of compound (1-1) in HPMCAS-MG were assessed for stability by exposure to moisture at elevated temperature. The glass transition temperature (Tg) as a function of relative humidity was determined at 75% relative humidity, 40 °C for 1, 2 and 3 months. The spray dried dispersion was stored in an LDPE bag inside a HDPE bottle to simulate bulk product packaging. The results are summarized in Table 6. At time zero, the Tg was 134 °C, at 1 month the Tg was 134 °C, at 2 months the Tg was 135 °C and at 3 months the Tg was 134 °C and only a single inflection point was observed for each measurement. X-ray diffraction patterns were also obtained for each sample. Figure 9 illustrates a powder X-ray diffraction profile of solid dispersions of compound (1-1) in HPMCAS-MG at time zero of a stability test. Figures 10, 11 and 12 illustrate powder X-ray diffraction profiles of solid dispersions of compound (1-1) in

[00166] HPMCAS-MG after 1 month, 2 months and 3 months, respectively, after exposure at 40 °C and 75 % relative humidity. The patterns did not show any diffraction lines associated with compound (1-1).

[00167] It will be appreciated by those skilled in the art that changes could be made to the exemplary embodiments shown and described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the exemplary embodiments shown and described, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the claims. For example, specific features of the exemplary embodiments may or may not be part of the claimed invention and features of the disclosed embodiments may be combined. Unless specifically set forth herein, the terms “a”, “an” and “the” are not limited to one element but instead should be read as meaning “at least one”.

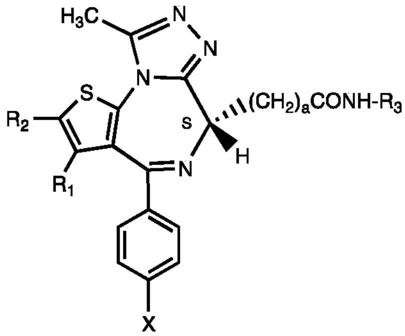
[00168] It is to be understood that at least some of the figures and descriptions of the invention have been simplified to focus on elements that are relevant for a clear understanding of the invention, while eliminating, for purposes of clarity, other elements that those of ordinary skill in the art will appreciate may also comprise a portion of the invention. However, because such elements are well known in the art, and because they do not necessarily facilitate a better understanding of the invention, a description of such elements is not provided herein.

[00169] Further, to the extent that the method does not rely on the particular order of steps set forth herein, the particular order of the steps should not be construed as limitation on the claims. The claims directed to the method of the present invention should not be limited to the performance of their steps in the order written, and one skilled in the art can readily appreciate that the steps may be varied and still remain within the spirit and scope of the present invention.

CLAIMS

I/we claim:

1. A solid dispersion comprising an amorphous thienotriazolodiazepine compound of the Formula (1)



wherein X is a halogen, R_1 is C_1-C_4 alkyl, R_2 is C_1-C_4 alkyl, a is an integer of 1-4, R_3 is C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 alkoxy, phenyl optionally having substituent(s), or heteroaryl optionally having substituent(s), a pharmaceutically acceptable salt thereof or a hydrate thereof; and a pharmaceutically acceptable polymer.

2. The solid dispersion of claim 1, wherein Formula (1) is selected from the group consisting of: (i) (S)-2-[4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo- [4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide or a dihydrate thereof, (ii) methyl (S)-{4-(3'-cyanobiphenyl-4-yl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]tri- azolo[4,3-a][1,4]diazepin-6-yl}acetate, (iii) methyl (S)-{2,3,9-trimethyl-4-(4-phenylaminophenyl)-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate; and (iv) methyl (S)-{2,3,9-trimethyl-4-[4-(3-phenylpropionylamino)phenyl]-6H-thieno[3,2-f-][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl}acetate.

3. The solid dispersion of claim 1, wherein Formula (1) is (S)-2-[4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,- 4]triazolo[4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide.

4. The solid dispersion according to any of claims 1-3, wherein the pharmaceutically acceptable polymer is hydroxypropylmethylcellulose acetate succinate.

5. The solid dispersion of claim 4, wherein the solid dispersion has a thienotriazolodiazepine compound to hydroxypropylmethylcellulose acetate succinate (HPMCAS), weight ratio of 1:3 to 1:1.

6. The solid dispersion according to any of claims 1-3, wherein the pharmaceutically acceptable polymer is PVP.

7. The solid dispersion according to claim 6, wherein the solid dispersion has a thienotriazolodiazepine compound to PVP weight ratio of 1:3 to 1:1.

8. The solid dispersion according to any of claims 1-7, wherein the solid dispersion is obtained by spray drying.

9. The solid dispersion according to any of claims 4 and 5, wherein the solid dispersion exhibits a single glass transition temperature (Tg) inflection point ranging from about 130 °C to about 140 °C .

10. The solid dispersion according to claim 9, wherein the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month.

11. The solid dispersion according to claim 10, wherein a concentration of the thienotriazolodiazepine compound after exposure to the relative humidity of 75 % at 40 °C for at least one month is at least 90 % of the concentration the amorphous thienotriazolodiazepine compound prior to such exposure.

12. The solid dispersion according to any of claims 6 and 7, wherein the solid dispersion exhibits a single glass transition temperature (Tg) inflection point ranging from about 175 °C to about 185 °C .

13. The solid dispersion according to claim 12, wherein the solid dispersion was exposed to a relative humidity of 75 % at 40 °C for at least one month.

14. The solid dispersion according to claim 13, wherein a concentration of the thienotriazolodiazepine compound after exposure to the relative humidity of 75 % at 40 °C for at least one month is at least 90 % of the concentration the amorphous thienotriazolodiazepine compound prior to such exposure.

15. The solid dispersion according to any of claims 1-14, wherein the solid dispersion exhibits an X-ray powder diffraction pattern substantially free of diffraction lines associated with crystalline thienotriazolodiazepine compound of Formula (1).

16. The solid dispersion according to any of claims 1-15, the solid dispersion provides an area under the curve (AUC) value that is at least 0.5 times that of a corresponding AUC value provided by a control composition administered intravenously, wherein the control composition comprises an equivalent quantity of a crystalline thienotriazolodiazepine compound of Formula (1).

17. The solid dispersion according to any of claims 1-15, wherein the solid dispersion provides a concentration, of the amorphous thienotriazolodiazepine compound, in an aqueous in vitro test medium at pH between 5.0 to 7.0, of at least 5-fold greater than a concentration of a crystalline thienotriazolodiazepine compound of Formula (1) without polymer, in a control in vitro test medium at pH between 5.0 to 7.0 test medium.

18. The solid dispersion according to any of claims 1-15, wherein a concentration of the amorphous thienotriazolodiazepine compound, from the solid dispersion, in an aqueous in vitro test medium having a pH of 1.0 to 2.0, is at least 50% higher than a concentration of a crystalline thienotriazolodiazepine compound of Formula (1) without polymer in an in vitro test medium having a pH between 5.0 and 7.0.

19. The solid dispersion according to any of claims 4 and 5, wherein concentration of the amorphous thienotriazolodiazepine compound, is at least 50% higher compared to a concentration of thienotriazolodiazepine compound of Formula (1), from a solid dispersion of thienotriazolodiazepine compound of the Formula (1) and a pharmaceutically acceptable polymer selected from the group consisting of: hypromellose phthalate and ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer, wherein each solid dispersion was placed in an aqueous in vitro test medium having a pH of 1.0 to 2.0.

20. The solid dispersion according to any of claims 6 and 7, wherein a concentration of the amorphous thienotriazolodiazepine compound of Formula (1), is at least 50% higher compared to a concentration of thienotriazolodiazepine compound of Formula (1), from a solid dispersion of thienotriazolodiazepine compound of the Formula (1) and a pharmaceutically acceptable polymer selected from the group consisting of: hypromellose phthalate, and Eudragit, wherein each solid dispersion was placed in an aqueous in vitro test medium having a pH of 1.0 to 2.0.

21. A pharmaceutical formulation comprising a solid dispersion, according to any of claims 1-20, and one or more pharmaceutically acceptable excipients selected from the group consisting of: lactose monohydrate; microcrystalline cellulose; croscarmellose sodium; colloidal silicon dioxide; magnesium stearate; and combinations thereof;
wherein said pharmaceutical formulation has a bulk density ranging from 0.55 g/cc to 0.60 g/cc.

22. A pharmaceutical capsule comprising the solid dispersion according to any of claims 1-20.

23. A pharmaceutical tablet comprising the solid dispersion according to any of claims 1-20.

24. A pharmaceutical formulation comprising 10-15 wt. % of a solid dispersion according to any of claims 1-20 ;45 -50 wt. % of lactose monohydrate; 35-40 wt. % of microcrystalline cellulose; 4-6 wt. % of croscarmellose sodium; 0.8-1.5 wt. % of colloidal silicon dioxide; and 0.8-1.5 wt. % of magnesium stearate.

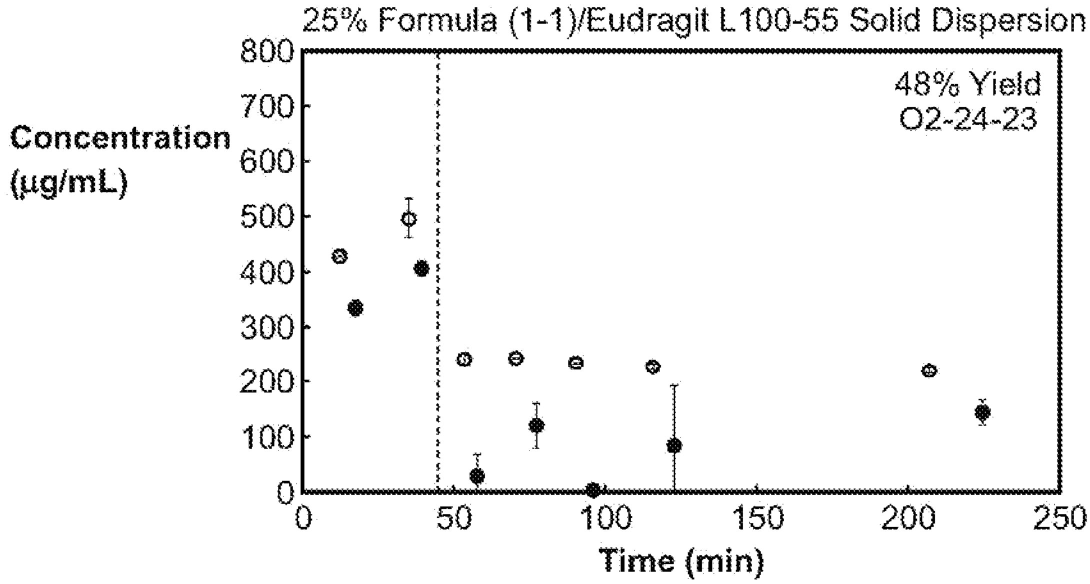

25% Formula (1-1)/Eudragit L100-55 Solid Dispersion
48% Yield
O2-24-23
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (min)

FIG. 1A

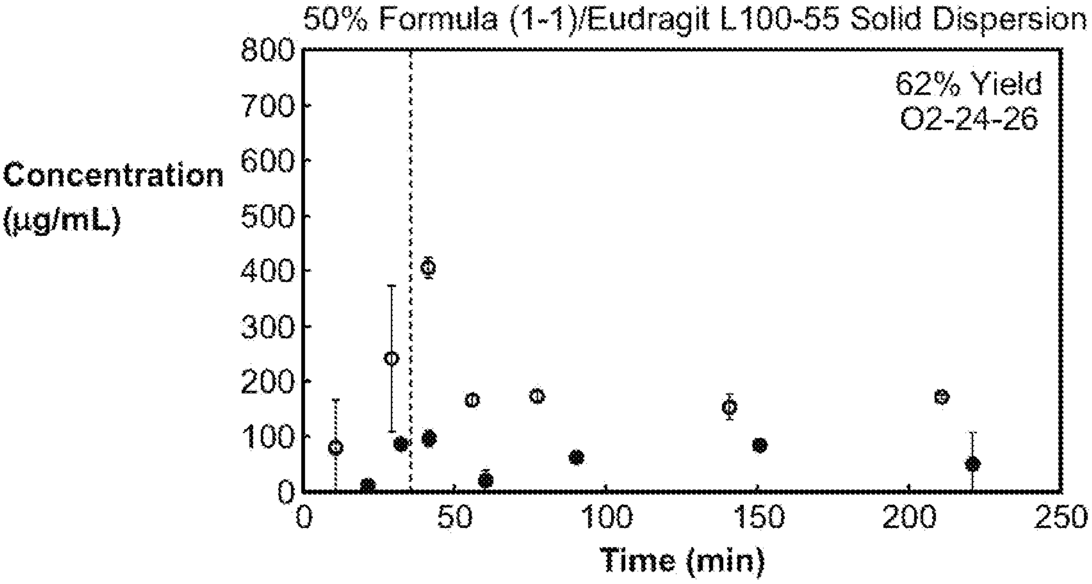

50% Formula (1-1)/Eudragit L100-55 Solid Dispersion
62% Yield
O2-24-26
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (min)

FIG. 1B

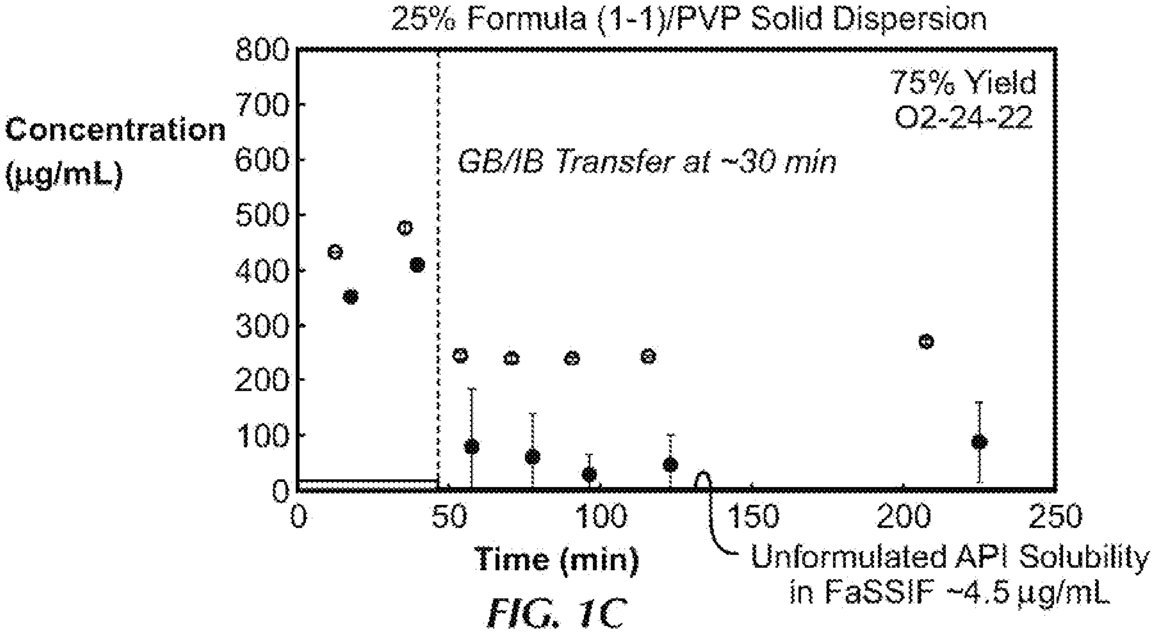

25% Formula (1-1)/PVP Solid Dispersion
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
75% Yield
O2-24-22
GB/IB Transfer at ~30 min
0
50
100
150
200
250
Time (min)
Unformulated API Solubility in FaSSIF ~4.5 µg/mL

FIG. 1C

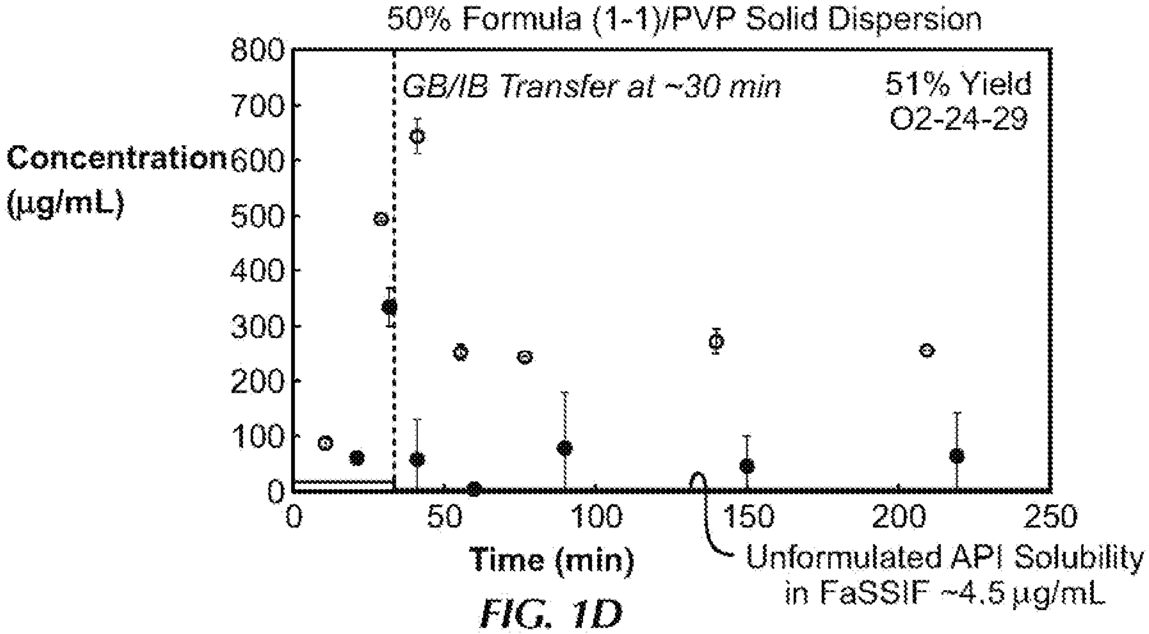

50% Formula (1-1)/PVP Solid Dispersion
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
GB/IB Transfer at ~30 min
51% Yield
O2-24-29
0
50
100
150
200
250
Time (min)
Unformulated API Solubility in FaSSIF ~4.5 µg/mL

FIG. 1D

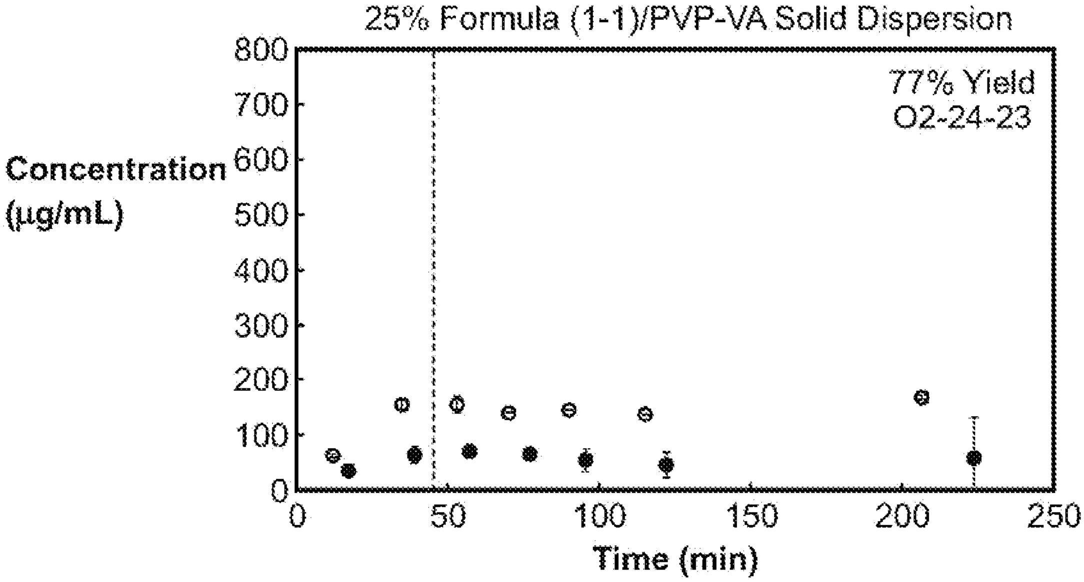

25% Formula (1-1)/PVP-VA Solid Dispersion
77% Yield
O2-24-23
Concentration (µg/mL)
0
100
200
300
400
500
600
700
800
Time (min)
0
50
100
150
200
250

FIG. 1E

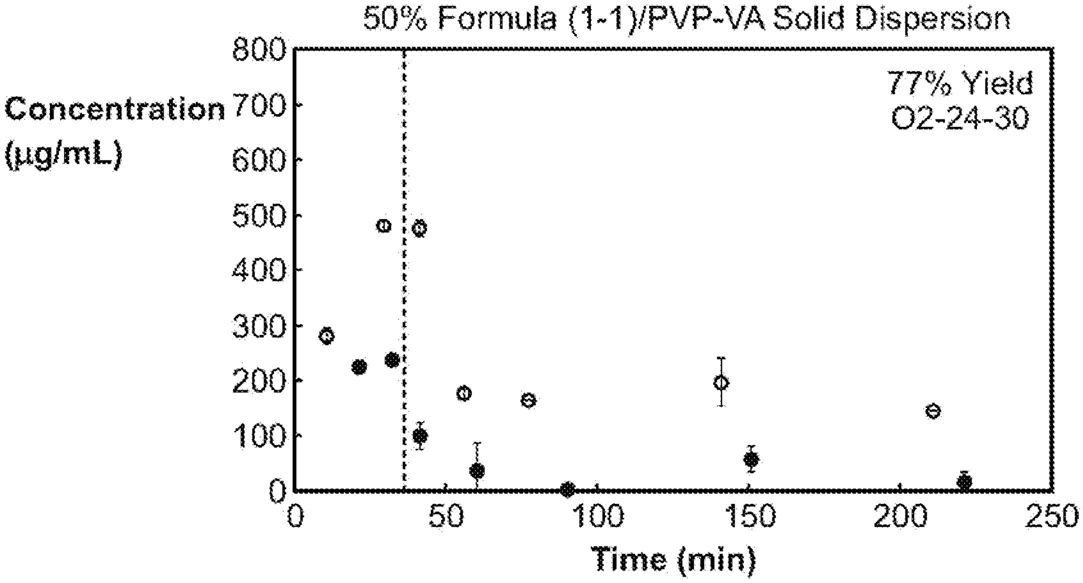

50% Formula (1-1)/PVP-VA Solid Dispersion
77% Yield
O2-24-30
Concentration (µg/mL)
0
100
200
300
400
500
600
700
800
Time (min)
0
50
100
150
200
250

FIG. 1F

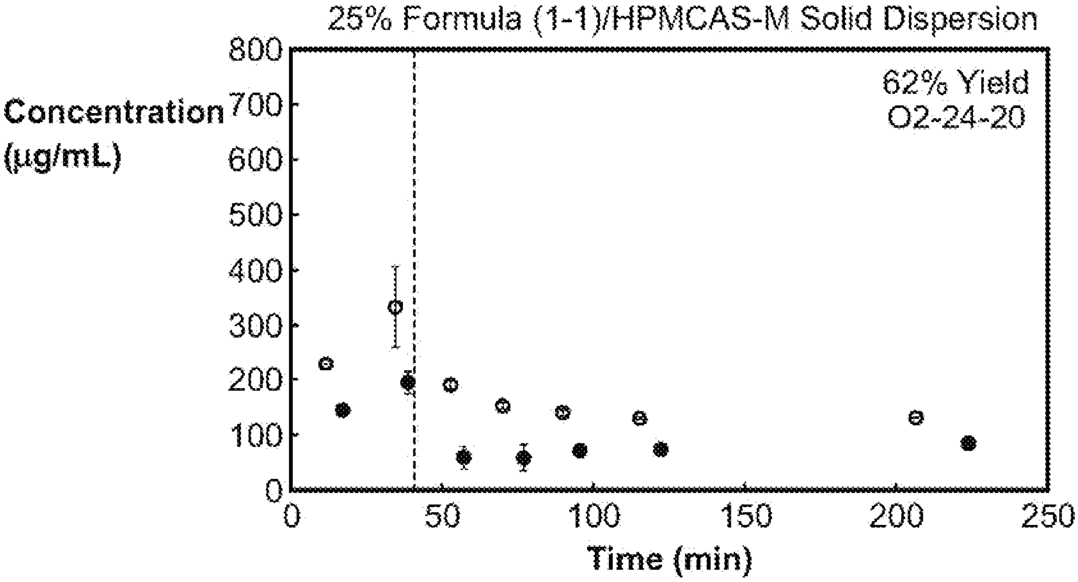

25% Formula (1-1)/HPMCAS-M Solid Dispersion
62% Yield
O2-24-20
Concentration (µg/mL)
0
100
200
300
400
500
600
700
800
0
50
100
150
200
250
Time (min)

FIG. 1G

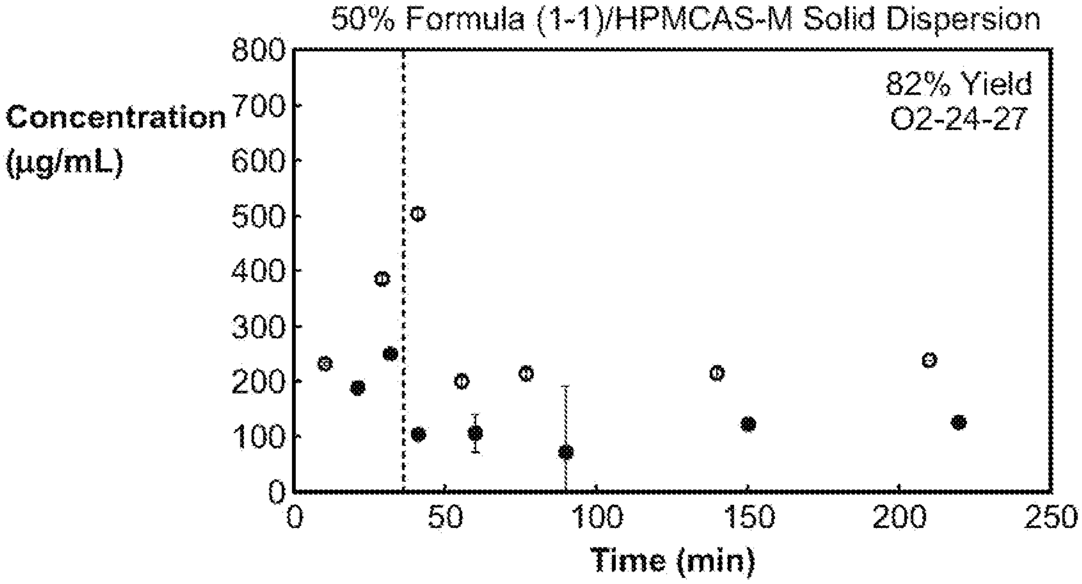

50% Formula (1-1)/HPMCAS-M Solid Dispersion
82% Yield
O2-24-27
Concentration (µg/mL)
0
100
200
300
400
500
600
700
800
0
50
100
150
200
250
Time (min)

FIG. 1H

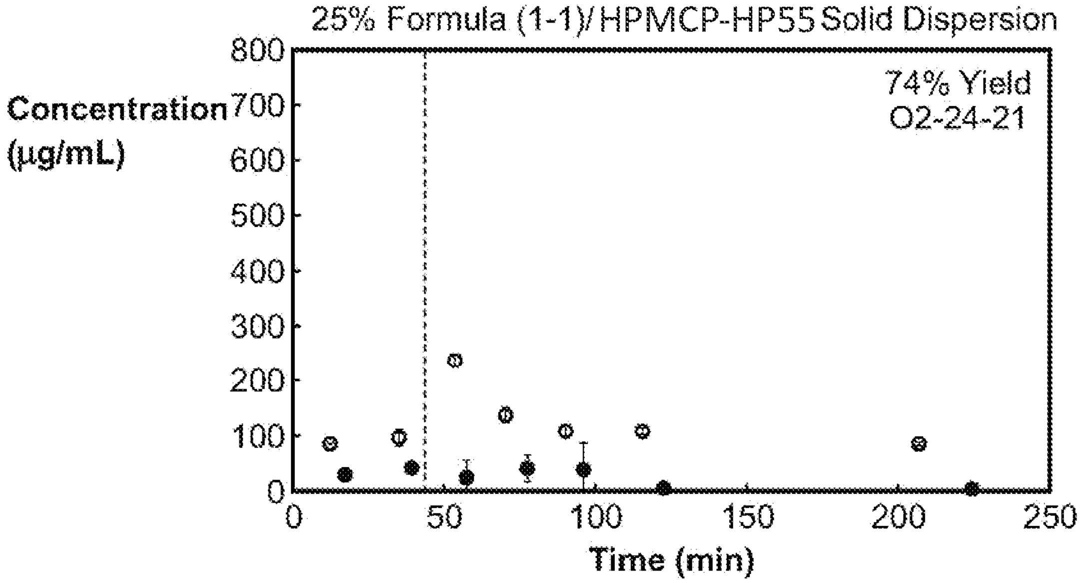

25% Formula (1-1)/HPMCP-HP55 Solid Dispersion
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (min)
74% Yield
O2-24-21

FIG. 1I

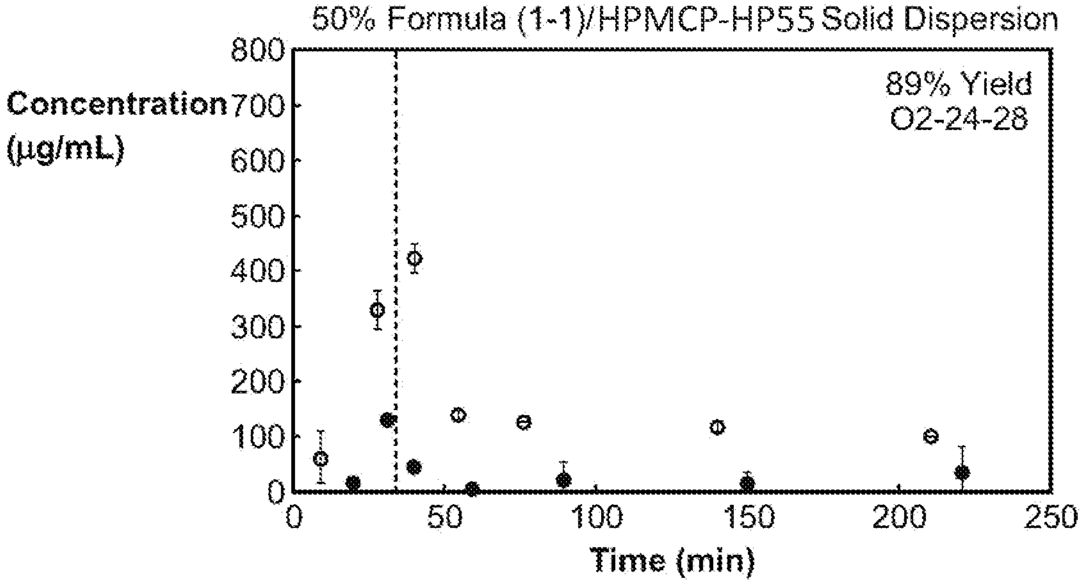

50% Formula (1-1)/HPMCP-HP55 Solid Dispersion
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (min)
89% Yield
O2-24-28

FIG. 1J

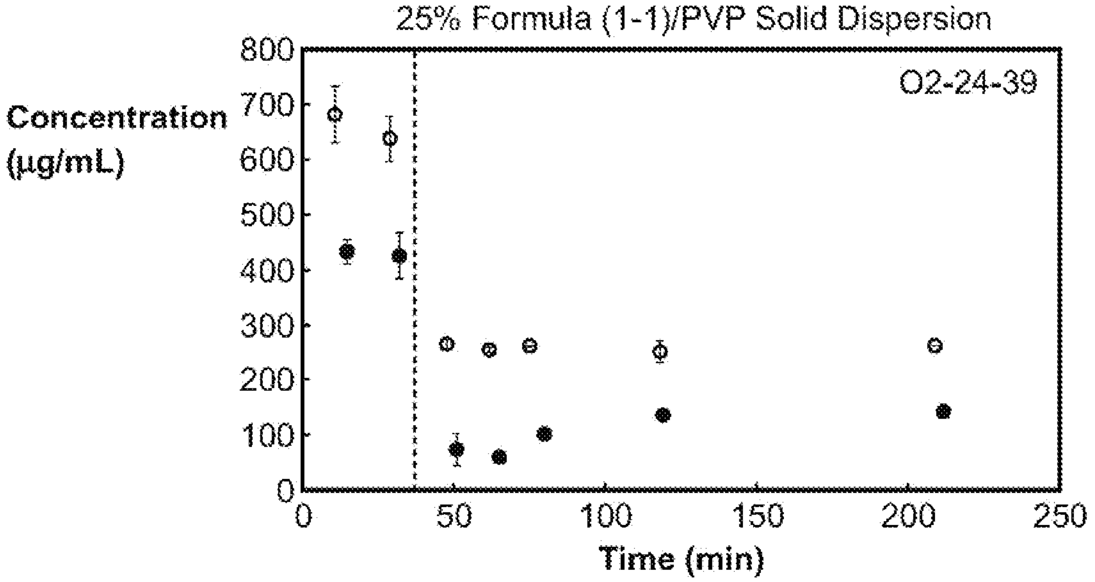

25% Formula (1-1)/PVP Solid Dispersion
O2-24-39
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (min)

