FORMULATIONS FOR STABILIZING DISSOLUTION OF MEDICAMENTS

FIELD OF THE INVENTION

[0001] The present disclosure provides a pharmaceutical composition. The pharmaceutical composition can include a granule for suspension.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This is an International Application that claims priority to JP 2024-039505 filed March 13, 2024, which is incorporated by reference in its entirety.

DISCUSSION OF THE BACKGROUND

[0003] International Publication No. WO 2009/061744 discloses a method of treating or suppressing mitochondrial diseases such as Friedreich's ataxia (FRDA), Leber hereditary optic neuropathy (LHON), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS), Kearns-Sayre syndrome (KSS), and other disorders such as amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease, and pervasive developmental disorders such as autism, and describes compounds that are useful in the method, such as a 4-(p-quinolyl)-2-hydroxybutanamide derivative. The document also describes that that racemic 2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide is synthesized from racemic Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid).

[0004] International Publication No. WO 2016/100579 describes polymorphic and amorphous forms of anhydrate, hydrate, and solvates of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide and methods of using such compositions for treating or suppressing oxidative stress disorders, including mitochondrial disorders, impaired energy processing disorders, neurodegenerative diseases and diseases of aging, as well as methods of making such polymorphic and amorphous forms.

[0005] International Publication No. WO 2021/167095 describes an optically resolved Trolox intermediate and a method for producing same.

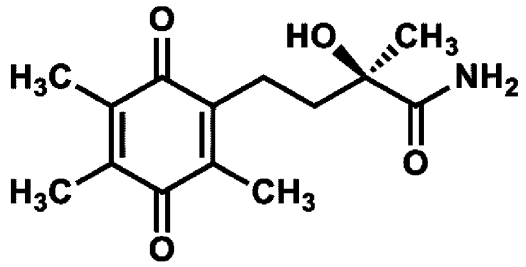
[0006] Additional references include: International Publication No. WO 2009/061744, International Publication No. WO 2016/100579, and International Publication No. WO 2021/167095.

SUMMARY

[0007] The inventors have found granules for suspension containing a compound represented by Formula 1 or a pharmaceutically acceptable salt or solvate thereof, which has good dissolution characteristics after suspension.

[0008] The present disclosure provides the following:

[0009] [1] Granules comprising a compound set forth in Formula 1:



or pharmaceutically acceptable salt or solvate thereof, wherein 20% or less by weight of particles constituting the granules have a particle size of 500 μm or greater.

[00010] [2] The granules of any one of the above item, which is a powder for oral solusion (or suspension).

[00011] [3] The granules of any one of the above items, wherein the particles contain a binder.

[00012] [4] The granules of any one of the above items, wherein the particles contain a dispersant.

[00013] [5] The granules of any one of the above items, wherein the particles contain a sweetener.

[00014] [6] The granules of any one of the above items, wherein the particles contain a suspending agent.

[00015] [7] The granules of any one of the above items, wherein the particles contain a binder, a dispersant, and a sweetener.

[00016] [8] The granules of any one of the above items, wherein the particles contain a binder, a dispersant, a sweetener and a suspending agent.

[00017] [9] The granules of any one of the above items, wherein the binder includes at least one binder selected from the group consisting of hydroxypropylcellulose, hypromellose (hydroxypropylmethylcellulose), copovidone, methylcellulose, povidone, polyvinyl alcohol, polyvinyl alcohol/polyethylene glycol graft copolymer, and xanthan gum.

[00018] [10] The granules of any one of the above items, wherein the binder is hydroxypropylcellulose or copovidone.

[00019] [11] The granules of any one of the above items, wherein the binder is hypromellose.

[00020] [12] The granules of any one of the above items, wherein the binder is hydroxypropyl cellulose.

[00021] [13] The granules of any one of the above items, wherein the dispersant includes at least one dispersant selected from the group consisting of light silicic anhydride, magnesium metasilicate aluminate, polyethylene glycol 6000, corn starch, microcrystalline cellulose and carboxymethylcellulose sodium, carmellose, calcium carmellose, and sodium stearyl fumarate.

[00022] [14] The granules of any one of the above items, wherein the dispersant is light anhydrous silicic acid.

[00023] [15] The granules of any one of the above items, wherein the sweetener is sucralose.

[00024] [16] The granules of any one of the above items, wherein the suspending agent is a carboxyvinyl polymer.

[00025] [17] The granules of any one of the above items, wherein the binder is hydroxypropyl cellulose, the suspending agent is a carboxyvinyl polymer, and the sweetener is sucralose.

[00026] [18] The granules of any one of the above items, wherein the binder is hydroxypropyl cellulose, the suspending agent is a carboxyvinyl polymer, the sweetener is sucralose, and the dispersant is light anhydrous silicic acid.

[00027] [19] The granules of any one of the above items, wherein the binder is hypromellose, the suspending agent is a carboxyvinyl polymer, the sweetener is sucralose.

[00028] [20] The granules of any one of the above items, wherein the binder is hypromellose, the suspending agent is a carboxyvinyl polymer, the sweetener is sucralose, and the dispersant is light anhydrous silicic acid.

[00029] [21] The granules of any one of the above items, wherein the binder is copovidone, the suspending agent is a carboxyvinyl polymer, and the sweetener is sucralose.

[00030] [22] The granules of any one of the above items, wherein the binder is copovidone, the suspending agent is a carboxyvinyl polymer, the sweetener is sucralose, and the dispersant is light anhydrous silicic acid.

[00031] [23] The granules of any one of the above items, wherein 15% or less by weight of the particles constituting the granules have a particle size of 500 μm or larger.

[00032] [24] The granules of any one of the above items, wherein 10% or less by weight of the particles constituting the granules have a particle size of 500 μm or greater.

[00033] [25] The granules of any one of the above items, wherein 5% or less by weight of the particles constituting the granules have a particle diameter of 500 μm or greater.

[00034] [26] The granules of any one of the above items, wherein the granules of any one of the above items, wherein the granule contains 1 mg to 1000 mg of a binder with respect to 1000 mg of a compound represented by Formula 1 or a pharmaceutically acceptable salt or solvate thereof.

[00035] [27] The granules of any one of the above items, wherein the granules contain 0.01 to 10% by weight of a dispersant with respect to the weight of the entire granules.

[00036] [28] The granules of any one of the above items, wherein the granules contain 1 mg to 1000 mg of sweetener with respect to 1000 mg of the compound represented by Formula 1 or pharmaceutically acceptable salt or solvate thereof.

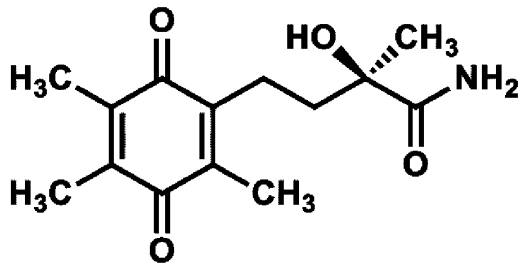
[00037] [29] The granules of any one of the above items, wherein the granule contains 1 mg to 1000 mg of suspension for 1000 mg of the compound represented by Formula 1 or pharmaceutically acceptable salt or solvate thereof.

[00038] [30] The granules of any one of the above items, wherein the granules is produced via a granulation liquid spraying process.

[00039] [31] The granules of any one of the above items, characterized by improved dissolution stability after storage.

[00040] [32] A method for manufacturing granules comprising a compound or pharmaceutically acceptable salt or solvate thereof represented by

Formula 1:



the method comprises the steps of:

admixing the compound or pharmaceutically acceptable salt or solvate thereof with other materials constituting the granules;

preparing a granule from the admixed material, wherein 20% or less by weight of the particles constituting the granules are prepared to have a particle size of 500 μm or greater,

wherein 20% or less by weight of the particles constituting the granule have a particle size of 500 μm or greater.

[00041] [33] The method according to any of the above items, wherein the step of preparing the granules includes a granulation liquid spraying process.

[00042] [34] The granules according to any one of the above items, or the granules manufactured by the method according to any one of the above items, which are used for manufacturing granules for suspension.

[00043] [35] Granules for suspension comprising the granules according to any of the above items.

[00044] [36] The granules according to any one of the above items, which is used for preparing a suspension liquid.

[00045] [37] A suspension liquid comprising the granules according to any one of the above items.

[00046] [38] A method of treating or preventing a disease in a subject in need thereof, comprising the step of administering to the subject in need thereof an effective amount of the suspension liquid according to any one of the above items.

[00047] [39] A method for producing granules for suspension according to any one of the above items, comprising the step of admixing the compound or a pharmaceutically acceptable salt or solvate thereof with the binder.

[00048] [40] A method for preparing a suspension liquid for administration to a subject at a medical setting, comprising the process of admixing the granules of any one of the above items with a necessary additive and/or a suspension solvent (including, for example, a water-soluble medium such as purified water).

[00049] [41] The granules according to any one of the above items, the suspension liquid according to the above item, or the method as described in any one of the above items, which is/are for use in treating or inhibiting oxidative stress disorders, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, or enhancing one or more energy biomarkers.

[00050] [42] The granules according to any one of the above items, the suspension liquid according to the above item, or the method as described in any one of the above items, which is/are for use in treating or inhibiting mitochondrial disorders; hereditary mitochondrial disease; Alpers disease; Barth syndrome; beta-oxidation defect; carnitine-acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndrome; coenzyme Q10 deficiency; complex I deficiency; complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive

