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(71) Applicant: **APRECIA PHARMACEUTICALS COMPANY** [US/US]; 2010 Cabot Blvd. West, Suite F, Langhorne, PA 19047 (US).

(72) Inventors: **JACOB, Jules**; 1008 N. Elbow LN, Yardley, PA 19067 (US). **COYLE, Norman**; 303 North Bethlehem Pike, Fort Washington, PA 19034 (US). **WEST, Thomas, G.**; 13135 East Run Dr., Lawrenceville, NJ 08648 (US). **MONKHOUSE, Donald, C.**; 439 King of Prussia Road, Radnor, PA 19087 (US). **SURPRENANT, Henry, L.**; 30 Summerhill Lane, Phoenixville, PA 19460 (US). **JAIN, Nemichand, B.**; 18 Abbington LN, Princeton Junction, NJ 08550 (US).

(74) Agent: **MATOS, Rick**; INNOVAR, LLC, P.O. Box 250647, Plano, TX 75025-0647 (US).

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(54) Title: RAPID DISPERSE DOSAGE FORM CONTAINING LEVETIRACETAM

(57) Abstract: A high dose rapidly dispersing three-dimensionally printed dosage form comprising a high dose of levetiracetam in a porous matrix that disperses in water within a period of less than about 10 seconds is disclosed. Also disclosed are methods of preparing the dosage form and of treating a condition, disease or disorder that is therapeutically responsive to levetiracetam. A process for preparing the dosage form is also provided

RAPID DISPERSE DOSAGE FORM CONTAINING LEVETIRACETAM

Field of the Invention

[0001] The present invention relates to a rapidly dispersing (orodispersible) dosage form of levetiracetam. In particular, the dosage form disperses within a period of less than about fifteen seconds when placed in the mouth of subject. The invention also relates to methods of use of the dosage form for the treatment of diseases, disorders or conditions that are therapeutically responsive to levetiracetam. A process for preparing the dosage form is also provided.

Background of the Invention

[0002] Solid oral dosage forms containing levetiracetam (LEV; (S)-2-(2-oxopyrrolidin-1-yl)butanamide; (-)-(S)- α -ethyl-2-oxo-1-pyrrolidine acetamide; described in U.S. 4,943,639) are known (FDA Electronic Orange Book). Solid tablets are currently available under the trademark KEPPRA® (NDA N021035, UCB, Inc., approval date Nov. 30, 1999; package insert available at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=9870). These tablets are known to contain 250, 500, 750 or 1000 mg of levetiracetam and the following excipients (inactive ingredients): colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, polyethylene glycol 3350, polyethylene glycol 6000, polyvinyl alcohol, talc, titanium dioxide, and additional agents listed below: 250 mg tablets contain FD&C Blue #2/indigo carmine aluminum lake; 500 mg tablets contain iron oxide yellow; 750 mg tablets contain FD&C yellow #6/sunset yellow FCF aluminum lake, iron oxide red. KEPPRA® oral solution dosage form is also available.

[0003] Levetiracetam is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane.

[0004] LEV has been found to be chemically stable in a wide range of pharmaceutical formulations. Ingredients included in commercially available tablets of LEV include corn starch, croscarmellose sodium, povidone, colloidal silicon dioxide, talc, magnesium stearate, polyethylene glycol, titanium dioxide, iron oxide and polyvinyl alcohol, among others. However, under accelerated (60° C) conditions of stress (acidic,

alkaline, aqueous, oxidative, thermal or photo), it has been demonstrated that LEV undergoes substantial degradation (Shah, *Der Pharmacia Sinica* (2012), 3(5), 576-589). Shah reports that the rate constant for oxidative degradation is smaller than for acidic hydrolysis, base hydrolysis, water hydrolysis and UV photolysis. Prohotsky et al. (Am. J. Health Syst. Pharm. (2014), 71(3), 219-22) disclose the results of a study on the stability of an oral solution of levetiracetam. They conclude that the solution is stable for up to six months.

[0005] Ensom et al. (Can. J. Hosp. Pharm. (2011), 64(3), 207-211) disclose the results of a study on the stability of extemporaneously compounded solutions of levetiracetam in ORA-SWEET and ORA-PLUS. They report that all samples were unchanged over a period of at least 91 days.

[0006] LEV is indicated for treating epilepsy, as adjunctive treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy, as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy, and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy. It has also been suggested for improving cognitive function in subjects that exhibit age-related cognitive impairment or are at risk thereof, including subjects having or at risk for Mild Cognitive Impairment (MCI), Age-related Cognitive Decline (ARCD) or Age-Associated Memory Impairment (AAMI).

[0007] LEV is dosed at high levels such as 250-1000 mg per tablet for the treatment of epilepsy and seizures. Treatment is initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Doses greater than 3000 mg/day have been used in open-label studies for periods of 6 months and longer. However, young and elderly patients typically experience difficulty in swallowing solid oral dosage forms containing such high doses, especially because of the large amount of excipients included in known dosage forms. Difficulty in swallowing leads to poor patient compliance. Attempts to resolve this problem have lead to the development of oral liquid and injectable formulations. Stability, contamination and inaccurate dosing problems, however, are still associated with such dosage forms.

[0008] Given the high doses of LEV required per tablet, it is difficult to formulate rapidly dispersible solid oral dosage forms with sufficient hardness and friability

suitable for storage and handling. Attempts to resolve such problems are disclosed. U.S. 8,187,635 to Karavas et al. discloses tablets that contain dicalcium phosphate and disintegrate in about 30 min. WO 2007/012439 to UCB Pharma, S.A. discloses tablets that disintegrate in about 15-45 min. WO 2006/102750 to Genpharm Inc. discloses tablets that are made by granulation and fluid-bed drying and disintegrate in about 3 to 8 min. Such tablets do not meet the U.S. F.D.A. requirements of an orodispersible dosage form.

[0009] Orodispersible dosage forms disperse or disintegrate in the mouth in a minimal amount of saliva or water. Such dosage forms provide ease of swallowing, accuracy of dosing, and rapid therapeutic action. U.S. 7,749,533 to Fu et al. discloses a dosage form containing granules containing a drug, porous plastic substance, water penetration enhancer, binder and drug. The granules must be compressed in order to create the dosage form. U.S. 4,371,516 to Gregory et al. and U.S. 5,738,875 disclose freeze-dried dosage forms. U.S. 5,178,878 to Wehling et al. discloses a soft-compress orodispersible dosage form. Effervescent dosage forms and quick release coatings of insoluble microparticles are described in U.S. 5,578,322 and 5,607,697. Freeze dried foams and liquids are described in U.S. 4,642,903 and U.S. 5,631,023. Melt-spun dosage forms are described in U.S. 4,855,326, 5,380,473 and 5,518,730. U.S. 20070218129 discloses an immediate release dispersible and orodispersible solid pharmaceutical composition having the form of particles with a size lower than 710 μm upon dispersion into water, wherein the formulation is made by wet granulation; however, the disintegration times range from 53 to 60 sec.

[0010] U.S. 6,471,992, U.S. 2012-0207929 and U.S. 2003-0133975 disclose three-dimensionally printed rapidly dispersing dosage forms. Even so, an orodispersible three-dimensionally printed dosage form containing LEV has not been suggested. It is not possible to predict *a priori* whether a three-dimensionally printed dosage form containing substantial amounts of LEV can be made to disperse in a minimal amount of aqueous fluid in 15 sec or less 10 sec or less or 5 sec or less while at the same time possessing sufficient hardness to endure handling and storage.

[0011] None of the above discloses a rapidly dissolving solid oral dosage form containing levetiracetam. WO 2011/136751 to Mahmut discloses a compressed effervescent tablet made from a granulate containing LEV; however, the tablet dissolves in about five minutes or less. CN102085194A to Beijing Yiling Bioengineering Co. Ltd. discloses an orally distintegrating freeze-dried dosage form containing LEV, PEG 600,

maltodextrin and hydrolyzed gelatin. Freeze-dried dosage forms, however, are physically very unstable and exhibit extremely high friability since they are not hard.