FIG. 2A

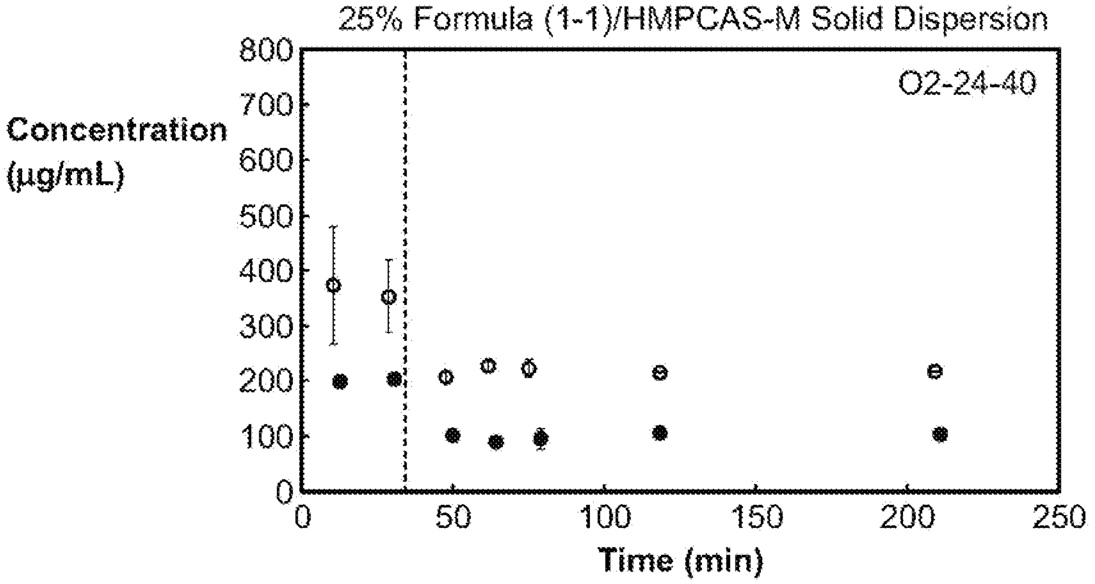

25% Formula (1-1)/HMPCAS-M Solid Dispersion
O2-24-40
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (min)

FIG. 2B

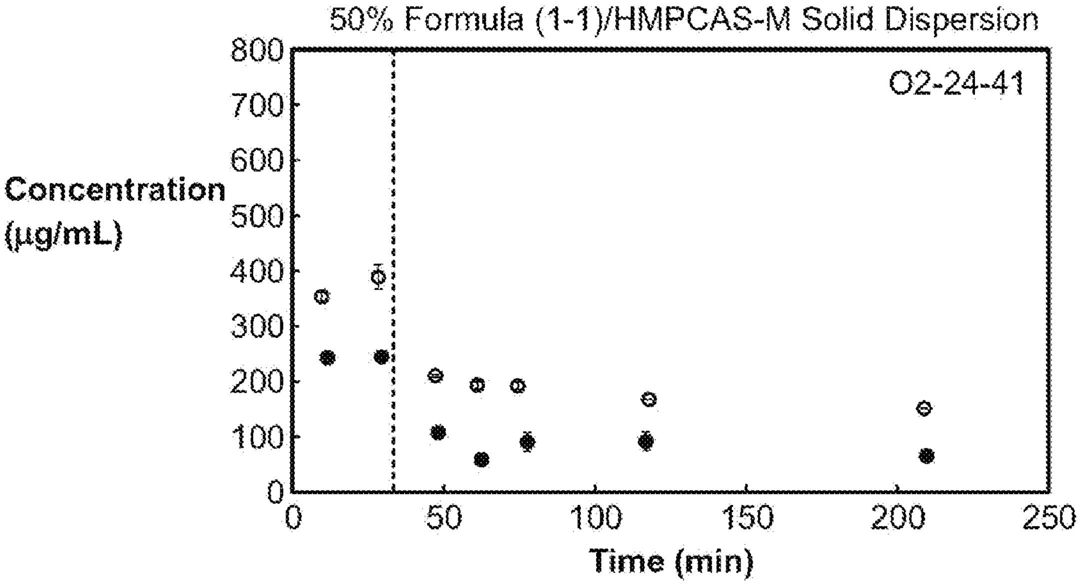

50% Formula (1-1)/HMPCAS-M Solid Dispersion
O2-24-41
Concentration (µg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
Time (min)

FIG. 2C

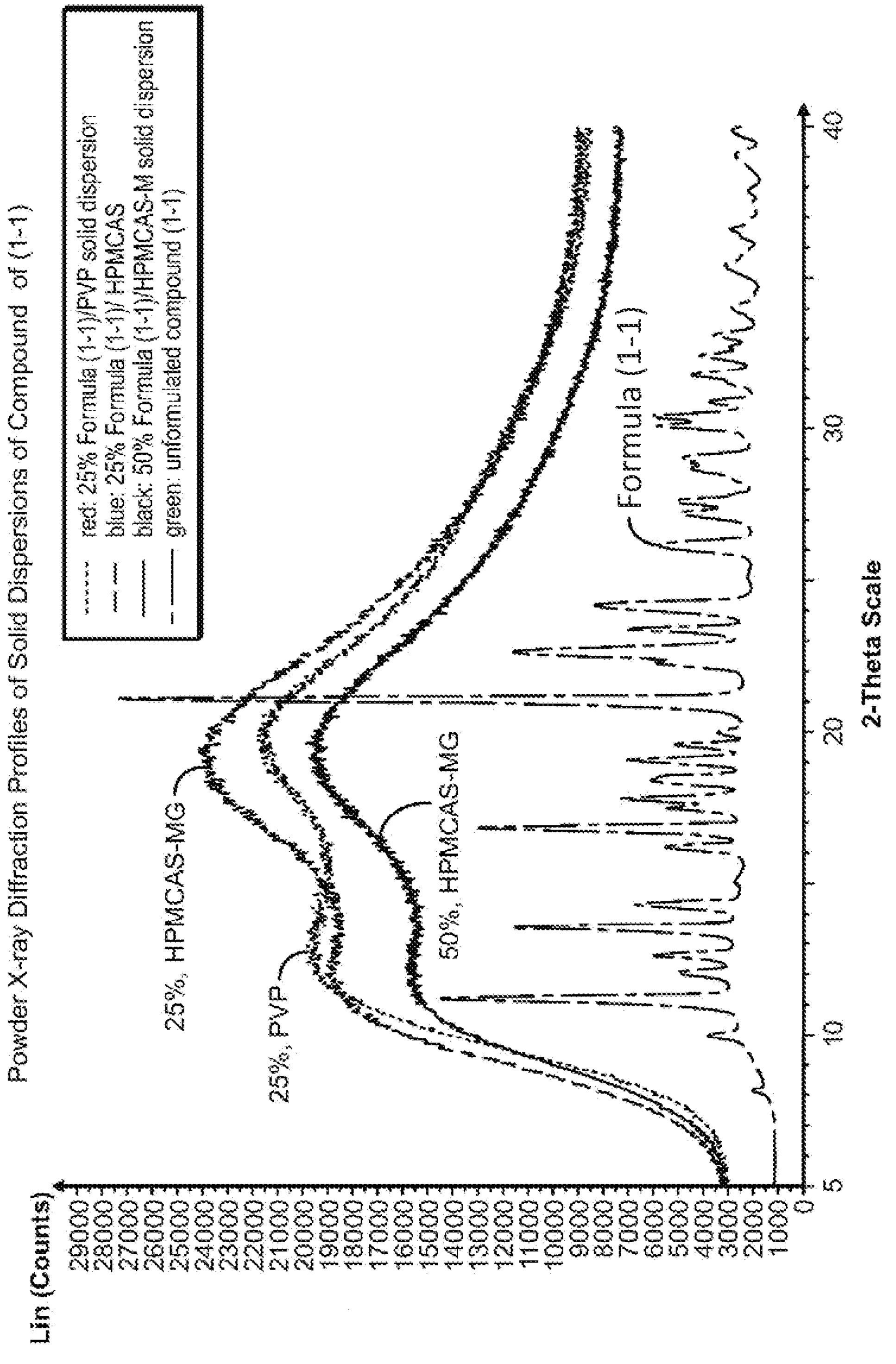

Powder X-ray Diffraction Profiles of Solid Dispersions of Compound of (1-1)
red: 25% Formula (1-1)/PVP solid dispersion
blue: 25% Formula (1-1)/ HPMCAS
black: 50% Formula (1-1)/HPMCAS-M solid dispersion
green: unformulated compound (1-1)
Lin (Counts)
29000
28000
27000
26000
25000
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
10
20
30
40
2-Theta Scale
25%, HPMCAS-MG
25%, PVP
50%, HPMCAS-MG
Formula (1-1)

FIG. 3

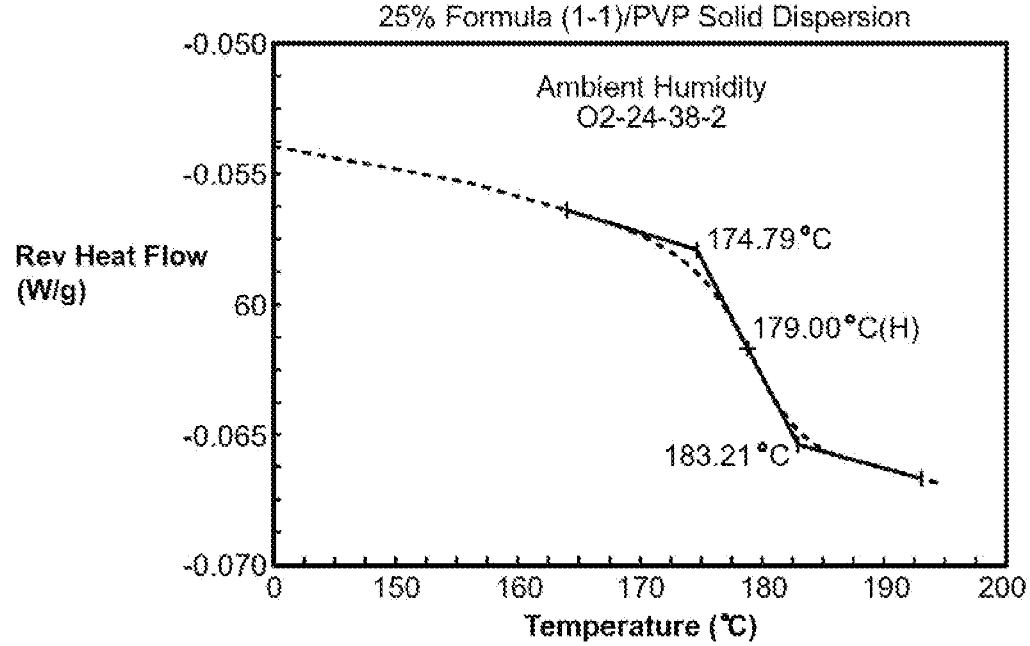

25% Formula (1-1)/PVP Solid Dispersion
Ambient Humidity
O2-24-38-2
Rev Heat Flow (W/g)
-0.050
-0.055
60
-0.065
-0.070
174.79°C
179.00°C(H)
183.21°C
0
150
160
170
180
190
200
Temperature (℃)

FIG. 4A

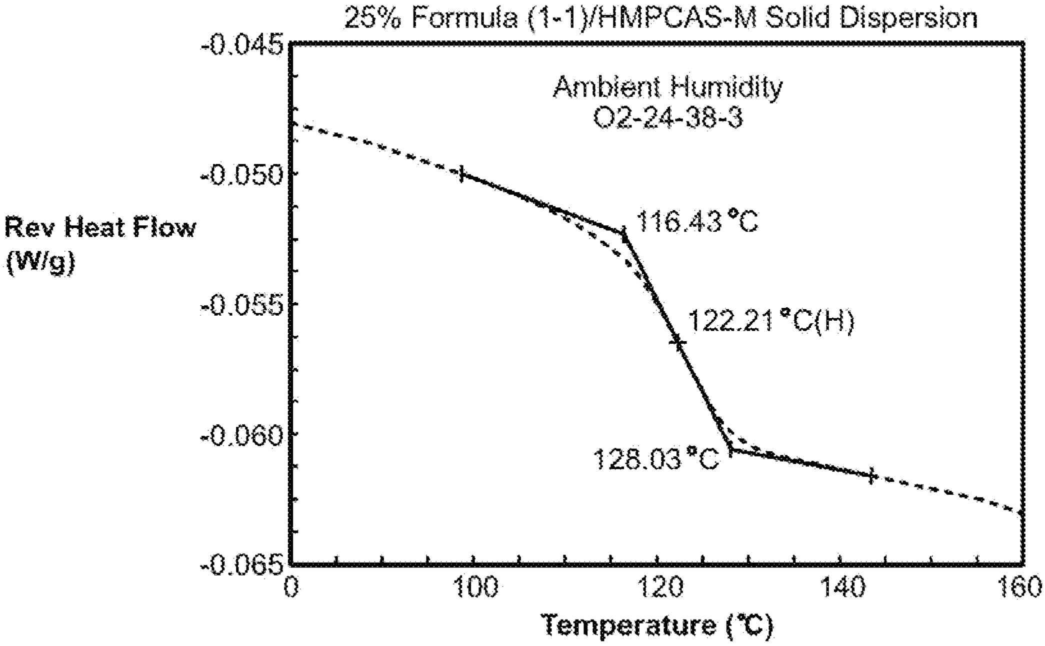

25% Formula (1-1)/HMPCAS-M Solid Dispersion
Ambient Humidity
O2-24-38-3
Rev Heat Flow (W/g)
-0.045
-0.050
-0.055
-0.060
-0.065
116.43°C
122.21°C(H)
128.03°C
0
100
120
140
160
Temperature (℃)

FIG. 4B

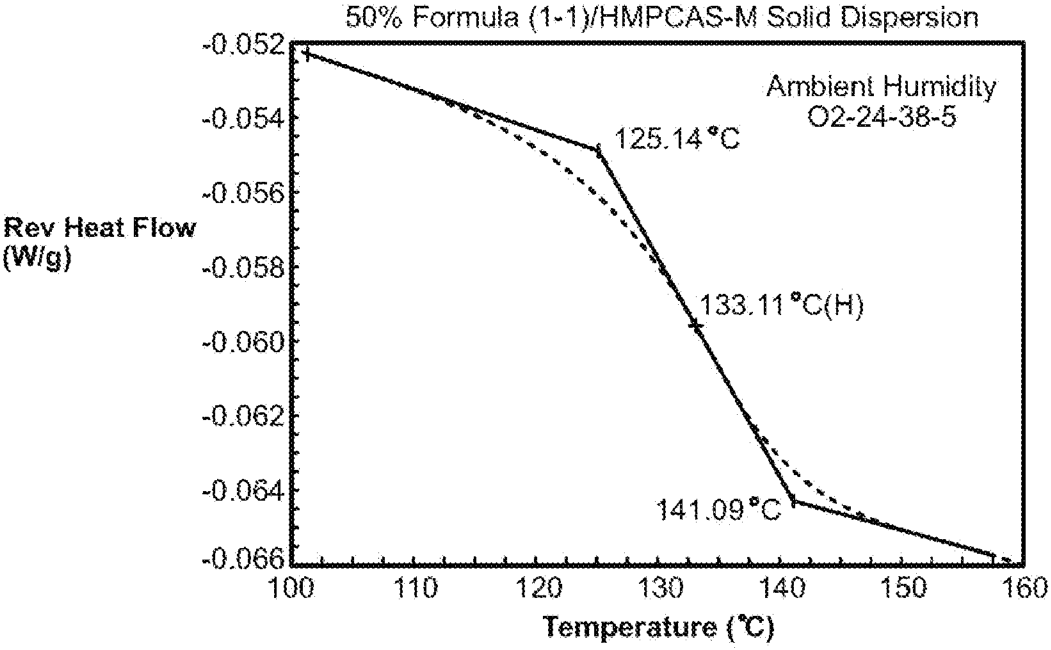
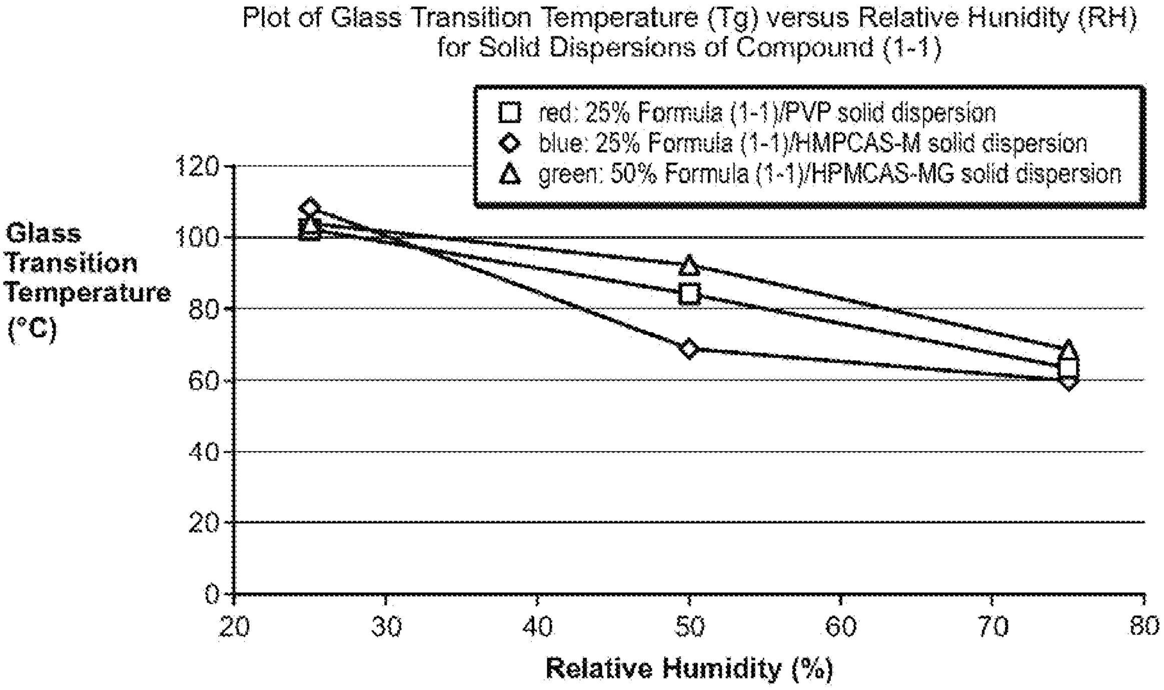
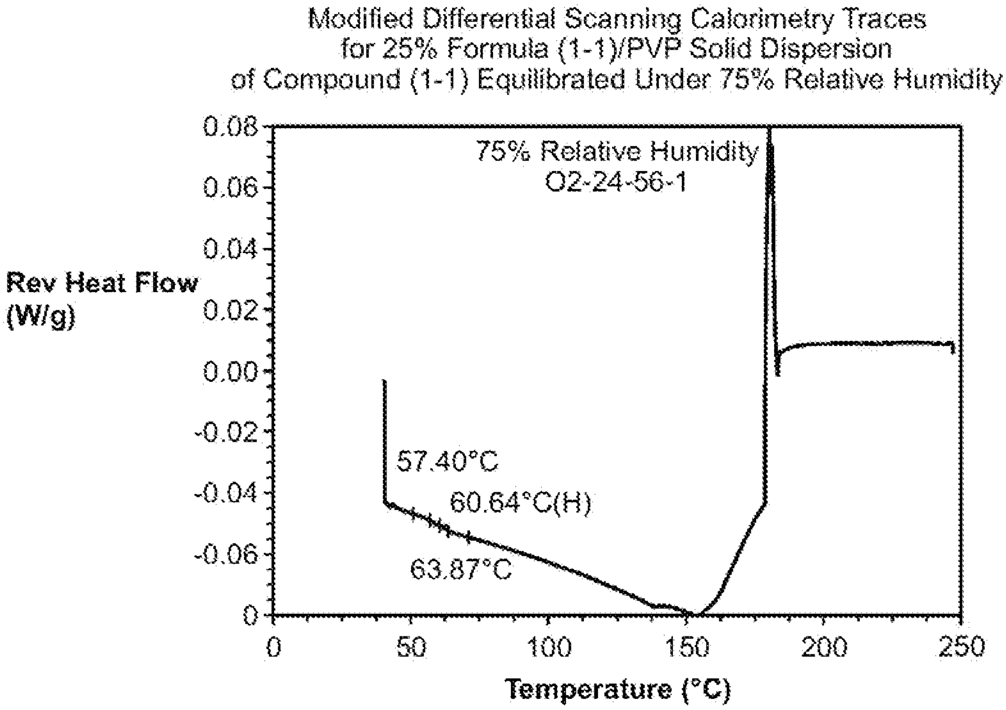

50% Formula (1-1)/HMPCAS-M Solid Dispersion
Ambient Humidity
O2-24-38-5
Rev Heat Flow (W/g)
-0.052
-0.054
-0.056
-0.058
-0.060
-0.062
-0.064
-0.066
125.14°C
133.11°C(H)
141.09°C
100
110
120
130
140
150
160
Temperature (°C)

FIG. 4C



Plot of Glass Transition Temperature (Tg) versus Relative Hunidity (RH) for Solid Dispersions of Compound (1-1)

FIG. 5



Modified Differential Scanning Calorimetry Traces for 25% Formula (1-1)/PVP Solid Dispersion of Compound (1-1) Equilibrated Under 75% Relative Humidity

FIG. 6

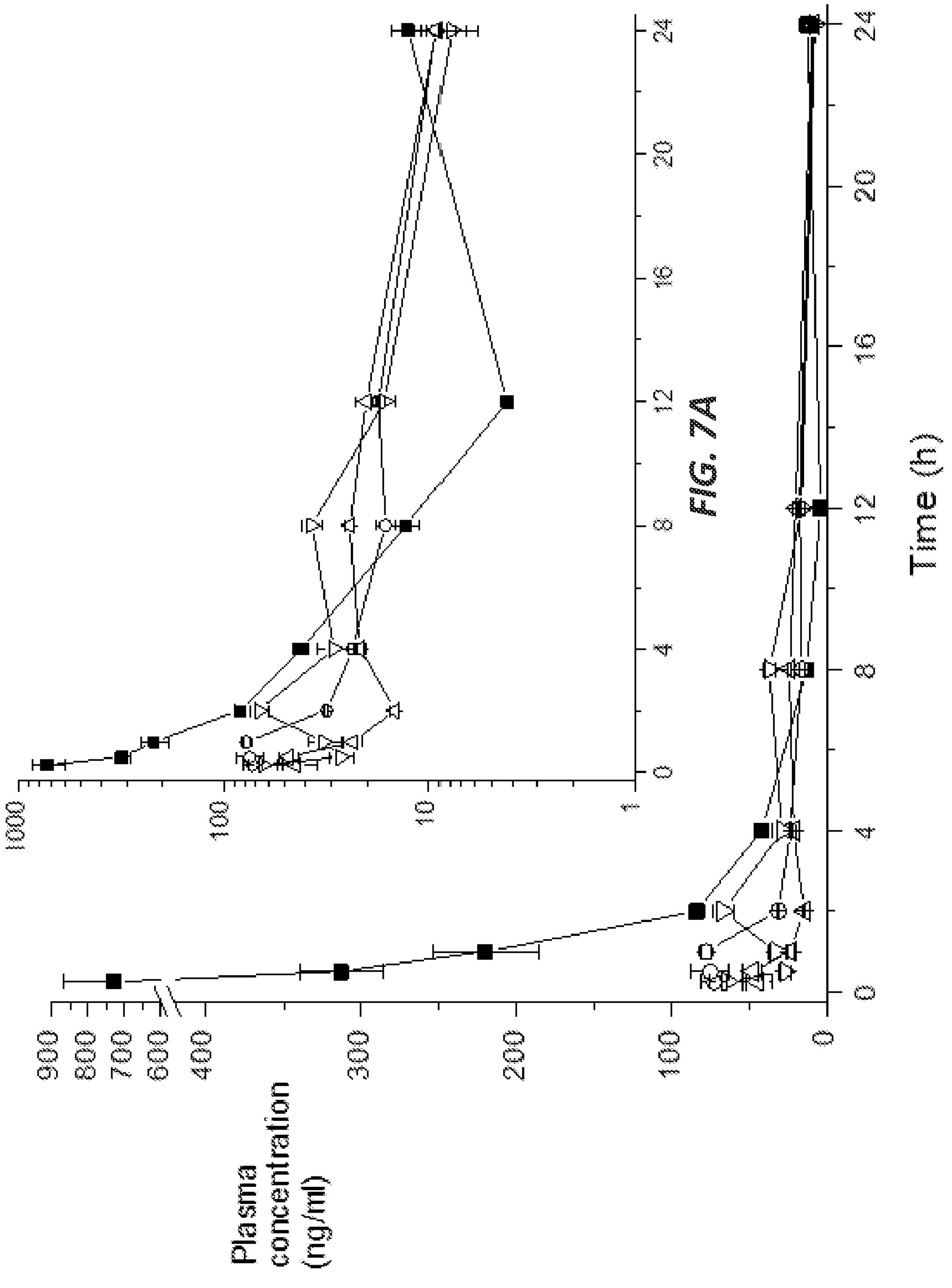

1000
100
10
1
0
4
8
12
16
20
24
Plasma concentration (ng/ml)
900
800
700
600
400
300
200
100
0
0
4
8
12
16
20
24
Time (h)

FIG. 7A

FIG. 7B

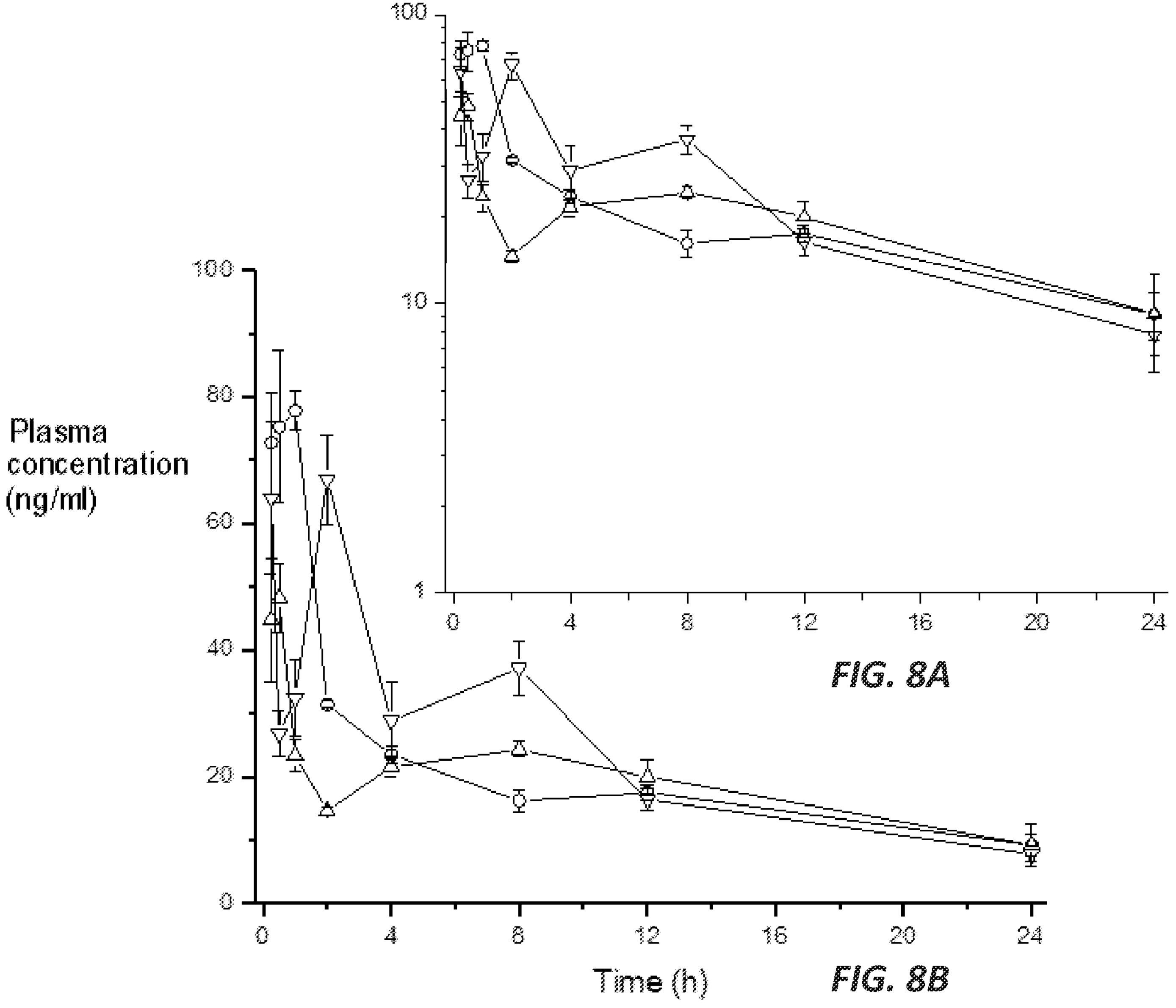

100
10
1
0
4
8
12
16
20
24
Plasma concentration (ng/ml)
100
80
60
40
20
0
0
4
8
12
16
20
24
Time (h)

FIG. 8A

FIG. 8B

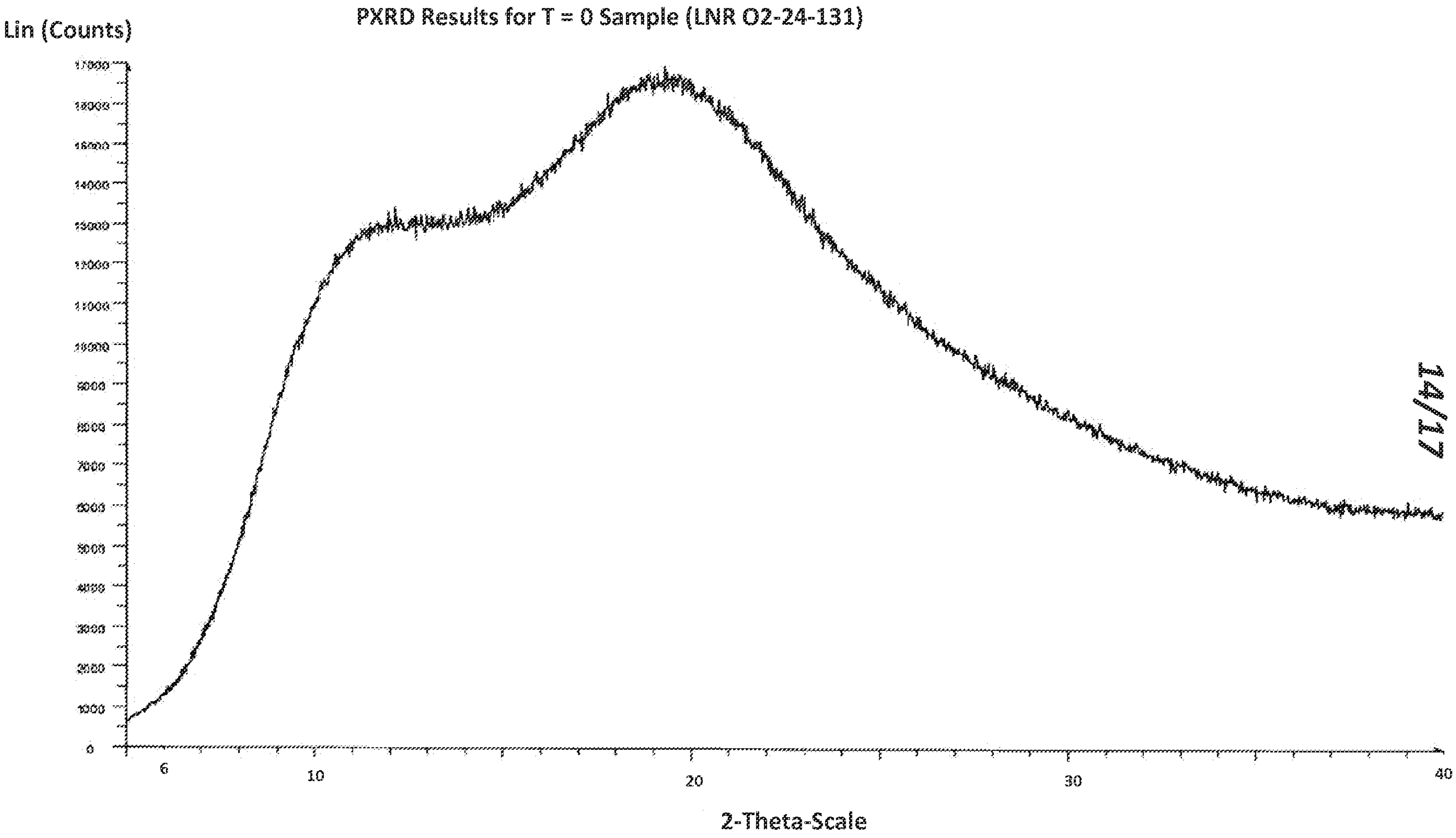

PXRD Results for T = 0 Sample (LNR O2-24-131)
Lin (Counts)
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
6
10
20
30
40
2-Theta-Scale