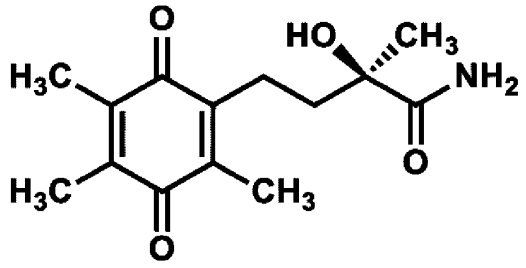
external ophthalmoplegia (CPEO); CPT I deficiency; CPT II deficiency; Friedreich's ataxia (FA); glutaric aciduria type II; Kearns-Sayre syndrome (KSS); lactic acidosis; long chain acyl CoA dehydrogenase deficiency (LCAD); LCHAD; Leigh syndrome; Leigh-like syndrome; Leber hereditary optic neuropathy (LHON); lethal infantile cardiomyopathy (LIC); Luft disease; multiple acyl CoA dehydrogenase deficiency (MAD); medium chain acyl CoA dehydrogenase deficiency (MCAD); mitochondrial MCAD); mitochondrial myopathy, encephalopathy, lactoacidosis, and stroke (MELAS); myoclonus epilepsy with red ragged fibers (MERRF); mitochondrial recessive ataxia syndrome (MIRAS); mitochondrial cell disease, mitochondrial DNA depletion; mitochondrial encephalopathy; mitochondrial myopathy; mitochondrial neurogastrointestinal encephalopathy (MNGIE); neuropathy, ataxia, retinitis pigmentosa (NARP); Pearson syndrome; pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; a disorder associated with a POLG mutation; respiratory chain disorders; short chain acyl CoA dehydrogenase deficiency (SCAD); SCHAD; very long chain acyl CoA dehydrogenase deficiency (VLCAD); myopathy; cardiomyopathy; encephalomyopathy; neurodegenerative disease; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis (ALS); motor neuron disease; neurological disease; epilepsy; age-related diseases; macular degeneration; diabetes; metabolic syndromes; cancer; brain cancer; genetic disorders; Huntington's disease; mood disorders; schizophrenia; bipolar disorder; pervasive developmental disorder; autistic disorder; Asperger's syndrome; childhood disintegrative disorder (CDD); Rett disorder or Rett syndrome; PDD not otherwise specified (PDD-NOS); cerebrovascular accidents; stroke; visual impairment; optic neuropathy; dominantly inherited juvenile optic atrophy; toxic-induced optic neuropathy; glaucoma; Stargardt macular dystrophy; diabetic retinopathy; diabetic maculopathy; retinopathy of prematurity; ischemia-reperfusion related retinal damage; oxygen toxicity; abnormal hemoglobinopathy; thalassemia; sickle cell anemia; seizures; ischemia; renal tubular acidosis; attention deficit hyperactivity disorder (ADHD); neurodegenerative disorders leading to hearing or balance impairment; dominant optic atrophy (DOA); maternally inherited diabetes mellitus with deafness (MIDD); chronic fatigue; contrast-induced renal injury; contrast-induced retinopathy damage; no beta lipoproteinemia; retinal pigmentary degeneration; Wolfram disease;

Tourette syndrome; cobalamin c deficiency; methylmalonic aciduria; glioblastoma; Down syndrome; acute tubular necrosis; muscular dystrophy; white matter dystrophy; progressive supranuclear palsy; spinal muscular atrophy; hearing loss; noise-induced hearing loss; traumatic brain injury; juvenile Huntington disease; multiple sclerosis; NGLY1; NGLY1 deficiency; NGLY1-congenital disorder of deglycosylation; multiple system atrophy; adrenoleucodystrophy; and adrenospinal neuropathy, to treat or inhibit an oxidative stress disorder selected from the group consisting of adrenoleucodystrophy; and adrenospinal neuropathy.

[00051] [43] The granules according to any one of the above items, the suspension liquid according to the above item, or the method as described in any one of the above items, which is/are for use in treating or inhibiting treating or preventing amyotrophic lateral sclerosis (ALS).

[00052] [44] Granules comprising particles of a compound represented by the following:

Formula 1:



or a pharmaceutically acceptable salt or solvate thereof, and hypromellose or a hypromellose analogue.

[00053] [45] The granules according to any one of above item, wherein the hypromellose or hypromellose analog is hypromellose.

[00054] [46] The granules according to any one of above items, wherein the granules have the characteristics described in any one or more of the items from item 1-43.

[00055] It is intended that in the present disclosure, one or more of the above features may be provided in further combinations in addition to the explicitly stated combinations. Further embodiments and advantages of the present disclosure will be recognized by those skilled in the art upon reading and understanding the following detailed description, if necessary. The features and significant actions and effects of the present disclosure other than those described above will become clear to those skilled in the art by referring to the following sections and drawings of embodiments of the invention.

[00056] The present disclosure provides granules for suspension with good dissolution characteristics after suspension.

BRIEF DESCRIPTION OF THE DRAWINGS

[00057] Figure 1 depicts particle size distribution is Example 1 and Comparison Example 1.

[00058] Figure 2 depicts results of Examples 2-5.

DETAILED DESCRIPTION

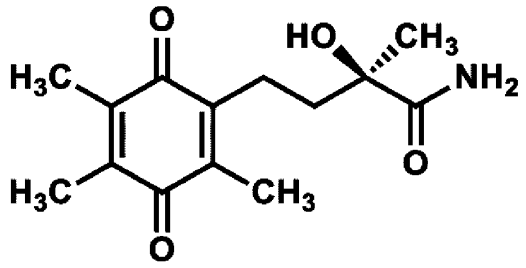
[00059] The present disclosure is described hereinafter in more detail. Throughout the entire specification, a singular expression should be understood as encompassing the concept thereof in the plural form, unless specifically noted otherwise. Thus, singular articles (e.g., “a”, “an,” “the,” and the like. in the case of English) should also be understood as encompassing the concept thereof in the plural form, unless specifically noted otherwise. Further, the terms used herein should be understood as being used in the meaning that is commonly used in the art, unless specifically noted otherwise. Therefore, unless defined otherwise, all terminologies and scientific technical terms that are used herein have the same meaning as the general understanding of those skilled in the art to which the present invention pertains. In case of a contradiction, the present specification (including the definitions) takes precedence.

[00060] The abbreviations used herein have the conventional meaning within the scope of the art unless specifically noted otherwise.

[00061] The term "about" for a value or parameter herein includes variations about the value or parameter itself. Unless specifically noted otherwise, "about X" for example includes "X" itself as well as values with an acceptable error of ± 10% therefrom.

[00062] Compound 1 as used herein is a compound of the following formula:

[00063] Formula 1:



[00064] "Granules" herein refers to dosage forms composed of particles with a certain range in size, which are obtained by granulating raw materials such as powder, bulk, solution, or molten liquid by wet granulation, dry granulation, or heated granulation methods. As used herein, the particles comprising granules may contain, in addition to the active ingredient, any ingredient that causes the particles to be composed. Such ingredients may include binders, dispersants, surfactants, disintegrants, sweeteners, and various other additives. Granules are typically "granules" as described in the Pharmacopoeia, and may also be powders for oral solution or suspension (or suspension), and the like., as described in other pharmacopoeias.

[00065] As used herein, granules can be characterized by the particle size of the particles that make up or constituting the granules. Granules are also characterized by the weight ratio of the particles that make up the granules. The granules may be expressed in terms of the ratio of particle diameters above a specific particle diameter (e.g., 750 μm, 500 μm, 250 μm, and the like) of the particles that make up the granules. Typically, the weight ratio of the particles that make up The granules is 20% or less, 19% or less, 18% or less, 17% or less, 16% or less, 15% or less, 14% or less, 13% or less, 12% or less, 11% or less, 10% or less, 9 or less, 8wt% or less, 7wt% or less, 6wt% or less, 5wt% or less, 4wt% or less, 3wt% or less, 2wt% or less, 1wt% or less, and the like. Without wishing to be bound by theory, it has been found that reducing the ratio of particles larger than a

specific particle size improves the dissolution stability, especially after storage, when looking at the dissolution stability when preparing suspension liquids using granules containing the active ingredient of the present disclosure. In particular, as a result of intensive research, it has been found that lowering the weight ratio of particles larger than 500 μm in diameter resulted in better dissolution stability after storage.

[00066] As used herein, "binders" are additives used to form powder mixtures containing active pharmaceutical ingredients (APIs) and additives by imparting binding power thereto. The binders are additives that fix the ratio of APIs and additives in a formulation and make the content uniform, or improve flowability by increasing the size of formulation particles in solid state. Examples include: cellulose binders, povidone binders, vinyl alcohol binders, and thickening polysaccharide binders.

[00067] Examples of cellulosic binders include hydroxypropyl cellulose, hypromellose, methylcellulose, hypromellose phthalate, hypromellose acetate succinate, carmellose, hydroxyethyl cellulose, and alginic acid.

[00068] Hypromellose is a type of hydroxyalkylalkyl cellulose, used as an abbreviation for hydroxypropyl methylcellulose, also called "HPMC" The methoxy group content in HPMC is preferably from 16.5 to 30.0 mass% from the viewpoint of providing good binding properties. The content of methoxy groups in HPMC is preferably from 16.5 to 30.0 mass%, and more preferably from 28.0 to 30.0 mass%. The content of hydroxypropoxy groups in HPMC is preferably 4.0 to 32.0 mass%, and more preferably 7.0 to 12.0 mass% from the viewpoint of imparting good binding properties. The content of hydroxypropoxy and methoxy groups in HPMC can be measured by the assay method described in the monograph of "Hypromellose" in the 18th edition of the Japanese Pharmacopoeia.

[00069] The term "hypromellose analogues" herein refers to any substance that has similar dissolution characteristics when suspended with hypromellose.

[00070] Examples of povidone binders include povidone and copovidone. Povidone is a linear polymer of 1-vinyl-2-pyrrolidone. Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate. Povidone and copovidone can be distinguished by their viscosity characteristic values (K-values), which can be determined by the K-value

measurement methods specified in the respective sections for "povidone" and "copovidone" in "the 18th edition of Japanese Pharmacopoeia."

[00071] Examples of vinyl alcohol binders include polyvinyl alcohol, polyvinyl alcohol-polyethylene glycol graft copolymers, and polyvinyl alcohol-acrylic acid/methyl methacrylate copolymers.

[00072] Examples of polysaccharide thickening binders include xanthan gum, gellan gum, guar gum, carrageenan, gum arabic, pectin, and pullulan.

[00073] As used herein, the content of the "binder" is not particularly limited, but is, for example, 1 mg to 1000 mg for 1000 mg of a compound represented by Formula 1 or a pharmaceutically acceptable salt or solvate thereof. Preferably, it is from 2 mg to 500 mg, more preferably from 5 mg to 300 mg, and more preferably from 20 mg to 200 mg.

[00074] As used herein, "dispersants" are substances that improve the flow and dispersion of particles in the solid state, prevent a certain degree of agglomeration between particles when the formulation comes into contact with water, improve the dispersion of the formulation in water when it comes into contact with water, and prevent strong re-agglomeration between particles of the formulation in water. Examples of inorganic salt dispersants, ether dispersants, starch dispersants, cellulose dispersants, and fatty acid ester salt dispersants.

[00075] Examples of inorganic salt dispersants include light anhydrous silicic acid and magnesium metasilicate aluminate.

[00076] Examples of ether dispersants include polyethylene glycols (polyethylene glycol 600, polyethylene glycol 4000, polyethylene glycol 6000, and the like.) and propylene glycol.

[00077] Examples of starch dispersants include corn starch, rice starch, sodium starch glycolate, and partially alpha starch.

[00078] Examples of cellulosic dispersants include microcrystalline and carboxymethylcellulose sodium carmellose, carmellose, and calcium carmellose.

[00079] Examples of fatty acid ester salt dispersants include sucrose fatty acid esters and sodium stearyl fumarate.