[0012] The use of glycerin in the manufacture of a three-dimensionally printed article is disclosed in U.S. 20080281019, U.S. 20080187711, U.S. 20070168815, U.S. 20040187714, U.S. 20030207959, U.S. 20070146734, U.S. 20050197431, U.S. 20040056378, U.S. 5,902,441, U.S. 6,416,850, and U.S. 6,838,035. There is no prior disclosure of the use of glycerin in the manufacture of a three-dimensionally printed rapidly dispersible dosage form.

[0013] It would be beneficial to provide a rapidly-dispersing orodispersible solid oral dosage form containing levetiracetam that exhibits low friability and sufficient hardness to withstand storage and handling while at the same time exhibiting an extremely rapid disintegration rate; however, no such suitable dosage form containing LEV has been disclosed in the art.

Summary of the Invention

[0014] The present invention seeks to overcome some or all of the disadvantages inherent in the art. The present invention provides an orodispersible solid dosage form, as described herein, comprising levetiracetam as the primary or sole active ingredient, wherein the dosage form comprises a bound matrix that disperses in about 15 sec or less in a volume of about 10 ml or less of water or saliva. The matrix disperses in the mouth of a subject to which it is administered, thereby facilitating swallowing and administration. It would be a substantial improvement in the art to provide an orodispersible solid dosage form, as described herein, comprising levetiracetam as the primary or sole active ingredient, wherein the dosage form comprises a bound matrix that disperses in 20 sec or less in a volume of 5 ml or less of water or saliva. The matrix very rapidly disperses in the mouth of a subject to which it is administered, thereby facilitating swallowing and administration.

[0015] The dosage form is self-preserved and does not require the addition of a preservative, even though a preservative can be included if desired. Accordingly, some embodiments of the invention provide a preservative-free rapidly orodispersible dosage of LEV.

[0016] The inventors have discovered that levetiracetam undergoes oxidative degradation during formulation by three-dimensional printing; however, no degradation

products corresponding to acid-catalyzed or based-catalyzed hydrolysis or photolytic or thermolytic degradation were observed. These results are surprising because (Shah, *supra*) teaches that oxidative degradation of LEV occurs at a much slower rate than hydrolysis or photolysis under accelerated conditions. The inventors have discovered that inclusion of an antioxidant in the orodispersible dosage form of the invention provides protection against oxidative degradation of LEV during manufacture and storage of the 3DP orodispersible dosage form. The inventors have succeeded in preparing a 3DP orodispersible dosage form comprising LEV, wherein the content of any individual oxidative degradant in the dosage form is less than 0.1% wt based upon the weight of LEV in the dosage form, wherein the dosage form comprises LEV, antioxidant, and water soluble binder comprising peroxide as impurity. The content of any individual oxidative degradant remains at or below 0.1% wt even after storage at 21° C for six months at 75% RH.

[0017] Accordingly, some embodiments of the invention provide a stable rapidly orodispersible three-dimensionally printed solid porous matrix comprising LEV, antioxidant, disintegrant and binder, wherein the matrix is stable to oxidative degradation of LEV when stored at 21° C for six months at 75% RH. The invention also provides a stable rapidly orodispersible three-dimensionally printed solid porous matrix comprising LEV, antioxidant, disintegrant and binder, wherein the matrix comprises 0.1% or less of an oxidative degradant of LEV after being stored at 21° C for six months at 75% RH. In some embodiments, the antioxidant is selected from the group consisting of butylated hydroxyanisole (BHA), butylated hydroxytoluene, sodium sulfite, sodium bisulfite, methionine, vitamin E, or combinations thereof.

[0018] In some aspects, the invention provides a rapidly dispersible, i.e. orodispersible, dosage form and administration thereof for the treatment of diseases, conditions or disorders that are therapeutically responsive to levetiracetam. The rapidly dispersible solid dosage form comprises a three-dimensionally printed matrix comprising LEV, antioxidant and bulk material. The matrix is formed by deposition of a printing fluid to a powder, whereby the particles of the powder become bound by LEV and/or binder. The matrix is porous with a defined overall bulk density, disintegration (dispersion) time in aqueous fluid, dissolution time in aqueous fluid, and moisture content. The matrix provides a balance of improved chemical stability, sufficient hardness, low friability and extremely rapid dispersion time in a small volume of aqueous liquid.

[0019] Increasing the content of many different types of water soluble excipients in the 3DP orodispersible dosage form generally results in increased hardness and increased dispersion time. For example, increasing the content of water soluble binder and LEV results in increased hardness and dispersion time. The inventors have discovered that increasing the content of glycerin in the 3DP dosage form increases hardness but unexpectedly decreases dispersion time.

[0020] Accordingly, another aspect of the invention provides use of a printing fluid comprising glycerin and at least one pharmaceutically acceptable solvent for the manufacture of a rapidly dispersible dosage form. The invention also provides a three-dimensional printing system comprising a glycerin-containing printing fluid, and provides a method of three-dimensionally printing an orodispersible dosage form, the method comprising: a) depositing an incremental layer of drug-containing powder onto a surface; b) depositing a sufficient amount of printing fluid onto the incremental layer to bind particles in the powder, wherein the printing fluid comprises glycerin and at least one pharmaceutically acceptable solvent; and c) repeating a) and b) thereby forming a rapidly orodispersible.

[0021] Some embodiments of the invention include those wherein: a) the drug is water soluble drug; b) the powder and/or printing fluid comprises water soluble binder; c) the content of glycerin in the printing fluid ranges from >0% to 20% wt or about 0.05% to about 10% wt or about 0.05% to about 5% wt; and/or d) the content of glycerin in the dosage form ranges from about 0.05%-3%, or about 0.1%-2%, or 0.5%-1.0% wt based upon final weight of the dosage form.

[0022] Some aspects of the invention provide an orodispersible solid dosage form comprising a three-dimensionally printed porous matrix comprising bound particles of LEV and bulk material, wherein the particles are bound by LEV and/or binder. The invention also provides an orodispersible dosage form comprising a three-dimensionally printed matrix comprising bound particles of LEV, disintegrant, binder, and antioxidant, wherein the particles are bound by LEV and/or binder.

[0023] In some embodiments, LEV is present in crystalline form. All polymorphs thereof are contemplated. The crystallinity of LEV or any other material can be determined by differential scanning calorimetry (DSC) to determine the presence of amorphous material. In some embodiments, LEV is present in amorphous form in the bulk powder or in the matrix

[0024] Embodiments of the invention include those wherein: a) the dosage form is not compressed; b) the matrix is not compressed; c) the hardness of the exterior surfaces of the dosage form is greater than the hardness of an interior portion (one or more interior incremental printed layers thereof) of the dosage form, i.e. the exterior of the dosage form is harder than the interior; d) the dissolution time of LEV is slower than the dispersion time of the matrix when placed in an aqueous fluid; e) the matrix disperses in about 10 seconds or less when placed in a small volume of aqueous fluid; f) at least 75%, at least about 90, or at least about 95% of the LEV dissolves in about 2 minutes or less when placed in an aqueous fluid; g) LEV is present in a form selected from the group consisting of hydrate, hemi-hydrate, crystalline, amorphous, anhydrate or a combination thereof; h) the dosage form comprises not more than 10% wt and not less 0.1% moisture as determined by loss on drying at 120° C; i) the hardness of the matrix is substantially uniform; j) the dosage form comprises one or more other medicaments; and/or k) a combination thereof.

[0025] The invention also provides a three-dimensionally printed orodispersible dosage form comprising a three-dimensionally printed orodispersible matrix of bound particles, the matrix comprising LEV, disintegrant, one or more binders, one or more surfactants, one or more antioxidants, glycerin and optionally one or more of the following: one or more glidants (free-flow additive), one or more flavorants, one or more preservatives; wherein, the matrix comprises particles bound by binder and LEV; the matrix is porous and non-compressed; the matrix disperses in less than 15 sec in a volume of 10 ml of aqueous fluid; and the content of LEV in the matrix ranges from 50-80 % wt based upon the total weight of the matrix. The matrix maintains a fixed and rigid three-dimensional structure when not placed in an aqueous fluid but disperses in a short period of time (as defined herein) when placed in a small volume of aqueous fluid (as defined herein).