FIG. 9

PXRD Results for 1 month Stability Sample (LNR O2-41-73)

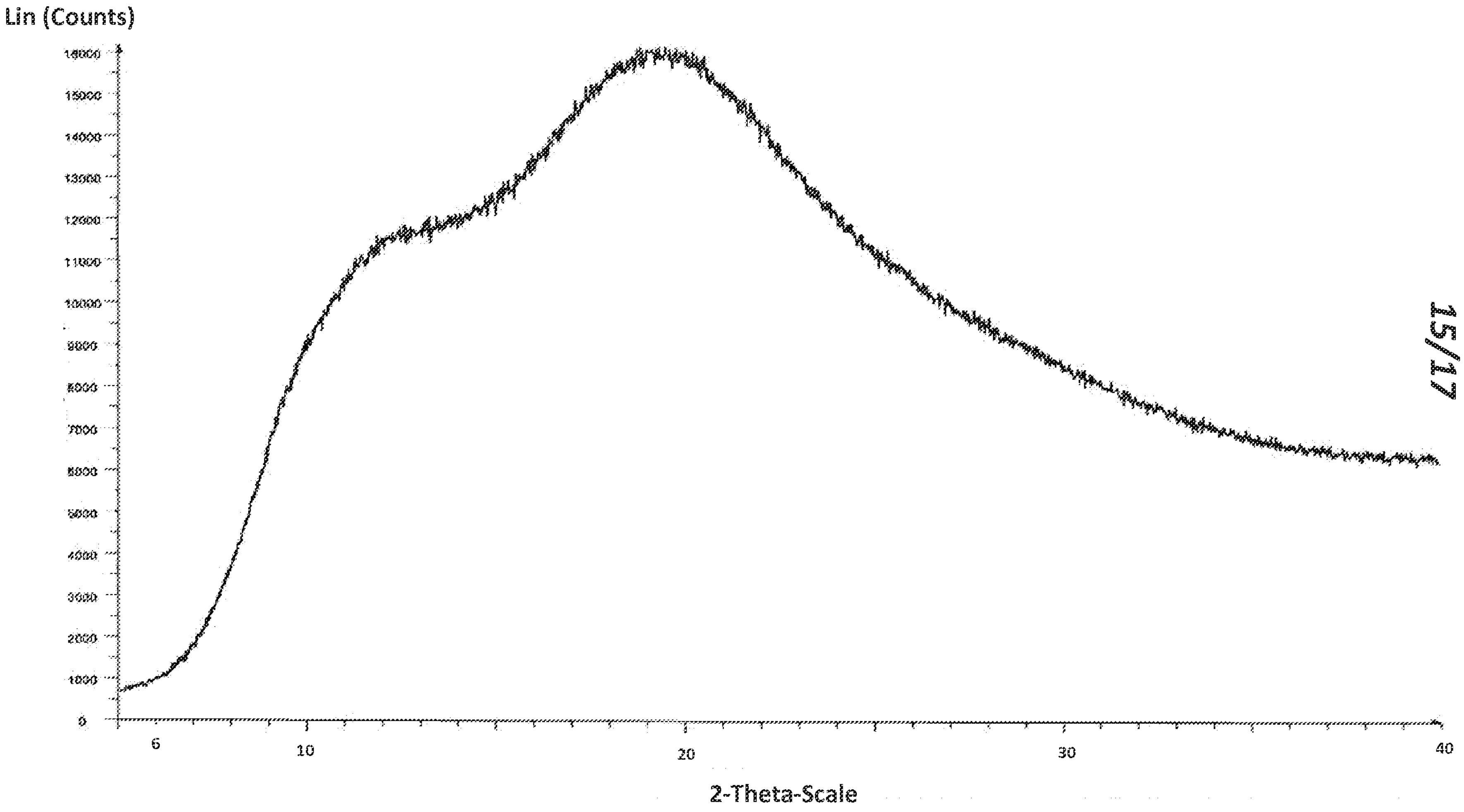


FIG. 10

PXRD Results for 2 month Stability Sample (LNR O2-37-107)

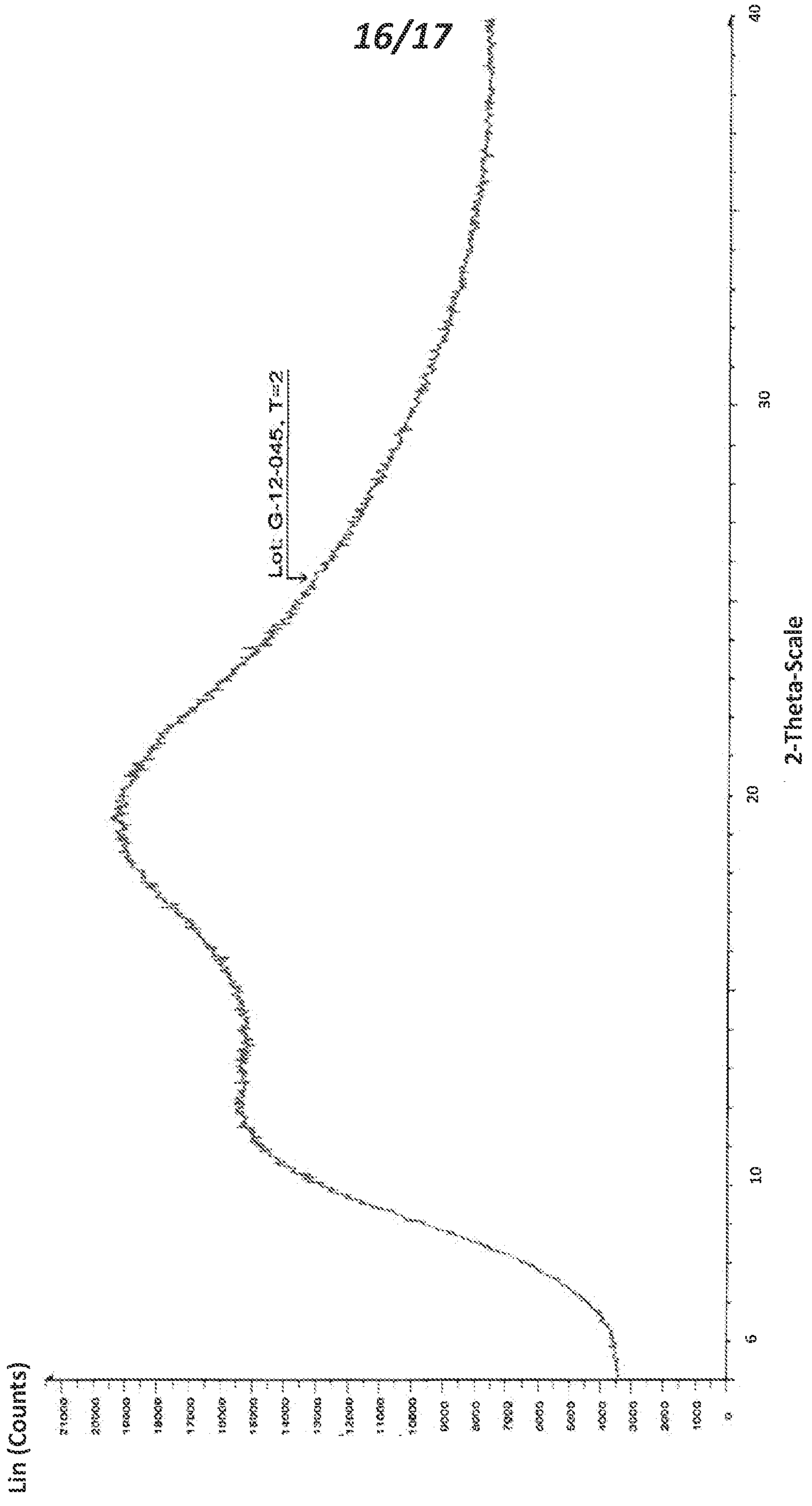


FIG. 11

PXRD Results for 3 month Stability Sample (LNR O2-37-120)

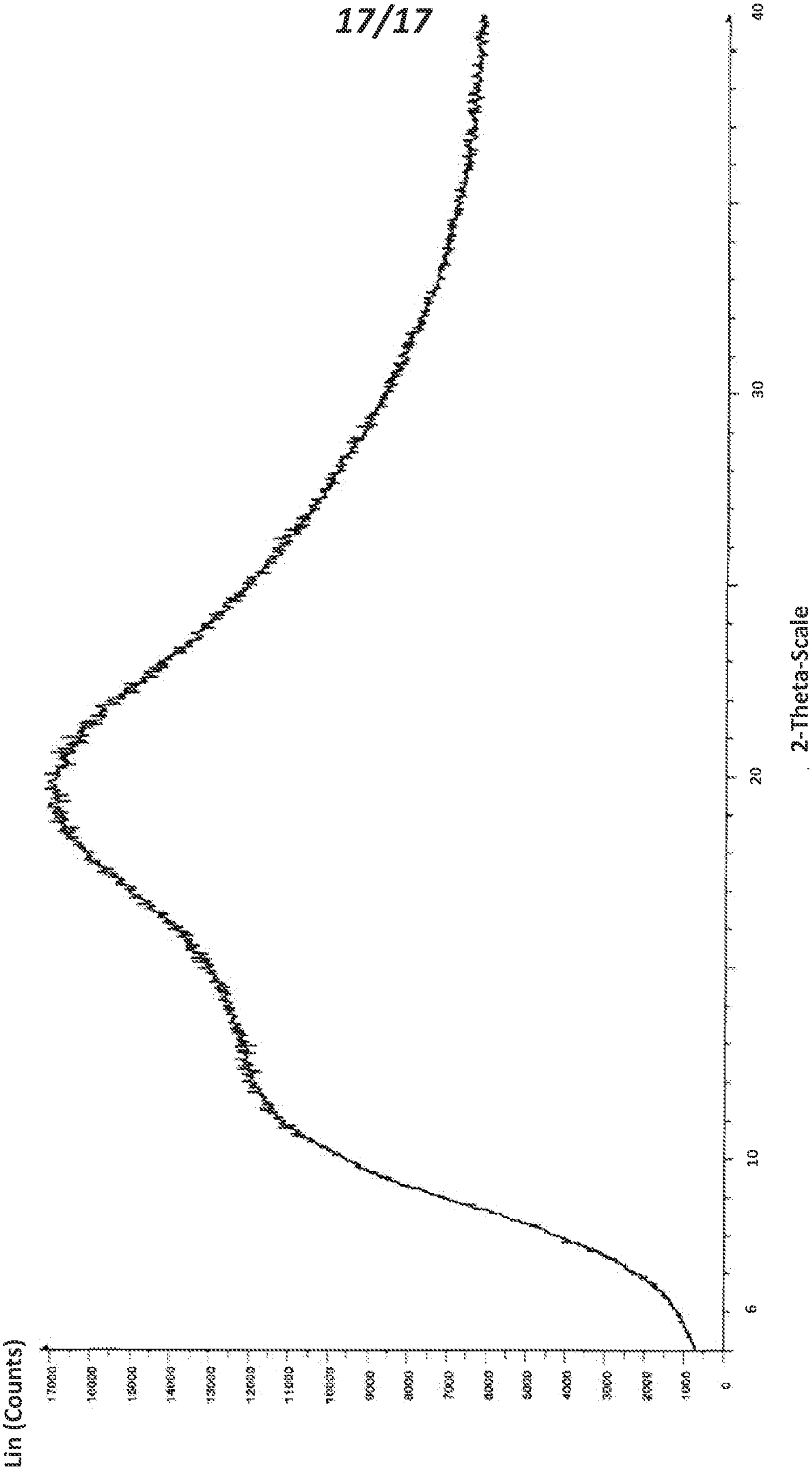


FIG. 12

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权利要求书3页　说明书34页　附图17页

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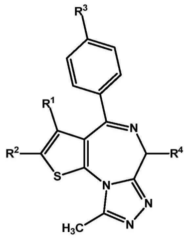
(54) 发明名称

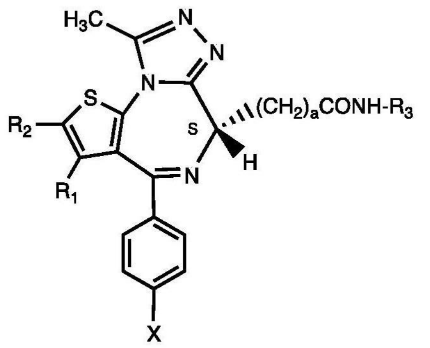
包含噻吩并三唑并二氮杂卓化合物的药物制剂

(57) 摘要

本发明提供一种固体分散体，包含：无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物、其药学可接受的盐或其水合物；以及药学可接受的聚合物：

(I) 其中X为卤素，R^1为C_1-C_4烷基，R^2为C_1-C_4烷基，a为1-4的整数，R^3为C_1-C_4烷基、C_1-C_4羟基烷基、C_1-C_4烷氧基、任选地具有一个或多个取代基的苯基、或者任选地具有一个或多个取代基的杂芳基。在一个实施方案中，所述的药学可接受的聚合物为HPMCAS。所述的固体分散体可以通过喷雾干燥来制备。

1.一种固体分散体，包含：无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物、其药学可接受的盐或其水合物；以及药学可接受的聚合物：



(I)

其中X为卤素，R_1为C_1-C_4烷基，R_2为C_1-C_4烷基，a为1-4的整数，R_3为C_1-C_4烷基、C_1-C_4羟基烷基、C_1-C_4烷氧基、任选地具有一个或多个取代基的苯基、或者任选地具有一个或多个取代基的杂芳基。

2.权利要求1所述的固体分散体，其中式(1)选自由如下化合物组成的组：(i)(S)-2-[4-(4-氯代苯基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,4]三唑并-[4,3-a][1,4]二氮杂卓-6-基]-N-(4-羟苯基)乙酰胺或其二水合物；(ii)甲基(S)-{4-(3’-氰基联苯-4-基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯；(iii)甲基(S)-{2,3,9-三甲基-4-(4-苯基氨基苯基)-6H-噻吩并[3,2-f][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯；以及(iv)甲基(S)-{2,3,9-三甲基-4-[4-(3-苯基丙酰氨基)苯基]-6H-噻吩并[3,2-f-][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯。

3.权利要求1所述的固体分散体，其中式(1)为(S)-2-[4-(4-氯代苯基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,4]三唑并-[4,3-a][1,4]二氮杂卓-6-基]-N-(4-羟苯基)乙酰胺。

4.根据权利要求1-3中任意一项所述的固体分散体，其中所述药学可接受的聚合物为醋酸羟丙基甲基纤维素琥珀酸酯。

5.权利要求4所述的固体分散体，其中所述固体分散体中噻吩并三唑并二氮杂卓化合物与醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)的重量比为1:3至1:1。

6.根据权利要求1-3中任意一项所述的固体分散体，其中所述药学可接受的聚合物为PVP。

7.权利要求6所述的固体分散体，其中所述固体分散体中噻吩并三唑并二氮杂卓化合物与PVP的重量比为1:3至1:1。

8.根据权利要求1-7中任意一项所述的固体分散体，其中所述固体分散体是通过喷雾干燥获得的。

9.根据权利要求4和5中任意一项所述的固体分散体，其中所述固体分散体在约130℃至约140℃范围内表现出单一的玻璃化转变温度(Tg)拐点。

10.根据权利要求9所述的固体分散体，其中所述固体分散体在40℃以及75％的相对湿度下暴露至少1个月。

11.根据权利要求10所述的固体分散体，其中在于40℃以及75％的相对湿度下暴露至

少 1 个月之后，所述噻吩并三唑并二氮杂卓化合物的浓度为经过所述暴露之前无定形噻吩并三唑并二氮杂卓化合物的浓度的至少 90％。

12. 根据权利要求 6 或 7 所述的固体分散体，其中所述固体分散体在约 175℃至约 185℃范围内表现出单一的玻璃化转变温度 (Tg) 拐点。

13. 根据权利要求 12 所述的固体分散体，其中所述固体分散体在 40℃以及 75％的相对湿度下暴露至少 1 个月。

14. 根据权利要求 13 所述的固体分散体，其中在于 40℃以及 75％的相对湿度下暴露至少 1 个月之后，所述噻吩并三唑并二氮杂卓化合物的浓度为经过所述暴露之前所述无定形噻吩并三唑并二氮杂卓化合物的浓度的至少 90％。

15. 根据权利要求 1-14 中任意一项所述的固体分散体，其中在所述固体分散体展示出的 X 射线粉末衍射图案中，基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

16. 根据权利要求 1-15 中任意一项所述的固体分散体，所述固体分散体产生的曲线下面积 (AUC) 值为经静脉给药的对照组合物产生的相应 AUC 值的至少 0.5 倍，其中所述对照组合物包含等价量的结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物。

17. 根据权利要求 1-15 中任意一项所述的固体分散体，其中，相比于不含聚合物的结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物在 pH 值为 5.0 至 7.0 的对照体外测试介质中的浓度，所述固体分散体在 pH 值为 5.0 至 7.0 的体外水性测试介质中提供的无定形噻吩并三唑并二氮杂卓化合物的浓度大至少 5 倍。

18. 根据权利要求 1-15 中任意一项所述的固体分散体，其中，相比于不含聚合物的结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物在 pH 值为 5.0 至 7.0 的体外测试介质中的浓度，由所述固体分散体在 pH 值为 1.0 至 2.0 的体外水性测试介质中得到的无定形噻吩并三唑并二氮杂卓化合物的浓度高至少 50％。

19. 根据权利要求 4 和 5 的任意一项所述的固体分散体，其中所述无定形的噻吩并三唑并二氮杂卓化合物的浓度比由下列固体分散体得到的式 (1) 所示的噻吩并三唑并二氮杂卓化合物的浓度高至少 50％，其中该固体分散体为由式 (1) 所示的噻吩并三唑并二氮杂卓化合物、以及选自由邻苯二甲酸羟丙基甲基纤维素酯和丙烯酸乙酯 - 甲基丙烯酸甲酯 - 三甲基铵乙基丙烯酸酯氯化物共聚物组成的组中的药学可接受的聚合物形成的，并且所述各固体分散体被放置在 pH 值为 1.0 至 2.0 的体外水性测试介质中。

20. 根据权利要求 6 和 7 中任意一项所述的固体分散体，其中所述无定形的式 (1) 所示的噻吩并三唑并二氮杂卓化合物的浓度比由下列固体分散体得到的式 (1) 所示的噻吩并三唑并二氮杂卓化合物的浓度高至少 50％，其中该固体分散体为由式 (1) 所示的噻吩并三唑并二氮杂卓化合物、以及选自由邻苯二甲酸羟丙基甲基纤维素酯和 Eudragit 组成的组中的药学可接受的聚合物形成的，并且所述各固体分散体被放置在 pH 值为 1.0 至 2.0 的体外水性测试介质中。

21. 一种药物制剂，其包含根据权利要求 1-20 中任意一项所述的固体分散体，以及一种或多种药学可接受的赋形剂，其中所述赋形剂选自由乳糖一水合物、微晶纤维素、交联羧甲基纤维素钠、胶体二氧化硅、硬脂酸镁及其组合所组成的组 ；其中所述药物制剂的堆密度范围为 0.55g/cc 至 0.60g/cc。

22.一种药物胶囊，其包含根据权利要求1-20中任意一项所述的固体分散体。

23.一种药片，其包含根据权利要求1-20中任意一项所述的固体分散体。

24.一种药物制剂，包含：10重量-15重量％的根据权利要求1-20中任意一项所述的固体分散体、45重量％-50重量％的乳糖一水合物、35重量％-40重量％的微晶纤维素、4重量％-6重量％的交联羧甲基纤维素钠、0.8重量％-1.5重量％的胶体二氧化硅和0.8重量％-1.5重量％的硬脂酸镁。

包含噻吩并三唑并二氮杂卓化合物的药物制剂

[0001]　相关申请的交叉引用

[0002]　本申请要求2012年9月28日提交的美国临时申请No.61/707,465、2013年3月14日提交的美国临时申请No.61/782,882、以及2013年6月6日提交的美国临时申请No.61/831,811的权益，所有这些申请的全文均以引用方式并入本文。

技术领域

[0003]　本申请公开描述了具有改善的溶解度和生物利用率的噻吩并三唑并二氮杂卓(thienotriazolodiazepine)化合物的固体分散体。

背景技术

[0004]　下文所述的式(1)的化合物已经显示出抑制乙酰化的组蛋白H4与包含串联的溴区结构域(BRD)的转录调控因子家族（称为BET（溴区结构域和特别终端）蛋白质，包括BRD2、BRD3和BRD4)的结合。参见美国专利申请公开No.2010/0286127 A1，其全文以引用方式并入本文。Denis,G.V.在“Bromodomain coactivators in cancer,obesity,type 2 diabetes,and inflammation,”Discov Med 2010；10:489-499（该文献的全部内容以引用方式并入本文）中报告了如下内容：BET蛋白质作为增殖和分化的主要的表观遗传调节子而出现，并且还与倾向于血脂障碍或脂肪生成调节不当、心血管病和2型糖尿病的炎症性质和风险升高、以及自体免疫疾病（例如类风湿性关节炎和系统性红斑狼疮）的易感性增加有关。因此，式(II)所示的化合物可以用于治疗多种癌症、心血管疾病、2型糖尿病和自体免疫病症（例如类风湿性关节炎和系统性红斑狼疮）。

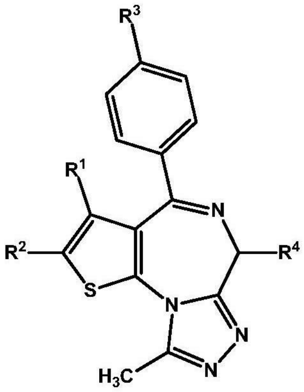
[0005]　下文所述的式(1)所示的噻吩并三唑并二氮杂卓化合物表现出与盖伦组合物的常规给药和制备有关的特定的困难，尤其包括药品生物利率以及患者间和患者内的剂量应答的差异性的特定问题，由此需要针对噻吩并三唑并二氮杂卓的实际非水溶性而研发出非常规的剂型。

[0006]　之前，如美国专利申请公开No.20090012064 A1中所报告（该文献的全部内容以引用方式并入本文)，已经发现式(1)的噻吩并三唑并二氮杂卓可以用载体丙烯酸乙酯-甲基丙烯酸甲酯-三甲基铵乙基丙烯酸酯氯化物(trimethylammonioethyl methacrylate chloride)的共聚物(Eudragit RS，由Rohm公司生产）配制，从而提供在下肠道中优先释放药物组分以用于治疗炎性肠病（溃疡性结肠炎和克罗恩病）的口服制剂。通过多个试验（包含动物测试），发现就炎性肠病而言，式(1)的噻吩并三唑并二氮杂卓化合物在病变中的释放以及其对炎性病变的直接作用比式(1)的噻吩并三唑并二氮杂卓化合物由胃肠道吸收至血液循环中更为重要。但是，对于许多其他的病症而言，则要求将式(1)的噻吩并三唑并二氮杂卓化合物由胃肠道高度吸收至血液循环中。因此，需要一种式(1)的噻吩并三唑并二氮杂卓化合物的制剂，该制剂可以使式(1)的噻吩并三唑并二氮杂卓化合物由胃肠道高度吸收至血液循环中。

[0007]　发明概述

[0008] 在一个实施方案中，本发明公开提供了固体分散体，包含：无定形的式（1）所示的噻吩并三唑并二氮杂卓化合物、其药学可接受的盐或其水合物；以及药学可接受的聚合物，其中式（1）为：

[0009]



[0010] 其中 X 为卤素，R^1为 C_1-C_4烷基，R^2为 C_1-C_4烷基，a 为 1-4 的整数，R^3为 C_1-C_4烷基、C_1-C_4羟基烷基、C_1-C_4烷氧基、任选地具有一个或多个取代基的苯基、或者任选地具有一个或多个取代基的杂芳基。

[0011] 在一个实施方案中，式（1）选自由如下化合物组成的组：(i)(S)-2-[4-(4-氯代苯基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,4]三唑并-[4,3-a][1,4]二氮杂卓-6-基]-N-(4-羟苯基)乙酰胺或它们的二水合物；(ii)甲基(S)-{4-(3'-氰基联苯-4-基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯；(iii)甲基(S)-{2,3,9-三甲基-4-(4-苯基氨基苯基)-6H-噻吩并[3,2-f][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯；以及(iv)甲基(S)-{2,3,9-三甲基-4-[4-(3-苯基丙酰氨基)苯基]-6H-噻吩并[3,2-f-][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯。在一个此类的实施方案中，式（1）为(S)-2-[4-(4-氯代苯基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,-4]三唑并[4,3-a][1,4]二氮杂卓-6-基]-N-(4-羟苯基)乙酰胺。

[0012] 在一些实施方案中，药学可接受的聚合物为醋酸羟丙基甲基纤维素琥珀酸酯。在一些此类的实施方案中，固体分散体中噻吩并三唑并二氮杂卓化合物与醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)的重量比为 1:3 至 1:1。在一些此类的实施方案中，固体分散体在约 130℃至约 140℃的范围内表现出单一的玻璃化转变温度(Tg)拐点。在一些此类的实施方案中，噻吩并三唑并二氮杂卓化合物在 40℃下、相对湿度为 75％的环境中暴露至少 1 个月后的浓度为无定形噻吩并三唑并二氮杂卓化合物在如此暴露之前的浓度的至少 90％。

[0013] 在其他的实施方案中，药学可接受的聚合物为 PVP。在一些此类的实施方案中，固体分散体中噻吩并三唑并二氮杂卓化合物与 PVP 的重量比为 1:3 至 1:1。在一些此类的实施方案中，固体分散体在约 175℃至约 185℃范围内表现出单一的玻璃化转变温度(Tg)拐点。在一些此类的实施方案中，噻吩并三唑并二氮杂卓化合物在 40℃下、相对湿度为 75％的环境下暴露至少 1 个月后的浓度为无定形噻吩并三唑并二氮杂卓化合物在如此暴露之前的浓度的至少 90％。

[0014] 在另一个实施方案中，固体分散体是通过喷雾干燥获得的。

[0015] 在另一个实施方案中，在固体分散体所展示出的 X 射线粉末衍射图案中，基本上

不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0016] 在另一个实施方案中，该固体分散体的曲线下面积(AUC)值为由静脉给药的对照组合物提供的相应AUC值的至少0.5倍，其中该对照组合物包含等价量的结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物。

[0017] 在又另一个实施方案中，相比于不含聚合物时结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物在pH值为5.0至7.0的对照体外测试介质中的浓度，所述固体分散体在pH值为5.0至7.0的体外水性测试介质中提供的无定形噻吩并三唑并二氮杂卓化合物的浓度大至少5倍。

[0018] 在另一个实施方案中，相比于不含聚合物时结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物在pH值为5.0至7.0的体外测试介质中的浓度，由所述固体分散体在pH值为1.0至2.0的体外水性测试介质中得到的无定形噻吩并三唑并二氮杂卓化合物的浓度高至少50％。

[0019] 在一个实施方案中，无定形噻吩并三唑并二氮杂卓化合物的浓度比由下列固体分散体得到的式(1)所示的噻吩并三唑并二氮杂卓化合物的浓度高至少50％，其中该固体分散体为由式(1)所示的噻吩并三唑并二氮杂卓化合物和药学可接受的聚合物形成的，该药学可接受的聚合物选自由邻苯二甲酸羟丙基甲基纤维素酯和丙烯酸乙酯-甲基丙烯酸甲酯-三甲基铵乙基丙烯酸酯氯化物共聚物构成的组，并且其中各固体分散体均置于pH值为1.0至2.0的体外水性测试介质中。

[0020] 在一个实施方案中，所述无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物的浓度比由下列固体分散体得到的式(1)所示的噻吩并三唑并二氮杂卓化合物的浓度高至少50％，其中该固体分散体为由式(1)所示的噻吩并三唑并二氮杂卓化合物和药学可接受的聚合物形成的，该药学可接受的聚合物选自由邻苯二甲酸羟丙基甲基纤维素酯和丙烯酸乙酯-甲基丙烯酸甲酯-三甲基铵乙基丙烯酸酯氯化物共聚物构成的组，并且其中各固体分散体均置于pH值为1.0至2.0的体外水性测试介质中。

[0021] 本发明公开进一步提供了药物制剂，其包含本文所述的喷雾干燥的固体分散体以及选自下组中的一种或多种药学可接受的赋形剂：乳糖一水合物；微晶纤维素；交联羧甲基纤维素钠；胶体二氧化硅；硬脂酸镁；和它们的组合。在一些实施方案中，药物制剂的堆密度范围为0.55g/cc至0.60g/cc。在一些实施方案中，药物形式可以为药物胶囊。在一些实施方案中，药物形式可以为药片。

[0022] 本发明公开进一步提供了药物制剂，其包含：10重量％-15重量％的本文所述的喷雾干燥的固体分散体和醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)，其中所述噻吩并三唑并二氮杂卓化合物在分散体中是无定形的，并且噻吩并三唑并二氮杂卓化合物与醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)的重量比为1:3至1:1；45重量％-50重量％的乳糖一水合物；35重量％-40重量％的微晶纤维素；4重量％-6重量％的交联羧甲基纤维素钠；0.8重量％-1.5重量％的胶体二氧化硅；和0.8重量％-1.5重量％的硬脂酸镁。

[0023] 附图简述

[0024] 当参照示例性实施方案的附图来阅读时，将会更好地理解前面的发明概述以及如下的本发明包含噻吩并三唑并二氮杂卓制剂的药物组合物和方法的实施方案的详述。但是，应该理解的是本发明不限于所示的精确的安排和手段。

[0025] 在附图中：

[0026] 图 1A 示出了包含固体分散体的比较制剂的溶解图，其中所述的固体分散体包含 25％的化合物（1-1）和 Eudragit L100-55；

[0027] 图 1B 示出了包含固体分散体的比较制剂的溶解图，其中所述的固体分散体包含 50％的化合物（1-1）和 Eudragit L100-55；

[0028] 图 1C 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 25％的化合物（1-1）和聚乙烯吡咯烷酮（PVP）；

[0029] 图 1D 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 50％的化合物（1-1）和 PVP；

[0030] 图 1E 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 25％的化合物（1-1）和 PVP- 乙酸乙烯酯（PVP-VA）；

[0031] 图 1F 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 50％的化合物（1-1）和 PVP-VA；

[0032] 图 1G 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 25％的化合物（1-1）和醋酸羟丙基甲基纤维素琥珀酸酯（HPMCAS-M）；

[0033] 图 1H 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 50％的化合物（1-1）和 HPMCAS-M；

[0034] 图 1I 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 25％的化合物（1-1）和邻苯二甲酸羟丙基甲基纤维素酯（HPMCP-HP55）；

[0035] 图 1J 示出了包含固体分散体的示例性制剂的溶解图，其中所述的固体分散体包含 50％的化合物（1-1）和 HPMCP-HP55；

[0036] 图 2A 示出了示例性制剂的体内筛选结果，该示例性制剂包含 25％的化合物（1-1）和 PVP 的固体分散体；

[0037] 图 2B 示出了示例性制剂的体内筛选结果，该示例性制剂包含 25％的化合物（1-1）和 HPMCAS-M 的固体分散体；

[0038] 图 2C 示出了示例性制剂的体内筛选结果，该示例性制剂包含 50％的化合物（1-1）和 HPMCAS-M 的固体分散体；

[0039] 图 3 示出了化合物（1-1）的固体分散体的 X 射线粉末衍射图谱；

[0040] 图 4A 示出了更改的差示扫描量热示踪线，其用于在环境条件下平衡的 25％化合物（1-1）和 PVP 的固体分散体；

[0041] 图 4B 示出了更改的差示扫描量热示踪线，其用于在环境条件下平衡的 25％化合物（1-1）和 HPMCAS-M 的固体分散体；

[0042] 图 4C 示出了更改的差示扫描量热示踪线，其用于在环境条件下平衡的 50％化合物（1-1）和 HPMCAS-M 的固体分散体；

[0043] 图 5 示出了对于 25％的化合物（1-1）和 PVP 或 HPMCAS-M 的固体分散体、以及 50％的化合物（1-1）和 HPMCAS-MG 的固体分散体，其玻璃化转变温度（Tg）与相对湿度（RH）的关系图；