[00080] As used herein, the content of the "dispersant" is not particularly limited, but is, for example, 0.01 to 10% by weight of the total composition. Preferably, it is from

0.1 to 8% by weight, more preferably from 0.5 to 5% by weight, more preferably from 1 to 5% by weight, and especially from 2 to 5% by weight.

[00081] As used herein, "suspending agent" refers to a substance added to granules when it is dispersed or suspended in water to form a suspension, for the purpose of maintaining the dispersion of suspended particles and improving dosing. Viscous or viscous substances may be used as a suspending agent.

[00082] Examples of suspending agents include thickening polysaccharides such as xanthan gum, guar gum, locust bean gum, tragacanth gum, sodium alginate, carrageenan; acrylic acid copolymers such as carboxyvinyl polymer; carboxymethyl cellulose, hypromellose, cellulose derivatives such as hydroxypropyl cellulose, methylcellulose; polyvinyl alcohol, povidone (polyvinylpyrrolidone), and combinations thereof.

[00083] As ushed herein, the content of the "suspending agent" is not particularly limited, but is, for example, 0.1 to 600 mg for 1000 mg of a compound represented by Formula 1 or a pharmaceutically acceptable salt or solvate thereof. Preferably, it is from 1.25 to 300 mg, more preferably from 2.5 to 300 mg, and even more preferably from 6.25 to 300 mg.

[00084] As used herein, "sweetener" means a corrective substance that adds sweetness to a drug product, improves the sensation of taking the drug product, or masks the unpleasant taste of the ingredients contained in the drug product.

[00085] Examples of sweeteners include aspartame, neotame, advantame, sucralose, sodium saccharin, dipotassium glycyrrhizate, acesulfame K, maltitol, erythritol, xylitol, trehalose, thaumatin and stevia.

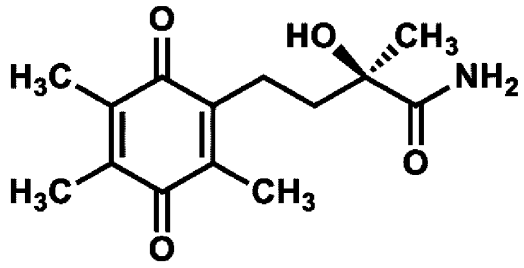
[00086] As used herein, the amount of "sweetener" is not particularly limited, and it is desirable to include an amount sufficient to impart an appropriate corrective effect when in suspension, for example, 0.125 to 900 mg for 1000 mg of a compound represented by Formula 1 or a pharmaceutically acceptable salt or solvate thereof. The following are examples. Preferably 1.25 to 600 mg, more preferably 6.25 to 300 mg.

[00087] The pharmaceutical compositions of the present disclosure may containadditives that can be used in ordinary pharmaceutical formulations as long as they do not interfere with the effects of the present disclosure. Examples of such additives

include, but are not limited to, thickeners, preservatives, stabilizers, buffers, colorants, and fragrances.

[00088] The present disclosure relates to all forms (e.g., tautomers, amorphous, crystalline, various forms of (R)-2-hydroxy-2-methyl-4-(2,4,5-trimethyl-3,6-dioxocyclohexa-1,4-dienyl)butanamide (compound of Formula 1) in all forms (e.g., tautomeric, amorphous, crystalline, various crystal polymorphs, and the like.). They typically refers to:

Formula 1:



[00089] The present disclosure also encompasses optical isomers thereof or mixtures thereof.

[00090] In the case of such mixtures, the percentage of the R-body is not particularly limited, but is preferably 60% or more by weight. More preferably, it is 80% or more by weight, more preferably 90% or more by weight, especially preferably 95% or more by weight, and most preferably 99% or more by weight.

[00091] Compounds of Formula 1 and pharmaceutically acceptable salts thereof may also exist in the form of hydrates and/or solvates, so solvates such as hydrates or ethanol solvates of these are also included in the present disclosure.

[00092] Examples of "pharmaceutically acceptable salts" include, but are not limited to, alkali metal salts such as sodium and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; inorganic metal salts such as zinc salts; organic base salts such as triethylamine, triethanolamine, organic bases such as triethylamine, triethanolamine, trihydroxymethylaminomethane, and amino acids; inorganic acids such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; acetate, propionate, succinate, lactate, malate, tartrate, citrate, maleate, fumarate, methane sulfonate, p organic

acid salts such as methane sulfonate, p-toluenesulfonate, benzenesulfonate, and ascorbate.

[00093] A compound of Formula 1 used in the present disclosure may be crushed as needed.

[00094] In the present disclosure, "medical setting" refers to any site where the pharmaceutical compositions of the present disclosure are used, including hospitals, clinics, nursing facilities, and homes (e.g., home healthcare).

[00095] As used herein, "modulation" of, or to "modulate," an energy biomarker means to change the level of the energy biomarker towards a desired value, or to change the level of the energy biomarker in a desired direction (e.g., increase or decrease). International Publication No. WO 2016/100579 is incorporated by reference. Modulation can include, but is not limited to, normalization and enhancement as defined below.

[00096] "Normalization" of, or to "normalize," an energy biomarker is defined as changing the level of the energy biomarker from a pathological value towards a normal value, where the normal value of the energy biomarker can be 1) the level of the energy biomarker in a healthy person or subject, or 2) a level of the energy biomarker that alleviates one or more undesirable symptoms in the person or subject. That is, to normalize an energy biomarker which is depressed in a disease state means to increase the level of the energy biomarker towards the normal (healthy) value or towards a value which alleviates an undesirable symptom; to normalize an energy biomarker which is elevated in a disease state means to decrease the level of the energy biomarker towards the normal (healthy) value or towards a value which alleviates an undesirable symptom.

[00097] "Enhancement" of, or to "enhance," energy biomarkers means to intentionally change the level of one or more energy biomarkers away from either the normal value, or the value before enhancement, in order to achieve a beneficial or desired effect. For example, in a situation where significant energy demands are placed on a subject, it may be desirable to increase the level of ATP in that subject to a level above the normal level of ATP in that subject. Enhancement can also be of beneficial effect in a subject suffering from a disease or pathology such as a mitochondrial disorder, in that normalizing an energy biomarker may not achieve the optimum outcome for the subject; in such cases, enhancement of one or more energy biomarkers can be beneficial, for

example, higher-than-normal levels of ATP, or lower-than-normal levels of lactic acid (lactate) can be beneficial to such a subject.

[00098] By modulating, normalizing, or enhancing the energy biomarker Coenzyme Q means modulating, normalizing, or enhancing the variant or variants of Coenzyme Q which is predominant in the species of interest. For example, the variant of Coenzyme Q which predominates in humans is Coenzyme Q10. If a species or subject has more than one variants of Coenzyme Q present in significant amounts (i.e., present in amounts which, when modulated, normalized, or enhanced, can have a beneficial effect on the species or subject), modulating, normalizing, or enhancing Coenzyme Q can refer to modulating, normalizing or enhancing any or all variants of Coenzyme Q present in the species or subject.

[00099] By the term "respiratory chain disorder," it means a disorder which results in the decreased utilization of oxygen by a mitochondrion, cell, tissue, or individual, due to a defect or disorder in a protein or other component contained in the mitochondrial respiratory chain. By "protein or other component contained in the mitochondrial respiratory chain," it means the components (including, but not limited to, proteins, tetrapyrroles, and cytochromes) comprising mitochondrial complex I, II, III, IV, and/or V. "Respiratory chain protein" refers to the protein components of those complexes, and "respiratory chain protein disorder" means a disorder which results in the decreased utilization of oxygen by a mitochondrion, cell, tissue, or individual, due to a defect or disorder in a protein contained in the mitochondrial respiratory chain.

[000100] The term "Parkinson's," (also called "Parkinsonism" and "Parkinsonian syndrome") ("PD") is intended to include not only Parkinson's disease but also drug-induced Parkinsonism and post-encephalitic Parkinsonism. Parkinson's disease is also known as paralysis agitans or shaking palsy. It is characterized by tremor, muscular rigidity and loss of postural reflexes. The disease usually progresses slowly with intervals of 10 to 20 years elapsing before the symptoms cause incapacity. Due to their mimicry of effects of Parkinson's disease, treatment of animals with methamphetamine or MPTP has been used to generate models for Parkinson's disease. These animal models have been used to evaluate the efficacy of various therapies for Parkinson's disease.

[000101] The term "Friedreich's ataxia" is intended to embrace other related ataxias, and is also sometimes referred to as hereditary ataxia, familial ataxia, or Friedreich's tabes.

[000102] The term "ataxia" is an aspecific clinical manifestation implying dysfunction of parts of the nervous system that coordinate movement, such as the cerebellum. People with ataxia have problems with coordination because parts of the nervous system that control movement and balance are affected. Ataxia may affect the fingers, hands, arms, legs, body, speech, and eye movements. The word ataxia is often used to describe a symptom of incoordination which can be associated with infections, injuries, other diseases, or degenerative changes in the central nervous system. Ataxia is also used to denote a group of specific degenerative diseases of the nervous system called the hereditary and sporadic ataxias. Ataxias are also often associated with hearing impairments.

[000103] There are three types of ataxia, cerebellar ataxia, including vestibulo-cerebellar dysfunction, spino-cerebellar dysfunction, and cerebro-cerebellar dysfunction; sensory ataxia; and vestibular ataxia. Examples of the diseases which are classifiable into spinocerebellar ataxia or multiple system atrophy are hereditary olivopontocerebellar atrophy, hereditary cerebellar cortical atrophy, Friedreich's ataxia, Machado-Joseph diseases, Ramsay Hunt syndrome, hereditary dentatorubral-pallidoluysian atrophy, hereditary spastic paraplegia, Shy-Drager syndrome, cortical cerebellar atrophy, striato-nigral degeneration, Marinesco-Sjogren syndrome, alcoholic cortical cerebellar atrophy, paraneoplastic cerebellar atrophy associated with malignant tumor, toxic cerebellar atrophy caused by toxic substances, Vitamin E deficiency due to mutation of a Tocopherol transfer protein (aTTP) or lipid absorption disorder such as Abetalipoproteinemia, cerebellar atrophy associated with endocrine disturbance and the like.