[0026] Some embodiments of the invention include those wherein: a) the at least one surfactant is present in an amount ranging from about 0.05 to about 1%, about 0.1 to about 0.8%, and about 0.2 to about 0.5 % wt based upon the final weight of the dosage form; b) the at least one antioxidant is present in an amount range from about 0.005 to about 5.0%, about 0.01 to about 1.0%, and about 0.08 to about 0.8% based upon the final weight of the dosage form; c) the at least one binder is present in an amount range from about 0.5 to about 20%, about 5 to about 15%, and about 7 to about 13% based upon

the final weight of the dosage form; d) the at least one disintegrant is present in an amount range from about 3 to about 35%, about 10 to about 30%, and about 20 to about 26% based upon the final weight of the dosage form; and/or e) the at least one glidant is present in an amount range from about 0.1 to about 2.0%, about 0.25 to about 1.5%, and about 0.5 to about 1.0% wt, based upon the final weight of the dosage form.

[0027] The LEV particles have an average, mean or median particle size in the range of about 50 to about 400 microns, about 50 to about 300 microns, about 50 to about 250 microns, about 60 to about 250 microns, about 60 to about 100 microns, or about 75 to about 250 microns. The particle size can be expressed as VMD. In some embodiments, the particle size range is defined as: a) Dv10 is about 20-60 microns, Dv50 is about 50 to 200 microns, and Dv90 is about 100-500 microns; b) Dv10 is about 50-60 microns, Dv50 is about 150 to 200 microns, and Dv90 is about 350-510 microns; c) Dv10 is about 20-30 microns, Dv50 is about 50 to 60 microns, and Dv90 is about 100-120 microns; d) Dv10 is about 30-40 microns, Dv50 is about 70-80 microns, and Dv90 is about 160-190 microns; or e) Dv10 is about 40-50 microns, Dv50 is about 125 to 150 microns, and Dv90 is about 300-350 microns. In some embodiments, the VMD ranges from about 60 to about 240 microns, from 50-70 microns, from 80-100 microns, from 150 to 175 microns, from 200 to 250 microns.

[0028] Some embodiments of the invention include those wherein the matrix comprises about 250 to about 1000 mg, about 250 mg, about 500 mg, about 750 mg, about 1000 mg of LEV.

[0029] The matrix rapidly disperses (disintegrates) in a small amount of aqueous fluid. Some embodiments of the invention include those wherein the matrix disperses in about 30 sec or less, about 20 sec or less, about 15 sec or less, about 10 sec or less, or about 5 sec or less when placed in a small amount of aqueous fluid.

[0030] Some embodiments of the invention include those wherein: a) the hardness of the matrix ranges from about 1 to about 10 kp, about 2 to about 6 kp or about 3 to about 9 kp; b) the matrix disperses in 10 sec or less when placed in 15 ml of water or saliva; c) binder is introduced into the matrix by way of printing fluid used to form the matrix; d) binder is introduced into the matrix by way of bulk powder used to form the matrix; e) the matrix comprises about 250 mg to about 1000 mg of LEV; f) the matrix comprises 15 to 50 or 25 to 50 of printed incremental layers; g) the thickness (height) of an

incremental layer ranges from 0.008 to 0.012 inches; and/or h) the matrix is porous and non-compressed.

[0031] The invention also provides a method of preparing a three-dimensionally printed orodispersible dosage form comprising LEV. The method comprises: a) providing an incremental layer of bulk powder comprising LEV, disintegrant, binder, antioxidant, optional flavorant, optional sweetener, and optional glidant; b) according to a predetermined saturation level, applying a printing fluid to the layer of bulk powder to form an incremental printed layer, wherein the fluid comprises water, alcohol, binder, antioxidant, glycerin, surfactant (emulsifier), optional sweetener, optional preservative; and c) repeating a) and b) at least two times, thereby forming the three-dimensionally printed orodispersible dosage form comprising at least three stacked incremental printed layers. The antioxidant can be included in the binding fluid, the powder or both.

[0032] Some embodiments of the invention include those wherein: a) the process further comprises forming an indicum or indicia on the surface of the dosage form in embossed (raised) or debossed (recessed) form during the 3DP process; b) the process further comprises removing water and alcohol from the dosage form to reduce its moisture content to within a range as described herein; c) the process further comprises separating the dosage form from bulk powder that has not been printed upon; d) a higher printing fluid saturation level is used for the upper and lower incremental layers of the dosage form than for the rest of the dosage form to provide, in the finished dosage form, increased hardness for the upper and lower incremental surfaces and reduced hardness for incremental layers there between; e) a higher printing fluid saturation level is used for the upper and lower incremental layers and for the periphery of the intermediate incremental layers of the dosage form than for the rest of the dosage form to provide, in the finished dosage form, increased hardness for its upper and lower incremental surfaces and for the periphery of its intermediate incremental layers and to provide reduced hardness for incremental layers there between; f) the process further comprises heating the dosage form to remove and reduce the amount of printing fluid therein; and/or g) the process further comprises preparing the bulk powder by mixing the ingredients thereof to form a mixture that is then sieved.

[0033] Some embodiments of the invention include those wherein the printing fluid saturation level used to prepare the incremental printed layers ranges from 40% to 120%.

[0034] A method of treating a disease or disorder that is therapeutically responsive to LEV is provided. The method comprises daily administration of one, two or three dosage forms of the invention to a subject in need thereof over a treatment period lasting days, weeks or months thereby reducing or eliminating one or more symptoms of the disease or disorder. In some embodiments, a 3DP dosage form described herein comprising a dose of about 250 to about 1000 mg is administered twice daily for a treatment period. The invention also provides a method of treating epilepsy, or other disease, disorder or condition that is therapeutically responsive to LEV, comprising: orally administering to a subject in need thereof a LEV-containing three-dimensionally printed orodispersible dosage form as described herein.

[0035] A method of preparing an orodispersible dosage form is also provided. The method comprises forming a non-compressed porous matrix as described herein by forming incremental layers of powders and depositing printing fluid on each incremental layer to bind disintegrant, binder, surfactant, antioxidant, glidant and LEV into a rapidly orodispersible non-compressed porous matrix.

[0036] The invention includes all combinations of the aspects, embodiments and sub-embodiments of the invention disclosed herein.

Brief Description of the Drawings

[0037] The following figures form part of the present description and describe exemplary embodiments of the claimed invention. The skilled artisan will, in light of these figures and the description herein, be able to practice the invention without undue experimentation.

[0038] FIG. 1 depicts a sectional front elevation of an orodispersible dosage form made from a three-dimensionally printed matrix comprising sequentially-formed incremental layers of bound bulk material.

[0039] FIG. 2 depicts a sectional front elevation of an alternate embodiment of an orodispersible dosage form made from a three-dimensionally printed matrix.

[0040] FIGS. 3A-3E depict various different printing patterns that can be used to apply printing fluid to incremental layers of powder.

Detailed Description of the Invention

[0041] As used herein and unless otherwise specified, the term levetiracetam (LEV) refers to the drug in underivatized form ((S)-2-(2-oxopyrrolidin-1-yl)butanamide; (-)-(S)- α -ethyl-2-oxo-1-pyrrolidine acetamide; described in U.S. 4,943,639) or derivatized form. Levetiracetam is available from TEVA (Jerusalem, Israel) and Hetero Labs (Hyderabad, India), Esteve (Tarragona, Spain), Aurobindo (Hyderabad, India), Matrix Labs (Karachi, Pakistan), Srini (Hyderabad, India). LEV can be present in crystalline or amorphous form. All polymorphs of crystalline LEV and mixtures thereof can be used.

[0042] The dosage form of the invention undergoes immediate and very rapid disintegration/ dispersion of its solid matrix, and LEV and excipients in the matrix undergo a rapid dispersion even when placed in a small volume of aqueous fluid, such as water, saliva, juice, milk, beverage, body fluid, soda or a combination thereof. Dispersion (used interchangeably with disintegration) typically, but not necessarily, overlaps with the dissolution. The matrix comprises a three-dimensional shape that is dispersed within the desired time period upon contact of the composition with at least a small volume of aqueous fluid.