[0044] 图 6 示出了更改的差示扫描量热示踪线，其用于 75％相对湿度下平衡的 25％化合物（1-1）和 PVP 的固体分散体；

[0045] 图7示出了血浆浓度与时间的关系曲线，其用于1mg/kg静脉定量给药后的化合物(1-1)（实心长方形）、3mg/kg口服定量给药的25％化合物(1-1):PVP（空心圆圈）、25％化合物(1-1):HPMCAS-MG（空心三角形）和50％化合物(1-1):HPMCAS-MG（空心的倒三角）。插图描绘了在半对数标度上绘出的相同的数据；

[0046] 图8示出了血浆浓度与时间的关系曲线，其用于以25％化合物(1-1):PVP（空心圆圈）、25％化合物(1-1):HPMCAS-MG（空心三角形）和50％化合物(1-1):HPMCAS-MG（空心的倒三角）形式在3mg/kg口服定量给药后的化合物(1-1)。插图描绘了在半对数标度上绘出的相同的数据；

[0047] 图9示出了在稳定性测试的0时，化合物(1-1)和HPMCAS-MG的固体分散体的X射线粉末衍射图谱；

[0048] 图10示出了在40℃和相对湿度75％的环境下暴露1个月后，化合物(1-1)在HPMCAS-MG中的固体分散体的X射线粉末衍射图谱；

[0049] 图11示出了在40℃和相对湿度75％的环境下暴露2个月后，化合物(1-1)在HPMCAS-MG中的固体分散体的X射线粉末衍射图谱；

[0050] 图12示出了在40℃和相对湿度75％的环境下暴露3个月后，化合物(1-1)在HPMCAS-MG中的固体分散体的X射线粉末衍射图谱。

[0051] 发明详述

[0052] 现在，下文将参照附图和实施例来更全面地描述本发明的主题，其中示出了代表性的实施方案。但是，本发明的主题可以以不同的形式体现，并且不应该解释成局限于本发明列出的实施方案。而是，描述这些实施方案并使本领域的任一技术人员能够实施。除非另作说明，否则本发明所用的所有技术和科学术语都具有所述主题所属技术领域的任一普通技术人员通常所理解的相同的含义。本发明中提及的所有公开、专利申请、专利和其他参考文献均以引用方式全文并入本文。

[0053] I. 定义

[0054] 本文所用的术语“烷基”是指饱和的直链或支链烃。

[0055] 术语“取代的烷基”是指具有一个或多个取代基的烷基部分，其中所述的取代基替代了烃主链上的氢或者一个或多个碳。

[0056] 无论术语“烯基”是单独使用还是作为取代基的一部分（例如“C_{1-4}烯基（芳基）”）使用，其是指具有至少一个碳-碳双键的部分不饱和支链或直链一价烃基团，其中所述的双键是通过由母体烷基分子的2个相邻碳原子的每个碳原子上除去一个氢原子而得到的，并且所述基团是通过由一个碳原子上除去一个氢原子而得到的。原子可以在双键周围以顺式(Z)或反式(E)构象来排布。典型的烯基基团包括但不限于乙烯基、丙烯基、烯丙基(2-丙烯基)、丁烯基等。其实例包括C_{2-8}烯基或C_{2-4}烯基。

[0057] 术语“$C_{(j-k)}$”（其中j和k为整数，其是指碳原子的指定数量）是指烷基、烯基、炔基、烷氧基或环烷基基团，或者指基团中的烷基部分，其中，烷基以前置代号的脚注来显示，包含j至k个碳原子（包含端值）。例如$C_{(1-4)}$表示包含1、2、3或4个碳原子的基团。

[0058] 如本文所用，术语“卤代”或“卤素”是指F、Cl、Br或I。

[0059] 术语“药学可接受的盐”是本领域公认的，并且是指化合物的相对无毒性的无机酸和有机酸加成盐、或者无机碱或有机碱加成盐，包括（例如）在本发明的组合物中所包含的

那些。

[0060] 如本文所用，术语“固体分散体”是指一组固体产物，其由至少 2 种不同的成分组成，通常为亲水性载体和疏水性药品（活性组分）。

[0061] 术语“手性的”是本领域公认的，并且是指具有镜像对应部分的非重叠性性质的分子，而术语“非手性”是指可重叠在它们的镜像对应部分上的分子。“前手性分子”是指在特定的过程中具有转化成手性分子的潜力的分子。

[0062] 符号“⎓”用于表示键，其可以是单键、双键或三键。

[0063] 如本文所用，术语“对映异构体”和用于描绘对映异构体的结构式是包含“纯的”对映异构体，其不包含光学异构体以及对映异构体及其光学异构体的混合物，其中对映异构体以对映异构体过量而存在，例如至少 10％，25％，50％，75％，90％，95％，98％或 99％对映异构体过量。

[0064] 当术语“立体异构体”在本文中使用时，由所有的几何异构体、对映异构体或非对映异构体组成。本发明涵盖了这些化合物和它们的混合物的多种立体异构体。此外，所公开的化合物的构象异构体和旋转异构体也被考虑在内。

[0065] 如本文所用，术语“立体选择合成”是指化学或酶反应，其中单一的反应物在建立新的立构中心的过程中或者在转化现有的立构中心的过程中形成了立体异构体的不均匀的混合物，并且这些反应是本领域公知的。立体选择合成涵盖了对映选择性和非对映选择性的转化。例如参见 Carreira，E.M.and Kvaerno，L.，Classics in Stereoselective Synthesis，Wiley-VCH:Weinheim，2009。

[0066] 术语“喷雾干燥”是指其中涉及将供料悬液或溶液雾化成小滴并在处理室（其中具有用于蒸发的强驱动力，例如热干气、部分真空或它们的组合）中快速除去混合物中的溶剂的工艺。

[0067] 如本文所用，术语“治疗有效量”是指本发明的噻吩并三唑并二氮杂卓或者任何其他药物活性试剂的任何量，与未接受此量的噻吩并三唑并二氮杂卓或其他药物活性试剂的相应患者相比，所述的量的噻吩并三唑并二氮杂卓或其他药物活性试剂会改善性地治疗、治愈、预防或减轻疾病紊乱或副作用，或者降低疾病或紊乱的进展的速率。

[0068] 术语“约”是指 +/-10％。

[0069] 在本申请及随附的权利要求书的全文中，除非上下文必须另外说明，否则词语“包括”或其变体（例如“包含”或“包含有”）都应该解释为包括所述的整数或步骤、或者一组整数或步骤，并且排除了任何其他的整数或步骤、或者一组整数或步骤。

[0070] 目前已经发现，下文所述的式 (1) 的噻吩并三唑并二氮杂卓化合物可以与药学可接受的聚合物一同配制为固体分散体，从而提供可以使药物组分由胃肠道高度地吸收至血液循环中的口服制剂。在一个实施方案中，药学可接受的盐为醋酸琥珀酸酯羟丙基甲基纤维素（也称为醋酸羟丙基甲基纤维素琥珀酸酯或 HPMCAS)。在一个实施方案中，药学可接受的聚合物为聚乙烯吡咯烷酮 (PVP)。

[0071] 在一些实施方案中，醋酸羟丙基甲基纤维素琥珀酸酯 (HPMCAS) 可以包括：具有 9％乙酰基 /11％琥珀酰基的 M 级（例如，具有平均粒径为 5μm 的 HPMCAS（即 HPMCAS-MF，细粉级）或者具有平均粒径为 1mm 的 HPMCAS（即 HPMCAS-MG，颗粒级））；具有 12％乙酰基 /6％琥珀酰基的 H 级（例如，具有平均粒径为 5μm 的 HPMCAS（即 HPMCAS-HF，细粉级）或者

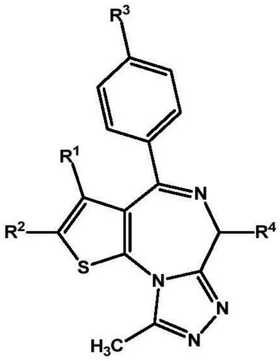
具有平均粒径为1mm的HPMCAS(即HPMCAS-HG,颗粒级));和具有8%乙酰基/15%琥珀酰基的L级(例如,具有平均粒径为5μm的HPMCAS(即HPMCAS-LF,细粉级)或者具有平均粒径为1mm的HPMCAS(即HPMCAS-LG,颗粒级))。

[0072] 在一些实施方案中,聚乙烯吡咯烷酮的分子量可以为约2,500(Kollidon® 12 PF,重均分子量为2,000至3,000)、约9,000(Kollidon® 17 PF,重均分子量为7,000至11,000)、约25,000(Kollidon® 25,重均分子量为28,000至34,000)、约50,000(Kollidon® 30,重均分子量为44,000至54,000)、和约1,250,000(Kollidon® 90或Kollidon® 90F,重均分子量为1,000,000至1,500,000)。

[0073] II. 噻吩并三唑并二氮杂卓化合物:

[0074] 在一个实施方案中,在本发明的制剂中使用的噻吩并三唑并二氮杂卓化合物由式(1)表示(包括其任意的盐、异构体、对映异构体、外消旋物、水合物、溶剂化物、代谢物和多形体):

[0075]



(1)

[0076] 其中:

[0077] R^1为碳数为1-4的烷基;R^2为氢原子、卤素原子或碳数为1-4且任选地被卤素原子或羟基取代的烷基;R^3为卤素原子、任选地被卤素原子取代的苯基、碳数为1-4的烷基、碳数量为1-4的烷氧基、氰基、$—NR^5—(CH_2)_m—R^6$(其中R^5为氢原子或碳数为1-4的烷基,m为0-4的整数,并且R^6为任选地被卤素原子取代的苯基或者吡啶基)、或者$-NR^7—CO—(CH_2)_n—R^8$(其中R^7为氢原子或碳数为1-4的烷基,n为0-2的整数,并且R^8为任选地被卤素原子取代的苯基或者吡啶基);并且R^4为$—(CH_2)_a—CO—NH—R^9$(其中a为1-4的整数,并且R^9为碳数为1-4的烷基),碳数为1-4的羟烷基,碳数量为1-4的烷氧基,或者任选地被碳数为1-4的烷基、碳数为1-4的烷氧基、氨基或羟基取代的苯基或吡啶基,或者$—(CH_2)_b—COOR^{10}$(其中b为1-4的整数,R^{10}为碳数为1-4的烷基)。

[0078] 在一个实施方案中,合适的烷基包括含有1个碳原子至4个碳原子的线性或支链烷基基团。在一个实施方案中,合适的烷基包括含有1个碳原子至3个碳原子的线性或支链烷基基团。在一个实施方案中,合适的烷基包括含有1个碳原子至2个碳原子的线性或支链烷基基团。在一个实施方案中,示例性的烷基基团包括但不限于甲基、乙基、丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基。在一个实施方案中,示例性的烷基包括但不限于甲基、乙基、丙基、异丙基、2-甲基-1-丙基、和2-甲基-2-丙基。

[0079] 在一些实施方案中,本发明提供了本发明所述的噻吩并三唑并二氮杂卓化合物的药学可接受的盐、溶剂化物(包括水合物)和同位素标记的形式。在一个实施方案中,噻吩

并三唑并二氮杂卓化合物的药学可接受的盐包括与无机酸形成的酸加成盐。在一个实施方案中，噻吩并三唑并二氮杂卓的药学可接受的无机酸加成盐包括盐酸、氢溴酸、氢碘酸、磷酸、偏磷酸、硝酸和硫酸的盐。在一个实施方案中，噻吩并三唑并二氮杂卓化合物的药学可接受的盐包含与有机酸形式的酸加成盐。在一个实施方案中，噻吩并三唑并二氮杂卓化合物的药学可接受的有机酸加成盐包括酒石酸、乙酸、三氟乙酸、柠檬酸、苹果酸、乳酸、富马酸、苯甲酸、甲酸、丙酸、乙醇酸、葡萄糖酸、马来酸、琥珀酸、樟脑磺酸、异硫碳酸、粘液酸、龙胆酸、异烟酸、葡萄糖二酸、葡萄糖醛酸、糠酸、谷氨酸、抗坏血酸、氨茴酸、水杨酸、苯乙酸、扁桃酸、帕莫酸（扑酸）、甲磺酸、乙磺酸、泛酸、硬脂酸、磺胺酸、褐藻酸、半乳糖醛酸和芳基磺酸（例如苯磺酸和4-甲基苯磺酸）的盐。

[0080] 本发明提供了本发明所述的噻吩并三唑并二氮杂卓化合物的药学可接受的同位素标记形式，其中一个或多个原子被原子数相同、但是原子质量或质量数与天然常见的原子质量或质量数不同的原子所替代。适于包含在噻吩并三唑并二氮杂卓化合物中的同位素的实例包括以下元素的同位素：氢，例如 ^{2}H 和 ^{3}H；碳，例如 ^{11}C、^{13}C 和 ^{14}C；氯，例如 ^{36}Cl；氟，例如 ^{18}F；碘，例如 ^{123}I 和 ^{125}I；氮，例如 ^{13}N 和 ^{15}N；氧，例如 ^{15}O、^{17}O 和 ^{18}O；以及硫，例如 ^{35}S。噻吩并三唑并二氮杂卓化合物的同位素标记形式通常可以通过本领域那些技术人员已知的常规技术来制备。

[0081] 式(1)所示化合物的某些同位素标记形式（例如引入了放射性同位素的那些）可用于药品和/或底物的组织分布研究中。由于放射性同位素氚(^{3}H)和碳-14(^{14}C)易于引入和即时的检测手段，所以它们特别适用于上述目的。使用较重的同位素（例如氘(^{2}H)）进行取代可以提供由于更高的代谢稳定性而产生的某些治疗益处，例如体内半衰期增长或者剂量需求降低，因此，在一些环境中可以是优选的。使用发射正电子的同位素（例如 ^{11}C、^{18}F、^{15}O 和 ^{13}N）进行取代可以用于正电子成像术研究(PET)中，以用于检测底物受体的占用。

[0082] 在一些实施方案中，本发明公开的噻吩并三唑并二氮杂卓化合物可以与药学可接受的溶剂形成溶剂化以及非溶剂化的形式存在。本领域的技术人员应该理解的是，溶剂化物为溶质（在这种情况下为本发明所述的噻吩并三唑并二氮杂卓化合物）和溶剂形成的化学计量可变的复合物。优选的是此类溶剂不会干扰溶质（所述的噻吩并三唑并二氮杂卓化合物）的生物活性。用于形成溶剂化物的合适溶剂的实例包括但不限于水、甲醇、二甲基亚砜、乙醇和乙酸。所用的合适的溶剂为药学可接受的溶剂。合适的是，所用的溶剂为水。在一个实施方案中，本发明所述的噻吩并三唑并二氮杂卓化合物的药学可接受的溶剂化物包括乙醇溶剂化物、异丙醇溶剂化物、二氧戊烷溶剂化物、四氢呋喃溶剂化物、二甲基亚砜溶剂化物、叔丁醇溶剂化物、2-丁醇溶剂化物、二氧戊烷溶剂化物、1,3-二甲基-3,4,5,6-四氢-2(1H)-嘧啶酮（“DMPU”）溶剂化物、1,3-二甲基咪唑啉酮（“DMI”）溶剂化物、和1,3-二甲基咪唑啉酮（“DMP”）溶剂化物、或它们的混合物。

[0083] 在一些实施方案中，本发明所述的噻吩并三唑并二氮杂卓化合物可以包含一个或多个手性中心和/或双键，因此可以以几何异构体、对映异构体或非对映异构体的形式存在。可以根据Cahn-Ingold-Prelog规则来命名噻吩并三唑并二氮杂卓化合物的对映异构体和非对映异构体，所述的规则将“R”或“S”描述符号指定给每个立构中心（通常也称为手性中心），并将E或Z描述符号指定给每个碳-碳双键（以命名几何异构体），这样可以通过在系统名中包含描述符号而独特地描述整个分子的构造。

[0084] 在一些实施方案中，本发明所述的噻吩并三唑并二氮杂卓化合物可以以外消旋混合物或外消旋物的形式存在，其可以包含手性分子的等量的左旋和右旋对映异构体。可以通过前缀（±）- 或 dl- 来表示此类外消旋混合物，表明右旋和左旋异构体的相等（1:1）的混合物。此外，前缀 rac-（或 racem-）或符号 RS 和 SR 可以用于命名外消旋混合物。

[0085] 此外，由取代基围绕碳 - 碳双键的排列或者取代基围绕环烷基或杂环的排列而产生的几何异构体也可以存在于本发明的化合物中。在一些实施方案中，符号$\overline{-\!-\!-\!-}$可以用于表示可以为单键、双键或三键的键。围绕碳 - 碳双键的取代基可以命名为呈“Z”或“E”构型，其中术语“Z”和“E”根据 IUPAC 标准使用。除非另作说明，否则描述双键的结构涵盖了“Z”和“E”异构体。围绕碳 - 碳双键的取代基也可以称为“顺式（cis）”或“反式（trans）”，其中“顺式”表示取代基在双键的同侧上，而“反式”表示取代基在双键的对侧上。取代基围绕碳环的排列还可以命名为“顺式”或“反式”。术语“顺式”表示取代基在环的平面的同侧上，而术语“反式”表示取代基在环的平面的对侧上。其中取代基置于环的平面的同侧和对侧上的化合物所形成的混合物命名为“顺式 / 反式”或“Z/E”。

[0086] 在一些实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物可以以单晶或多晶形式或多型物存在。在一个实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物包含其无定形形式。在一个实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物包含其单一多晶型。在另一个实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物包含其多晶型的混合物。在另一个实施方案中，所述的化合物为结晶形式。

[0087] 在一些实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物可以以单一对映异构体或者对映异构体富集形式存在。在一个实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物以对映异构体过量百分比超过 80％的形式存在。在一个实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物以对映异构体过量百分比超过 90％的形式存在。在一个实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物以对映异构体过量百分比超过 98％的形式存在。在一个实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物以对映异构体过量百分比超过 99％的形式存在。在一些实施方案中，本发明所公开的噻吩并三唑并二氮杂卓化合物以选自由至少 10％、至少 25％、至少 50％、至少 75％、至少 90％、至少 95％、至少 98％和至少 99％所组成的组中的对映异构体过量百分比的形式存在。

[0088] 对于对映异构体对而言，可以使用以下等式（等式（1））来计算对映异构体 E1 相对于对映异构体 E2 的对映异构体过量百分比：

[0089]

$$\text{对映异构体E1的过量百分比}\ \% = \frac{(E1\text{-}E2)\times 100\%}{(E1+E2)}$$

[0090] 等式（1）

[0091] 可以通过手性高效液相色谱（HPLC）、核磁共振（NMR）或任何其他合适的方法来测定 E1 和 E2 的相对量。在一些实施方案中，对映异构体化合物的纯度可以指对映异构体 E1 和 E2 相对于其他材料的量，这些其他材料特别包括副产物和 / 或未反应的反应物或试剂。

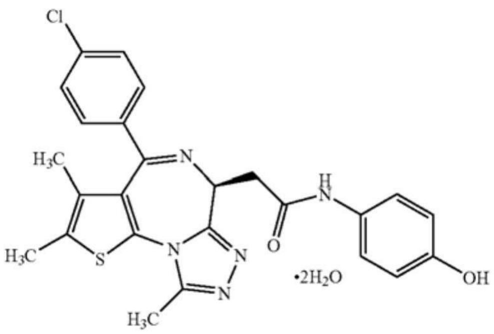
[0092] 在一些实施方案中，式（1）所示的噻吩并三唑并二氮杂卓化合物包括但不限于噻

吩并三唑并二氮杂卓化合物（1-1）至（1-18），其列于下表 A 中。

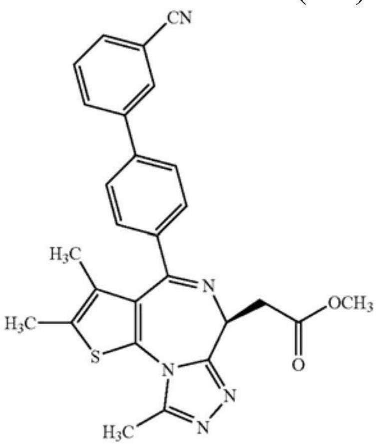
[0093]　表 A：可以用于本发明所述的制剂中的示例性化合物：

[0094]

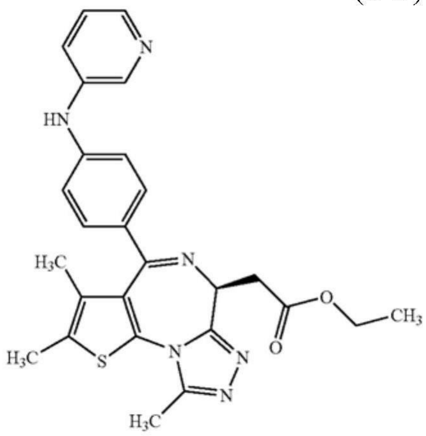
(1-1)



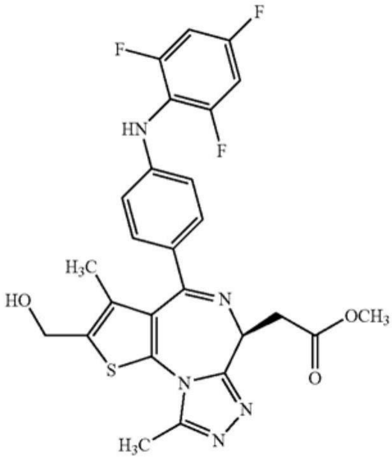
(1-2)



(1-3)



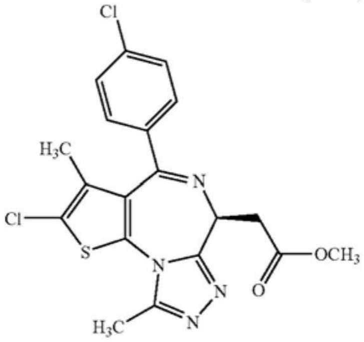
(1-4)



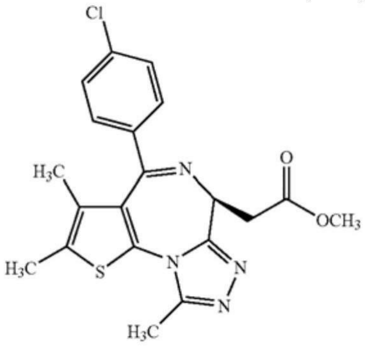
[0095]　表 A（接上表）：

[0096]

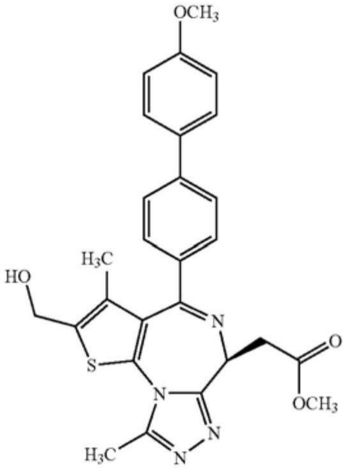
(1-5)



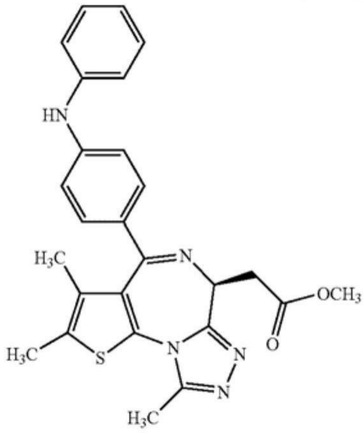
(1-6)



(1-7)



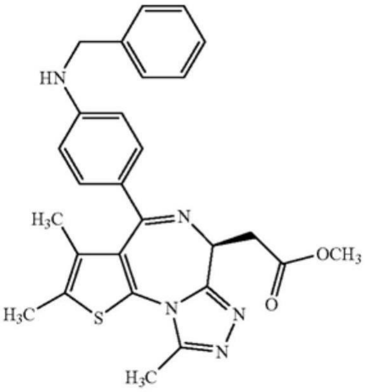
(1-8)



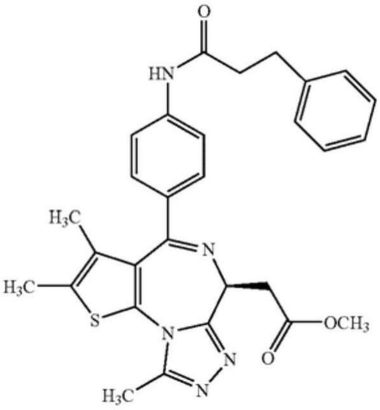
[0097] 表 A（接上表）：

[0098]

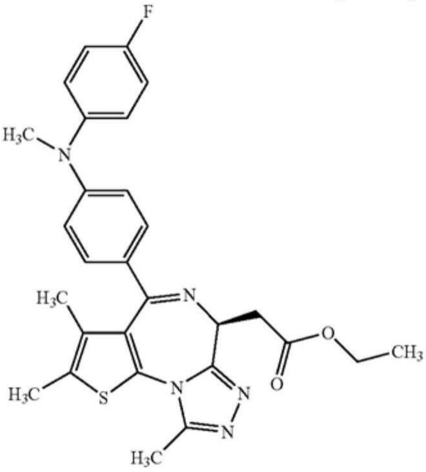
(1-9)



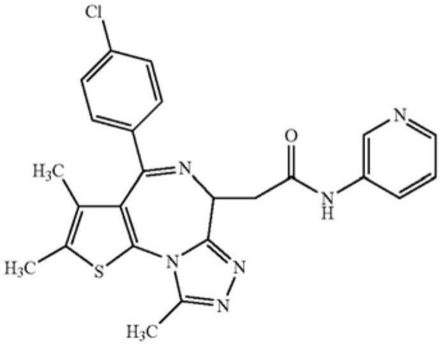
(1-10)



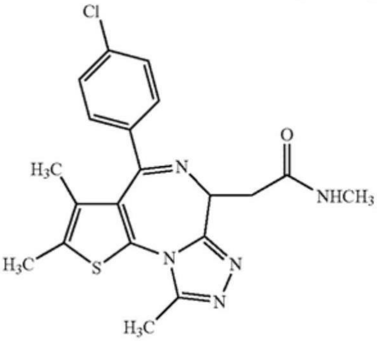
(1-11)



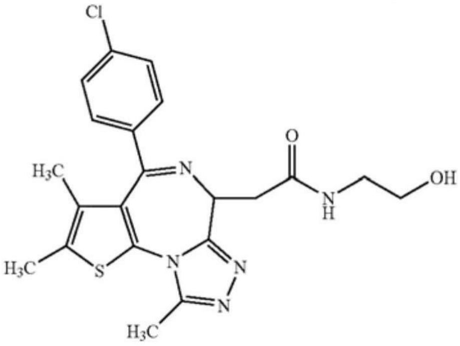
(1-12)



(1-13)



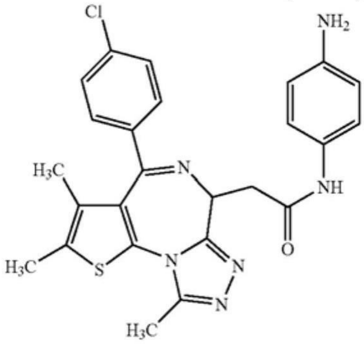
(1-15



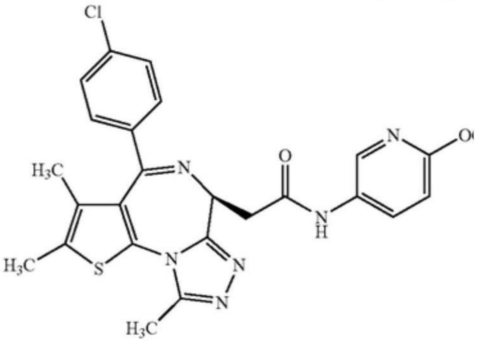
[0099] 表 A（接上表）：

[0100]

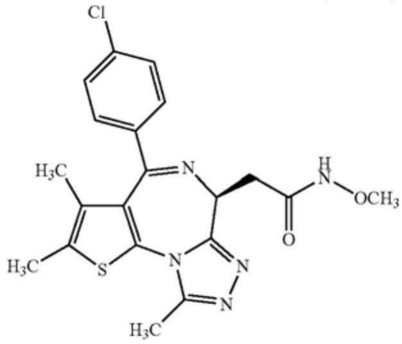
(1-15)



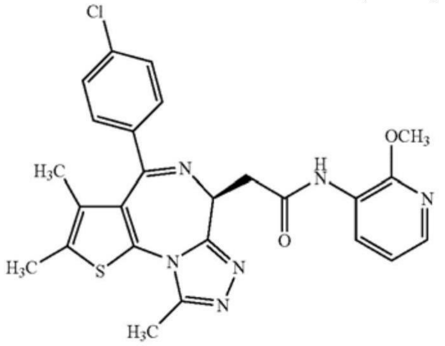
(1-16)



(1-17)



(1-18)



[0101] 在一些实施方案中，式(1)所示的噻吩并三唑并二氮杂卓化合物包括：(i)(S)-2-[4-(4-氯代苯基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,4]三唑并-[4,3-a][1,4]二氮杂卓-6-基]-N-(4-羟苯基)乙酰胺或它们的二水合物；(ii)甲基(S)-{4-(3'-氰基联苯-4-基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯；(iii)甲基(S)-{2,3,9-三甲基-4-(4-苯基氨基苯基)-6H-噻吩并[3,2-f][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯；以及(iv)甲基(S)-{2,3,9-三甲基-4-[4-(3-苯基丙酰氨基)苯基]-6H-噻吩并[3,2-f-][1,2,4]三唑并[4,3-a][1,4]二氮杂卓-6-基}乙酸酯。

[0102] 在一些实施方案中，式(1)所示的噻吩并三唑并二氮杂卓化合物包括(S)-2-[4-(4-氯代苯基)-2,3,9-三甲基-6H-噻吩并[3,2-f][1,2,-4]三唑并[4,3-a][1,4]二氮杂卓-6-基]-N-(4-羟苯基)乙酰胺。

[0103] III. 制剂

[0104] 式(1)所示的化合物在与盖伦组合物的常规给药和制备方面表现出非常特殊的困难，包括药品生物利率以及患者间和患者内的剂量应答的变化性的特定问题，由此需要针对几乎为非水溶性的噻吩并三唑并二氮杂卓研发出非常规的剂型。

[0105] 之前，已经发现可以利用载体丙烯酸乙酯-甲基丙烯酸甲酯-三甲基铵乙基丙烯酸酯氯化物共聚物(Eudragit RS，由Rohm制造)将式(1)所示的化合物配制成固体分散体，从而提供在下肠道中优先释放药物组分以用于治疗炎性肠病(溃疡性结肠炎和克罗恩病)的口服制剂(美国专利申请20090012064 A1，2009年1月8日公开)。通过多个试验(包含动物测试)，发现就炎性肠病而言，式(1)的噻吩并三唑并二氮杂卓化合物在病变中的释放以及其对炎性病变的直接作用比式(1)的噻吩并三唑并二氮杂卓化合物由胃肠道吸收至血液循环中更为重要。

[0106]　目前，意外地发现根据式(1)所示的噻吩并三唑并二氮杂卓化合物、其药学可接受的盐、溶剂化物(包含水合物)、外消旋物、对映异构体、同位素标记的形式可以使用药学可接受的聚合物而配制成固体分散体，从而提供口服制剂，该口服制剂能够使药物组分由胃肠道高度吸收至血液循环中，以治疗炎性肠病以及其他疾病。在狗和人类中的研究证明，与之前研发用于治疗炎性肠病的Eudragit固体分散体制剂相比，所述这些固体分散体的口服生物利用率较高。

[0107]　固体分散体为改善水溶性差的药品的口服生物利用率的一种手段。

[0108]　如本文所用，术语“固体分散体”是指一组固体产物，其包含至少2种不同的成分，通常为亲水性载体和疏水性药品(即，根据式(1)所示的噻吩并三唑并二氮杂卓化合物。基于药品在分散体内的分子排列，可以区分为6种不同类型的固体分散体。通常，固体分散体分为：简单低共熔混合物、固溶体、玻璃溶液(glass solution)和悬液、以及结晶载体中的无定形沉淀。此外，可存在某些组合，例如在同一样品中，一些分子可以簇状存在，而一些分子以分子形式分散。

[0109]　在一个实施方案中，根据式(1)所示的噻吩并三唑并二氮杂卓化合物可以以分子形式分散于无定形颗粒(簇)中。在另一个实施方案中，根据式(1)所示的噻吩并三唑并二氮杂卓化合物可以以结晶颗粒形式分散。在一个实施方案中，载体可以具有结晶性。在另一个实施方案中，载体可以是无定形的。