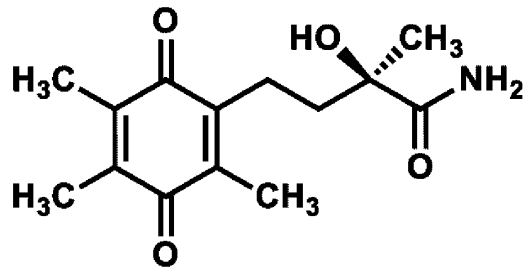
[000104] Examples of ataxia symptoms are motor ataxia, trunk ataxia, limb ataxia and the like, autonomic disturbance such as orthostatic hypotension, dysuria, hypohidrosis, sleep apnea, orthostatic syncope and the like, stiffness of lower extremity, ocular nystagmus, oculomotor nerve disorder, pyramidal tract dysfunction, extrapyramidal symptoms (postural adjustment dysfunction, muscular rigidity, akinesia,

tremors), dysphagia, lingual atrophy, posterior funiculus symptom, muscle atrophy, muscle weakness, deep hyperreflexia, sensory disturbance, scoliosis, kyphoscoliosis, foot deformities, anarthria, dementia, manic state, decreased motivation for rehabilitation and the like.

[000105]

Embodiment: One embodiment of the present disclosure provides a pharmaceutical composition including:

a compound represented by formula 1:



or a pharmaceutically acceptable salt or solvate thereof. The granules of the present disclosure have a particle diameter of 500 μm or greater for 20% or less by weight of the particles constituting the granules.

[000106] In one embodiment, 15% or less by weight of the particles constituting the granules have a particle size of 500 μm or greater, and preferably 10% or less by weight of the particles constituting the granules have a particle size of 500 μm or greater and preferably 5% or less by weight of the particles constituting the granules have a particle size of 500 μm or greater.

[000107] In one embodiment, the granules are a powder for oral solution or suspension.

[000108] In one embodiment, the granules of the present disclosure or the particles comprising the same contain at least one of a binder, a dispersant, a sweetener, and a suspending agent.

[000109] In one embodiment, the granules of the present disclosure or the particles constituting the same contain a binder. Any type of binder may be used, as long as it can form particles stably, preferably one known to be pharmaceutically acceptable.

[000110] In one embodiment, the granules of the present disclosure or the particles constituting the same contain a dispersant.

[000111] In one embodiment, the granules of the present disclosure or the particles constituting the same contain a sweetener.

[000112] In one embodiment, the granules of the present disclosure or the particles constituting the same contain a suspending agent.

[000113] In certain embodiments, in the present disclosure, the binders can include binders selected from the group consisting of cellulosic binders, povidone binders, vinyl alcohol binders, and thickened polysaccharide binders.

[000114] In the present disclosure, examples of the cellulosic binders can include hydroxypropylcellulose, hypromellose, and methylcellulose.

[000115] In the present disclosure, examples of the povidone-based binders can include povidone, and copovidone, and the like.

[000116] In the present disclosure, examples of the vinyl alcohol binders can include polyvinyl alcohol, and polyvinyl alcohol-polyethylene glycol graft copolymers, etc.

[000117] In the present disclosure, examples of the thickened polysaccharide binder can include xanthan gum and the like.

[000118] In the present disclosure, the binder can include a binder selected from the group consisting of hydroxypropylcellulose, hypromellose, copovidone, methylcellulose, povidone, polyvinyl alcohol, polyvinyl alcohol/polyethylene glycol graft copolymer, and xanthan gum.

[000119] In the present disclosure, the binder can include hydroxypropylcellulose or copovidone.

[000120] In the present disclosure, the binder can include hydroxypropyl cellulose.

[000121] In the present disclosure, examples of the dispersants can be inorganic salt dispersants, ether dispersants, starch dispersants, cellulose dispersants, and fatty acid ester salt dispersants.

[000122] In the present disclosure, the inorganic salt dispersants can be light silicic anhydride, and magnesium metasilicate aluminate, and the like.

[000123] In the present disclosure, examples of the ether dispersant can be polyethylene glycol 6000 or the like.

[000124] In the present disclosure, examples of the starch dispersant can be corn starch or the like.

[000125] In the present disclosure, examples of the cellulosic dispersants can be microcrystalline and carboxymethylcellulose sodium carmellose, carmellose, and calcium carmellose, and the like.

[000126] In the present disclosure, the fatty acid ester salt dispersant can be sodium stearyl sodium fumarate or the like.

[000127] In the present disclosure, examples of the dispersants can be light silicic anhydride, magnesium metasilicate aluminate, polyethylene glycol 6000, corn starch, crystalline cellulose sodium carmellose, carmellose, calcium carmellose, and sodium stearyl fumarate, and the like.

[000128] In the present disclosure, the dispersant is light anhydrous silicic acid.

[000129] In the present disclosure, examples of binders can include a cellulosic binder or povidone binder, and the dispersant can include a dispersant selected from the group consisting of inorganic salt dispersants, ether dispersants, starch dispersants, cellulosic dispersants, and fatty acid ester salt dispersants.

[000130] In the present disclosure, examples of binders can include a cellulosic binder, and the dispersant can include a dispersant selected from the group consisting of inorganic salt dispersants, ether dispersants, starch dispersants, and cellulosic dispersants.

[000131] In the present disclosure, examples of binders includes a binder selected from the group consisting of hydroxypropyl cellulose, hypromellose, copovidone, methylcellulose, povidone, polyvinyl alcohol, polyvinyl alcohol/polyethylene glycol graft copolymer, and xanthan gum and the dispersant can include a dispersant selected from the group consisting of light silicic anhydride, magnesium metasilicate aluminate, polyethylene glycol 6000, corn starch, microcrystalline and carboxymethylcellulose sodium carmellose, carmellose, calcium carmellose, and sodium stearyl fumarate.

[000132] In the present disclosure, examples of binders can include a binder selected from the group consisting of hydroxypropylcellulose or copovidone, and the dispersant can include light anhydrous silicic acid.

[000133] In the present disclosure, examples of binders can include hydroxypropyl cellulose and the dispersant can include light anhydrous silicic acid.

[000134] In the present disclosure, examples of binders can include hypromellose and the dispersant can include light anhydrous silicic acid.

[000135] In the present disclosure, examples of binders can include a povidone binder, and the dispersant can include a dispersant selected from the group consisting of inorganic salt dispersants, ether dispersants, starch dispersants, cellulose dispersants, and fatty acid ester salt dispersants.

[000136] In the present disclosure, examples of binders can include a povidone binder, and the dispersant can include a dispersant selected from the group consisting of an inorganic salt dispersant and a cellulosic dispersant.

[000137] In the present disclosure, examples of the binder can include copovidone and the dispersant can include light anhydrous silicic acid.

[000138] In the present disclosure, the binder can include a cellulosic binder and the dispersant can include an inorganic salt dispersant.

[000139] In the present disclosure, examples of the binder can include hydroxypropylcellulose or hypromellose, and the dispersant can include light anhydrous silicic acid.

[000140] In the present disclosure, examples of the binder can include a binder selected from the group consisting of hydroxypropylcellulose and hypromellose, and the dispersant can include light anhydrous silicic acid.

[000141] In the present disclosure, the binder can include a povidone binder and the dispersant can include a cellulose dispersant.

[000142] In the present disclosure, examples of the binder can include copovidone and the dispersant can include light anhydrous silicic acid.

[000143] In the present disclosure, examples of the binder can include a povidone binder and the dispersant can include an inorganic salt dispersant.

[000144] In the present disclosure, examples of the sweetener can include sucralose.

[000145] In the present disclosure, examples of the suspending agent can include carboxyvinyl polymers.

[000146] The present disclosure provides granules wherein the binder is hydroxypropyl cellulose, the suspending agent is carboxy vinyl polymer, and the sweetener is sucralose.

[000147] The present disclosure provides granules wherein the binder is hydroxypropyl cellulose, the suspending agent is carboxy vinyl polymer, the sweetener is sucralose, and the dispersant is light anhydrous silicic acid.

[000148] The present disclosure provides granules wherein the binder is hypromellose, the suspending agent is carboxyvinyl polymer, and the sweetener is sucralose.

[000149] In the present disclosure, the granules are provided wherein the binder is hypromellose, the suspending agent is carboxy vinyl polymer, the sweetener is sucralose, and the dispersant is light anhydrous silicic acid.

[000150] The present disclosure provides granules in which the binder is copovidone, the suspending agent is carboxyvinyl polymer, and the sweetener is sucralose.

[000151] The present disclosure provides granules in which the binder is copovidone, the suspending agent is carboxyvinyl polymer, the sweetener is sucralose, and the dispersant is light anhydrous silicic acid.

[000152] In the present disclosure, 15% or less by weight of the particles constituting the granules have a particle size of 500 μm or larger, preferably 10% or less by weight of the particles constituting the granules have a particle size of 500 μm or larger, more preferably 5% or less by weight of the particles constituting the granules have a particle diameter of 500 μm or larger.

[000153] In the present disclosure, examples of the pharmaceutical compositions, granules or particles comprising the same may contain from 1 mg to 1000 mg of a binder for 1000 mg of a compound represented by Formula 1 or a pharmaceutically acceptable salt or solvate thereof.

[000154] In the present disclosure, examples of the pharmaceutical compositions, granules or particles comprising the same can contain 0.01 to 10% by weight of a dispersant relative to the weight of the entire composition, granules or particles.

[000155] In the present disclosure, examples of the pharmaceutical compositions, granules or particles comprising the same may contain from 1 mg to 1000 mg of suspension for 1000 mg of the compound represented by Formula 1 or pharmaceutically acceptable salt or solvate thereof.

[000156] In the present disclosure, examples of the pharmaceutical compositions, granules or particles comprising the same may contain from 1 mg to 1000 mg of sweetener with respect to 1000 mg of the compound represented by Formula 1 or pharmaceutically acceptable salt or solvate thereof.

[000157] In one embodiment of the present disclosure, granules for suspension for the manufacture of pharmaceutical compositions, comprising the granules described in any of the above.

[000158] In the present disclosure, the product can be a suspension granule for suspension preparation.

[000159] In one embodiment of the present disclosure, a granule formulation for suspension for the manufacture of pharmaceutical compositions is provided, having the granules features of the present disclosure.

[000160] In the present disclosure, the granules can be a suspension granule formulation for suspension preparation.

[000161] In one embodiment of the present disclosure, a pharmaceutical composition is provided that is granules for suspension for the manufacture of pharmaceutical compositions.

[000162] In one embodiment of the present disclosure, the disclosure provides a suspension liquid containing the pharmaceutical composition of any one of the above, which is a suspension granule formulation for manufacturing pharmaceutical compositions.

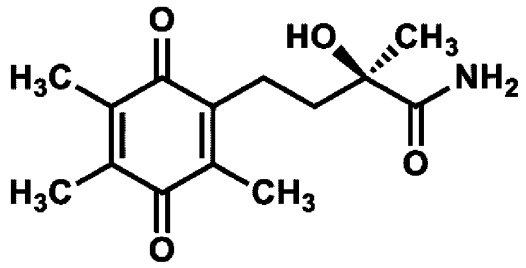
[000163] In the present disclosure, the disclosure can be provided in suspension.