[0043] The present invention provides a pharmaceutical composition suitable for administration to a subject, the composition comprising LEV contained in a rapidly dispersing, non-compressed solid matrix, the matrix having a fixed three-dimensional shape and comprising a bulk material and a binder, the bulk material comprising a pharmaceutically acceptable compound in particulate form and the binder comprising a pharmaceutically acceptable, substantially water-soluble substance having the capacity to adhere to and bind together the particles of the bulk material, to maintain the three-dimensional shape of the matrix, when not placed in an aqueous liquid, and to permit the composition to exhibit hardness and friability characteristics adequate for storage and handling. In some embodiments, the matrix comprises LEV, binder, disintegrant, glycerin, and surfactant.

[0044] Three-dimensionally printed (3DP) dosage forms comprising the matrix were prepared according to Example 1. The resulting 3DP dosage forms were evaluated (Example 3) for hardness, dispersion time and friability to determine which of the drug-containing particles provided suitable 3DP orodispersible dosage forms with very rapid dispersion times, adequate hardness and minimal friability.

[0045] It has been determined that inclusion of a surfactant in the printing fluid, bulk powder and drug-containing particles aids in ensuring rapid dispersion of the 3DP dosage form when placed in a minimal amount of water. The surfactant serves to enhance wetting of the particles. The surfactant need only be present in an amount sufficient to enhance dispersion as compared to another 3DP dosage form excluding the surfactant. If the surfactant is present in too high of an amount, however, it will negatively impact mouth feel, performance and/or physical properties of the dosage form. The surfactant can be included in the bulk powder and/or printing fluid. In some embodiments, the amount of surfactant present in the printing fluid ranges from about 0.1 to about 4%, about 1 to about 3% or about 1.5 to about 2.5 % wt. based upon the weight to the printing fluid.

[0046] The rapidly dispersible dosage form can disperse (disintegrate) in about 20 seconds or less, in about 15 seconds or less, in about 10 seconds or less, in about 5 sec or less, in about 4 sec or less, or in about 3.5 sec or less when placed in a small volume of aqueous fluid, such as a saliva, gastric fluid and/or a sip of water. In some embodiments, the dispersion (disintegration) time is measured in a small volume of 20 ml or less, 15 ml or less, 10 ml or less, 5 ml or less, 3 ml or less and at least 1 ml of an aqueous fluid. In some embodiments, the disintegration time is determined according to USP <701>.

[0047] The small volume of aqueous fluid can be a sip such as a volume less than 50 ml, less than 40 ml, less than 30 ml, less than 20 ml, less than 10 ml, less than 5 ml, less than 2.5 ml, or less than 1 ml. The small volume can be at least 0.1 ml, at least 0.25 ml, at least 0.5 ml, at least 0.75 ml, at least 1 ml, at least 1.5 ml or at least 2 ml. All possible combinations of these volumes are contemplated. Suitable ranges for the small volume include 0.1 to 50 ml, 0.1 to 40 ml, 0.1 to 30 ml, 0.1 to 20 ml, 0.1 to 10 ml, 0.2 to 10 ml, 0.3 to 10 ml, 0.5 to 10 ml, 1 to 10 ml, 1 to 7.5 ml, 1 to 5 ml, 0.5 to 3 ml, or other such ranges. Preferably a sip is about 2 to about 30 ml, about 10 to about 15 ml (1 tablespoon) or about 13 ml of water (fluid).

[0048] In some embodiments, the dosage form comprises not more than 10% wt., not more than 7.5% wt., not more than 5% wt., not more than 4% wt., not more than 3% wt., not more than 2.5% wt., not more than 2% wt. or not more than 1.5% wt. moisture as determined by loss on drying (LOD) at 120° C. In some embodiments, the dosage form comprises at least 0.1% wt., at least 0.2% wt., at least 0.5% wt., at least 0.75% wt., at least 1% wt., at least 1.5% wt., at least 2% wt., at least 2.5% wt., at least 3% wt., at least 4%

wt., or at least 5% wt. moisture as determined by loss on drying at 120° C. In some embodiments, the dosage form comprises 0.1 to 10% wt, 0.2 to 7.5% wt, 0.5 to 5% wt, 0.5 to 4% wt or 1 to 3% wt moisture. All combinations of these various limits are within the scope of the invention.

[0049] The dosage form is a rapidly dispersing dosage form having superior overall hardness and friability characteristics. The hardness of the matrix can be the same (uniform) throughout the matrix, or it can vary. In some embodiments, the hardness of the exterior surfaces of the dosage form (or matrix) is greater than the hardness of an interior portion of the dosage form (or matrix), i.e. the exterior of the dosage form is harder than the interior. The exterior hardness can be at least 1.05-fold, at least 1.1-fold, at least 1.2-fold, at least 1.3-fold, at least 1.4-fold, at least 1.5-fold, at least 1.75-fold, at least 2-fold, at least 2.5-fold, at least 3 fold, at least 5-fold, at least 7-fold, or at least 10-fold higher than the interior hardness. In some embodiments, the upper and lower exterior surfaces have a greater hardness than the interior portion (one or more interior layers) of the dosage form. Methods of achieving uniform hardness and varying hardness of the matrix are discussed herein. In some embodiments, the dosage form has a shelf life of at least six months or at least one year.

[0050] In some embodiments, the overall hardness (as determined by a tablet breaking force assay according to USP <127>) of the matrix ranges from 1 kp to about 20 kp, from about 1 kp to about 10 kp, from about 1 kp to about 7 kp, from about 3 to about 9 kp, about 1 to about 3 kp, about 4.5 to about 6 kp, about 2.5 to about 6.5 kp, about 3 to about 6 kp, or from about 1 kp to about 5 kp. In some embodiments, the overall hardness is at least 1kp, at least 2kp, or at least 3kp. In some embodiments, the overall hardness is no more than 10kp, no more than 8kp or no more than 6kp.

[0051] The term friability refers to the tendency of the matrix to lose material from its outer edges and surfaces upon mechanical insult. Friability is reduced by increasing the hardness. In some embodiments, the dosage form possesses a friability of less than about 25%, preferably less than about 10% as determined according to USP <1216> and as further described below.

[0052] In some embodiments, the porosity of the matrix ranges from about 10% to about 90% or from about 30% to about 70% of the dosage form volume.

[0053] In some embodiments, the bulk density of the matrix (as determined by measurement and/or calculation) ranges from 150 (mg/mL) to about 1300 (mg/mL) or from about 400 (mg/mL) to about 1000 (mg/mL).

[0054] Dissolution time of the LEV is slower than dispersion time of the matrix of the dosage form when placed in an aqueous fluid. Some embodiments of the invention include those wherein not less than 75% wt. (or wherein at least 75% wt.) of LEV present in the dosage form dissolves in 20 min or less, 10 min or less, 5 min or less, 4 min or less, 3 min or less, 2 min or less or 1 min or less when placed in an aqueous environment. Other embodiments of the invention include those wherein not less than 95% wt. (or wherein at least 95% wt.) of LEV present in the dosage form dissolves in 20 min or less, 10 min or less, 5 min or less, 4 min or less, 3 min or less, 2 min or less or 1 min or less when placed in an aqueous environment or in water. In some embodiments, the dissolution times above may be achieved in aqueous environments characterized by a pH of 1.2 or 4.5 or 6.8, and tested within a USP paddle apparatus at 50 RPM or 75 RPM or 100 RPM and a volume of 900 mL or 950 mL or 1000 mL.

[0055] The rapidly dispersible dosage form of the invention is made by a three-dimensional printing (3DP) process. Suitable equipment assemblies for three-dimensional printing of articles are commercially available or are already in use: Massachusetts Institute of Technology Three-Dimensional Printing Laboratory (Cambridge, MA), Z Corporation's 3DP and HD3DP™ systems (Burlington, MA), The Ex One Company, L.L.C. (Irwin, PA), Soligen (Northridge, CA), Specific Surface Corporation (Franklin, MA), TDK Corporation (Chiba-ken, Japan), Therics L.L.C. (Akron, OH, now a part of Integra Lifesciences), Phoenix Analysis & Design Technologies (Tempe, AZ), Stratasys, Inc.'s Dimension™ system (Eden Prairie, MN), Objet Geometries (Billerica, MA or Rehovot, Israel), Xpress3D (Minneapolis, MN), and 3D Systems' Invision™ system (Valencia, CA). Other suitable 3DP systems are disclosed in U.S. No. 20080281019, No. 20080277823, No. 20080275181, No. 20080269940, No. 20080269939, No. 20080259434, No. 20080241404, No. 20080231645, No. 20080229961, No. 20080211132, No. 20080192074, No. 20080180509, No. 20080138515, No. 20080124464, No. 20080121172, No. 20080121130, No. 20080118655, No. 20080110395, No. 20080105144, No. 20080068416, No. 20080062214, No. 20080042321, No. 20070289705, No. 20070259010, No. 20070252871, No. 20070195150, No. 20070188549, No. 20070187508, No. 20070182799, No.