[0110]　在一个实施方案中，本发明提供了包含固体分散体的药物组合物，其中所述固体分散体包含：根据式(1)所示的噻吩并三唑并二氮杂卓化合物，或者其药学可接受的盐、溶剂化物(包括水合物)、外消旋物、对映异构体、异构体或其同位素标记形式；以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为醋酸琥珀酸酯羟丙基甲基纤维素(也称为醋酸羟丙基甲基纤维素琥珀酸酯或HPMCAS)。在一个实施方案中，分散体中噻吩并三唑并二氮杂卓化合物与醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)的重量比为1:3至1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一些实施方案中，固体分散体表现出玻璃化转变温度(Tg)的单一拐点。在一些实施方案中，单一的Tg在130℃至140℃之间发生。在其他此类的实施方案中，单一的Tg在约135℃下发生。在一些此类的实施方案中，固体分散体在40℃、相对湿度为75%的环境下暴露至少1个月。在一些实施方案中，在固体分散体的X射线粉末衍射图案中，基本上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约21°的2θ处，在无定形晕(amorphous halo)上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0111]　在一个实施方案中，本发明提供了药物组合物，其包含式(1)所示的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物(包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式在药学可接受的聚合物中形成的固体分散体。在一个实施方案中，药学可接受的聚合物为聚乙烯吡咯烷酮(也称为聚乙烯吡啶酮或PVP)。在一个实施方案中，分散体中噻吩并三唑并二氮杂卓化合物与PVP的重量比为1:3至1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一

些实施方案中，固体分散体表现出玻璃化转变温度 (Tg) 的单一拐点。在一些实施方案中，单一的 Tg 在 175℃至 185℃之间发生。在其他此类的实施方案中，单一的 Tg 在约 179℃处发生。在一些此类的实施方案中，固体分散体在 40℃下、相对湿度为 75％的环境下暴露至少 1 个月。在一些实施方案中，在固体分散体的 X 射线粉末衍射图案中，基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约 21° 的 2θ 处，在无定形晕上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0112] 在一个实施方案中，本发明的药物组合物包含固体分散体，该固体分散体包含无定形的式 (1) 所示的形式的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或其同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为醋酸琥珀酸酯羟丙基甲基纤维素。在一个实施方案中，式 (1) 所示的羟丙基甲基纤维素醋酸琥珀酸与醋酸琥珀酸酯羟丙基甲基纤维素的重量比范围为 1:3 至 1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一些实施方案中，固体分散体表现出玻璃化转变温度 (Tg) 的单一拐点。在一些实施方案中，单一的 Tg 在 130℃至 140℃之间发生。在其他此类的实施方案中，单一的 Tg 在约 135℃下发生。在一些此类的实施方案中，固体分散体在 40℃下、相对湿度为 75％的环境下暴露至少 1 个月。在一些实施方案中，在固体分散体的 X 射线粉末衍射图案中，基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约 21° 的 2θ 处，在无定形晕上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0113] 在一个实施方案中，本发明的药物组合物包含固体分散体，该固体分散体包含无定形的式 (1) 所示的形式的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为聚乙烯吡咯烷酮。在一个实施方案中，式 (1) 所示的噻吩并三唑并二氮杂卓化合物与聚乙烯吡咯烷酮的重量比范围为 1:3 至 1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一些实施方案中，固体分散体表现出玻璃化转变温度 (Tg) 的单一拐点。在一些实施方案中，单一的 Tg 在 175℃至 185℃之间发生。在其他此类的实施方案中，单一的 Tg 在约 179℃处发生。在一些此类的实施方案中，固体分散体在 40℃、相对湿度为 75％的环境下暴露至少 1 个月。在一些实施方案中，在固体分散体的 X 射线粉末衍射图案中，基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约 21° 的 2θ 处，在无定形晕上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0114] 在一个实施方案中，本发明的药物组合物包含固体分散体，该固体分散体包含结晶形式的式 (1) 所示的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物（包含水合物）、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为醋酸琥珀酸酯羟丙基甲基纤维素。在一

个实施方案中，式(1)所示的噻吩并三唑并二氮杂卓化合物与醋酸琥珀酸酯羟丙基甲基纤维素的重量比范围为1:3至1:1。

[0115] 在一个实施方案中，本发明的药物组合物包含固体分散体，该固体分散体包含式(1)所示的结晶形式的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物(包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为聚乙烯吡咯烷酮。在一个实施方案中，式(1)所示的噻吩并三唑并二氮杂卓化合物与聚乙烯吡咯烷酮的重量比范围为1:3至1:1。

[0116] 在一些实施方案中，通过喷雾干燥来制备包含固体分散体的药物组合物。

[0117] 在一个实施方案中，本发明的药物组合物包含喷雾干燥的固体分散体，该固体分散体包含式(1)所示的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物(包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为醋酸琥珀酸酯羟丙基甲基纤维素。在一个实施方案中，式(1)所示的化合物与醋酸琥珀酸酯羟丙基甲基纤维素的重量比范围为1:3至1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一些实施方案中，固体分散体表现出玻璃化转变温度(Tg)的单一拐点。在一些实施方案中，单一的Tg在130℃至140℃之间发生。在其他此类的实施方案中，单一的Tg在约135℃下发生。在一些此类的实施方案中，固体分散体在40℃、相对湿度为75%的环境下暴露至少1个月。在一些实施方案中，在固体分散体的X射线粉末衍射图案中，基本上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约21°的2θ处，在无定形晕上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0118] 在一个实施方案中，本发明的药物组合物包含喷雾干燥的固体分散体，该固体分散体包含式(1)所示的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物(包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为聚乙烯吡咯烷酮。在一个实施方案中，式(1)所示的化合物与聚乙烯吡咯烷酮的重量比范围为1:3至1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一些实施方案中，固体分散体表现出玻璃化转变温度(Tg)的单一拐点。在一些实施方案中，单一的Tg在175℃至185℃之间发生。在其他此类的实施方案中，单一的Tg在约179℃下发生。在一些此类的实施方案中，固体分散体在40℃、相对湿度为75%的环境下暴露至少1个月。在一些实施方案中，在固体分散体的X射线粉末衍射图案中，基本上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约21°的2θ处，在无定形晕上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0119] 在一个实施方案中，本发明的药物组合物包含喷雾干燥的固体分散体，该固体分散体包含无定形的式(1)所示的形式的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物(包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式，以及

药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为醋酸琥珀酸酯羟丙基甲基纤维素。在一个实施方案中，式 (1) 所示的噻吩并三唑并二氮杂卓化合物与醋酸琥珀酸酯羟丙基甲基纤维素的重量比范围为 1:3 至 1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一些实施方案中，固体分散体表现出玻璃化转变温度 (Tg) 的单一拐点。在一些实施方案中，单一的 Tg 在 130℃至 140℃之间发生。在一些此类的实施方案中，固体分散体在 40℃、相对湿度为 75％的环境下暴露至少 1 个月。在其他此类的实施方案中，单一的 Tg 在约 135℃下发生。在一些实施方案中，在固体分散体的 X 射线粉末衍射图案中，基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约 21° 的 2θ 处，在无定形晕上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0120] 在一个实施方案中，本发明的药物组合物包含喷雾干燥的固体分散体，该固体分散体包含无定形的式 (1) 所示的形式的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为聚乙烯吡咯烷酮。在一个实施方案中，式 (1) 所示的噻吩并三唑并二氮杂卓化合物与聚乙烯吡咯烷酮的重量比范围为 1:3 至 1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一些实施方案中，固体分散体表现出玻璃化转变温度 (Tg) 的单一拐点。在一些实施方案中，单一的 Tg 在 175℃至 185℃之间发生。在其他此类的实施方案中，单一的 Tg 在约 179℃下发生。在一些此类的实施方案中，固体分散体在 40℃、相对湿度为 75％的环境下暴露至少 1 个月。在一些实施方案中，在固体分散体的 X 射线粉末衍射图案中，基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约 21° 的 2θ 处，在无定形晕上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

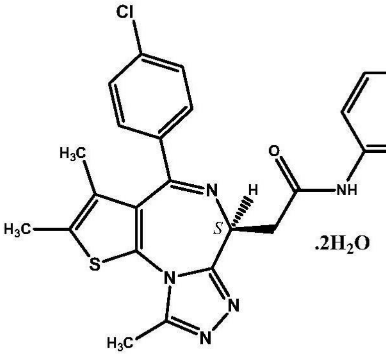
[0121] 在一个实施方案中，本发明的药物组合物包含喷雾干燥的固体分散体，该固体分散体包含式 (1) 所示的结晶形式的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为醋酸琥珀酸酯羟丙基甲基纤维素。在一个实施方案中，式 (1) 所示的噻吩并三唑并二氮杂卓化合物与醋酸琥珀酸酯羟丙基甲基纤维素的重量比范围为 1:3 至 1:1。

[0122] 在一个实施方案中，本发明的药物组合物包含喷雾干燥的固体分散体，该固体分散体包含式 (1) 所示的结晶形式的噻吩并三唑并二氮杂卓化合物或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式，以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为聚乙烯吡咯烷酮。在一个实施方案中，式 (1) 所示的噻吩并三唑并二氮杂卓化合物与聚乙烯吡咯烷酮的重量比范围为 1:3 至 1:1。

[0123] 在一个优选的实施方案中，本发明提供了一种药物组合物，其包含固体分散体，该

固体分散体包含 :2-[(6S)-4-(4- 氯代苯基)-2,3,9- 三甲基 -6H- 噻吩并 [3,2-f]-[1,2,4] 三唑并 [4,3-a][1,4] 二氮杂卓 -6- 基]-N-(4- 羟苯基) 乙酰胺二水合物 (化合物 (1-1)) 或者其药学可接受的盐、溶剂化物 (包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式 ;以及药学可接受的聚合物,其中所述的化合物 (1-1) 如下 :

[0124]



(1-1)

。

[0125] 在一个实施方案中,药学可接受的聚合物为 HPMCAS。在一个实施方案中,分散体中式 (1) 所示的化合物与 HPMCAS 的重量比为 1:3 至 1:1。在一个实施方案中,至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中,噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一个实施方案中,固体分散体是喷雾干燥的。在一些实施方案中,固体分散体表现出玻璃化转变温度 (Tg) 的单一拐点。在一些实施方案中,单一的 Tg 在 130℃至 140℃之间发生。在其他此类的实施方案中,单一的 Tg 在约 135℃下发生。在一些此类的实施方案中,固体分散体在 40℃、相对湿度为 75%的环境下暴露至少 1 个月。在一些实施方案中,在固体分散体的 X 射线粉末衍射图案中,基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言,“基本不存在”是指在约 21° 的 2θ 处,在无定形晕上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0126] 在另一个实施方案中,所述的药物组合物包含固体分散体,该固体分散体包含 :化合物 (1-1) 或者其药学可接受的盐、溶剂化物 (包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式 ;以及药学可接受的聚合物。在一个实施方案中,药学可接受的聚合物为 PVP。在一个实施方案中,分散体中化合物 (1-1) 与 PVP 的重量比为 1:3 至 1:1。在一个实施方案中,至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中,噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一个实施方案中,固体分散体是喷雾干燥的。在一些实施方案中,固体分散体表现出玻璃化转变温度 (Tg) 的单一拐点。在一些实施方案中,单一的 Tg 在 175℃至 185℃之间发生。在其他此类的实施方案中,单一的 Tg 在约 179℃下发生。在一些此类的实施方案中,固体分散体在 40℃、相对湿度为 75%的环境下暴露至少 1 个月。在一些实施方案中,在固体分散体的 X 射线粉末衍射图案中,基本上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言,“基本不存在”是指在约 21° 的 2θ 处,在无定形晕上不存在与结晶性的式 (1) 所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0127] 在一个实施方案中,本发明的药物组合物包含固体分散体,该固体分散体包含 :无定形形式的噻吩并三唑并二氮杂卓化合物 (1-1) 或者其药学可接受的盐、溶剂化物 (包括

水合物）、外消旋物、对映异构体、异构体或同位素标记的形式；以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为HPMCAS。在一个实施方案中，分散体中化合物(1-1)与HPMCAS的重量比为1:3至1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一个实施方案中，固体分散体是喷雾干燥的。在一些实施方案中，固体分散体表现出玻璃化转变温度(Tg)的单一拐点。在一些实施方案中，单一的Tg在130℃至140℃之间发生。在其他此类的实施方案中，单一的Tg在约135℃下发生。在一些此类的实施方案中，固体分散体在40℃、相对湿度为75％的环境下暴露至少1个月。在一些实施方案中，在固体分散体的X射线粉末衍射图案中，基本上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约21°的2θ处，在无定形晕上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0128] 在一个实施方案中，本发明的药物组合物包含固体分散体，该固体分散体包含：无定形形式的噻吩并三唑并二氮杂卓化合物(1-1)或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式；以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为PVP。在一个实施方案中，分散体中化合物(1-1)与PVP的重量比为1:3至1:1。在一个实施方案中，至少一部分噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在另一个实施方案中，噻吩并三唑并二氮杂卓化合物均匀地分散于整个固体分散体中。在一个实施方案中，固体分散体是喷雾干燥的。在一些实施方案中，固体分散体展现出玻璃化转变温度(Tg)的单一拐点。在一些实施方案中，单一的Tg在175℃至185℃之间发生。在其他此类的实施方案中，单一的Tg在约189℃下发生。在一些此类的实施方案中，固体分散体在40℃、相对湿度为75％的环境下暴露至少1个月。在一些实施方案中，在固体分散体的X射线粉末衍射图案中，基本上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。就本申请的目的而言，“基本不存在”是指在约21°的2θ处，在无定形晕上不存在与结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物有关的衍射线。

[0129] 在一个实施方案中，本发明的药物组合物包含固体分散体，该固体分散体包含：结晶形式的噻吩并三唑并二氮杂卓化合物(1-1)或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式；以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为HPMCAS。在一个实施方案中，分散体中化合物(1-1)与HPMCAS的重量比为1:3至1:1。在一个实施方案中，固体分散体是喷雾干燥的。

[0130] 在一个实施方案中，本发明的药物组合物包含固体分散体，该固体分散体包含：结晶形式的噻吩并三唑并二氮杂卓化合物(1-1)或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式；以及药学可接受的聚合物。在一个实施方案中，药学可接受的聚合物为PVP。在一个实施方案中，分散体中化合物(1-1)与PVP的重量比为1:3至1:1。在一个实施方案中，固体分散体是喷雾干燥的。

[0131] 当经口施用本发明所述的固体分散体时，其展现出特别有利的性质。当在动物或人类中在标准的生物利用率试验中施用时，固体分散体的有利性质的例子包括但不限于一致的且高水平的生物利用率。本发明的固体分散体可以包括含有式(1)所示的噻吩并三唑

并二氮杂卓化合物、聚合物以及添加剂的固体分散体。在一些实施方案中，固体分散体可以实现式(1)所示噻吩并三唑并二氮杂卓化合物在血流中的吸收，而这是不可能通过仅仅将式(1)所示的噻吩并三唑并二氮杂卓化合物与添加剂混合而获得的，这是因为式(1)所示的噻吩并三唑并二氮杂卓化合物药品在水和大部分的水性介质中溶解度可忽略不计。可以使用多种体外和/或体内研究来测量式(1)所示的噻吩并三唑并二氮杂卓化合物或者噻吩并三唑并二氮杂卓化合物(1-1)的生物利用率。体内研究还可以使用例如大鼠、狗或人类来进行。

[0132] 可以通过沿着横坐标(X轴)的时间在纵坐标(Y轴)上绘制式(1)所示的噻吩并三唑并二氮杂卓化合物或者噻吩并三唑并二氮杂卓化合物(1-1)的血清或血浆浓度，从而获得曲线下面积(AUC)值，由此测量生物利用率。然后，将所述固体分散体中的式(1)所示的噻吩并三唑并二氮杂卓化合物或者噻吩并三唑并二氮杂卓化合物(1-1)的AUC值与不包含聚合物的等价浓度的结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物或者结晶性噻吩并三唑并二氮杂卓化合物(1-1)的AUC值比较。在一些实施方案中，当将所述固体分散体经口施用给狗时，该固体分散体的曲线下面积(AUC)值为由静脉施用给狗的对照组合物的相应AUC值的至少0.4倍、0.5倍、0.6倍、0.8倍、1.0倍，其中所述对照组合物包含等价量的结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物。

[0133] 可以通过模拟胃部环境和肠内环境的pH值的体外测试来测量生物利用率。可以通过将式(1)所示的噻吩并三唑并二氮杂卓化合物或噻吩并三唑并二氮杂卓化合物(1-1)的固体分散体悬浮在pH值为1.0至2.0的体外水性测试介质中，并且随后将对照用体外测试介质的pH值调节为5.0至7.0。可以在pH值调节后的最初2个小时中的任何时间来测量无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物或无定形噻吩并三唑并二氮杂卓化合物(1-1)的浓度。在一些实施方案中，与不包含聚合物的结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物或结晶噻吩并三唑并二氮杂卓化合物(1-1)的浓度相比，在pH值为5.0至7.0的体外水性测试介质中，固体分散体中无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物或无定形噻吩并三唑并二氮杂卓化合物(1-1)的浓度高至少5倍以上、至少6倍以上、至少7倍以上、至少8倍以上、至少9倍以上或者至少10倍以上。

[0134] 在其他的实施方案中，与不包含聚合物的结晶性的式(1)所示的噻吩并三唑并二氮杂卓化合物的浓度相比，在pH值为1.0至2.0中的体外水性测试介质中，所述固体分散体中无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物或无定形噻吩并三唑并二氮杂卓化合物(1-1)的浓度高至少40%、至少50%、至少60%、至少70%、至少80%。在一些此类的实施方案中，固体分散体的聚合物为HPMCAS。在一些此类的实施方案中，固体分散体的聚合物为PVP。

[0135] 在其他的实施方案中，所述固体分散体中的无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物或无定形噻吩并三唑并二氮杂卓化合物(1-1)的浓度比下述固体分散体中的式(1)所示的噻吩并三唑并二氮杂卓化合物浓度高至少40%、至少50%以上、至少60%、至少70%、至少80%，其中上述固体分散体包含式(1)所示的噻吩并三唑并二氮杂卓化合物、以及选自由邻苯二甲酸羟丙基甲基纤维素酯和丙烯酸乙酯-甲基丙烯酸甲酯-三甲基铵乙基丙烯酸酯氯化物共聚物组成的组中的药学可接受的聚合物；其中所述各固体分散体被放置在pH值为1.0至2.0的体外水性测试介质中。在一些此类的实施方案中，所

述固体分散体的聚合物为HPMCAS。在一些此类的实施方案中，所述固体分散体的聚合物为PVP。

[0136] 在一些实施方案中，本发明所述的固体分散体在一定的湿度和温度下暴露一段时间时，其表现出抵抗式(1)所示的噻吩并三唑并二氮杂卓化合物或噻吩并三唑并二氮杂卓化合物(1-1)的重结晶的稳定性。在一个实施方案中，无定形的式(1)所示的噻吩并三唑并二氮杂卓化合物或保持无定形的噻吩并三唑并二氮杂卓化合物(1-1)的浓度选自：至少90％、至少91％、至少92％、至少93％、至少94％、至少95％、至少96％、至少97％、至少98％和至少99％。

[0137] IV. 剂型

[0138] 可以用于本发明的固体分散体的合适的剂型包括但不限于胶囊、片剂、小片剂、珠丸、珠、丸剂、小颗粒(granule)、颗粒(granulate)和粉末。可以使用例如肠溶衣来包裹合适的剂型。合适的包衣可以包括但不限于邻苯二甲酸乙酸纤维素、羟丙基甲基纤维素(HPMC)、邻苯二甲酸羟丙基甲基纤维素、聚甲基丙烯酸共聚物、或醋酸羟丙基甲基纤维素琥珀酸酯(HPMCAS)。在一些实施方案中，可存在某些组合，例如，在相同的样品中，本发明的噻吩并三唑并二氮杂卓的一些分子可以以簇状存在，而一些分子则以分子形式分散于载体中。

[0139] 在一些实施方案中，本发明的固体分散体可以配制成片剂、囊片或胶囊。在一些实施方案中，本发明的固体分散体可以配制成小片剂或倒入口中(pour-into-mouth)的小颗粒、或者组分(constitution)的口服粉末。在一些实施方案中，本发明的固体分散体与其他的赋形剂（例如，抑制重结晶/沉淀的聚合物、掩味成分等）组合并分散于合适的稀释剂中，从而得到即用型的悬浮制剂。在一些实施方案中，本发明的固体分散体可以配制用于小儿治疗。

[0140] 在一个实施方案中，本发明的药物组合物被配制用于口服给药。在一个实施方案中，所述的药物组合物包含根据本发明所述的多个实施方案的固体分散体，其包含：式(1)所示的噻吩并三唑并二氮杂卓化合物，或者其药学可接受的盐、溶剂化物（包括水合物）、外消旋物、对映异构体、异构体或同位素标记的形式；以及聚合物载体。在一个实施方案中，所述的药物组合物还包含一种或多种添加剂，例如崩解剂、润滑剂、助流剂、粘结剂、和填料。

[0141] 合适的药学可接受的润滑剂和药学可接受的助流剂（用于所述的药物组合物）的实例包括但不限于硅胶、三硅酸镁、淀粉、滑石、磷酸三钙、硬脂酸镁、硬脂酸铝、硬脂酸钙、碳酸镁、氧化镁、聚乙二醇、纤维素粉末、甘油二十二烷酸酯、硬脂酸、氢化蓖麻油、甘油单硬脂酸酯、和硬脂酰醇富马酸钠。

[0142] 合适的药学可接受的粘结剂（用于所述的药物组合物）的实例包括但不限于：淀粉；纤维素及其衍生物，例如微晶纤维素（例如AVICEL PH，得自FMC）、羟丙基纤维素、羟乙基纤维素、和羟丙基甲基纤维素(HPMC，例如METHOCEL得自Dow Chemical)；蔗糖、右旋糖、玉米糖浆；多糖；和凝胶。

[0143] 合适的药学可接受的填料和药学可接受的稀释剂（用于所述的药物组合物）的实例包括但不限于甜食制造商的糖、可压缩糖、葡萄糖结合剂、糊精、右旋糖、乳糖、甘露醇、微晶纤维素(MCC)、纤维素粉末、山梨醇、蔗糖、和滑石。

[0144] 在一些实施方案中，在所述的药物组合物中，赋形剂可以发挥多于一种的功能。例如填料或粘结剂还可以为崩解剂、助流剂、抗粘附剂、润滑剂、甜味剂等。

[0145] 在一些实施方案中，本发明的药物组合物可以进一步包含添加剂或组分，例如抗氧化剂（例如抗坏血酸棕榈酸酯、丁基化羟基茴香醚（BHA）、二丁基化羟基甲苯（BHT）、α-生育酚、丙基没食子酸、和富马酸）、抗微生物剂、酶抑制剂、稳定剂（例如丙二酸）和/或防腐剂。

[0146] 通常，本发明的药物组合物可以配制成任何合适的固体剂型。在一些实施方案中，本发明的固体分散体混合在单位剂型中，例如胶囊或片剂、或者多微粒系统（例如小颗粒或颗粒、或者粉末），以用于给药。

[0147] 在一个实施方案中，药物组合物包含：固体分散体，该固体分散体包含根据本发明所述的固体分散体的多个实施方案的式（1）所示噻吩并三唑并二氮杂卓化合物，和醋酸羟丙基甲基纤维素琥珀酸酯（HPMCAS），其中所述的噻吩并三唑并二氮杂卓化合物在固体分散体中是无定形的，并且噻吩并三唑并二氮杂卓化合物与醋酸羟丙基甲基纤维素琥珀酸酯（HPMCAS）的重量比为 1:3 至 1:1；45 重量％ -50 重量％的乳糖一水合物；35 重量％ -40 重量％的微晶纤维素；4 重量％ -6 重量％的交联羧甲基纤维素钠；0.8 重量％ -1.5 重量％的胶体二氧化硅；和 0.8 重量％ -1.5 重量％的硬脂酸镁。

[0148] V. 剂量

[0149] 在一个实施方案中，本发明提供了可以配制成任何合适的固体剂型的药物组合物。在一个实施方案中，根据本发明的药物组合物包含本发明所述式（1）的噻吩并三唑并二氮杂卓的多个实施方案中的一个或多个，其中所述式（1）的噻吩并三唑并二氮杂卓的剂量在约 10mg 至约 100mg 范围内。在一个实施方案中，根据本发明的药物组合物包含本发明所述式（1）的噻吩并三唑并二氮杂卓的多个实施方案中的一个或多个，其中所述式（1）的噻吩并三唑并二氮杂卓的剂量选自由如下剂量组成的组：约 10mg 至约 100mg、约 10mg 至约 90mg、约 10mg 至约 80mg、约 10mg 至约 70mg、约 10mg 至约 60mg、约 10mg 至约 50mg、约 10mg 至约 40mg、约 10mg 至约 30mg、和约 10mg 至约 20mg。在一个实施方案中，根据本发明的药物组合物包含本发明所述式（1）的噻吩并三唑并二氮杂卓的多个实施方案中的一个或多个，其中所述式（1）的噻吩并三唑并二氮杂卓的剂量选自由约 10mg、约 50mg、约 75mg、约 100mg 所构成的组。

[0150] 根据治疗的具体目的、治疗的阶段等，这种单位剂型适于每日给药 1 至 5 次。在一个实施方案中，有需要的受试者可以至少连续两天每日至少 1 次施用该剂型。在一个实施方案中，有需要的受试者可以隔日并且每日至少 1 次施用该剂型。在一个实施方案中，有需要的受试者可以至少每周施用该剂型，并且将该剂型分成相等的和/或不等的剂量。在一个实施方案中，有需要的受试者可以每周施用该剂型，每隔 3 天和/或每周 6 次施用。在一个实施方案中，有需要的受试者可以每隔一天、每隔 3 天、每隔 4 天、每隔 5 天和/或每周施用该剂型。在一个实施方案中，有需要的受试者可以每个月服用该剂型的 2 个或多个均分剂量或非均分剂量。

[0151] 例如可以使用肠溶衣来包裹所用的剂型，例如胶囊、片剂、小片剂、珠丸、珠、丸剂、小颗粒、颗粒和粉末。合适的包衣可以包括但不限于邻苯二甲酸乙酸纤维素、羟丙基甲基纤维素（HPMC）、邻苯二甲酸羟丙基甲基纤维素、聚甲基丙烯酸共聚物、或醋酸羟丙基甲基纤维

素琥珀酸酯(HPMCAS)。

[0152] VI. 工艺

[0153] 本发明所公开的噻吩并三唑并二氮杂卓化合物可以以游离碱或酸加成盐的形式存在,该游离碱或酸加成盐可以根据美国专利申请公开No.2010/0286127(其全部内容以以引用方式并入本文或本申请中)中所述的工序来获得。本发明的噻吩并三唑并二氮杂卓化合物的各对映异构体和非对映异构体可以由包含不对称中心或立体异构中心的市售可得的起始材料以合成方式制备,或者通过制备外消旋的混合物、然后通过本领域的那些普通技术人员公知的拆分方法来制备。这些拆分方法例如有:(1)使对映异构体的混合物附着在手性助剂上,通过重结晶或色谱法分离所得的非对映异构体的混合物,并由助剂上释放光学纯产物;(2)使用光学活性拆分剂形成盐;(3)在手性液相色谱柱上直接分离光学对映异构体的混合物;或者(4)使用立体选择性化学品或酶试剂进行动力学拆分。此外,外消旋的混合物还可以通过公知的方法而拆分成它们的构成成分的对映异构体,例如手性相气相色谱法或使化合物在手性溶剂中结晶。

[0154] 如果需要,本发明所公开的噻吩并三唑并二氮杂卓化合物的特定对映异构体可以通过不对称合成或者通过使用手性助剂衍生来制备,其中所得的非对映异构体的混合物被分离并且辅助基团被切割,从而提供所需的纯的对映异构体。或者,在所述分子包含碱性官能团(例如氨基)或酸性官能团(例如羧基)的情况下,非对映异构体的盐是通过以下过程形成的:使用合适的光学活性的酸或碱,然后对非对映异构体(通过本领域公知的分级结晶或色谱手段而由此形成)进行拆分,并在随后回收纯的对映异构体。可使用本领域公知的多种方法来制备式(1)所示的噻吩并三唑并二氮杂卓化合物,其中对映异构体的过量百分比通常超过约80%。有利的是,优选的对映异构体的过量百分比大于80%,优选大于90%,更优选大于95%,并且最优选为99%以上。

[0155] 本发明的固体分散体可以通过多种方法来制备,包括熔融和溶剂蒸发方法。此外,本发明的固体分散体还可以根据如下文中所描述的工序制备:Chiou WL,Riegelman S:“Pharmaceutical applications of solid dispersion systems”,J.Pharm.Sci.1971;60:1281-1302;Serajuddin ATM:“Solid dispersion of poorly water-soluble drugs:early promises,subsequent problems,and recentbreakthroughs”,J.Pharm.Sci.1999;88:1058-1066;Leuner C,Dressman J:“Improving drug solubility for oral delivery using solid dispersions”,Eur.J.Pharm.Biopharm.2000;50:47-60;和Vasconcelos T,Sarmento B,Costa P:“Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs”,Drug Discovery Today 2007;12:1068-1075,所有这些文献均以引用方式全文并入本文。

[0156] 在一个实施方案中,本发明的固体分散体是通过熔融工艺制备的。在一个实施方案中,熔融工艺包括在载体中将式(1)所示的噻吩并三唑并二氮杂卓的多个实施方案的一个或多个熔融。在一个实施方案中,熔融工艺包括使本发明的熔融化合物和载体冷却。在一个实施方案中,熔融工艺包括将熔融的化合物和载体粉碎。在一个实施方案中,在冷却步骤之后将本发明的熔融的化合物和载体粉碎。

[0157] 在一些实施方案中,式(1)所示的噻吩并三唑并二氮杂卓或者其药学可接受的盐、溶剂化物(包括水合物)、外消旋物、对映异构体、异构体或同位素标记的形式与载体间

不相容，在这种情况中，可以在熔融步骤中加入表面活性剂，从而防止在加热的混合物中形成2个液相或悬液。在一些实施方案中，式(1)所示的噻吩并三唑并二氮杂卓的多个实施方案中的一个或多个实施方案悬浮于之前熔融的载体中，而并未使用熔融状态的药品和载体，由此降低了工艺的温度。在一个实施方案中，在冰浴搅拌下冷却熔融的药品和载体的混合物。在一个实施方案中，通过喷雾冷却（或者通过喷雾冷凝）冷却并固化熔融的药品和载体混合物。

[0158] 在一个实施方案中，通过将熔融物喷雾至冷却室（使环境温度或冷却温度的低温空气通过该冷却室）中从而将熔融物形成颗粒，从而冷却和固化熔融的药品和载体的混合物。在一个实施方案中，通过在合适的流化床处理器中使熔融分散体雾化和再固化，从而冷却和固化熔融的药品和载体混合物。在一个实施方案中，通过在可加热的高剪切力混合器中进行熔融制粒，从而冷却并固化熔融的药品和载体的混合物。

[0159] 在一些实施方案中，可以采用热阶段挤出(hot-stage extrusion)或熔融团聚来避免药品的熔融局限。热阶段挤出包括如下过程：在熔融温度下将预先混合的药品和载体以高转速在短时间内挤出；在室温下冷却后收集所得的产物并研磨。

[0160] 在一个实施方案中，将式(1)所示的噻吩并三唑并二氮杂卓的多个实施方案中的一个或多个实施方案在校对的温度下加工，从而避免任何热不稳定的化合物发生降解。在一个实施方案中，通过将热阶段挤出与暂时性增塑剂（例如二氧化碳）结合而得到较低的处理温度。在一个实施方案中，在根据本发明的固体分散体的制备中，在常规的高剪切力混合器或旋转处理器中使用了熔融团聚。在一个实施方案中，通过将包含根据本发明的噻吩并三唑并二氮杂卓化合物的熔融载体加入至加热的赋形剂中，从而制备根据本发明的固体分散体。在一个实施方案中，通过将熔融载体加入到根据本发明的噻吩并三唑并二氮杂卓与一种或多种赋形剂的加热混合物中，从而制备根据本发明的固体分散体。在一个实施方案中，通过将根据本发明的噻吩并三唑并二氮杂卓化合物、载体和一种或多种赋形剂的混合物加热至载体的熔融范围内或以上的温度，从而制备根据本发明的固体分散体。

[0161] 在一些实施方案中，通过溶剂蒸发方法来制备根据式(1)所示的噻吩并三唑并二氮杂卓的制剂多个实施方案中的一个或多个实施方案。在一个实施方案中，溶剂蒸发方法包括使根据式(1)所示的噻吩并三唑并二氮杂卓和载体溶解于挥发性溶剂中，然后使挥发性溶剂蒸发。在一个实施方案中，挥发性溶剂可以为一种或多种赋形剂。在一个实施方案中，一种或多种赋形剂包括但不限于抗粘剂、惰性填料、表面润湿剂、pH调节剂和添加剂。在一个实施方案中，赋形剂可以溶解于挥发性溶剂中，或者在挥发性溶剂中呈悬浮或膨胀状态。