[000164] In the present disclosure, the granules of the present disclosure are characterized by improved dissolution stability after storage.

[000165] In the present disclosure, granules of the present disclosure can be produced through a granulation liquid spraying process. The granulation liquid spraying includes, for example, the one fluid spray method, in which a liquid is misted under pumping pressure, and the two-fluid spray method, in which a liquid is misted under gas pressure. The granulation liquid spraying can be any method. Granules of the present disclosure can also be produced by adjusting the particle size by sieving.

[000166] In one aspect, the present disclosure provides a method for manufacturing granules comprising particles of a compound or pharmaceutically acceptable salt or solvate thereof represented by

Formula 1:



the method comprises the steps of:

admixing the compound or pharmaceutically acceptable salt or solvate thereof with other materials comprising the particles;

preparing a granule from the admixed material, wherein 20% or less by weight of the particles constituting the granules are prepared to have a particle size of 500 μm or greater, wherein 20% or less by weight of the particles constituting the granule formulation have a particle size of 500 μm or greater.

[000167] In the present disclosure, the process for preparing granules used in the present disclosure includes a granulation liquid spraying process.

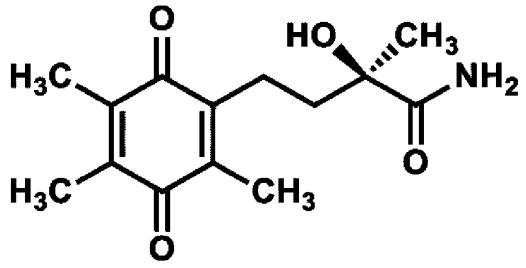
[000168] In the present disclosure, the granules of the present disclosure are used to produce granules for suspension.

[000169] In the present disclosure, the present disclosure provides granules for suspension liquid containing the granules of the present disclosure.

[000170] In the present disclosure, the granules of the present disclosure are used to prepare suspension liquids.

[000171] In another aspect, the present disclosure provides granules comprising particles of a compound represented by the following:

Formula 1:



or a pharmaceutically acceptable salt or solvate thereof, and hypromellose or a hypromellose analogue.

[000172] In one embodiment the hypromellose or hypromellose analog is hypromellose.

[000173] In one embodiment of the present disclosure, there is provided a method of treating or preventing a disease in a subject in need thereof, comprising the process of administering to the subject in need thereof an effective amount of granules, pharmaceutical composition or suspension liquid described in the present disclosure.

[000174] In one embodiment of the present disclosure, there is provided a method of producing a granule, pharmaceutical composition or suspension liquid as described in the present disclosure, comprising the process of mixing the compound or pharmaceutically acceptable salt or solvate thereof, the binder, and necessary ingredients such as a dispersant and a sweetener.

[000175] In one embodiment of the present disclosure, there is provided a method of producing granules, pharmaceutical composition or suspension liquid, comprising the process of mixing granules of the present disclosure with a necessary additive and/or suspension solvent (including, for example, a water soluble medium such as purified water).

[000176] In one embodiment of the present disclosure, there is provided a method of preparing a pharmaceutical composition or suspension for administration to a subject at a medical setting, comprising the process of mixing granules described in the present disclosure with a necessary additive and/or suspension solvent (including, for example, a water soluble medium such as purified water).

[000177] In one embodiment of the present disclosure, granules, pharmaceutical composition, suspension liquid, or method of the present disclosure is for treating or inhibiting a stress disorder, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, enhancing one or to enhance one or more energy biomarkers.

[000178] In one embodiment of the present disclosure, granules, pharmaceutical composition, suspension liquid, or method of the present disclosure is a mitochondrial disorder; hereditary mitochondrial disease; Alpers disease; Barth syndrome; beta oxidation defect; carnitine-acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndrome; coenzyme Q10 deficiency; complex I deficiency; complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive external ophthalmoplegia (CPEO); CPT I deficiency; CPT II deficiency; Friedreich ataxia (FA); glutaric aciduria type II; Kearns-Sayre syndrome (KSS); lactic acidosis; long-chain acyl CoA dehydrogenase deficiency (LCAD); LCHAD; Leigh syndrome; Leigh-like syndrome; Leber's hereditary optic neuropathy (LHON); lethal infantile cardiomyopathy (LIC); Luft's disease; multiple acyl CoA dehydrogenase deficiency (MAD); medium chain acyl CoA dehydrogenase deficiency (MCAD); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS); myoclonus epilepsy with red ragged fibers (MERRF); mitochondrial recessive ataxia syndrome (MIRAS); mitochondrial cytosis, mitochondrial DNA depletion; mitochondrial encephalopathy; mitochondrial myopathy; mitochondrial neurogastrointestinal encephalopathy (MNGIE); neuropathy, ataxia, retinitis pigmentosa (NARP); Pearson syndrome; pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; a disorder associated with a POLG mutation; respiratory chain disorders; short-chain acyl CoA dehydrogenase deficiency (SCAD); SCHAD; very long-chain acyl CoA dehydrogenase deficiency (VLCAD); myopathies; cardiomyopathies; encephalomyopathies; neurodegenerative disorders; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis (ALS); motor neuron disease; neurological disorders; epilepsy; age-related diseases; macular degeneration; diabetes; metabolic syndromes; cancer; brain cancer; genetic disorders; Huntington's disease; mood disorders; schizophrenia; bipolar disorder; pervasive developmental disorder; autistic disorder; Asperger's syndrome; childhood disintegrative disorder (CDD); Rett disorder or

Rett syndrome; specific Disabling PDD (PDD-NOS); cerebrovascular accident; stroke; visual impairment; optic neuropathy; dominantly inherited juvenile optic atrophy; toxic-induced optic neuropathy; glaucoma; Stargardt macular dystrophy; diabetic retinopathy; diabetic maculopathy; retinopathy of prematurity; ischemia-reperfusion related retinal damage; oxygen intoxication; abnormal hemochromatosis; thalassemia; sickle cell anemia; seizures; ischemia; renal tubular acidosis; attention deficit hyperactivity disorder (ADHD); neurodegenerative disorders leading to hearing loss or balance disorders; dominant optic atrophy (DOA); maternally inherited diabetes with deafness (MIDD); chronic fatigue; contrast medium-induced renal injury; contrast-induced retinopathy damage; no beta lipoproteinemia; retinitis pigmentosa; Wolfram's disease; Tourette syndrome; cobalamin c deficiency; methylmalonic aciduria; glioblastoma; Down syndrome; acute tubular necrosis; muscular dystrophy; white matter dystrophy; progressive supranuclear palsy; spinal muscular atrophy; hearing loss ; noise-induced hearing loss; traumatic brain injury; juvenile Huntington's disease; multiple sclerosis; NGLY1; NGLY1 deficiency; NGLY1-congenital disorder of deglycosylation; multiple system atrophy; adrenoleucodystrophy; and adrenomyeloneuropathy to treat or inhibit oxidative stress disorders selected from the group consisting of.

[000179] In one embodiment of the present disclosure, granules, pharmaceutical composition, suspension liquid, or method of the present disclosure is for treating or preventing amyotrophic lateral sclerosis (ALS).

[000180] Diseases, various disorders/diseases (such as mitochondrial disorders, impaired energy processing disorders, neurodegenerative disorders, and aging disorders), to which treatment or suppression using the granules, pharmaceutical compositions, suspension liquids, or methods of the present disclosure are applicable, may be caused or aggravated by oxidative stress affecting the normal electron flow within cells and may be treated or suppressed using the compositions, suspensions, and methods of the present disclosure. It is believed that they arise or are exacerbated and can be treated or inhibited using the compositions, suspension liquids, and methods of the present disclosure.

[000181] Examples of oxidative stress disorders include, for example, mitochondrial disorders (including hereditary mitochondrial diseases) (Alpers disease, Barth syndrome, beta oxidation defects, carnitine-acyl-carnitine deficiency, carnitine

deficiency, creatine deficiency syndrome, coenzyme Q10 deficiency, complex I deficiency, complex II deficiency, complex III deficiency, complex IV deficiency, complex V deficiency, COX deficiency, chronic progressive external ophthalmoplegia (CPEO), CPT I deficiency, CPT II deficiency, Friedreich ataxia (FA), glutaric aciduria type II, Kearns-Sayre syndrome (KSS), lactic acidosis, long-chain acyl CoA dehydrogenase deficiency (LCAD), LCHAD, Leigh disease or Leigh syndrome, Leigh-like syndrome, Leber's hereditary optic neuropathy (LHON, Leber's disease, Leber's optic atrophy (LOA), or also known as LON), lethal infantile cardiomyopathy (LIC), Luft disease, multiple acyl CoA dehydrogenase deficiency (MAD), medium-chain acyl CoA dehydrogenase deficiency (MCAD), mitochondrial myopathy, encephalopathy, lactoacidosis, and stroke (MELAS), red ragged fiber with myoclonus epilepsy (MERRF), mitochondrial recessive ataxia syndrome (MIRAS), mitochondrial cytosis, mitochondrial DNA depletion, mitochondrial encephalopathy, mitochondrial myopathy, mitochondrial neurogastric encephalopathy (MNGIE), neuropathy, ataxia, retinitis pigmentosa (NARP), Pearson syndrome, pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, a disorder associated with a POLG mutation, respiratory chain disorders, short-chain acyl CoA dehydrogenase deficiency (SCAD), SCHAD, very long chain acyl CoA dehydrogenase deficiency (VLCAD), and the like); myopathies (cardiomyopathies and encephalomyopathy, and the like); neurodegenerative disorders (such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease)); motor neuron diseases; neurological disorders (such as epilepsy); age-related diseases, especially those in which CoQ10 has been proposed for treatment (macular degeneration, diabetes (e.g., type 2 diabetes mellitus), metabolic syndromes, and cancers (e.g., brain cancer)); genetic disorders (e.g., Huntington's disease (also a neurological disorder)); mood disorders (e.g., schizophrenia and bipolar disorder); pervasive developmental disorders (autistic disorders, Asperger's syndrome, childhood disintegrative disorder (CDD), Rett disorder or Rett syndrome, and PDD not otherwise specified (PDD-NOS)); cerebrovascular accidents (e.g., stroke); visual impairment (visual impairment caused by neurodegenerative diseases of the eye (optic neuropathy, Leber's hereditary optic neuropathy, dominant juvenile optic atrophy, toxic-induced glaucoma, age-related macular degeneration (both “dry,” i.e., non-exudative macular