20070182782, No. 20060268057, No. 20060268044, No. 20060230970, No. 20060141145, No. 20060127153, No. 20060111807, No. 20060110443, No. 20060099287, No. 20060077241, No. 20060035034, No. 20060030964, No. 20050247216, No. 20050204939, No. 20050179721, No. 20050104241, No. 20050069784, No. 20050061241, No. 20050059757, No. 20040265413, No. 20040262797, No. 20040252174, No. 20040243133, No. 20040225398, No. 20040183796, No. 20040145781, No. 20040145628, No. 20040143359, No. 20040141043, No. 20040141030, No. 20040141025, No. 20040141024, No. 20040118309, No. 20040112523, No. 20040012112, No. 20040005360, No. 20040005182, No. 20040004653, No. 20040004303, No. 20040003741, No. 20040003738, No. 20030198677, No. 20030143268, No. 20020125592, No. 20020114652, No. 20020079601, No. 20020064745, No. 20020033548, No. 20020015728, No. 20010028471, and No. 20010017085; U.S. Patents No. 5,490,962, No. 5,204,055, No. 5,121,329, No. 5,127,037, No. 5,252,264, No. 5,340,656, No. 5,387,380, No. 5,490,882, No. 5,518,680, No. 5,717,599, No. 5,851,465, No. 5,869,170, No. 5,879,489, No. 5,934,343, No. 5,940,674, No. 6,007,318, No. 6,146,567, No. 6,165,406, No. 6,193,923, No. 6,200,508, No. 6,213,168, No. 6,336,480, No. 6,363,606, No. 6,375,874, No. 6,508,971, No. 6,530,958, No. 6,547,994, No. 6,596,224, No. 6,772,026, No. 6,850,334, No. 6,905,645, No. 6,945,638, No. 6,989,115, No. 7,220,380, No. 7,291,002 No. 7,365,129, No. 7,435,368, No. 7,455,804, No. 7,828,022, No. 8,017,055; PCT International Publications No. WO 00/26026, No. WO 98/043762, No. WO 95/034468, No. WO 95/011007; and European Patent No. 1,631,440, which employs a cylindrical (radial or polar) coordinate-based system due to its construction. The entire disclosure of each of these references is hereby incorporated herein.

[0056] The 3DP process described herein requires a powder layering system that forms a layer of powder and printing system that applies a printing fluid to the layer of powder according to a predetermined pattern, thereby forming an incremental printed layer. The printing fluid serves to form bound particles of powder, i.e. particles that are adhered to one another by one or more pharmaceutical excipients and/or one or more active ingredients. Incremental printed layers are formed one on top of another to vertically build the dosage form of the invention, thereby forming a dosage form comprising plural incremental printed layers. The process of spreading powder and depositing droplets is repeated until the desired number of layers for the dosage form is

complete. The layers adhere to one another due to bleeding of printing fluid from one layer to an adjacent other layer such that one or more excipients and/or one or more active ingredients adhere to both adjacent layers. Following completion of the initial three-dimensional structure, residual printing fluid is removed from or reduced in the dosage form by drying. The evaporation of solvent during the drying process leaves a matrix having a three-dimensional architecture comprising the particles of bulk material bound by solidified binder and/or other components including one or more active ingredients and/or any optional pharmaceutically acceptable excipients.

[0057] The three-dimensional printing process is normally conducted at ambient temperatures. The process can utilize a variety of printing fluids, including biologically compatible organic and aqueous solvents. The process is additive, whereby microscopic features are incorporated layer by layer, allowing a wide range of possible architectures to be constructed precisely on a sub-millimeter scale. Using three-dimensional printing to control simultaneously both the microscopic features and the macroscopic shape, the unique drug delivery systems of the present invention are obtained.

[0058] A particularly suitable printing assembly for three-dimensional printing of the instant dosage form is described in U.S. application No. 61/696,839, filed September 5, 2012, the disclosure of which is hereby incorporated by reference in its entirety. The assembly includes build modules each having an incrementally height adjustable platform disposed within a cavity of the build modules, a powder layering system, a printing system, a printing fluid removal system and a dosage form handling system.

[0059] In general, at least two components are used in the three-dimensional printing process used to prepare the matrix of the rapidly dispersing dosage forms. The first component is the bulk powder material to be included in the incremental powder layers. The second component is the printing fluid (in some cases the fluid may also contain a binder) that is dispensed by a printhead onto the powder layer. In some embodiments, the bulk powder material is comprised of one or more pharmaceutically acceptable excipients, LEV, disintegrant, binder and surfactant.

[0060] At least one component of the matrix must serve as a "binding agent" that binds particles of bulk powder together in the completed three-dimensional matrix. The binding agent produces adhesion between particles of the bulk powder. It is this adhesion that enables the dosage form to maintain a fixed shaped (geometry) and maintain

its characteristics of hardness and friability adequate to permit handling and storage. The strength and extent of the particle binding depends on the proportion of the binding agent either in the powder layer or dissolved in the solvent, and is a function of the amount of fluid deposited. The term adhesion means the bonding or binding of particles of the bulk material to each other or to particles of another material present, such as particles of binder or active ingredient. There are various ways in which a binding agent can be included in the matrix. The invention contemplates a combination of one or of two or more of these different ways.

[0061] In some embodiments of the method of preparation of the matrix, binding agent is present in the bulk powder, the printing fluid, or both. A binding agent in the printing fluid can be the same as or different than a binding agent in the bulk powder.

[0062] The binding agent can be a binder, LEV, another pharmaceutical excipient, or a combination thereof. In some embodiments, the binding agent is: a) at least LEV; b) at least binder; or c) binder and LEV. In some embodiments, two or more binding agents are present in the matrix. Including a "binder" as the binding agent in the printing fluid will result in a different internal microstructure of the wafers, particularly the pore size, than the internal microstructure of an otherwise same wafer excluding binder in the binding solution. Upon printing, as the solvent evaporates, binder remains as a solid residue, which occupies void space in between powder particles, e.g. particles of disintegrant or drug. The resulting structure will have higher density compared to tablets fabricated without binder in the printing fluid.

[0063] The invention provides a process for the preparation of a rapidly dispersing solid dosage form comprising a three-dimensionally printed solid porous matrix comprising a bulk powder, binder and LEV, the process comprising: (a) providing a powdered mixture of one or more disintegrants, one or more binders, one or more glidants and LEV, together with any optional pharmaceutically acceptable excipients; (b) forming an incremental layer of the powdered mixture; (c) applying to the incremental layer droplets of printing fluid according to a predetermined pattern to form a printed incremental layer; (d) repeating (b) and (c) a predetermined number of times, thereby providing a three-dimensionally printed moist matrix; and (e) removing printing fluid from the moist matrix, thereby providing three-dimensionally printed solid porous matrix having a composition, moisture content, porosity, overall bulk density, hardness, matrix dispersion time, *in vitro* drug dissolution time, *in vitro* dispersion behavior, *in vivo*

pharmacokinetic behavior, structure, incremental layer thickness, drug particle size, disintegrant particle size, drug content, and/or friability within the ranges specified herein.

[0064] The dosage form of the present invention may be further shaped as desired to facilitate placement thereof in the buccal cavity of a subject. One such embodiment may be a wafer-like shape.

[0065] FIG. 1 depicts a sectional front elevation of an orodispersible dosage form (1) made from a three-dimensionally printed matrix comprising sequentially-formed incremental layers of bound bulk material (2-3). The exterior surfaces (3) envelope a middle portion (2). The exterior surfaces have a greater hardness than the interior portion. This dosage form is made by three-dimensionally printed plural incremental layers. The bottom incremental layer, which defines the lower surface, and the upper incremental layer, which defines the upper surface, and the circumferential surfaces (left and right of the middle portion) are harder than the interior portion. The increased hardness is achieved by using a higher saturation level, higher content of binder or as otherwise described herein. The increased hardness at the periphery of the incremental layers of the middle portion is achieved by increasing the saturation level and/or content of binder at the periphery, but not the center (non-peripheral portion) of the respective incremental layers.