[0162] 在一个实施方案中，根据本发明的固体分散体的制备包括使悬浮于挥发性溶剂中的一种或多种赋形剂干燥。在一个实施方案中，所述的干燥包括真空干燥、使挥发性溶剂在低温下缓慢蒸发、使用旋转蒸发仪、喷雾干燥、喷雾制粒、冷冻干燥或使用超临界流体。

[0163] 在一个实施方案中，使用了喷雾干燥制备根据式(1)所示的噻吩并三唑并二氮杂卓组合物的制剂，其包括使所述的组合物的悬液或溶液雾化形成小滴，然后快速除去制剂中的溶剂。在一个实施方案中，根据本发明的制剂的制备涉及喷雾制粒，其中将位于溶剂中的组合物的溶液或悬液喷雾至合适的化学惰性和/或物理惰性填料上，例如乳糖或甘露醇。在一个实施方案中，通过双通或三通喷嘴对所述的组合物的溶液或悬液进行喷雾制粒。

[0164] 在一些实施方案中,根据本发明的固体分散体的制备包括使用超临界流体。术语“超临界流体”是指在临界温度和临界压力以上以单一液相存在的物质。在一个实施方案中,根据本发明的制剂的制备包括使用超临界二氧化碳流体。在一个实施方案中,利用超临界流体技术的根据本发明的制剂制备包括 :将根据式 (1) 所示的噻吩并三唑并二氮杂卓化合物和载体溶解于常见溶剂中,该溶剂通过喷嘴与二氧化碳同时被引入至颗粒形成容器中 ;以及将所述溶液喷雾,从而使溶剂被超临界流体快速萃取,由此使得固体分散体颗粒沉淀在容器的壁上。

[0165] 在一些实施方案中,根据本发明的固体分散体的制备包括使用共沉淀方法。在一个实施方案中,在持续搅拌下将非溶剂滴加至根据式 (1) 所示的噻吩并三唑并二氮杂卓组合物和载体溶液中。在一个实施方案中,在加入非溶剂的过程中,使根据式 (1) 所示的噻吩并三唑并二氮杂卓组合物和载体进行共沉淀,从而形成微颗粒。在一个实施方案中,过滤并干燥所得的微颗粒,从而提供所需的固体分散体。

[0166] 式 (1) 所示的化合物与聚合物载体 (一种或多种) 的混合比例没有特别限定,只要其可以改善式 (1) 所示的化合物的生物利用率即可,并且该比例根据聚合物的种类而改变。

[0167] 在以下非限定性的实施例中说明本发明。

[0168] VII. 例子

[0169] 在以下非限定性的实施例中说明本发明。

[0170] 实施例 1 :<u>化合物 (1-1) 的固体分散体的体外筛选</u>

[0171] 使用化合物 (1-1) 以及 5 种聚合物中的一种来制备十种固体分散体,其中所述聚合物包括醋酸琥珀酸酯羟丙基甲基纤维素 (HPMCAS-M)、邻苯二甲酸羟丙基甲基纤维素酯 (HPMCP-HP55)、聚乙烯吡咯烷酮 (PVP)、PVP- 乙酸乙烯酯 (PVP-VA) 和 Euragit L100-55,并且对于每种聚合物,化合物 (1-1) 的负载率为 25%和 50%。通过溶剂蒸发方法来制备固体分散体 :使用喷雾干燥,然后在低温对流烤箱中进行二次干燥。通过非漏槽溶解性能测试 (non-sink dissolution performance test) 来评估各固体分散体的性能,其中所述测试测量了药品的总量和随时间的推移溶液中所存在的游离药品的量。选择非漏槽溶解是由于其能够最好地代表低溶解度化合物的体内情况。该测试包括在分散体被引入至测试介质 (该测试介质模拟了体内条件) 后的约 30 至 40 分钟,分散体由胃部 pH 值 (0.1N NaCl,pH 值为 1.0) 至肠内 pH 值 (FaFSSIF,pH 值为 6.5) 的“胃部转移”。[FaFSSIF 为禁食状态的人工肠液,其由 3mM 的牛黄胆酸钠、0.75mM 的卵磷脂、0.174g 的 NaOH 颗粒、1.977g 的 $NaH_2PO_4 \cdot H_2O$、3.093g 的 NaCl、和纯净水适量 500mL 组成]。使用高效液相色谱 (HPLC) 方法和 Agilent 1100 系列 HPLC 来定量溶解药品的量。制剂的溶解图 (图 1A-1J) 表明 :相对于相同介质中未配制的化合物而言,在所有的分散体候选物中,药品的溶解度均大幅升高。在所有的固体分散体中,根据在肠内 pH 值下所释放的游离药品的水平更高这一发现,25%化合物 (1-1) 在 PVP 中的分散体、25%化合物 (1-1) 在 HPMCAS-M 中的分散体、以及 50%化合物 (1-1) 在 HPMCAS-M 中的分散体所提供的口服吸收效果高于未配制的化合物。

[0172] 实施例 2 :<u>化合物 (1-1) 的固体分散体的体内筛选</u>

[0173] 以更大的规模制备化合物 (1-1) 的固体分散体,即 25%化合物 (1-1) 在 PVP 中的分散体、25%化合物 (1-1) 在 HPMCAS-MG 中的分散体、和 50%化合物 (1-1) 在 HPMCAS-M 中

的分散体以用于体内研究。各制剂均经过了实施例 1 所述的体外溶解测试的评估。为了确保这些分散体是无定形且均匀的,通过 X 射线粉末衍射法 (PXRD) 和更改的差示扫描量热法 (mDSC) 来评估这些分散体。X 射线衍射计为 Bruker D-2Phaser。此外,为了了解水对各种分散体的玻璃化转变温度 (Tg) 的影响,对在设定的相对湿度(即,25％、50％和 75％ RH) 下首先平衡至少 18 小时的样品实施 mDSC。[水可以用作固体分散体的增塑剂,并且体系由于活性化合物或聚合物的收湿性可以影响被这些体系吸收的水的量]。

[0174] 非漏槽溶解结果 (图 2A-2C) 与实施例 1 中分散体的结果相当。PXRD 结果 (图 3) 表明任意一种分散体中均未显示存在结晶性化合物,并且 mDSC 结果 (图 4A-4C) 表明各分散体均存在单一的玻璃化转变温度 (Tg),这表明各分散体是均匀的。对于各种分散体,观察到 Tg 与相对湿度之间呈反比关系 (图 5)。明显的是,对于在 75％ RH 下平衡的 25％化合物 (1-1) 在 PVP 中的固体分散体,出现了 2 个 Tg,这表明发生了相分离,并且该分散体还显示出在 75％ RH 下发生了熔融,这表明在 RH 平衡过程中发生了结晶 (图 6)。该发现表明 25％化合物 (1-1) 在 PVP 中的固体分散体的稳定性弱于 HPMCAS-M 分散体。

[0175] 为了评估这三种分散体的生物利用率,向多组雄性猎兔犬 (每组 3 只) 给予剂量为 3mg/kg 的化合物 (1-1) 的固体分散体的水性悬液 (通过口服填喂法给药),或者给予剂量为 1mg/kg 的溶解于水 : 乙醇 : 聚乙二醇 (PEG)400(60:20:20) 中的化合物 (1-1)(并以静脉推注给药至头静脉中)。在静脉给药后的 0 分钟 (预剂量)、5 分钟、15 分钟和 30 分钟、和 1 小时、2 小时、4 小时、8 小时、12 小时和 24 小时,以及在口服填喂给药后的 0 分钟 (预剂量)、15 分钟和 30 分钟、以及 1 小时、2 小时、4 小时、8 小时、12 小时、和 24 小时由各动物的颈静脉收集血液样品。使用定量 LC-MS/MS 方法检测各样品中存在的化合物 (1-1) 的量,并且定量下限为 0.5ng/mL。通过使用线性梯形法则 (直至最后可测量的浓度,而未将终末消除相外推至无穷大) 来测定血浆浓度 - 时间曲线的曲线下面积 (AUC)。通过对对数浓度 - 时间曲线的终末线性部分进行最小二乘回归分析来计算消除半衰期 ($t_{1/2}$)。由血浆浓度数据直接得到最大血浆浓度 (C_{max}) 和达到 C_{max} 的时间 (t_{max})。通过口服给药后的剂量归一化的 AUC 除以静脉给药后的剂量归一化的 AUC 来计算口服生物利用率 (F),并以百分率 (％) 形式报告。下表 1 中概括的结果分别给出了 25％化合物 (1-1) 在 PVP 中的固体分散体、25％化合物 (1-1) 在 HPMCAS-M 中的固体分散体和 50％化合物 (1-1) 在 HPMCAS-M 中的固体分散体的平均口服生物利用率 (58％、49％和 74％)。

[0176] 表 1 :狗口服 (po) 和静脉 (iv) 给药后的化合物 (1-1) 的药代动力学参数 (数值为 3 只狗的平均值)

[0177]

化合物（1-1）的制剂	剂量和途径	C_{max} (ng/L)	t_{max} (hr)	AUC (ng•min/mL)	$t_{1/2}$ (hr)	F (%)
水:乙醇:PEG400(60:20:20)中的溶液	1 mg/kg IV	769	0.083	53,312	1.5	----
25%化合物(1-1)/PVP固体分散体的水性悬液	3 mg/kg PO	487	1.0	93,271	1.6	58
25%化合物(1-1)/HPMCAS-M固体分散体的水性悬液	3 mg/kg PO	228	0.5	78,595	2.0	49
50%化合物(1-1)/HPMCAS-M固体分散体的水性悬液	3 mg/kg PO	371	1.0	118,174	1.5	74

[0178] AUC：血浆浓度－时间曲线下的面积；C_{max}：最大血浆浓度；F：生物利用率；HPMCAS：醋酸羟丙基甲基纤维素钠；IV：静脉；PEG：聚乙二醇；PO：经口，口服；PVP：聚乙烯吡咯烷酮；t_{max}：达到C_{max}的时间；$t_{1/2}$：血浆消除半衰期。

[0179] 实施例3：包含化合物(1-1)的固体分散体的胶囊的制备和临床用途

[0180] 制备10mg强度的凝胶胶囊，在患有恶性血液病的患者中进行初步的临床研究。基于实施例1和2中的化合物(1-1)的固体分散体的体外和体内测试结果，选择50％化合物(1-1)在HPMCAS-M中的固体分散体用于胶囊的研发。以3#尺寸的硬凝胶胶囊充装190mg的充装量为目标来开始胶囊的研发，因为这样的硬胶囊的构造可以通过充装更大尺寸的胶囊而潜在地增加胶囊的强度，同时保持药物组合物。根据经验，设计了4种胶囊制剂，其中具有不同量的崩解剂并且具有或不具有润湿剂。由于所有4种制剂都显示出相似的崩解测试和溶解测试结果，所以选择最简单的制剂（不具有润湿剂，并具有最少量的崩解剂）用于制造。进行制造工艺的研发和规模扩大的研究，从而确认固体分散体的喷雾干燥工艺和干燥后的时间；共混的参数；为获得约60g/cc的目标堆密度的共混物的辊压和研磨；以及胶囊充装的条件。

[0181] 将结晶性化合物(1-1)和聚合物醋酸琥珀酸酯羟丙基甲基纤维素(HPMCAS-M)溶解于丙酮中，并喷雾干燥，从而生产包含50％化合物(1-1)负载率的固体分散体中间体(SDI)颗粒。PXRD分析显示SDI是无定形的，mDSC分析显示SDI是均匀的（即在环境条件下具有单一的Tg）。在V型搅拌机的多个阶段(stages)中共混50％化合物(1-1)在HPMCAS-M中的固体分散体(1000g)和赋形剂（包括微晶纤维素填料－粘结剂(4428g)、交联羧甲基纤维素钠崩解剂(636g)、胶体二氧化硅分散剂/润滑剂(156g)、硬脂酸镁分散剂/润滑剂(156g)和乳糖一水合物填料(5364g)）。然后，将混合物压紧并制粒，从而得到约0.6g/mL的堆密度。使用自动化的充装机器将混合物分配至3#尺寸的硬凝胶胶囊（目标充装量：190mg)中，并使用胶囊剖光器将胶囊成品剖光。

[0182] 在口服给药10mg胶囊（包含50％化合物(1-1)在HPMCAS中的固体分散体）后进行药代动力学的评估，并将结果与对健康志愿者口服给药4x10mg胶囊（其包含化合物(1-1)的Eudragit固体分散体）后进行的药代动力学评估加以对比。

[0183] 在下表2A和2B中提供了这两种药物组合物的比较。前一Eudragit制剂在2009年1月8日出版的美国专利申请2009/0012064 A1中的实施例5中有所描述。该申请记

载：通过在水和乙醇的混合物中溶解和／或分散式(A)所示的噻吩并三唑并二氮杂卓和包裹用赋形剂(包含季胺基甲基丙烯酸酯共聚物B型(Eudragit RS)、甲基丙烯酸共聚物C型(Eudragit L100-55)、滑石和硅酸镁铝)来制备Eudragit固体分散体制剂。然后，使用离心流化床制粒机将上述的非均匀混合物施加在微晶纤维素球(Nonpareil 101，Freund)上，从而生产出分配至2#尺寸的羟丙基甲基纤维素胶囊中的颗粒。

[0184] 在这2个临床研究中，使用经验证的LC-MS/MS方法来测定化合物(1-1)的血液水平，并根据在胶囊给药后24小时内的各时间点测量的化合物(1-1)的血浆浓度来进行药代动力学分析。下表3中总结的结果显示，根据AUC，HPMCAS-M固体分散体制剂在人类中的生物利用率比Eudragit固体分散体制剂(924*4/1140，针对给药剂量的差异进行调节)高3倍以上。此外，根据观察到的T_{max}，HPMCAS制剂的吸收速度快于Eudragit制剂(T_{max}为1小时vs 4-6小时)。系统暴露于HPMCAS-M固体分散体制剂的明显改善是意料之外的。

[0185] 表2A：<u>用于临床用途的化合物(1-1)的固体分散体胶囊</u>

[0186] 包含化合物(1-1)的50％ HPMCAS固体分散体的药物组合物：10mg强度，3#尺寸的硬凝胶胶囊

[0187]

组分	功能	胶囊含量	
		mg	重量%
式(II)所示的化合物	活性剂	10.0*	5.56
醋酸琥珀酸酯羟丙基甲基纤维素(HPMCAS-M)	固体分散体的载体	10.0	5.56
乳糖一水合物	填料	85.0	47.22
微晶纤维素	填料-粘结剂	70.0	38.89
交联羧甲基纤维素钠	崩解剂	10.0	5.56
胶体二氧化硅	分散剂/润滑剂	2.5	1.39
硬脂酸镁	分散剂/润滑剂		
总计		190.0	100.0

[0188] 表2B：包含化合物(1-1)的Eudragit L100-55固体分散体的药物组合物：10mg强度，2#尺寸的硬凝胶树脂

[0189]

组分	功能	胶囊含量

[0190]

		mg	重量%
化合物(1-1)	活性剂	10.0*	3.8
芯：			
微晶纤维素球(Nonpareil 101, Freund, Inc)	媒介物	100.0	38.5
化合物/聚合物层：			
季胺基甲基丙烯酸酯共聚物B型(NF. PhEur)(Edragit RS, Evonik)	包衣试剂	10.8	4.2
甲基丙烯酸共聚物 C 型(NF)/甲基丙烯酸-丙烯酸乙酯共聚物(1:1)A 型(PhEur) (丙烯酸树脂 L100-55, Evonik)	包衣试剂	25.2	9.7
滑石	包衣试剂	88.2	33.9
硅酸镁铝(Neuslin, Fuji Chemical)	包衣试剂	20.0	7.7
柠檬酸三乙酯	增塑剂	5.0	1.9
二氧化硅	流化剂	0.8	0.3
		260.0	100.0

[0191] ＊为无水形式

[0192] 表 3 :<u>在将化合物 (1-1) 的固体分散体经口给药人类后的药代动力学参数</u>

[0193]

化合物(1-1)制剂	#患者	剂量和途径	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24h} (ng•h/mL)
Eudragit 固体分散体制剂	7	40 mg PO	83	4 至 6	1140
50% HMPCAS-M 固体分散体制剂	7	10 mg PO	286	1	925

[0194] AUC_{0-24h}:24 小时内 OTX015 血浆浓度与时间曲线下的面积

[0195] C_{max}:血浆中的最大浓度

[0196] hr :小时

[0197] HPMCAS :醋酸琥珀酸酯羟丙基甲基纤维素

[0198] mL :毫升

[0199] ng :毫微克

[0200] PO :经口，口服

[0201] T_{max}:达到 C_{max}的时间

[0202] 实施例 4.<u>在大鼠中的口服暴露</u>

[0203] 在大鼠中测定化合物 (1-1) 的固体分散体的 3 种制剂的口服生物利用率。所选的 3 种分散体为 25％化合物 (1-1) 在 PVP 中的分散体、25％化合物 (1-1) 在 HPMCAS-MG 中的分散体和 50％化合物 (1-1) 在 HPMCAS-MG 中的分散体。在该研究中使用的动物为得自图尔库大学（芬兰）的 Central Animal Laboratory 的无特异病原 (SPF) 的 Hsd:Sprague Dawley 大鼠。大鼠最初购自位于荷兰的 Harlan。大鼠为雌性，并且为 10 周龄，12 只大鼠用于该研究中。在聚碳酸酯 Makrolon II 笼中饲养该动物（每个笼中 3 只），动物室温为 21+/-3℃，动物室内的相对湿度为 55+/-15％，并且动物室内照明为人工照明，而且为 12 小时光暗周期的循环（暗周期为 18:00 至 06:00 小时）。杨树木屑 (Tapvei Oy,Estonia) 用

于垫料，并且每周至少1次更换垫料。在定量给药动物之前提供食物和水，但是在定量给药后最初的2个小时中移除食物和水。

[0204] 通过将预算量的注射用无菌水加入至装有适量分散体的容器中，获得浓度为0.75mg/mL的化合物(1-1)，由此制备包含25％化合物(1-1)在PVP中的分散体、25％化合物(1-1)在HPMCAS-MG中的分散体和50％化合物(1-1)在HPMCAS-MG中的分散体的口服定量给药溶液。在每次给药之前，将口服定量给药溶液进行涡流混合20秒。用于静脉给药的定量给药溶液包含0.25mg/mL的化合物(1-1)，该定量给药溶液是通过将5mg的化合物(1-1)溶解于混合物中来制备的，其中所述混合物包含4mL的平均分子量为400Da的聚乙二醇(PEG400)、4mL的乙醇(96％纯度)和12mL的注射用无菌水。在加入水后的30分钟之内使用含有25％化合物(1-1)在PVP中的分散体的定量给药溶液。在加入水后的60分钟之内使用包含25％化合物(1-1)在HPMCAS-MG中的分散体和50％化合物(1-1)在HPMCAS-MG中的分散体的定量给药溶液。使用4mL/kg定量给药量，从而使化合物(1-1)的静脉给药的给药水平为1mg/kg，口服给药的给药水平为3mg/kg。定量给药计划表在表4中给出。

[0205] 表4.用于大鼠口服暴露研究的定量给药计划表

[0206]

大鼠	重量	剂量(mL)	测试项目	途径
1	236.5	0.95	化合物(1-1)	静脉
2	221	0.88	化合物(1-1)	静脉
3	237.5	0.95	化合物(1-1)	静脉
4	255.5	1.02	25％化合物(1-1)在PVP中的分散体	口服
5	224.2	0.90	25％化合物(1-1)在PVP中的分散体	口服
6	219.2	0.88	25％化合物(1-1)在PVP中的分散体	口服
7	251.6	1.01	25％化合物(1-1)在HPMCAS-MG中的分散体	口服
8	240.4	0.96	25％化合物(1-1)在HPMCAS-MG中的分散体	口服
9	238	0.95	25％化合物(1-1)在HPMCAS-MG中的分散体	口服
10	226.6	0.91	50％化合物(1-1)在HPMCAS-MG中的分散体	口服
11	228.4	0.91	50％化合物(1-1)在HPMCAS-MG中的分散体	口服

12	228.5	0.91	50％化合物（1-1）在HPMCAS-MG中的分散体	口服

[0207] 在定量给药后的0.25小时、0.5小时、1小时、2小时、4小时、8小时、12和24小时的时间点时，将约50μL的血液样品收集至包含5μL乙二胺四乙酸（EDTA）溶液的Eppendorf管中，并且每个样品都是在距所述时间点5分钟时间窗内收集的。由各样品获得20μL血浆并储存在干冰温度下以用于分析。使用有效的液相色谱串联质谱（LC-MS/MS）法对各样品中化合物（1-1）的浓度进行分析，其定量下限为0.5ng/mL。

[0208] 使用Phoenix WinNonlin软件包（6.2.1版，Pharsight公司，美国，加利福尼亚州），通过标准的非房室模型方法来计算药代动力学参数。通过对数浓度-时间曲线的终末线性部分的最小二乘回归分析来计算消除相半衰期（$t_{1/2}$）。通过使用线性梯形法则（直至最后可测量的浓度，此后将终末消除相外推至无穷大）来测定血浆浓度-时间曲线下面积（AUC）。通过将药品浓度外推至无穷大来计算平均停留时间（MRT），其代表了化合物在房室或系统中保留的平均时间量。由血浆浓度数据直接得到最大血浆浓度（C_{max}）和达到C_{max}的时间（t_{max}）。通过将口服给药后剂量归一化AUC除以静脉给药后剂量归一化AUC来计算试验性口服生物利用率（F），即F＝（AUC（口服）/剂量（口服））/（AUC（静脉）/剂量（静脉）），并且报告为百分率（％）。

[0209] 药代动力学参数在表5中给出，并且血浆浓度与时间的图示于图7和8中。

[0210] 表5.在口服和静脉给药后化合物（1-1）之后的药代动力学参数。其中的数值为得自3只动物的平均值。

[0211]

化合物	**参数**	**1 mg/kg 静脉**	**3 mg/kg 口服**	**F(%)**
化合物(1-1)/水：乙醇:PEG400(60:20:20)	AUC (min*ng/ml)	74698		
	C_{max} (ng/ml)	730		
	T_{max} (hr)	0.25		
	$t_{1/2}$ (hr) 8.5	8.5		
	CI/F (ml/min/kg)	13.4		
	MRT (hr)	7.4		
25%化合物(1-1)在PVP中的分散体	AUC (min*ng/ml)		39920	18
	C_{max} (ng/ml)		77.9	
	T_{max} (hr)		1	
	$t_{1/2}$ (hr) 8.5		13.8	
	CI/F (ml/min/kg)		75.2	
	MRT (hr)		18.0	
25%化合物(1-1)在HPMCAS-MG中的分散体	AUC (min*ng/ml)		35306	16
	C_{max} (ng/ml)		48.3	
	T_{max} (hr)		0.5	
	$t_{1/2}$ (hr) 8.5		11.0	
	CI/F (ml/min/kg)		85.0	
	MRT (hr)		17.1	
50%化合物(1-1)在HPMCAS-MG中的分散体	AUC (min*ng/ml)		40238	18
	C_{max} (ng/ml)		67.0	
	T_{max} (hr)		2	
	$t_{1/2}$ (hr) 8.5		9.5	
	CI/F (ml/min/kg)		74.6	
	MRT (hr)		12.8	

[0212] 实施例5.喷雾干燥分散体的制备

[0213] 使用5种所选的聚合物来制备化合物(1-1)的喷雾干燥的分散体，这5中聚合物为：HPMCAS-MG(Shin Etsu Chemical公司)、HPMCP-HP55(Shin Etsu Chemical公司)、PVP(ISP,Ashland公司的分部)、PVP-VA(BASF公司)、和丙烯酸树脂L100-55(Evonik Industries AG)。使用各种聚合物制备25重量％和50重量％的所有的喷雾干燥溶液。除了PVP溶液以外，所有的溶液都是在丙酮中制备的，其中PVP溶液是在乙醇中制备的。对于各溶液而言，在10g溶剂中制备1.0g固体(聚合物和化合物(1-1))。使用具有1.5mm喷嘴的Büchi B-290、PE-024喷雾干燥器和Büchi B-295、P-002冷凝器将溶液喷雾干燥。将喷雾干燥器的喷嘴压力设定为80psi，目标出口温度设定为40℃，制冷机的温度设定至-20℃，泵速设定为100％，并且移液器设定为100％。在喷雾干燥后，收集固体分散体，并在低温对

流烤箱中过夜干燥，从而除去残余的溶剂。

[0214]

实施例6：　在一定的湿度和温度下的稳定性

表6

测试	过程	接受标准	T=O (初始)	T-1 个月(储存在40℃/75%RH)	T-2 个月(储存在40℃/75%RH)	T=3 个月(储存在40℃/75%RH)
外观	AM-0002	白色至米白色粉末	测试日期/参数： 06Aug2012/02-41-2	测试日期/参数： 24Sep2012/02-41-59	测试日期/参数： 24Oct2012/02-37-106	测试日期/参数： 17Dec2012/02-37-119
			白色粉末	白色粉末	白色粉末	白色粉末
效力(HPLC)	AM-0028	45.0 • 55.0 wt%	测试日期/参数： 25Jul2012/02-37-21	测试日期/参数： 25Sep2012/02-4HI0	测试日期/参数： 24Oct2012/02-37-105	测试日期/参数： 29Nov2012/02-34-107
			50.0	49.4	49.8	49.2
单个相关的物质(HPLC)	AM-0029	报告结果	测试日期/参数： 25Jul2012/02·34-49	测试日期/参数： 26Sep2012/02-41-64	测试日期/参数： 24Oct2012/02-37-105	测试日期/参数： 29Nov2012/02-34-107
			RRT %面积	RRT %面积	RRT %面积	RRT %面积
			无可报告的相关的物质	无可报告的相关的物质	0.68 0.06	0.68 0.07
					0.77 0.06	0.77 0.09
总体相关的物质(HPLC)	AM·0029	报告结果	测试日期/参数： 25Jul2012/02-34-49	测试日期/参数： 26Sep2012/02-41-64	测试日期/参数： 24Oct2012/02-37-105	测试日期/参数： 29Nov2012/02-34-107
			无可报告的相关的物质	无可报告的相关的物质	0.12%	0.16%
水含量(KF)	AM-0030 USP <921>	报告结果(wt%)	测试日期/参数： 02Aug2012/02-41-1	测试日期/参数： 27Sep2012/02-37-99	测试日期/参数： 25Oct2012102-37-110	测试日期/参数： 29Nov2012/02·37-116
			1.52	2.53	2.70	3.43
X射线粉末衍射法(XRPD)	USP <941>	符合无定形形式	测试日期/参数： 24Jul2012/02·24-131	测试日期/参数： 01Oct2012/02-41-73	测试日期/参数： 24Oct2012/02-37-107	测试日期/参数： 17Dec2012/02-37-120
			符合无定形形式，参见图9	符合无定形形式，参见图10	符合无定形形式，参见图11	符合无定形形式，参见图12
更改的差示扫描量热法(mDSC)	USP <891>(n = 2个重复)	报告单独的和平均的玻璃化转变温度(Tg, ℃)	测试日期/参数： 24Jul2012/02-24-130	测试日期/参数： 26Sep2012/02-37-98	测试日期/参数： 24Oct2012/02-37-108	测试日期/参数： 17Dec2012/02-37-121
			重复1 = 134.30℃，重复2 = 134.23℃，重复3 = 135.28℃，平均= 134.60℃	重复1 = 134.65℃，重复2 =134.43℃，平均=134.54℃	重复1 = 135.35℃，重复2 = 134.93℃，平均= 135.14℃	重复1 = 134.36℃. 重复2 = 137.16℃，平均= 135.76℃

[0215]　通过在高温下暴露于水分来评估化合物(1-1)在HPMCAS-MG中形成的喷雾干燥的分散体的稳定性。在1、2和3个月内，在75％相对湿度和40℃下，测定作为相对湿度的函数

的玻璃化转变温度(Tg)。将喷雾干燥的分散体储存在HDPE瓶中的LDPE袋内，从而模拟散货包装。结果概括于表6中。在0时，Tg为134℃，在1个月时，Tg为134℃，在2个月时，Tg为135℃，在3个月时，Tg为134℃，并且在各测量中仅观察到单一的拐点。此外，还获得的各样品的X射线衍射图案。图9示出了在稳定性测试的0时，化合物(1-1)在HPMCAS-MG中形成的固体分散体的X射线粉末衍射图谱。图10、11和12示出了化合物(1-1)在HPMCAS-MG中形成的固体分散体在40℃和75％相对湿度下分别暴露1个月、2个月和3个月后的X射线粉末衍射图谱。所述的图案未显示与化合物(1-1)有关的任何衍射线。

[0216] 本领域的那些技术人员应该理解的是在不脱离本发明的宽泛的发明理念的条件下可以对上文所示的并描述的示例性实施方案进行修改。因此，应该理解的是本发明不限于所示的并描述的示例性实施方案，但是其将涵盖在权利要求书所定义的本发明的精神和范围内的修改。例如示例性实施方案的特定特征可以为所要求的本发明的一部分或不是其一部分，并且所公开的实施方案的特征可以结合。除非本发明作出具体说明，术语“a”、“an”和“the”不限于一个元素，而是应该理解为“至少一个”。

[0217] 应该理解的是至少本发明的一些特征和描述可以被简化，从而集中于与清楚地理解本发明有关的元素，同时为了清晰起见，删除本领域的那些普通技术人员将理解的其他元素(其也可以包含本发明的一部分)。但是由于此类元素是本领域公知的，并且由于它们不一定会有利于更好地理解本发明，所以在本发明中未提供此类元素的描述。

[0218] 此外，所述的方法并非依赖于本发明列出的步骤的特定顺序，就此而言，步骤的特定顺序不应该解释为对权利要求的限定。定向于本发明的方法的权利要求不应该限于书写顺序的步骤的性能，并且本领域的技术人员可以容易地理解这些步骤可以改变并仍保持在本发明的精神和范围内。

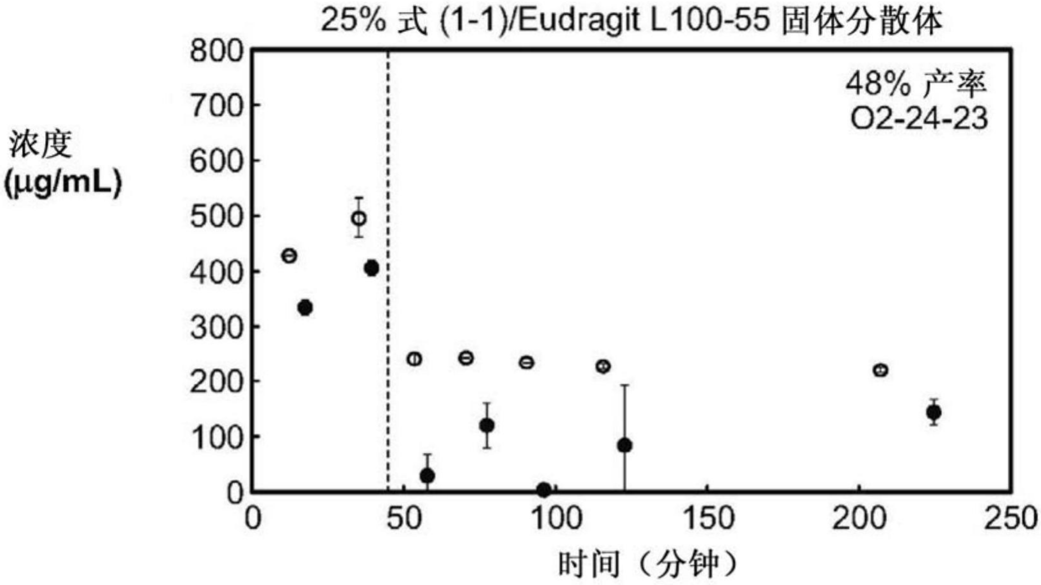

25% 式 (1-1)/Eudragit L100-55 固体分散体
48% 产率
O2-24-23
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
时间（分钟）