degeneration and "wet," i.e., exudative macular degeneration), Stargardt macular dystrophy, diabetic retinopathy, diabetic maculopathy, retinopathy of prematurity, or ischemia-reperfusion related retinal damage); and Disorders caused by energy disorders include oxygen deprivation, intoxication, or toxicity, as well as diseases resulting from qualitative or quantitative disruption of oxygen transport, such as hemoglobionopathies (e.g., thalassemia or sickle cell anemia); other diseases involving mitochondrial dysfunction diseases, such as excitotoxic neurologic damage (e.g., seizures, strokes, and ischemia-related damage); and other disorders involving renal tubular acidosis; attention deficit hyperactivity disorder (ADHD); neurodegenerative disorders leading to hearing or balance disorders; dominant optic atrophy (DOA); maternally inherited diabetes mellitus (MIDD) with hearing loss chronic fatigue; contrast-induced renal injury; contrast-induced retinopathy damage; ano beta-lipoproteinemia; retinitis pigmentosa; Wolfram's disease; Tourette syndrome; cobalamin c deficiency; methylmalonic aciduria; glioblastoma; Down syndrome; acute tubular necrosis; muscular dystrophy; white matter atrophy; progressive supranuclear palsy; spinal muscular atrophy; hearing loss (e.g., noise-induced hearing loss); traumatic brain injury; juvenile Huntington's disease; multiple sclerosis; NGLY1; multiple system atrophy; adrenoleucodystrophy; and adrenomyeloneuropathy. It should be understood that certain specific diseases or disorders can fall into more than one category; for example, Huntington's disease is a genetic disease as well as a neurological disease. Furthermore, certain oxidative stress diseases and oxidative stress disorders can also be considered mitochondrial disorders. International Publication No. 2016/100579 is cited by reference.

[000182] The compound represented by Formula 1 (Compound 1) is made into granules in which the particles are bound and granulated with a binder for ease of manufacture and handling during distribution in the formulations of the present disclosure. When a formulation with these characteristics is designed, it is found that the granules does not exhibit good dissolution stability, i.e., delayed dissolution, over time during storage.

[000183] Considering the impact of delayed dissolution of the active ingredient over time on the drug product's efficacy, a formulation that exhibits stable dissolution behavior is more desirable as a pharmaceutical product.

[000184] The pharmaceutical compositions of the present disclosure have good dissolution stability, which is beneficial during suspension preparation.

Formulation Method: A course crystal of Compound 1 is crushed as needed to obtain compound 1 for the preparation of a formulation. While the active pharmaceutical ingredient/raw material is also generally crushed as needed in order to design a homogenous and uniform formulation, the active pharmaceutical ingredient/raw material may be used directly when there is no issue in terms of the design of the formulation. Compound 1 can be obtained by, for example, the method described in WO 2021/167095.

[0152] Specific examples of the preparation method of the formulation are described below; however, the preparation method of the formulation is not limited thereto. Compound 1, a binding agent, a suspending agent, and a sweetener are mixed as the raw materials of a formulation. The mixture is loaded into a preparation mixer. Purified water is gradually added as granulation liquid, and the mixture was mixed/agitated, while repeating mixing/agitation of the mixture and addition of purified water, to obtain granules. The granules are subjected to wet sieving through a sieve and dried to obtain dried granules. The dried granules are subjected to dry sieving through a sieve to obtain granules.

[000185] Granules and a dispersant are mixed, and the entire amount is sifted with a sieve. The sifted product is mixed to obtain a formulation.

[000186] In addition to the preparation method described above, the formulation can also be prepared by, for example, the following method. Compound 1, a suspending agent, a sweetener, and, if necessary, a binding agent are mixed as formulation raw materials. This mixture is charged into a mixing granulator, purified water or an aqueous binding agent solution is added as granulation liquid, and the mixture is stirred and granulated to obtain granules. The granules are subjected to wet sieving, if necessary, and dried with a fluidized bed granulator or the like to obtain dried granules. The dried granules are subjected to dry sieving as necessary to obtain granules. A formulation can be obtained by mixing the granules and a dispersant.

[000187] As the granulation method, a wet granulation method is preferable, and examples thereof include mixing granulation method, fluidized bed granulation method, extrusion granulation method, and kneading granulation method. The binder can be added

as a powder together with the formulation ingredients, or dissolved in a solvent as a granulating liquid when other formulation ingredients are granulated.

[000188] The granulation liquid spraying process can be carried out as follows:

[000189] In the case of mixing granulation, purified water or a binder solution is sprayed onto the powder mixture of raw materials being agitated by the rotating blades from an optimal position and in an optimal direction that does not interfere with granulation.

[000190] In the case of fluidized bed granulation, purified water or a binder solution is sprayed onto the powder mixture of raw materials flowing by an air current from an optimal position and in an optimal direction that does not interfere with granulation.

[000191] In other granulation methods, purified water or a binder solution is sprayed onto the powder mixture of the formulation ingredients from an optimal position and in an optimal direction that does not cause granulation obstacles. The spray methods that can be employed in each granulation method are not desired to be limited to these, but for example, the one fluid spray method, in which the liquid is misted under pumping pressure, and the two-fluid spray method, in which the liquid is misted under gas pressure, are employed.

EXAMPLES

[000192] The present invention is described hereinafter in more detail with the Comparative Examples, Examples, Test Examples and the like, but the present disclosure is not limited thereto.

[000193] In the following comparative and examples, carboxy vinyl polymer, sucralose, hydroxypropyl cellulose, hypromellose, copovidone, and light anhydrous silicic acid were used, but the present invention is not limited to these.

- Carboxyvinyl polymer: Carbopol 971P (Lubrizol)
- Sucralose: Sucralose (Merck)
- Hydroxypropylcellulose: HPC-L fine (Nippon Soda Co., Ltd.)
- Hypromellose: TC-5R (Shin-Etsu Chemical Co., Ltd.)
- Copovidone: Kollidon VA64 (BASF)
- light anhydrous silicic acid: AEROSIL 200 (EVONIK)

In addition, the purified water used in the production of the formulation was "Japanese Pharmacopoeia Purified Water" (Takasugi Seiyaku Co., Ltd.).

[000194] Formulations of Comparative Example 1 and Examples 1-5 were prepared by the following method, using the amounts of Compound 1 and additives shown in Table 1 below.

[000195] (1) Preparation of Compound 1

In order to reduce the coarse crystals of Compound 1 to an appropriate particle size, the unmilled Compound 1 product was crushed using a QUADROCOMIL (Powrex Corporation) granulator to obtain Compound 1 for preparation of the formulation.

[000196] Test Example 1 (Particle size distribution measurement)

Specific evaluation methods are described below.

[000197] Ten grams of each formulation (Comparative Example 1 and Examples 1 to 5) was fractionated using a sieve shaker (AS 200 CONTROL: RETSCH Corporation) with metal test sieves of 710, 500, 250, 180, 125, 106, and 75 μm (inner diameter φ100 mm × height 40 mm, respectively), fractionation was performed under the following conditions. The amount of fractional mass remaining on each sieve was calculated from the mass of the sieve bottom before and after the measurement (empty mass and mass after the test). The fractional mass remaining on the sieve was divided by the total fractional mass (sum of fractional masses of each sieve), and the distribution frequency was expressed as a percentage.

[000198] Particle size distribution measurement conditions:

Amplitude: 1.00 mm

Interval time: 10 sec

Interval (interval on/off): on

Operating time: 10 min

[000199] Test Example 2 (Dissolution)

Storage of specimensFor each formulation (Comparative Example 1 and Examples 1-5), a quantity equivalent to 1000 mg of Compound 1 was weighed into a 30 mL volumetric clear glass bottle (Screw Tube Bottle 30 mL No. 6/Maruem Co., Ltd.) and stored in a constant temperature and humidity chamber set at 50 °C and 85% RH (Nagano Science Co., Ltd.) with the bottle opened. The product was stored in a constant

temperature and humidity chamber (Nagano Science Co., Ltd.) at 50 °C and 85%RH with the bottle open. After storage for the prescribed periods (1 week, 2 weeks, 1 month, and 5 weeks), the samples were removed and used as samples for dissolution evaluation. For the initial (at the start of storage) product, a quantity equivalent to 1000 mg of compound 1 was weighed into clear glass bottles of 30 mL volume each (screw tube bottle 30 mL No.6/MALEM Co., Ltd.) and used as samples for dissolution evaluation, and were not stored at 50 °C and 85% RH.

[000200]

Preparation and measurement of sample solutions:To each sample for dissolution evaluation, was added 20 mL of purified water, and each sample was mixed until homogeneous to make a sample solution.

[000201] For each sample solution, 870 mL of test solution was added to each vessel previously filled with 870 mL of test solution. 10 mL of test solution was washed in to initiate the elution test. Five mL of the eluate was taken at the time specified according to dissolution test conditions and filtered through a membrane filter. The first 2 mL or more of the filtrate was removed, and the next filtrate was used as the sample solution for HPLC. The table below shows the results of the elution rate measured 30 minutes after the start of the test. The elution rate of the stored product was evaluated as the ratio of the elution rate of the initial product (at the start of storage) to the initial elution, where the initial elution rate was 100%.

[000202]

Dissolution test conditions:Method: Dissolution test method of the Japanese Pharmacopoeia General Test Method (paddle method)

Rotation speed: 50 revolutions with respect to minute

Test solution: Dissolution test solution 2

Test solution volume: 900 mL

Test solution temperature: 37±0.5 °C

Duration (can be changed as needed): 5, 10, 15, 30, 45 and 60 minutes

Sampling volume: 5 mL

[000203]

Preparation of standard solutions:Approximately 55 mg of the standard of compound 1 was weighed, dissolution test solution 2 (pH 6.8) was added, sonicated, and 50 mL of the test solution was added to make the standard solution (1.1 mg/mL).

[000204] Analytical conditions:

Detector: UV absorbance spectrophotometer (measurement wavelength: 265 nm)

Column: Stainless steel tube 4.6 mm i.d. and 50 mm long filled with octadecylsilylated silica gel for liquid chromatography with a particle size of 1.8 m.

(Agilent ZORBAX Eclipse Plus C18 or equivalent)

Column temperature: Constant temperature around 40 °C

Mobile phase: Water/acetonitrile/trifluoroacetic acid mixture (1500:500:1)

Flow rate: 1.0 mL with respect to minute

Injection volume: 1 μL

Sample cooler temperature: constant temperature around 25 °C

[000205] Calculation of elution rate (%):

The elution rate (%) of compound 1 was determined by the following formula.

Elution rate (%) = MS / 1000 × AT / AS × D × 100

MS: Amount of compound 1 standard collected (mg)

AT: Peak area of compound 1 in sample solution

AS: Peak area of compound 1 in standard solution

D: Dilution correction factor 900 / 50

[000206] Experimentation for Comparison

(1) Preparation of Comparative Example 1: Compound 1 (2500 g), hydroxypropyl cellulose (412.5 g), carboxy vinyl polymer (25 g), and sucralose (62.5 g) were mixed in a plastic bag.