[0066] FIG. 2 depicts a sectional front elevation of an alternate embodiment of an orodispersible dosage form (5) made from a three-dimensionally printed matrix. The bottom incremental layer, which defines the lower surface (8), and the upper incremental layer, which defines the upper surface (7) are harder than the interior portion (6) comprising plural incremental layers. The dosage forms (1) and (5) differ primarily in the process used to print the middle incremental layers, the layers of (6) not having a periphery with increased hardness.

[0067] FIGS. 3A-3E depict the top plan view of three different print patterns that can be used to prepare the printed incremental layers of a 3DP orodispersible matrix of the invention. Even though each print pattern is depicted as being circular, substantially any geometry can be used, e.g. circle, oval, square, rectangle, oblong circle, etc. FIG. 3A depicts a first solid print pattern wherein substantially the same full, heavy or higher saturation level is used throughout the entire print area. FIG. 3B depicts a second solid print pattern wherein substantially the same medium, low, light or lower saturation level is used throughout the entire print area. This second solid pattern is referred to as a grayscale pattern since it has a reduced saturation level. Where solid printing is initially defined as a

saturation ranging from 90 to 120%, grayscale printing is defined as saturation of less than 90%, or saturation of about 20 to <90%, or about 20 to about 85%, or about 20 to about 80%, about 20%, about 35%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or any fractional or integer increments in these ranges.

[0068] FIG. 3C depicts an annular (hollow) print pattern wherein printing fluid is applied to the periphery of the print area but not toward the center of the print area. FIG. 3D depicts a combination annular and grayscale print pattern wherein printing fluid is applied to the periphery of the print area at a higher saturation level and toward the center of the print area at a grayscale (reduced) saturation level. The radial thickness (as measured from the center of the circle) of the peripheral ring in the print patterns in FIGS. 3D and 3D can be varied as needed. The ring thickness can range from about 0.05 to 10 mm depending upon the diameter of the dosage form. It can range from about 0.1 to about 7 mm, about 0.5 to about 7 mm, about 1 to about 5 mm, or about 1.5 to about 3.5 mm.

[0069] FIG. 3E depicts an indicum print pattern wherein substantially the same saturation level is used throughout the entire print area except in the indicum region(s) wherein no printing fluid is applied thereby forming a debossed indicum in the surface of the final dosage form.

[0070] In some embodiments, the dosage form comprises (consists essentially of or consists of) the following types of printed incremental layers: a) plural layers of first solid print pattern, and plural layers of combination annular and grayscale print pattern; b) plural layers of first solid print pattern, plural layers of annular print pattern, and plural layers of combination annular and grayscale print pattern; c) plural layers of first solid print pattern, plural layers of annular print pattern, plural layers of combination annular and grayscale print pattern, and plural layers of indicum print pattern; d) plural layers of first solid print pattern, plural layers of annular print pattern, plural layers of combination annular and grayscale print pattern, plural layers of first solid print pattern, and plural layers of indicum print pattern; e) plural layers of first solid print pattern, plural layers of grayscale print pattern, and plural layers of first solid print pattern; f) plural layers of grayscale print pattern; g) plural layers of combination annular and grayscale print pattern; h) plural layers of first solid print pattern; i) plural layers of first solid print pattern and plural layers of annular print pattern; or j) plural layers of first solid print pattern, plural

layers of combination annular and grayscale print pattern, and plural layers of indicum print pattern.

[0071] In some embodiments, the dosage form comprises (consists essentially of or consists of) the following types of incremental layers grouped into respective sections of the dosage form: a) a first end comprising plural layers of first solid print pattern; a middle portion comprising plural layers of annular print pattern and plural layers of combination annular and grayscale print pattern; and a second end comprising plural layers of indicum print pattern; b) a first end comprising plural layers of first solid print pattern; a middle portion comprising plural layers of combination annular and grayscale print pattern; and a second end comprising plural layers of first solid print pattern and/or plural layers of indicum print pattern; c) a first end comprising plural layers of first solid print pattern; a middle portion comprising plural layers of annular print pattern, plural layers of combination annular and grayscale print pattern; and a second end comprising plural layers of first solid print pattern and/or plural layers of indicum print pattern; or d) a first end comprising plural layers of first solid print pattern; a middle portion comprising alternating groups of layers, wherein one group comprises plural layers of annular print pattern, and another group comprises plural layers of combination annular and grayscale print pattern; and a second end comprising plural layers of first solid print pattern and/or plural layers of indicum print pattern.

[0072] The physical properties of the dosage form can be controlled by varying incremental powder layer thickness, powder composition, printing fluid composition, printing fluid saturation level (print density) on a layer, and identity and amount of the excipients included within the dosage form, e.g. identity and amount of disintegrant, binder, sweetener, surfactant. These variables exhibit different levels of effect upon dosage form hardness, bulk density, disintegration time, dissolution time, bioavailability, moisture content, mouthfeel and friability. It was determined that the result effective variables include, at least, the amount of drug, amount of disintegrant, amount of binder, identity of some components, and composition of the drug-containing particles.

[0073] Three-dimensional printing can have spatial descriptors in each of three different, typically orthogonal directions. In three-dimensional printing, fluid may be deposited in drops or in fluid units resembling drops. Drops may be deposited in a succession that forms a line corresponding to the motion of the printhead. The spacing between those drops is the drop-to-drop spacing. After completion of one line, another

line may be deposited adjacent to the earlier-deposited line and separated from the earlier-deposited line by a distance that is a line-to-line spacing. After completion of printing on a layer of powder, another powder layer may be deposited, with each powder layer having a layer thickness. The powder layer thickness is the third descriptor.

[0074] In some instances, the spacing of droplets may be described in terms of the resolution of the printing system, often expressed as dots per inch (dpi), which is the reciprocal of droplet spacing. For example, resolutions of 300 and 600 dpi correspond to droplet spacing's of about 84.7 microns and about 42.3 microns, respectively. The drop-to-drop spacing (within a line), or the line spacing (spacing of droplets from one line to the next), or any other spacing of droplets may be described in terms of resolution expressed in dpi. In some instances, layer-by-layer instructions for making the dosage forms may consist of a series of pixelated images characterized by a resolution in dots-per-inch in each of two orthogonal linear directions. In some instances, these pixelated images are 1-bit monochrome images, alternately referred to as binary or bi-level images in which each pixel contains one bit of information (0 or 1) that may be represented as either black or white onscreen.

[0075] In some instances, the relative amount of binding in localized regions of the dosage form is achieved by "grayscaling" (i.e., use of a grayscale print pattern) in the dosage form design. In the case of 1-bit monochrome images used for machine instructions, grayscaling is achieved by changing the number of "black" pixels relative to "white" pixels in a chosen region of a dosage form, or in a chosen layer of a dosage form, or throughout a dosage form. Any other regions that may be "solid" by using all black pixels. In some embodiments, the dosage form design includes a "solid" exterior and a "grayscaled" interior. In some embodiments, grayscaling may be achieved with equally spaced black pixels amongst white pixels to reach an overall ratio of black to white pixels in the grayscaled region. In other embodiments, grayscaling may be achieved with randomly placed black pixels amongst white pixels to achieve an overall ratio of black to white pixels in the grayscaled region. In still other embodiments, grayscaling may be achieved with a chosen pattern (e.g., parallel lines, hashed pattern, dot pattern) of black pixels amongst white pixels to achieve an overall ratio of black to white pixels in the grayscaled region.

[0076] In three-dimensional printing, a voxel or unit volume may be defined by one drop-to-drop spacing in the fast axis direction of motion, by one line-to-line spacing in

the slow axis direction of motion, and by one layer thickness in the vertical direction. Some of this unit volume is occupied by powder particles, and the remainder of the unit volume is empty space that collectively has a volume that is the void volume.