图 1A

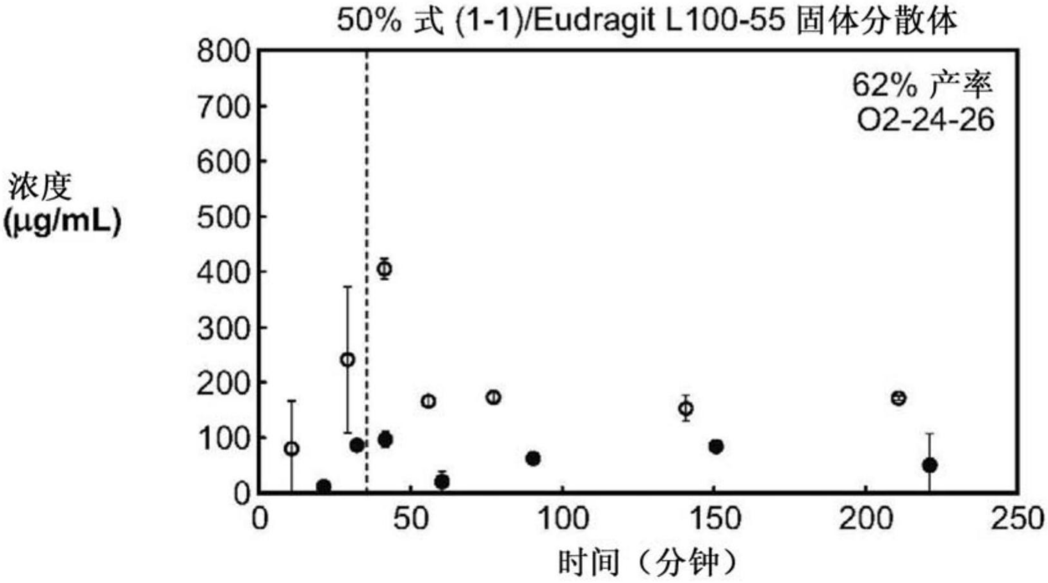

50% 式 (1-1)/Eudragit L100-55 固体分散体
62% 产率
O2-24-26
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
时间（分钟）

图 1B

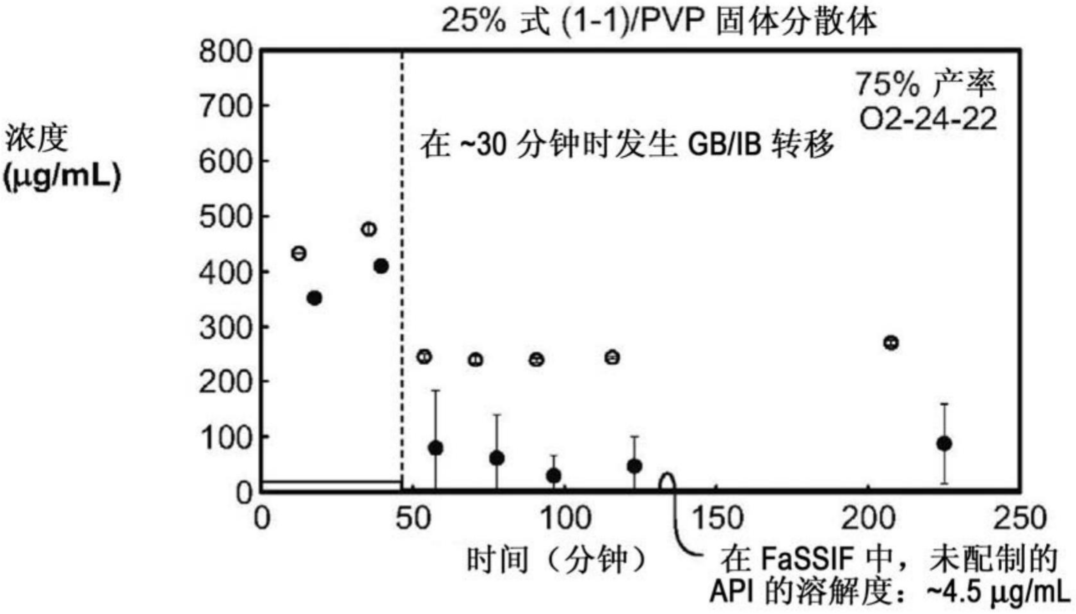

25% 式 (1-1)/PVP 固体分散体
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
在 ~30 分钟时发生 GB/IB 转移
75% 产率
O2-24-22
时间（分钟）
在 FaSSIF 中，未配制的
API 的溶解度：~4.5 μg/mL

图 1C

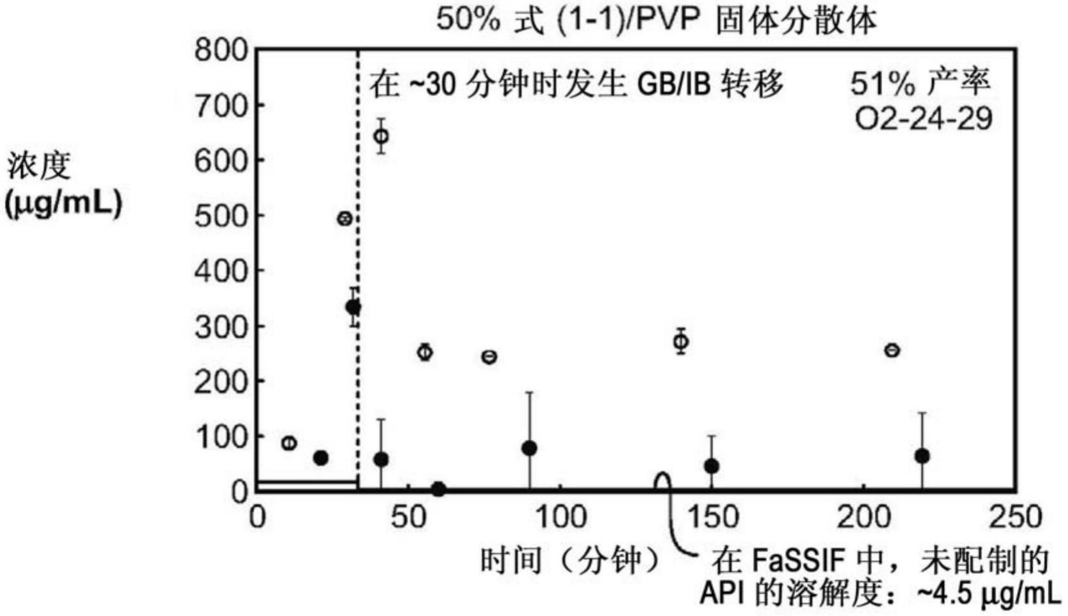

50% 式 (1-1)/PVP 固体分散体
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
在 ~30 分钟时发生 GB/IB 转移
51% 产率
O2-24-29
时间（分钟）
在 FaSSIF 中，未配制的
API 的溶解度：~4.5 μg/mL

图 1D

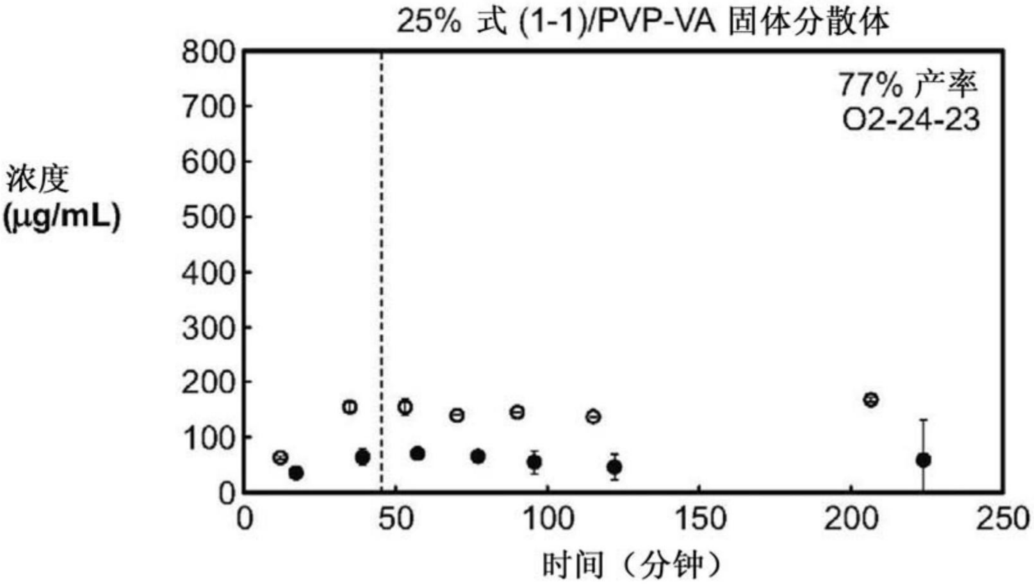

25% 式 (1-1)/PVP-VA 固体分散体
77% 产率
O2-24-23
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
时间（分钟）

图 1E

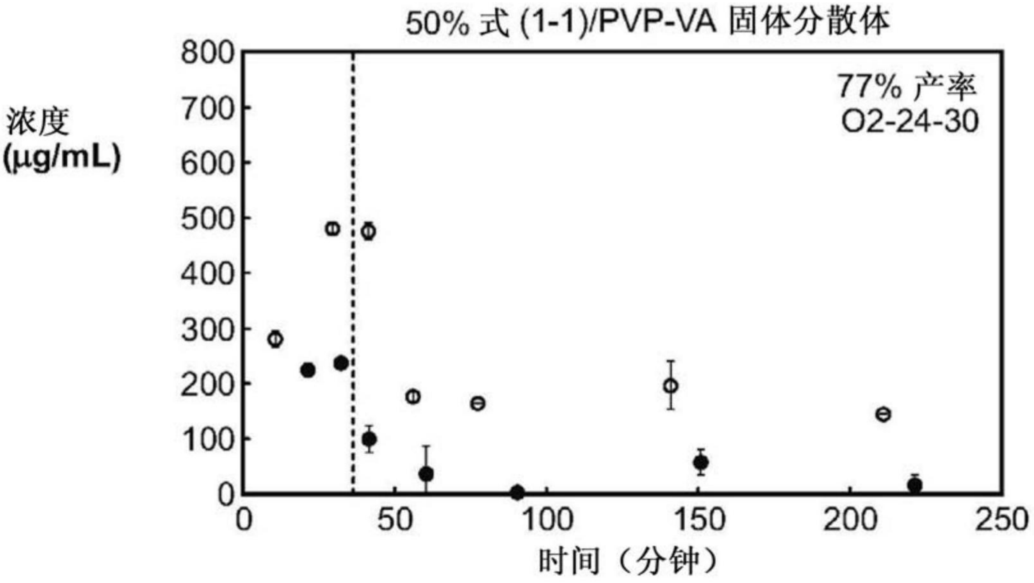

50% 式 (1-1)/PVP-VA 固体分散体
77% 产率
O2-24-30
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
时间（分钟）

图 1F

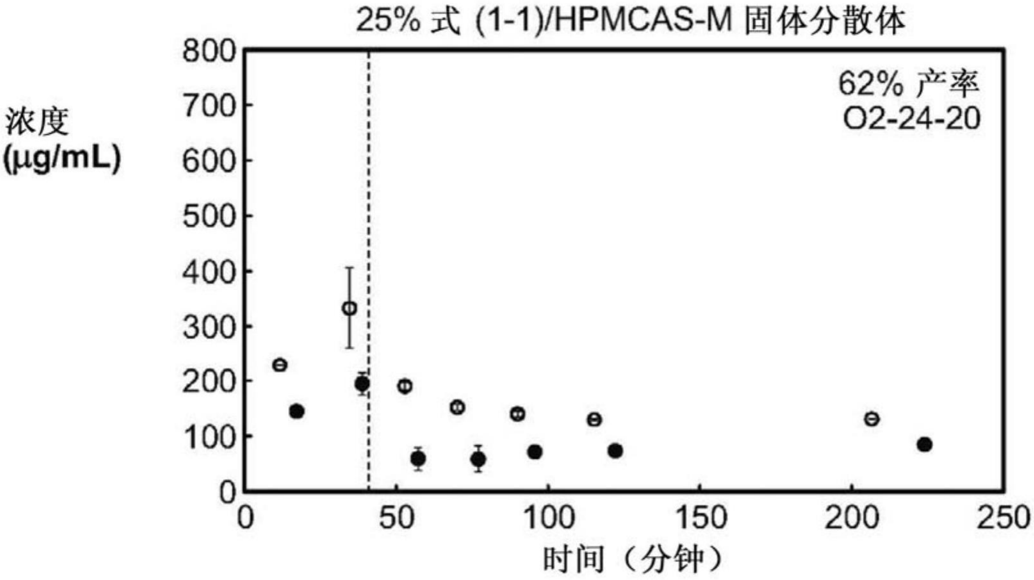

25% 式 (1-1)/HPMCAS-M 固体分散体
浓度 (μg/mL)
0
100
200
300
400
500
600
700
800
62% 产率
O2-24-20
0
50
100
150
200
250
时间（分钟）

图 1G

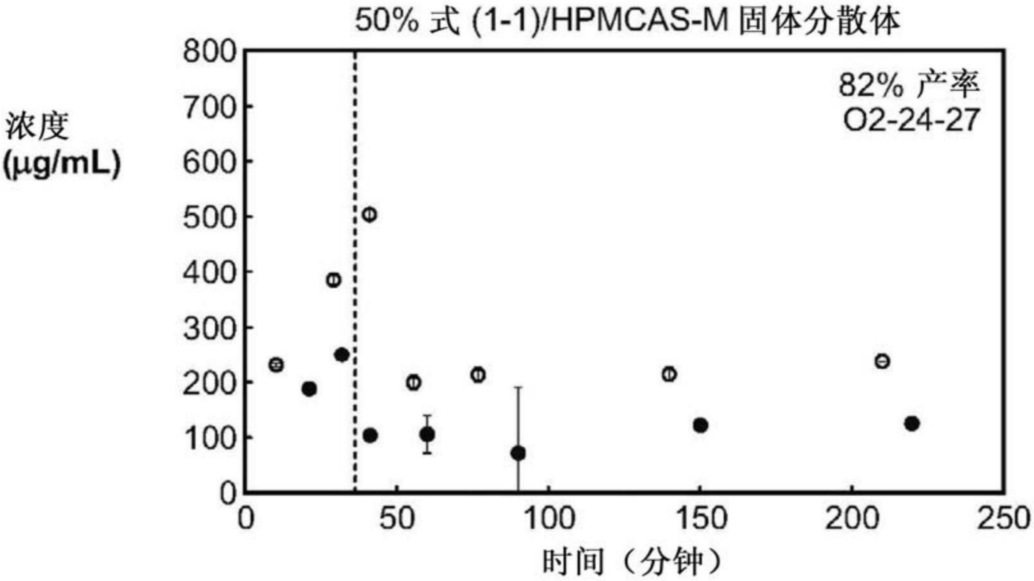

50% 式 (1-1)/HPMCAS-M 固体分散体
浓度 (μg/mL)
0
100
200
300
400
500
600
700
800
82% 产率
O2-24-27
0
50
100
150
200
250
时间（分钟）

图 1H

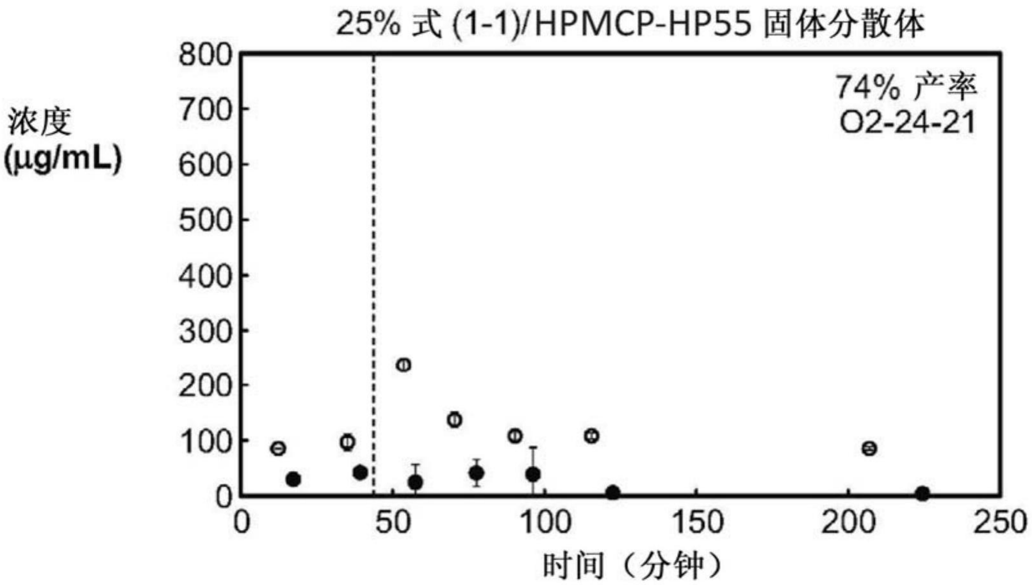

25% 式 (1-1)/HPMCP-HP55 固体分散体
浓度
(µg/mL)
800
700
600
500
400
300
200
100
0
74% 产率
O2-24-21
0
50
100
150
200
250
时间（分钟）

图 1I

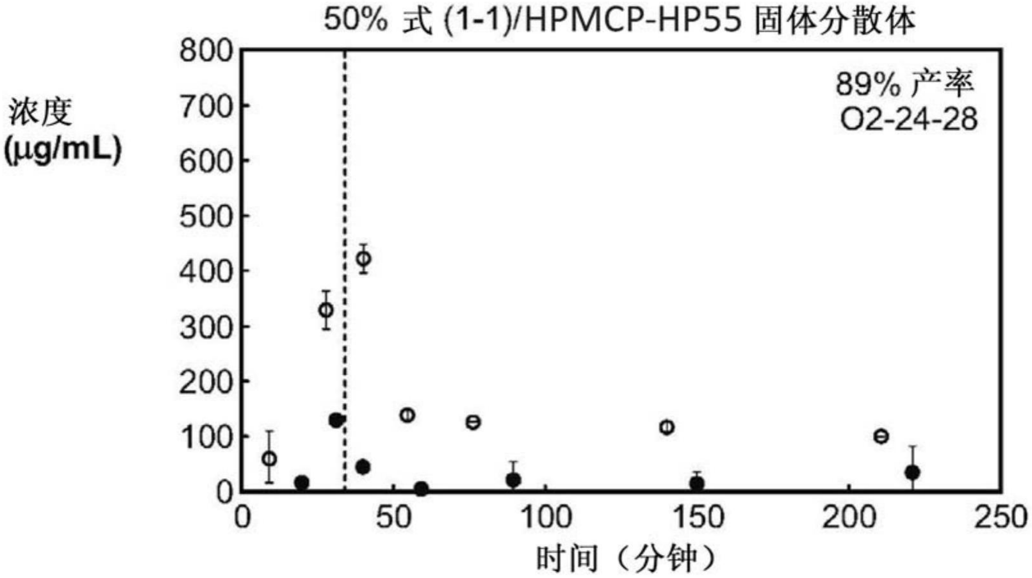

50% 式 (1-1)/HPMCP-HP55 固体分散体
浓度
(µg/mL)
800
700
600
500
400
300
200
100
0
89% 产率
O2-24-28
0
50
100
150
200
250
时间（分钟）

图 1J

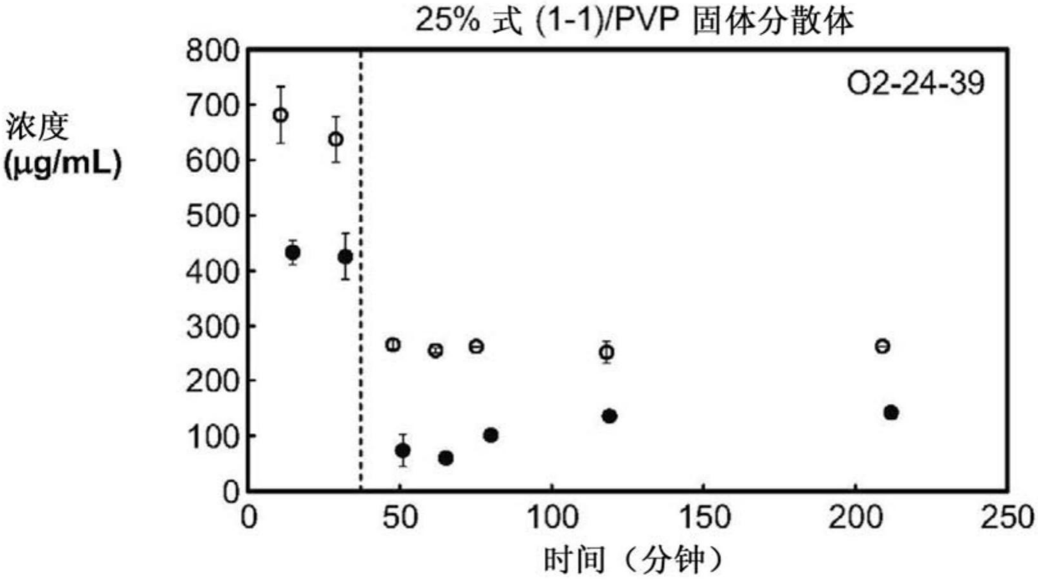

25% 式 (1-1)/PVP 固体分散体
O2-24-39
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
时间（分钟）

图 2A

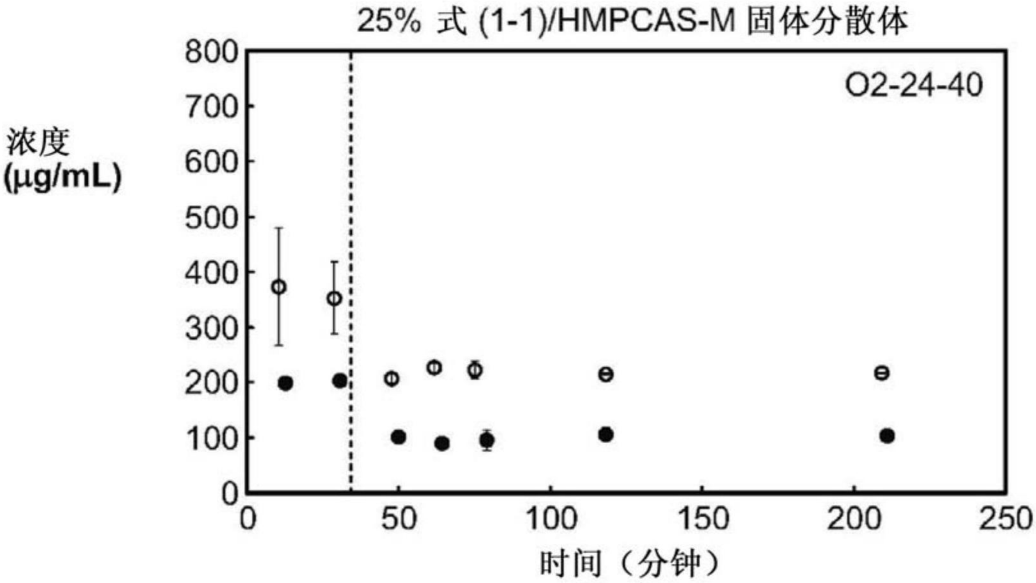

25% 式 (1-1)/HMPCAS-M 固体分散体
O2-24-40
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
时间（分钟）

图 2B

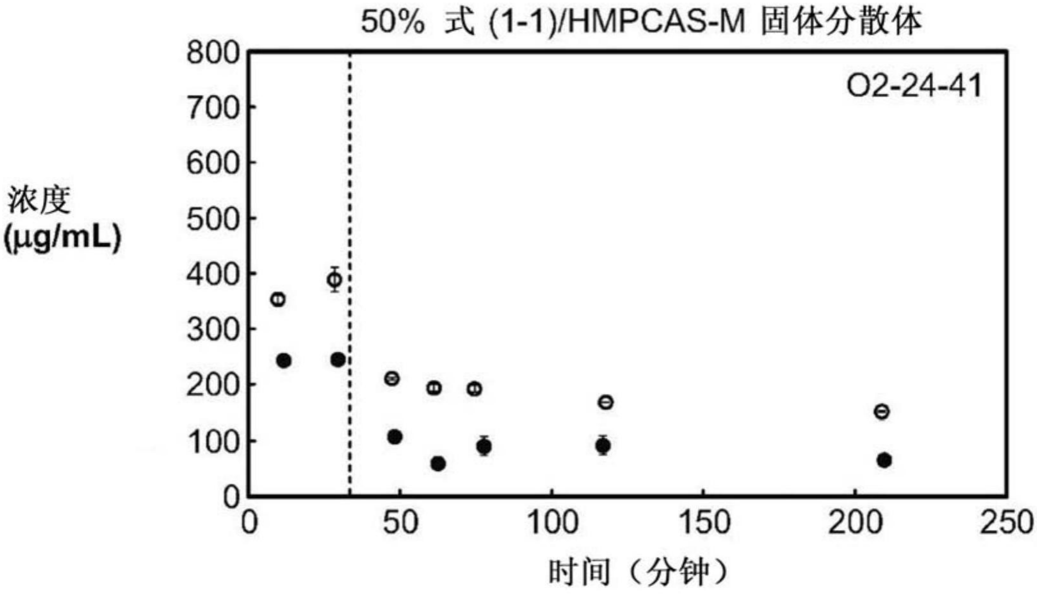

50% 式 (1-1)/HMPCAS-M 固体分散体
O2-24-41
浓度
(μg/mL)
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
时间（分钟）

图 2C

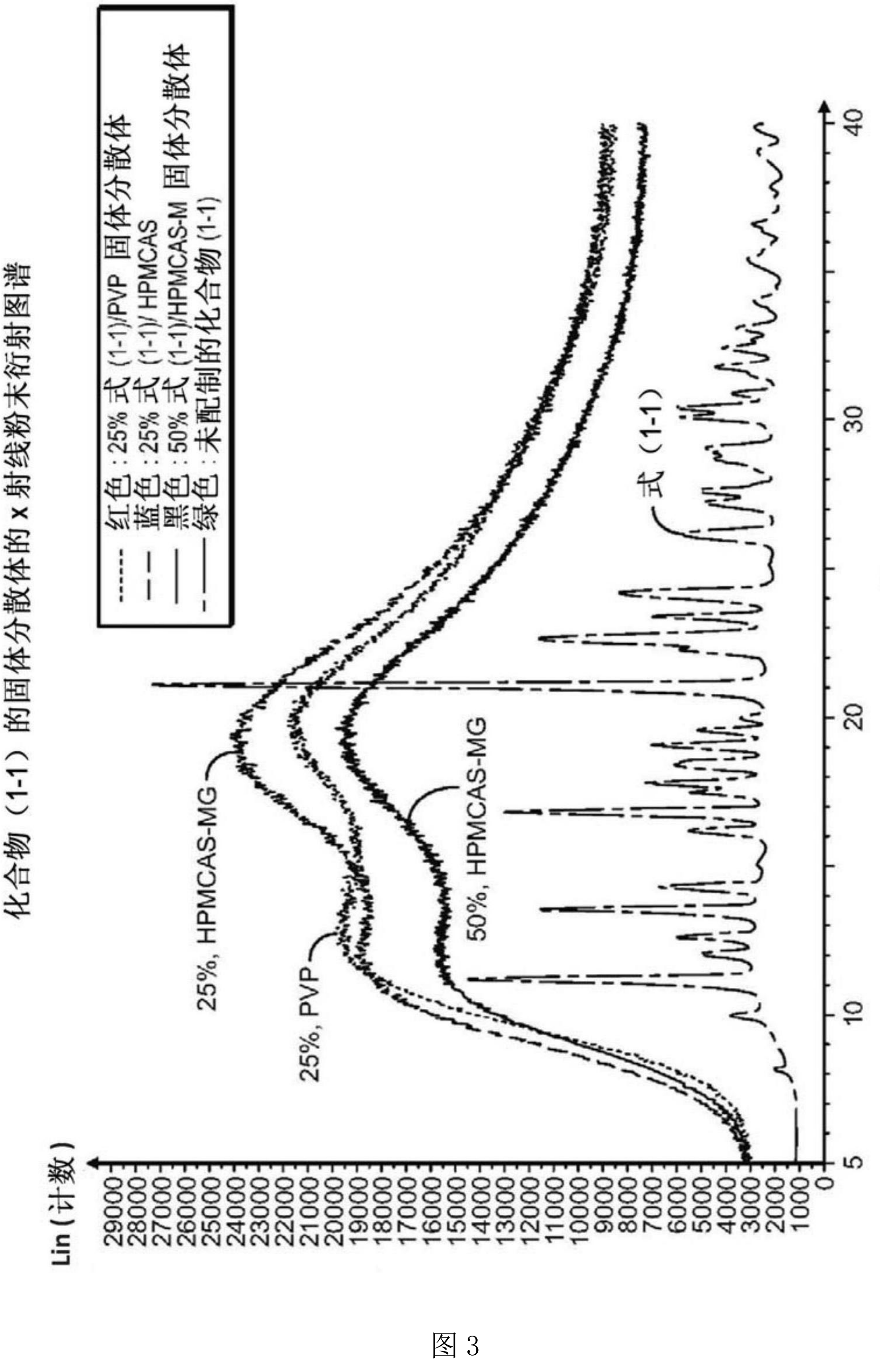

化合物（1-1）的固体分散体的x射线粉末衍射图谱
红色：25% 式（1-1)/PVP 固体分散体
蓝色：25% 式（1-1)/ HPMCAS
黑色：50% 式（1-1)/HPMCAS-M 固体分散体
绿色：未配制的化合物 (1-1)
25%, HPMCAS-MG
25%, PVP
50%, HPMCAS-MG
式（1-1）
Lin (计数)
29000
28000
27000
26000
25000
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
5
10
20
30
40
2θ

图 3

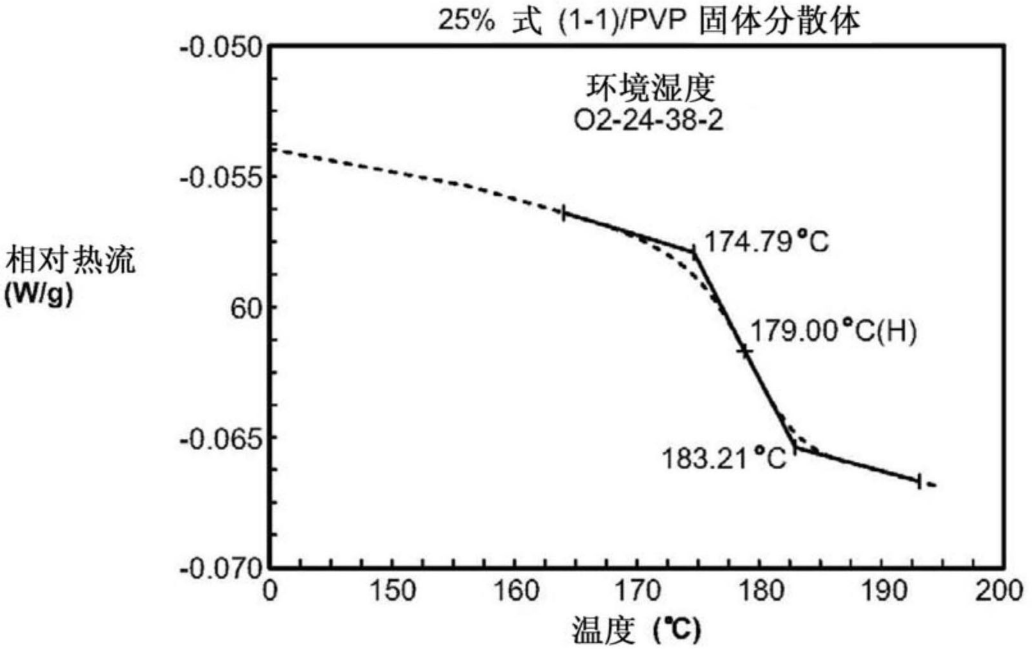

25% 式 (1-1)/PVP 固体分散体
环境湿度
O2-24-38-2
174.79°C
179.00°C(H)
183.21°C
相对热流
(W/g)
-0.050
-0.055
60
-0.065
-0.070
0
150
160
170
180
190
200
温度 (℃)

图 4A

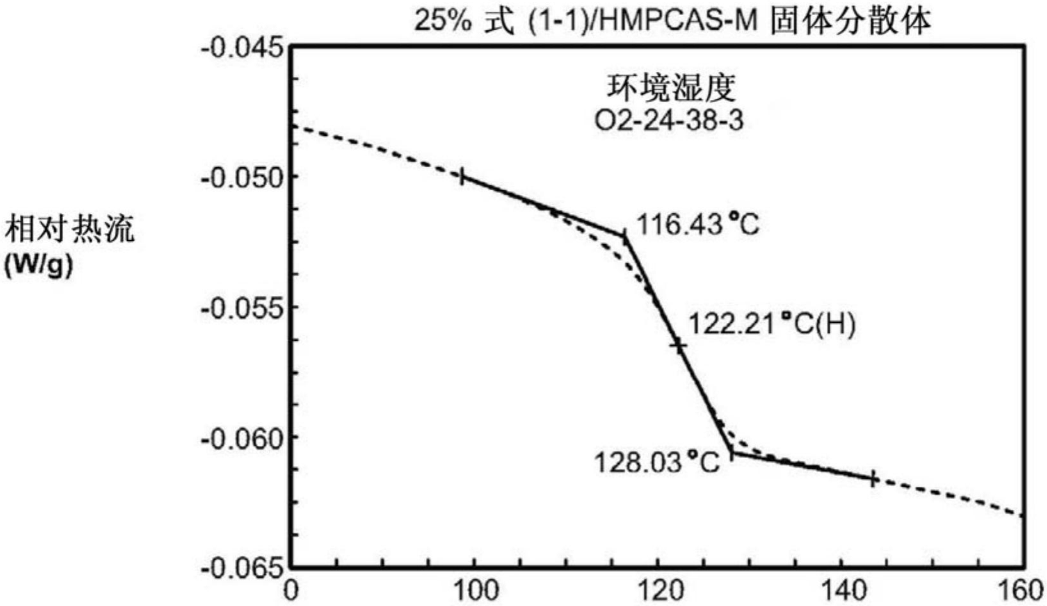

25% 式 (1-1)/HMPCAS-M 固体分散体
环境湿度
O2-24-38-3
116.43°C
122.21°C(H)
128.03°C
相对热流
(W/g)
-0.045
-0.050
-0.055
-0.060
-0.065
0
100
120
140
160
温度 (℃)