[000207] The mixture was placed in a stirring mixing granulator (Powrex Co., Ltd.), and the mixture was stirred and purified water (540 g) was dripped into the mixture until a granulated product was obtained. The resulting granules were regulated its particle size in a wet/dry particle size regulator (Powrex Co., Ltd.) and dried in a fluid bed granulator-dryer (Powrex Co., Ltd.) to obtain dried granules. The dried granules and light anhydrous silicic acid (50 g) were placed in a plastic bag, mixed in the bag, and then dry granulated

in a wet/dry particle size regulator (Powrex Co., Ltd.) to obtain the formulation of Comparative Example 1.

[000208] (2) Preparation of Example 1: Compound 1 (2500 g), hydroxypropyl cellulose (412.5 g), carboxy vinyl polymer (25 g), and sucralose (62.5 g) were mixed in a plastic bag.

[000209] The mixture was placed in a stirring mixing granulator (Powrex Co., Ltd.), and the mixture was stirred with a rotating blade. Purified water was sprayed onto the mixture using a gas-liquid two-fluid nozzle. Spraying was stopped as needed according to the granulation status, and only agitation and mixing were carried out, followed by spraying again. Depending on the granulation status, the gas pressure was adjusted accordingly, and the desired granules were obtained at a final purified water spray volume of 782 g. The obtained granules were regulated its particle size in a wet/dry particle size regulator (Powrex Co., Ltd.) and dried in a fluidized bed granulator-dryer (Powrex Co., Ltd.) to obtain dried granules. The dried granules and light anhydrous silicic acid (50 g) were placed in a plastic bag, mixed in the bag, and then dry granulated in a wet/dry particle size regulator (Powrex Co., Ltd.) to obtain the formulation of Example 1.

[000210] Table 1

Component	**Formulation (mg)**	
	Comparison Example 1	**Example 1**
Compound 1	1000	1000
hydroxypropyl cellulose	165	165
carboxy vinyl polymer	10	10
sucralose	25	25
hypromellose		
copovidone		
light anhydrous silicic acid	50	50

Component		**Formulation (mg)**	
		Comparison Example 1	**Example 1**
granulation liquid	Purified water	(as appropriate)	(as appropriate)
	Method of addition	drop	Spraying
total amount		1250	1250

[000211]

The results are shown below.

[000212] Table 2

Summary		**Comparison Example 1**	**Example 1**	**Difference**
Percentage of coarse grains (%)		(A1)	(B1)	(B1)-(A1)
	710 um or more	12.9	1.0	-
	500 um or more	20.8	4.3	-
	250 um or more	33.9	19.2	-
Elution rate vs. initial elution rate (%) (30 min value)		(A1)	(B1)	(B1)-(A1)
	initial	100.0	100.0	**0.0**
	1w	96.0	98.0	**2.0**
	2w	94.9	97.1	**2.2**
	1M	92.9	98.0	**5.1**

[000213] The particle size distribution is shown in Figure 1.

[000214] Based on the above results, we thought that reducing the particle size above 500 μm might be particularly effective, so we prepared the following various compositions and conducted a demonstration experiment on the effect of reducing the particle size above 500 μm.

[000215] Preparation Example 2: Experiments with various compositions

(3) Preparation of Example 2: Compound 1 (158.3 g), hydroxypropyl cellulose (26.1 g), carboxyvinyl polymer (1.6 g), and sucralose (4.0 g) were placed in a plastic bag and mixed in the bag.

[000216] The mixture was placed in an agitating mixing granulator (Powrex Co., Ltd.), and the agitation and mixing of the mixture and the dropping of purified water (37.8 g) were repeated until a granulated product was obtained. The resulting granules were regulated its particle size in a wet/dry particle size regulator (Powrex Co., Ltd.) and dried in Fluidized bed granulation dryer (Powrex Co., Ltd.) to obtain dry granules. The dried granules were then regulated its particle size in a wet/dry particle size regulator (Powrex Co., Ltd.) to obtain a formulation, which was then sieved through a sieve shaker (RETSCH Co., Ltd.) using a metallic sieve with a 500 μm gap to obtain the formulation of Example 2.

[000217] (4) Preparation of Example 3: The preparation of Example 3 was made in the same manner as in Example 2, except that Compound 1 (158.3 g), hydroxypropyl cellulose (26.1 g), and purified water (32.0 g) as granulation liquid were used as ingredients.

[000218] (5) Preparation of Example 4: The preparation of Example 4 was made in the same manner as in Example 2, except that Compound 1 (158.3 g), hypromellose (26.1 g), and purified water (50.4 g) as granulation liquid were used as the raw materials for the formulation.

[000219] (6) Preparation of Example 5: The preparation of Example 5 was made in the same manner as in Example 2, except that Compound 1 (158.3 g), copovidone (26.1 g), and purified water (35.2 g) granulation liquid were used as raw materials for the formulation.

[000220] Table 3

Component	**Formulation (mg)**			
	Example 2	**Example 3**	**Example 4**	**Example 5**
Compound 1	1000	1000	1000	1000
hydroxypropyl cellulose	165	165		

Component		Formulation (mg)			
		Example 2	**Example 3**	**Example 4**	**Example 5**
carboxy vinyl polymer		10			
sucralose		25			
hypromellose				165	
copovidone					165
light anhydrous silicic acid					
granulation liquid	Purified water	(as appropriate)	(as appropriate)	(as appropriate)	(as appropriate)
	Method of addition	drop	drop	drop	drop
total amount		1200	1165	1165	1165

[000221] A result is shown in Figure 2.

[000222] Results are shown below.

[000223] Table 4

		Example 2	**Example 3**	**Example 4**	**Example 5**
Summary		**HPC** + carboxyvinyl polymer + sucralose	**HPC**	**HPMC**	**copovidone**
Percentage of coarse grains (%)	710 um or more	0.8	0.1	1.8	0.4
	500 um or more	1.3	0.3	4.8	1.3
	250 um or more	17.6	17.2	53.1	36.8
	initial	100.0	100.0	100.0	100.0
	1w	96.9	99.0	102.1	100.0

		Example 2	Example 3	Example 4	Example 5
Summary		**HPC** + carboxyvinyl polymer + sucralose	**HPC**	**HPMC**	**copovidone**
Elution rate vs. initial elution rate (%) (30 min value)	2w	94.9	101.0	100.0	95.9
	5w	95.9	99.0	102.1	86.6

[000224] From the above results, it is understood that the dissolution stability is better in all cases. In all cases, if the composition is the same, the dissolution stability is better when the particle size is controlled than when the particle size is not controlled.

[000225] Example 6

[000226] (7) Preparation of Example 6: Compound 1 (158.3 g), hypromellose (26.1 g), and purified water (50.4 g) as granulation liquid were mixed in a plastic bag.

[000227] agitation and mixing of the mixture and dropping of purified water (37.8 g) were repeated until a granulated product was obtained. The resulting granules were regulated its particle size in a wet/dry particle size regulator (Powrex Co., Ltd.) and dried in a fluidized bed granulator (Powrex Co., Ltd.) to obtain dry granules. The dried granules were then wet regulated its particle size in a wet/dry particle size regulator (Powrex Co., Ltd.) to obtain the formulation of Example 6.

[000228] (8) Preparation of Comparative Example 2: Except for using Compound 1 (158.3 g), hydroxypropyl cellulose (26.1 g), carboxy vinyl polymer (1.6 g), and sucralose (4.0 g) as raw materials for the preparation, the preparation of Comparative Example 2 was made in the same way as the preparation of Example 6.

[000229] (9) Preparation of Comparative Example 3: The preparation of Comparative Example 3 was made in the same way as in Example 6, except that Compound 1 (158.3 g), hydroxypropylcellulose (26.1 g), and purified water (32.0 g) as granulation liquid were used as the raw materials for the formulation.

[000230] (10) Preparation of Comparative Example 4: The preparation in Comparative Example 4 was made in the same way as in Example 6, except that Compound 1 (158.3 g), copovidone (26.1 g), and purified water (35.2 g) as granulation liquid were used as raw materials for the formulation.

[000231] Table 5

Component		**Formulation (mg)**			
		Example 6	**Comparison Example 2**	**Comparison Example 3**	**Comparison Example 4**
Compound 1		1000	1000	1000	1000
hypromellose		165			
hydroxypropyl cellulose			165	165	
carboxy vinyl polymer			10		
sucralose			25		
copovidone					165
light anhydrous silicic acid					
granulation liquid	(as appropriate)		(as appropriate)	(as appropriate)	(as appropriate)
	drop		drop	drop	drop
total amount		1165	1200	1165	1165

[000232] Results are shown below.

Table 6

	Example 1	**Comparison Example 2**	**Comparison Example 3**	**Comparison Example 4**

Summary		HPMC	HPC + carboxyvinyl polymer + sucralose	HPC	Copovidone
Percentage of coarse grains (%)	Above 710 um	12.9	12.5	6.5	9.9
	500 um or more	26.6	21.9	13.6	22.2
	Above 250 um	59.7	37.9	26.6	48.2
Elution rate vs. initial elution rate (%) (30 min value)	initial	100.0	100.0	100.0	100.0
	1w	101.0	95.8	94.9	96.0
	2w	99.0	92.6	94.9	93.1
	5w	102.1	91.6	93.9	67.3

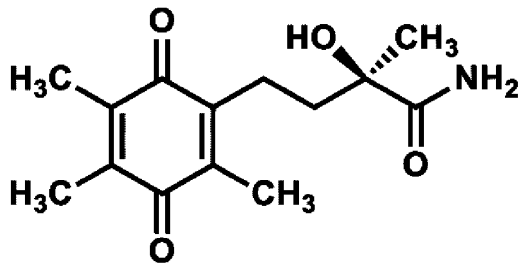
[000233] These results show that, unexpectedly, the use of hypromellose improves dissolution stability compared to other binders.

[000234] As described above, the present disclosure has been exemplified using preferred embodiments; however, it is understood that the scope of the present disclosure should be interpreted solely based on the claims. It is understood that the patents, patent applications, and other documents cited in this specification are incorporated herein by reference in the same manner as the contents are specifically described herein. This application is based on a patent application No. 2024-39505 filed in Japan (filing date: March 13, 2024), the contents of which are incorporated in its entirety herein.

[000235] Industrial applicability: The present disclosure provides pharmaceutical compositions.