[0077] The saturation level (print density) describes how much of the void space in this unit volume is occupied by liquid which is dispensed in a drop or fluid unit which is dedicated to that particular voxel. The saturation level is the ratio of the dispensed fluid volume to the volume of empty space in the voxel. In general, in three-dimensional printing, saturation levels may be chosen to be slightly less than, or somewhere approximately equal to, 1.0, also expressed as 100%. Excessively low saturation levels tend to result in poor structural integrity. Excessively high saturations levels tend to result in excessive bleeding of liquid beyond where the liquid was deposited. In the present dosage form, the saturation level during the step of applying printing fluid to a powder layer ranges from about 10% to about 110%, about 15% to about 80%, about 20% to about 50% or about 15% to about 35% in aggregate across the dosage form, or otherwise in selected regions of the dosage form.

[0078] Suitable printing devices include those having a continuous jet printhead or those having a drop-on-demand printhead. A continuous jet printhead provides a continuous jet (spray) of droplets while depositing printing fluid onto a powder layer. A drop-on-demand printhead only deposits droplets of printing fluid onto the powder layer if it receives an instruction (demand, operational command) to do so. A printhead scans (applies fluid to) the surface of powder layer from left to right at a predetermined rate, e.g. a scan rate, to form a line of droplets. A high scan rate will result in a lower saturation level, and a low scan rate with result in a higher saturation level when comparing printing fluid deposition at a constant volume per unit time. When considering the situation where binder is present in the binding solution, an increase in the print speed from 1.0 m/s to 2.0 m/s reduces the total volume of binder solution deposited in the tablets by half. As the print speed increases, the bulk density (theoretical, calculated from the weight and dimensions of the tablet) decreases. A simultaneous decrease in the dimensions and weight of the tablets is also seen. This decrease is attributed to the fact that a decrease in the total volume of binder droplets deposited onto the powder results in a decrease in the extent of binder solution spreading in the powder. Increasing the print speed also decreases the flash time and the hardness and increases the friability of the tablets. This result is obtained because the proportion of binder decreases in the tablets as

the print speed increases. An increase in the print speed also increases the void volume inside the tablets, as illustrated by an increase in the percent volume of the tablets penetrated by mercury at 30 psi (% intrusion).

[0079] When using a continuous jet printhead, the printhead scans at a rate of about 0.5 to 3.0 m/sec, and most preferably at about 1.75 m/sec. When using a drop-on-demand jet printhead, the printhead scans at a rate of 0.1 to 1 m/sec, most preferably at about 0.15 to about 0.5 m/sec.

[0080] The volume of individual droplets can be varied as desired, for example, by selection of a different three-dimensional printing machine, or different printhead components on the same machine, or different parameters on the same printhead and same machine. Increasing the volume of the droplet increases the saturation level and decreasing the volume of a droplet decreases the saturation level when comparing printing fluid deposition at a constant scan rate. When using a continuous jet printhead, the size of the fluid droplets delivered by the printhead preferably ranges from about 15 μm to about 150 μm in diameter. When using a drop-on-demand printhead, the size of the fluid droplets delivered by the printhead preferably ranges from about 50 μm to about 500 μm in diameter.

[0081] The flow rate of the fluid delivered by the printhead can be varied as desired. Increasing the flow rate will increases the saturation level and decreasing the flow rate decreases the saturation level when comparing printing fluid deposition at a constant scan rate. As discussed herein, the printhead deposits droplets of printing fluid to form parallel lines thereof in the powder layer. When using a continuous jet printhead, the line spacing ranges from about 20 to about 1000 μm, about 50 to about 500 μm, or and preferably about 100 to 200 μm. When using a drop-on-demand jet printhead, the line spacing ranges from about 20 to about 300 μm, about 40 to about 100 μm, or about 55 to 75 μm.

[0082] The powder layering system and the height adjustable platform cooperate to form thin incremental layers of powder in the build modules. The total thickness (height) of the dosage form will be a function of the number and thickness of the incremental layers. The number of printed incremental layers typically ranges from 5 to 50. In some embodiments, the number of printed incremental layers ranges from 10 to 50, 15 to 45 or 20 to 40. A matrix will typically comprise (consist essentially of or consist of)

20 to 50, 20 to 40, 25 to 40, 30 to 40 or 30 to 35 printed incremental layers. The "end" section of a dosage form will typically comprise 1 to 10, 1 to 7, 2 to 7, 2 to 5, or 4 to 6 printed incremental layers. An end section with an indicum will typically comprise 2 to 10, 2 to 7, 2 to 5, or 4 to 7 printed incremental layers. The balance of the printed incremental layers will comprise the middle portion, with respect to the vertical height, of the dosage form. The middle portion will typically comprise 5 to 40, 10 to 30, 10 to 20, or 20 to 30 printed incremental layers.

[0083] Wafers (matrices, dosage forms) produced by the 3DP process described herein vary in size according to the content of LEV and of excipients required to provide dosage forms exhibiting the desired properties. If the matrix comprises a higher dose of LEV, then a larger wafer is required as compared to another 3DP dosage form having the same percentage but lower dose of LEV. If a higher percentage of LEV is used, the dosage form weight can be decreased correspondingly and *vice versa*. Wafer-shaped dosage forms of the invention ranged in diameter from about 13-14 mm (lowest dose) to about 20-25 mm (highest dose) and in height from about 5-6 mm (lowest dose) to about 8-10 mm(highest dose).

[0084] The incremental layers are of a predetermined height (vertical thickness), which typically varies from 0.005 to 0.015 inches, 0.008 to 0.012 inches, 0.009 to 0.011 inches, about 0.01 inches, 100-300 μm, 100-500 μm, about 200 μm, or about 250 μm. As thicker incremental layers are used, an increasing amount of printing fluid must be deposited on that layer to ensure adequate binding both within the plane of the layer and layer-to-layer. Conversely, for a thinner incremental layer a lesser amount of printing fluid must be deposited to obtain the same extent of binding. For a given amount of printing fluid deposited per layer, using a larger layer thickness will reduce (worsen) dosage form handleability and reduce (improve) dispersion time. If too thick of a layer is used for a given amount of fluid, laminar defects may form that cause the dosage form to easily fracture along the plane of the layers (delamination), or the dosage form itself may not have adequate strength to handle at all. In some embodiments, the thickness of the incremental layers ranges from 100 – 400 microns, 150-300 microns, or 200-250 microns. In one preferred embodiment, the layer thickness is 200 microns. In another preferred embodiment, the layer thickness is 250 microns.

[0085] The stability of LEV to oxidative degradation when included in a 3DP dosage form of the invention was determined by exposing finished dosage forms to heat.

The formation of degradants was observed and monitored by HPLC/MS as detailed below. It was determined that LEV undergoes oxidative degradation to form oxo-levetiracetam whenever an antioxidant is absent and the formulation contains an oxidative excipient, e.g. povidone containing peroxide impurity or silica containing peroxide impurity. Povidone and silica, however, are important functional ingredients. Accordingly, the invention provides a stable rapidly dispersible dosage form comprising LEV, oxidative excipient, antioxidant, binder and disintegrant, wherein the matrix comprises 0.1% by wt or less of an oxidative degradant of LEV after storage for six months at 21° C and 75% RH.

[0086] The present inventors determined that some of the excipients commonly used in 3DP dosage forms can contain oxidizing compound (oxidants), which can result from the process of manufacture or the inherent instability of the excipient(s). Some of the oxidants are believed to be peroxides. It was determined that the level of oxidant in povidone increases during storage after exposure of the excipient to an oxygen-containing atmosphere. Regardless of the source of oxidant, it is surprising that levetiracetam is so sensitive to oxidation when included in a 3DP dosage form but not when included in other dosage forms, as note in the art cited above.

[0087] Stability studies were conducted according to Example 6. The present inventors have succeeded in identifying and selecting a group of preferred antioxidants that stabilize levetiracetam against oxidation that occurs upon storage at elevated temperature and/or upon exposure to elevated temperature during the drying step of the 3DP process used to prepare the dosage form of the invention. Suitable antioxidants include sodium sulfite, sodium bisulfite, Vitamin E, methionine, BHA and BHT. Preferred antioxidants include sodium bisulfite, sodium sulfite, BHA and BHT.