图 4B

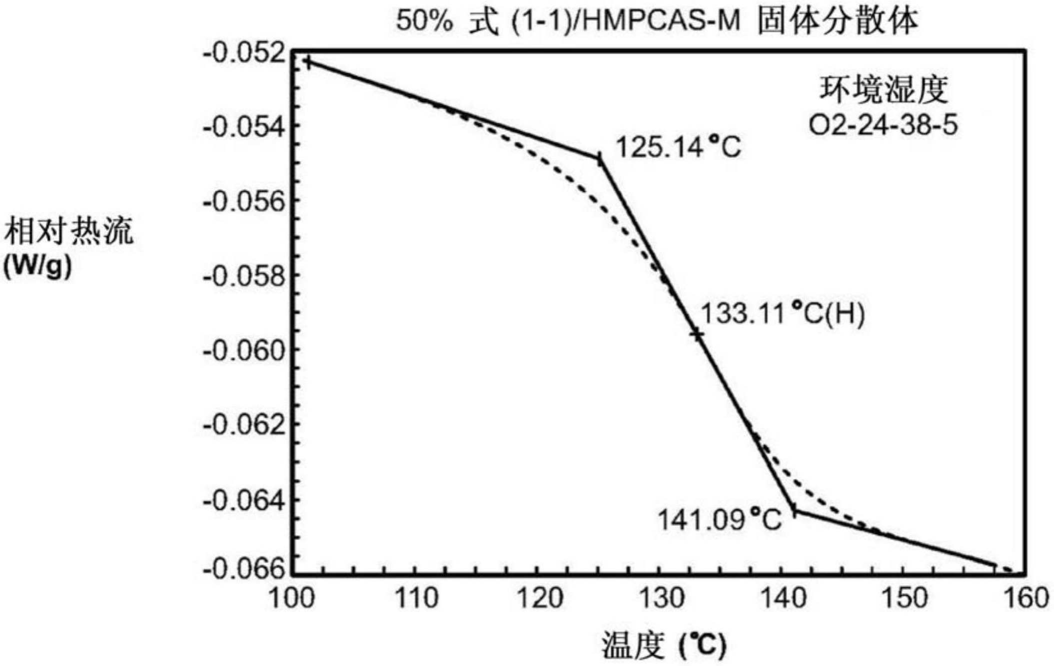

50% 式 (1-1)/HMPCAS-M 固体分散体
环境湿度
O2-24-38-5
125.14°C
133.11°C(H)
141.09°C
相对热流
(W/g)
-0.052
-0.054
-0.056
-0.058
-0.060
-0.062
-0.064
-0.066
100
110
120
130
140
150
160
温度 (°C)

图 4C

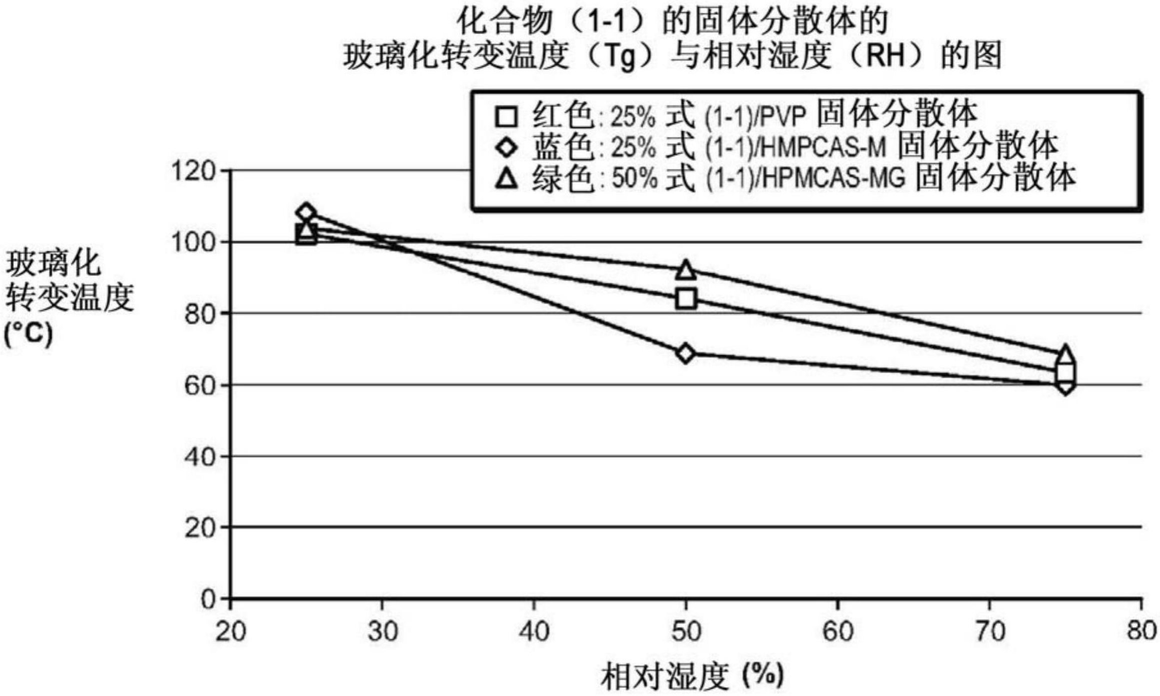

化合物（1-1）的固体分散体的
玻璃化转变温度（Tg）与相对湿度（RH）的图
□ 红色: 25% 式 (1-1)/PVP 固体分散体
◇ 蓝色: 25% 式 (1-1)/HMPCAS-M 固体分散体
△ 绿色: 50% 式 (1-1)/HPMCAS-MG 固体分散体
玻璃化
转变温度
(°C)
120
100
80
60
40
20
0
20
30
40
50
60
70
80
相对湿度 (%)

图 5

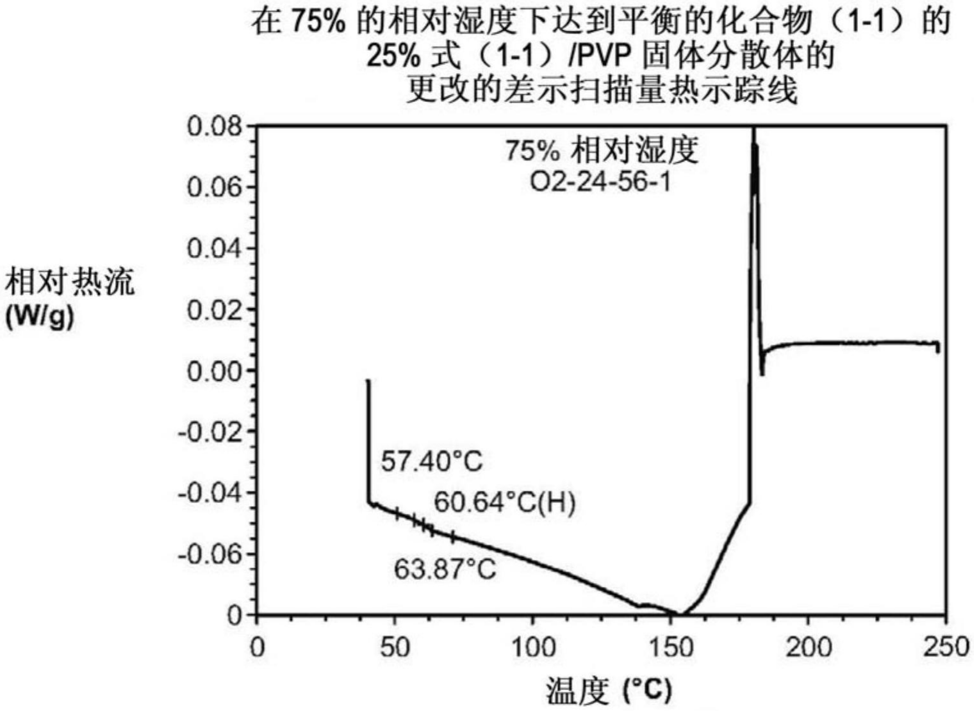

在 75% 的相对湿度下达到平衡的化合物（1-1）的
25% 式（1-1）/PVP 固体分散体的
更改的差示扫描量热示踪线
75% 相对湿度
O2-24-56-1
相对热流
(W/g)
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.06
0
57.40°C
60.64°C(H)
63.87°C
0
50
100
150
200
250
温度 (°C)

图 6

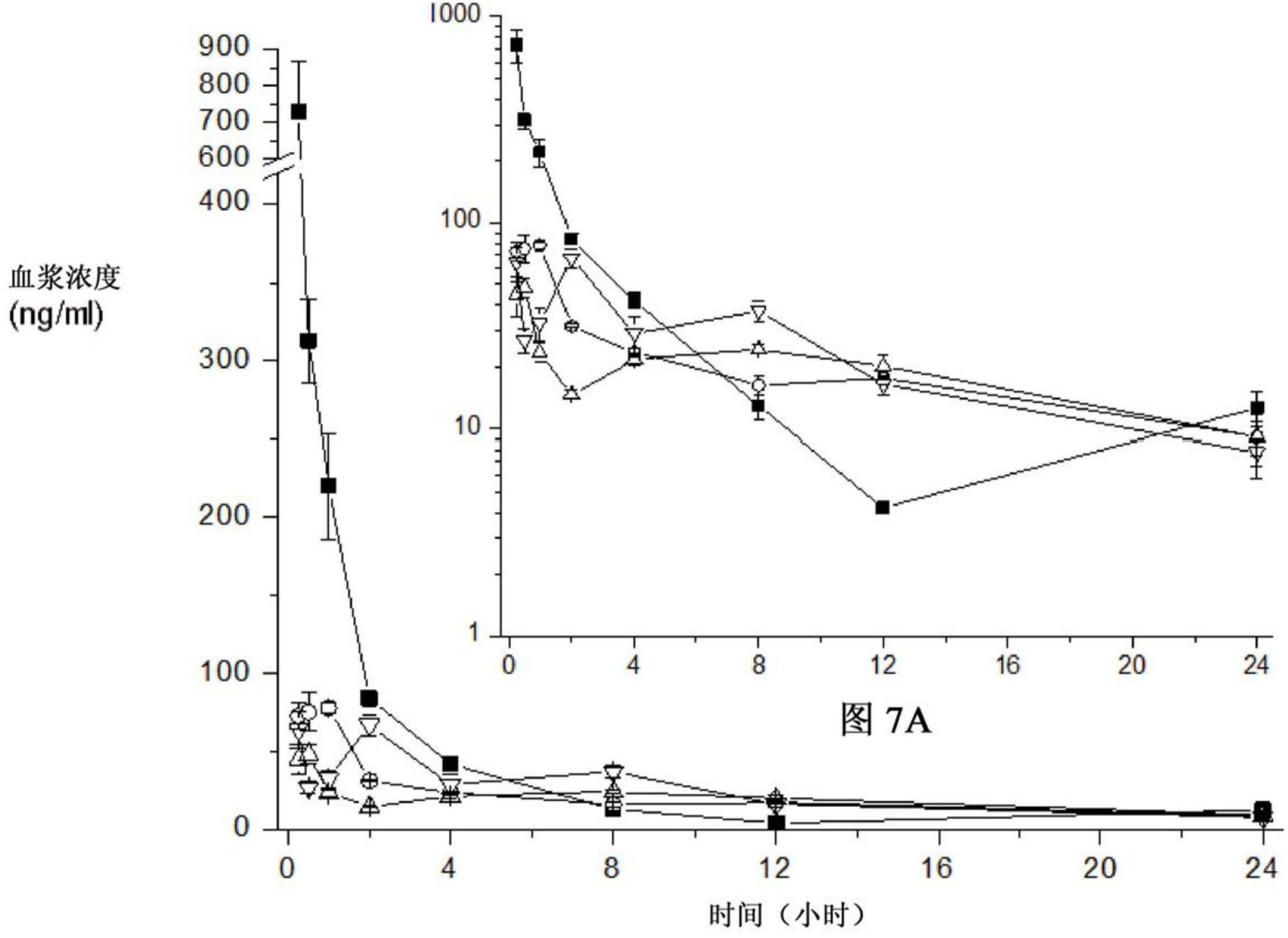

1000
100
10
1
0
4
8
12
16
20
24
血浆浓度
(ng/ml)
900
800
700
600
400
300
200
100
0
0
4
8
12
16
20
24
时间（小时）

图 7A

图 7B

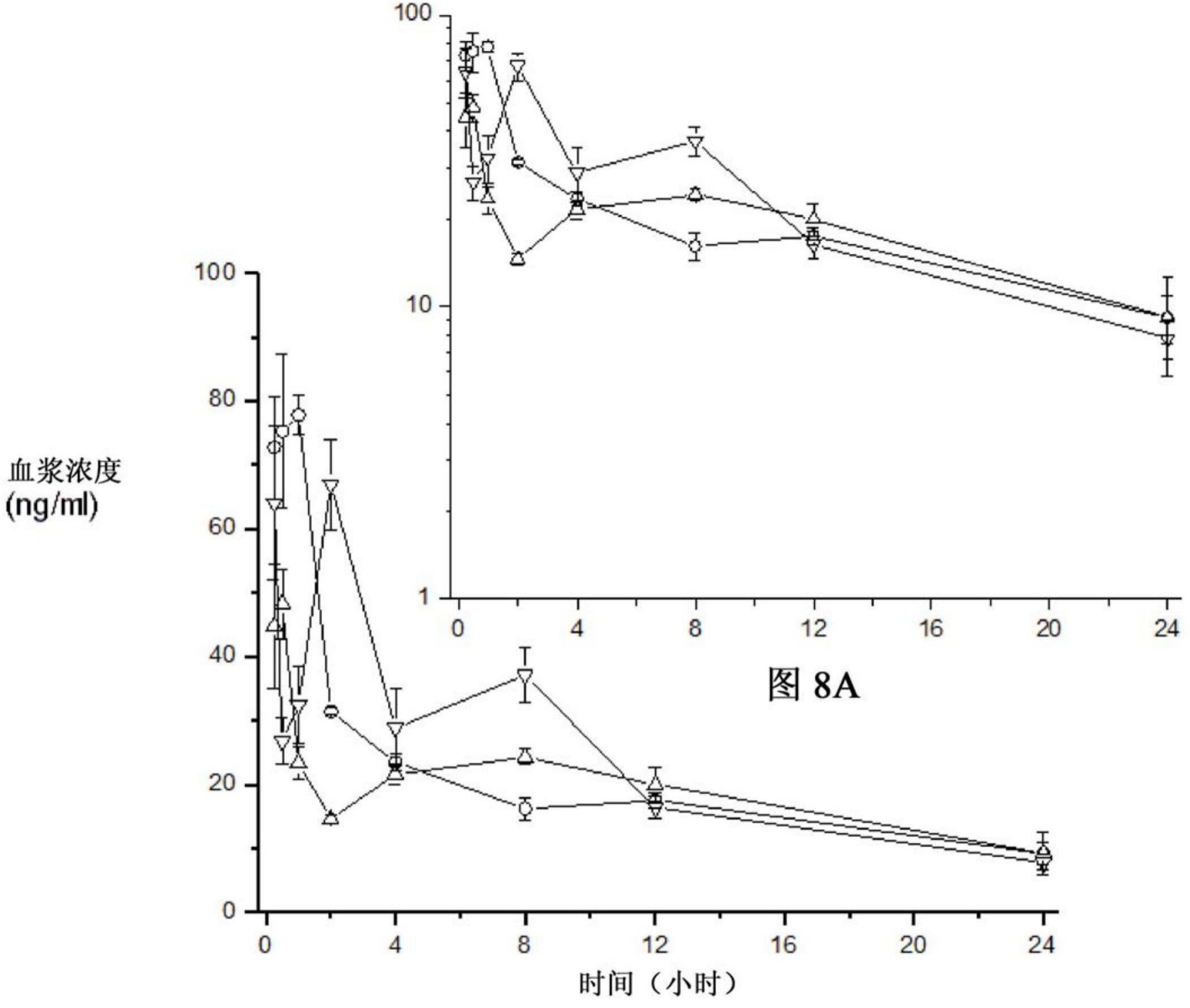

100
10
1
0
4
8
12
16
20
24
血浆浓度
(ng/ml)
100
80
60
40
20
0
0
4
8
12
16
20
24
时间（小时）

图 8A

图 8B

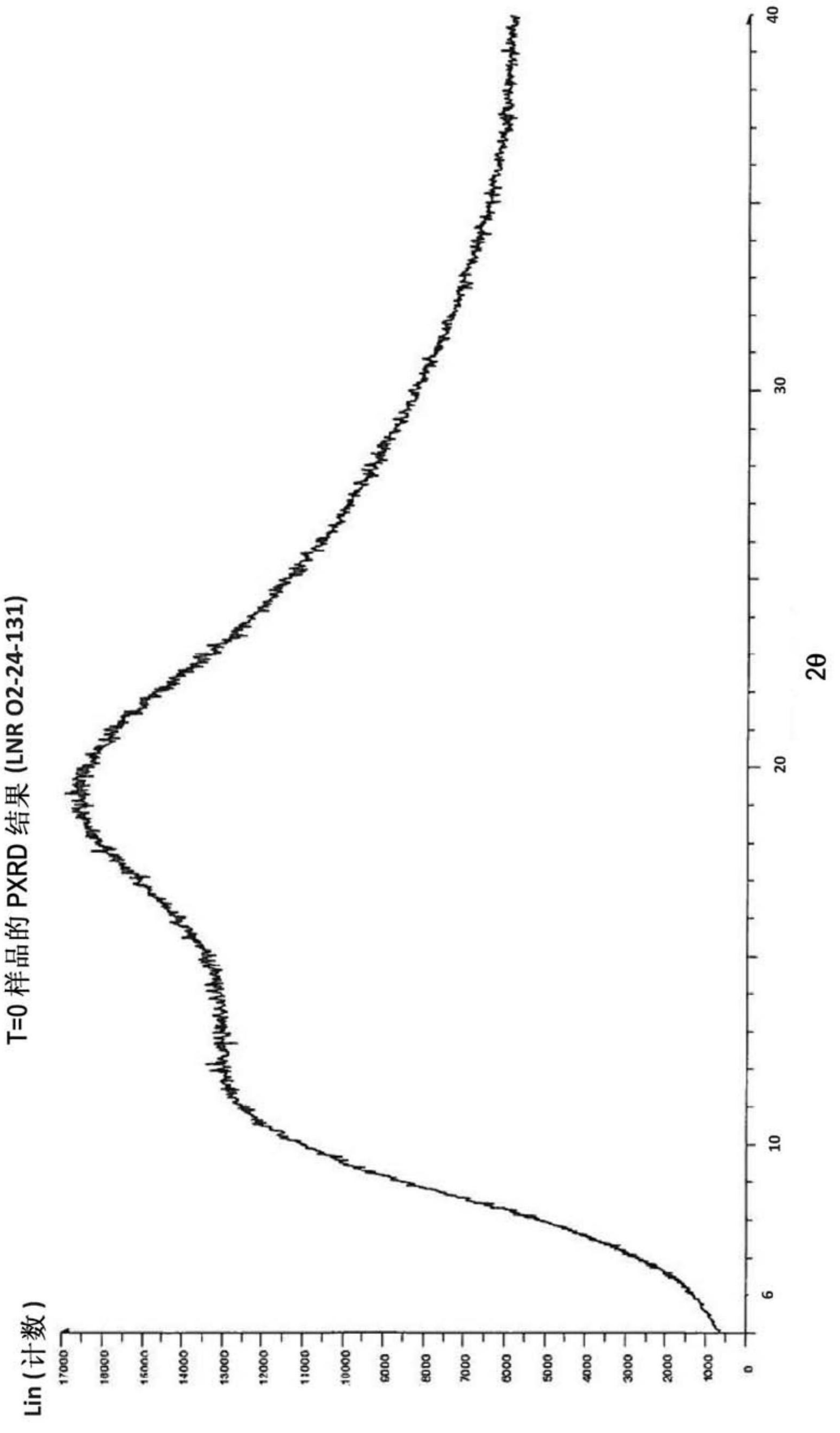
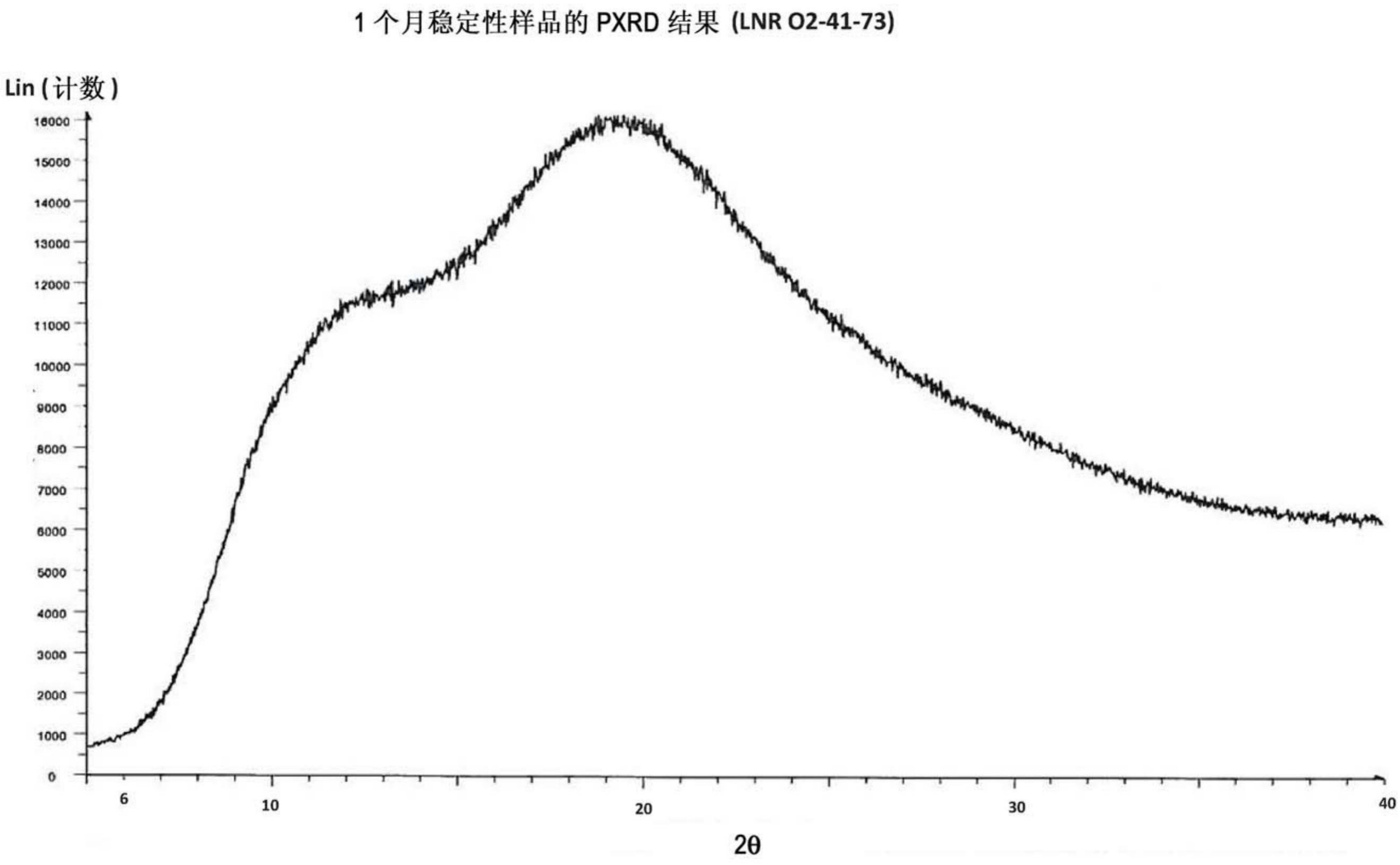

T=0 样品的 PXRD 结果 (LNR O2-24-131)
Lin (计数)
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
6
10
20
30
40
2θ

图 9



1 个月稳定性样品的 PXRD 结果 (LNR O2-41-73)

图 10

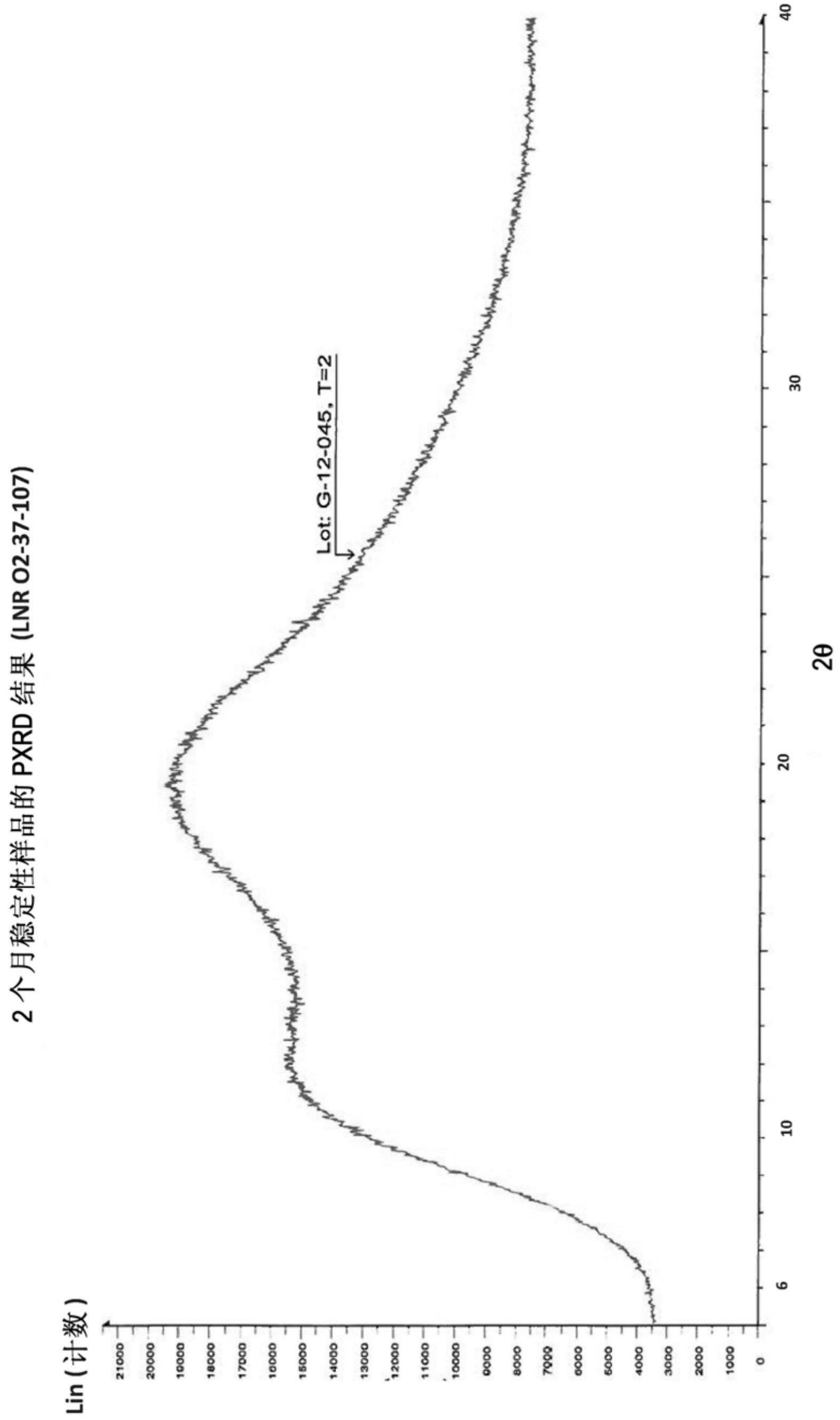

2 个月稳定性样品的 PXRD 结果 (LNR O2-37-107)
Lin (计数)
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
6
10
20
30
40
2θ
Lot: G-12-045, T=2

图 11

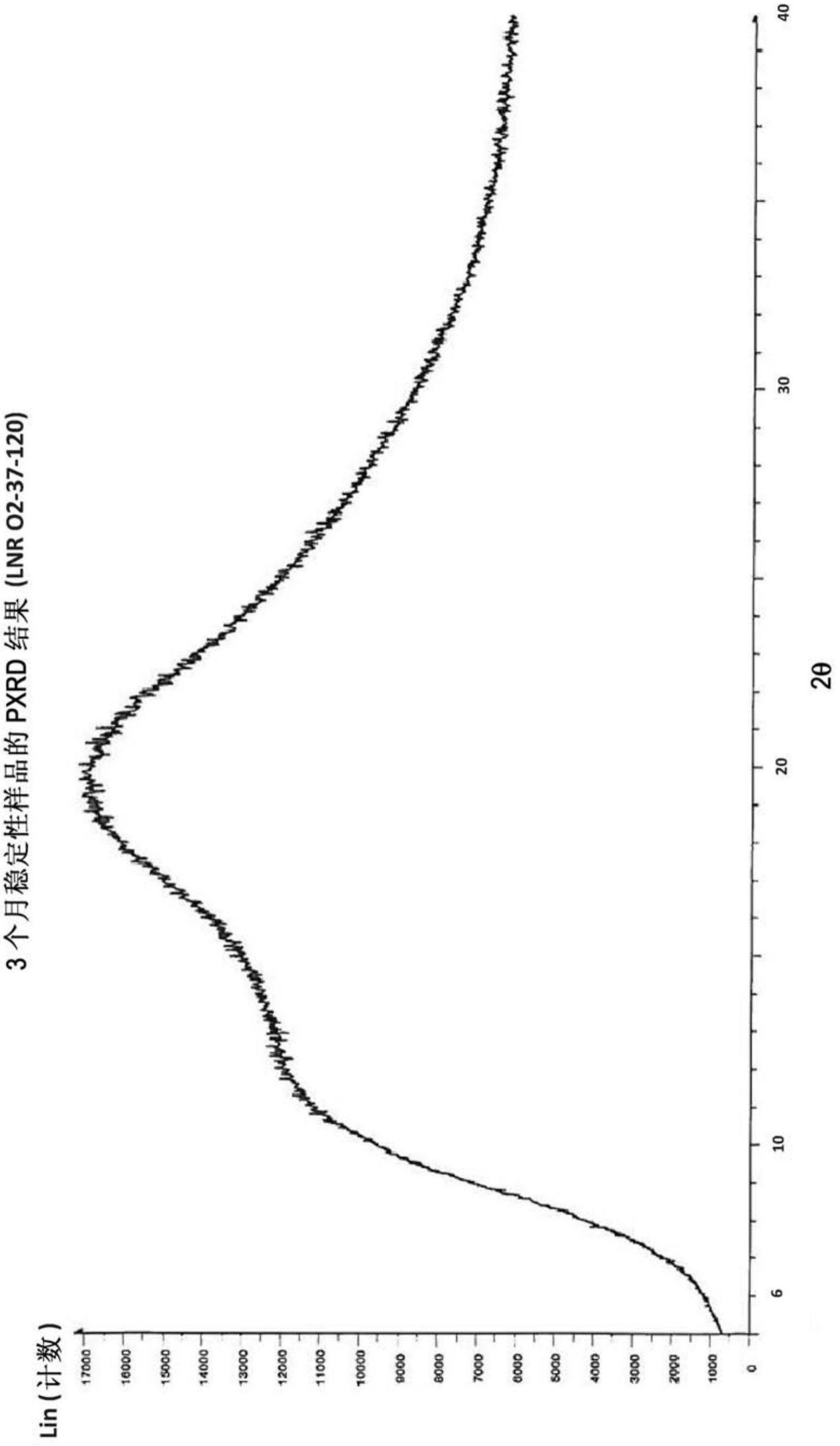

3 个月稳定性样品的 PXRD 结果 (LNR O2-37-120)
Lin (计数)
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
6
10
20
30
40
2θ

图 12

Abstract

A solid dispersion comprising an amorphous thienotriazolodiazepine compound of the Formula (I), wherein X is a halogen, R1 is C1-C4 alkyl, R2 is C1-C4 alkyl, a is an integer of 1-4, R3 is C1-C4 alkyl, C1-C4 hydroxyalkyl, C1-C4 alkoxy, phenyl optionally having substituent(s), or heteroaryl optionally having substituent(s), a pharmaceutically acceptable salt thereof or a hydrate thereof; and a pharmaceutically acceptable polymer. In one embodiment, the pharmaceutically acceptable polymer is HPMCAS. The solid dispersion may be made by spray drying.