CLAIMS

Claim 1. Granules comprising a compound according to Formula 1:



or pharmaceutically acceptable salt or solvate thereof, wherein 20% or less by weight of particles constituting the granules have a particle size of 500 μm or greater.

Claim 2. The granules of claim 1, wherein the particles contain a binder.

Claim 3. The granules according to claim 1 or 2, wherein the particles contain a dispersant.

Claim 4. The granules of any one of claims 1-3, wherein the particles contain a sweetener.

Claim 5. The granules of any one of claims 1-4, wherein the particles contain a suspending agent.

Claim 6. The granules of any one of claims 1-5, wherein the particles contain a binder, a dispersant, and a sweetener.

Claim 7. The granules of any one of claims 1-6, wherein the particles contain a binder, a dispersant, a sweetener, and a suspending agent.

Claim 8. The granules of any one of claims 2-7, wherein the binder comprises at least one binder selected from the group consisting of hydroxypropylcellulose,

hypromellose, copovidone, methylcellulose, povidone, polyvinyl alcohol, polyvinyl alcohol/polyethylene glycol/graft copolymer, and xanthan gum.

Claim 9. The granules of any one of claims 2-8, wherein the binder is hydroxypropyl cellulose or copovidone.

Claim 10. The granules of any one of claims 2-8, wherein the binder is hypromellose.

Claim 11. The granules of any one of claims 2-9, wherein the binder is hydroxypropyl cellulose.

Claim 12. The granules of any one of claims 3-11, wherein the dispersant comprises at least one dispersant selected from the group consisting of light silicic anhydride, magnesium metasilicate aluminate, polyethylene glycol 6000, corn starch, microcrystalline and carboxymethylcellulose sodium carmellose, carmellose, calcium carmellose, and sodium stearyl fumarate.

Claim 13. The granules of any one of claims 3-12, wherein the dispersant is light anhydrous silicic acid.

Claim 14. The granules of any one of claims 4-13, wherein the sweetener is sucralose.

Claim 15. The granules of any one of claims 5-14, wherein the suspending agent is a carboxyvinyl polymer.

Claim 16. The granules according to claim 7, wherein the binder is hydroxypropyl cellulose, the suspending agent is a carboxyvinyl polymer, and the sweetener is sucralose.

Claim 17. The granules according to claim 7, wherein the binder is hydroxypropyl cellulose, the suspending agent is a carboxyvinyl polymer, the sweetener is sucralose, and the dispersant is light anhydrous silicic acid.

Claim 18. The granules according to any one of claims 1-17, wherein 15% or less by weight of the particles constituting the granules have a particle size of 500 μm or greater.

Claim 19. The granules according to any one of claims 1-18, wherein 10% or less by weight of the particles constituting the granules have a particle size of 500 μm or greater.

Claim 20. The granules according to any one of claims 1-19, wherein 5% or less by weight of the particles constituting the granule formulation have a particle size of 500 μm or greater.

Claim 21. The granules according to any one of claims 2 to 20, wherein the granules contain 1 mg to 1000 mg of binder with respect to 1000 mg of the compound represented by Formula 1 or pharmaceutically acceptable salt or solvate thereof.

Claim 22. The granules according to any one of claims 3 to 21, wherein the granules comprise 0.01 to 10% by weight of dispersant relative to the weight of the entire granules.

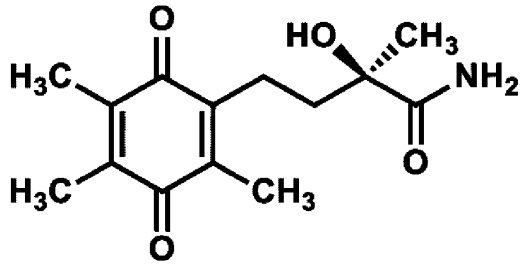
Claim 23. The granules according to any one of claims 4 to 22, wherein the granules comprise 1 mg to 1000 mg of sweetener with respect to 1000 mg of the compound represented by Formula 1 or pharmaceutically acceptable salt or solvate thereof.

Claim 24. The granules of any one of claims 5 to 23, wherein the granules contain 1 mg to 1000 mg of suspending agent for 1000 mg of the compound represented by Formula 1 or pharmaceutically acceptable salt or solvate thereof.

Claim 25. The granules of any one of claims 1 to 24, wherein the granules are produced via a granulation liquid spraying process.

Claim 26. Granules according to any one of claims 1 to 25, characterized by improved dissolution stability after storage.

Claim 27. A method for manufacturing granules comprising a compound or pharmaceutically acceptable salt or solvate thereof represented by
Formula 1:



the method comprises the steps of:

admixing the compound or pharmaceutically acceptable salt or solvate thereof with other materials to be comprised in the granules;

preparing granules from the admixed material, wherein not more than 20% by weight of the particles constituting the granules are prepared to have a particle size of 500 μm or greater.

wherein 20% or less by weight of the particles constituting the granules have a particle size of 500 μm or greater.

Claim 28. The method according to claim 27, wherein the step of preparing the granules include a granulation liquid spraying process.

Claim 29. The granules according to any one of claims 1 to 26, or granules manufactured by the method according to claim 27 or 28 used for preparing a suspension liquid.

Claim 30. A suspension liquid comprising granules according to any one of claims 1 to 26 and 29.

Claim 31. A method of treating or preventing a disease in a subject in need thereof, comprising the steps of administering to the subject in need thereof an effective amount of the suspension liquid according to claim 30.

Claim 32. A method of preparing a suspension liquid for administration to a subject at a medical setting, comprising the process of mixing granules according to any one of claims 1-26 with a necessary additive and/or a suspension solvent (including, for example, a water soluble medium such as purified water).

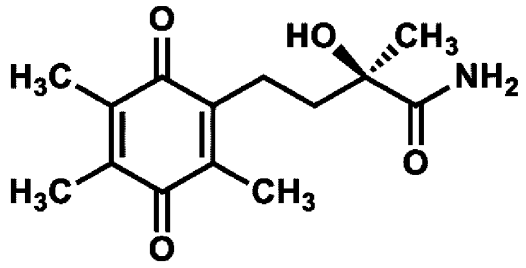
Claim 33. The granules according to any one of claims 1 to 26, the suspension liquid according to claim 30, or the method according to any one of claims 31 or 32 for use in treating or inhibiting oxidative stress disorders, modulating one or more energy biomarkers, normalizing one or more energy biomarkers, enhancing one or more energy biomarkers.

Claim 34. The granules according to any one of claims 1 to 26, the suspension liquid according to claim 30, or the method according to any one of claims 31 or 32 for use in treating or inhibiting: mitochondrial disorders; hereditary mitochondrial disease; Alpers disease; Barth syndrome; beta-oxidation defect; carnitine-acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndrome; coenzyme Q10 deficiency; complex I deficiency; complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive exophthalmoplegia (CPEO); CPT I deficiency; CPT II deficiency complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive external ophthalmoplegia (CPEO); CPT I deficiency; CPT II deficiency; Friedreich's ataxia (FA); glutaric aciduria type II; Kearns-Sayre syndrome (KSS); lactic acidosis; long chain acyl CoA dehydrogenase deficiency (LCAD); LCHAD; Leigh syndrome; Leigh-like syndrome; Leber hereditary optic neuropathy (LHON); lethal infantile cardiomyopathy (LIC); Luft disease; multiple acyl CoA dehydrogenase deficiency (MAD); medium chain acyl CoA dehydrogenase deficiency (MCAD) ; mitochondrial myopathy, encephalopathy, lactoacidosis, and stroke (MELAS); myoclonus epilepsy with red ragged fibers (MERRF); mitochondrial recessive ataxia syndrome (MIRAS); mitochondrial cell disease, mitochondrial DNA depletion; mitochondrial encephalopathy; mitochondrial myopathy Syndrome; mitochondrial neurogastrointestinal encephalopathy (MNGIE); neuropathy, ataxia, retinitis pigmentosa (NARP); Pearson syndrome; pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; a disorder associated with a POLG mutation; respiratory chain disorders; short-chain acyl CoA dehydrogenase deficiency (SCAD); SCHAD; very long chain acyl CoA dehydrogenase deficiency (VLCAD); myopathy; cardiomyopathy; encephalomyopathy; neurodegenerative disease; Parkinson's disease; Alzheimer's disease; amyotrophic lateral sclerosis (ALS); motor neuron disease; neurological disease; epilepsy; age-related diseases; macular degeneration; diabetes; metabolic syndrome; cancer; Brain cancer; Genetic disorders; Huntington's disease; Mood disorders; Schizophrenia; Bipolar disorder; Pervasive developmental disorder; Autistic disorder;

Asperger's syndrome; Childhood decompensation disorder (CDD); Rett disorder or Rett syndrome; PDD not otherwise specified (PDD-NOS); Cerebrovascular accident; Stroke; Visual impairment; Optic neuropathy; Dominant inherited juvenile optic atrophy; optic neuropathy caused by poisons; glaucoma; Stargardt macular dystrophy; diabetic retinopathy; diabetic maculopathy; retinopathy of prematurity; ischemia-reperfusion related retinal damage; oxygen toxicity; abnormal hemoglobinopathy; thalassemia; sickle cell anemia; seizures; ischemia; renal tubular acidosis; Attention Deficit Hyperactivity Disorder (ADHD); neurodegenerative disorders leading to hearing or balance impairment; Dominant Optic Atrophy (DOA); Maternally Inherited Diabetes with Deafness (MIDD); Chronic Fatigue; Contrast-induced renal injury; Contrast-induced retinopathy damage; Ano beta lipoproteinemia; Retinitis Pigmentosa; Wolfram's disease; Tourette syndrome; cobalamin c deficiency; methylmalonic aciduria; glioblastoma; Down syndrome; acute tubular necrosis; muscular dystrophy; leukodystrophy; progressive supranuclear palsy; spinal muscular atrophy; hearing loss; noise-induced hearing loss; traumatic brain injury; juvenile Huntington disease; multiple sclerosis; NGLY1; NGLY1 deficiency; NGLY1-congenital disorder of deglycosylation; multiple system atrophy; adrenal cerebral white matter dystrophy; and adrenal spinal neuropathy.

Claim 35. The granule formulation according to any one of claims 1-26, the suspension liquid according to claim 30, or the method according to any one of claims 31-34 for treating or preventing amyotrophic lateral sclerosis (ALS).

Claim 36. Granules comprising particles of a compound represented by the following Formula 1:



Formula 1

or a pharmaceutically acceptable salt or solvate thereof, and hypromellose or a hypromellose analogue.

Claim 37. The granules according to claim 36, wherein the hypromellose or hypromellose analog is hypromellose.

Claim 38. The granules according to claim 36 or 37, wherein the granules have the characteristics described in any one of the claims from 1 to 35.