[0088] One or more pharmaceutically acceptable excipients can be included in bulk powder material and/or the printing fluid. Each excipient may be independently selected upon each occurrence from a water soluble, aqueous fluid soluble, partially water soluble, partially aqueous fluid soluble, water insoluble or aqueous fluid insoluble excipient as needed to provide the required particle-to-particle binding in a printed matrix.

[0089] Most pharmaceutically acceptable excipients, both small molecules and polymers, can be employed, which allow a pharmaceutically active ingredient to be loosely encased in a porous structure (a matrix of bound particles) that is subject to rapid dispersion in the presence of an appropriate aqueous fluid, e.g., saliva. Some of these excipients, suitable for use in the three-dimensional printing process of the invention, are

listed in the Handbook of Pharmaceutical Excipients (Eds. A. Wade and P. J. Weller, Second edition, American Pharmaceutical Association, The Pharmaceutical Press, London, 1994).

[0090] Suitable types of excipients include binder, disintegrant, dispersant, sweetener, glidant, flavorant, surfactant, humectant, preservative, antioxidant and diluent. Although conventional pharmaceutical excipients may be used, they may not always function in precisely the same manner as with traditional pharmaceutical processing.

[0091] One or more binders can be included in the printed matrix. The binder may be included in either the powder material or in the printing fluid dispensed through the printhead. The binder is independently selected upon each occurrence. Adhesion of the particles to and/or by the binder occurs either when the binder is contacted by the printing fluid from the printhead or when it is present (i.e., soluble) in the printing fluid. The binder is preferably water soluble, aqueous fluid soluble, partially water soluble or partially aqueous fluid soluble. In some embodiments, the printing fluid comprises 1-20% wt, 5-15 % wt or 8-12 % wt of binder. In some embodiments, the bulk powder comprises >0 to 10% wt, 5 to 15% wt, 0 to 15 % wt, 8-14 % wt or 9-11 % wt of binder. In some embodiments, the printed matrix comprises 1-20 % wt, 5-14% wt or 8-12 % wt of binder. In some embodiments, binder is absent from the printing fluid or absent from the bulk material.

[0092] Suitable binders include water-soluble synthetic polymer, polyvinlypyrrolidone (povidone), sorbitol, mannitiol, xylitol, lactitol, erythritol, pregelatinized starch, modified starch, hydroxypropylmethylcellulose and others. The preferred binder is polyvinylpyrrolidone, e.g. PVP K30, modified starch (e.g., starch sodium octenylsuccinate), mannitol or a combination thereof. PVP with a K value different from 30 may be used, including without limitation PVP K25 and PVP K90.

[0093] The following materials are considered binders, even though they exhibit low strength binding: spray dried lactose, fructose, sucrose, dextrose, sorbitol, mannitol, or xylitol.

[0094] One or more disintegrants can be included in the printed matrix. The disintegrant can be present in the bulk powder. The disintegrant is independently selected upon each occurrence. In some embodiments, the bulk powder comprises 5 to 30% wt, 10 to 25% wt, 15 to 25% wt, 18 to 24% wt, 18 to 23.7% wt, 1-30% wt, 10-25% wt, 20-25% wt of disintegrant.

[0095] Suitable disintegrants include microcrystalline cellulose (MCC), crospovidone (cross-linked polyvinylpyrrolidone), croscarmellose, sodium starch glycolate or a combination thereof. The preferred disintegrant is microcrystalline cellulose. Suitable grades of AVICEL® are summarized in the table below. The dosage form can comprise one or a combination of the specified grades. All such embodiments containing single grades or a combination of grades are contemplated.

Product Grades	Nominal Particle Size, μm	Moisture, %	LooseBulk Density, g/cc
Avicel DG	45	NMT 5.0	0.25 - 0.40
Avicel PH-101	50	3.0 to 5.0	0.26 - 0.31
Avicel PH-102	100	3.0 to 5.0	0.28 - 0.33
Avicel HFE*-102	100	NMT 5.0	0.28 - 0.33
Avicel PH-102 SCG**	150	3.0 to 5.0	0.28 - 0.34
Avicel PH-105	20	NMT 5.0	0.20 – 0.30
Avicel PH-102 SCG	150	3.0 to 5.0	0.28 – 0.34
Avicel PH-200	180	2.0 to 5.0	0.29 - 0.36
Avicel PH-301	50	3.0 to 5.0	0.34 - 0.45
Avicel PH-302	100	3.0 to 5.0	0.35 - 0.46
Avicel PH-103	50	NMT 3	0.26 - 0.31
Avicel PH-113	50	NMT 2	0.27 - 0.34
Avicel PH-112	100	NMT 1.5	0.28 - 0.34
Avicel PH-200 LM	180	NMT 1.5	0.30 - 0.38
Avicel CE-15	75	NMT 8	N/A

NMT means “not more than”.

[0096] The binder and disintegrant are key ingredients for controlling the hardness, friability and dispersion time of the matrix. The greater the amount of binder, the higher the hardness, the lower the friability and the slower the dispersion time. On the

other hand, increasing the amount of disintegrant provides lower hardness, increased friability and a faster dispersion time. Accordingly, the matrix of the invention comprises a balanced amount of binder and disintegrant.

[0097] One or more sweeteners can be included in the printed matrix. The sweetener can be present in the bulk powder and/or in the printing fluid applied to the bulk powder. Better taste-masking is observed when at least one sweetener is present in at least the printing fluid. The sweetener is independently selected upon each occurrence. The printing fluid and the bulk powder can have at least one sweetener in common, e.g. the printing fluid and bulk powder each comprise the same sweetener and the bulk powder comprises an additional sweetener. In some embodiments, the bulk powder comprises >0 to 5% wt, or >0 to 2% wt, or >0 to 1.5% wt of sweetener. In some embodiments, the printing fluid comprises >0 to 5%, or 0.5 to 4%, or 1 to 3% wt sweetener.

[0098] Suitable sweeteners are selected from the group consisting of glycyrrhizinic acid derivative, e.g. magnasweet (monoammonium glycyrrhizinate), sucralose, aspartame, acesulfame potassium, neotame, and a combination thereof. The preferred sweetener in the printing fluid is sucralose. The sweetener is present in at least the printing fluid and can also be present in the bulk powder.

[0099] One or more flavorants can be included in the matrix. The flavorant can be present in the bulk powder and/or the printing fluid. The flavorant is independently selected upon each occurrence. The flavorant is preferably water soluble, aqueous fluid soluble, partially water soluble or partially aqueous fluid soluble. In some embodiments, the printing fluid comprises 0.01-5% wt, 0.1-1 % wt or 0.2-0.5 % wt of flavorant. In some embodiments, the flavorant may be provided on a powdered carrier. Suitable carriers may be chosen from starches, celluloses, and other excipients on which the flavorant could be absorbed, adsorbed, encapsulated, or otherwise loaded. In some embodiments, the bulk powder comprises 0.1 to 10% wt, or 1 to 9% wt, 2 to 8% wt of flavorant-loaded carrier. In some embodiments, the printed matrix comprises 0.1-10 % wt, or 1-9 % wt or 2-8 % wt of flavorant-loaded carrier. In some embodiments, the flavorant is absent from the printing fluid or absent from the bulk material.

[00100] Suitable flavorants include spearmint, peppermint, mint, vanilla, orange, lemon, citrus, lime, grape, cherry, strawberry, chocolate, coffee or a combination thereof.

[00101] One or more surfactants can be included in the printing fluid and/or bulk powder. The surfactant is independently selected upon each occurrence. In some embodiments, the printing fluid comprises 0.1 to 4 % wt, 1 to 3 % wt or 1.5 to 2.5% wt of surfactant.

[00102] Suitable surfactants include polysorbate (PEG-ylated sorbitan (a derivative of sorbitol) esterified with fatty acid), poloxamer or a combination thereof. Suitable polysorbates include polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (Polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (Polyoxyethylene (20) sorbitan monostearate), polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate), sodium lauryl sulfate, poloxamer (comprising a central (poly(propylene oxide)) flanked by two chains of (poly(ethylene oxide), e.g. LUTROL), low molecular weight polyethylene glycol (e.g. PEG 400). Suitable poloxamers may include poloxamers 124, 188, 237, 338, or 407.

[00103] Even though the dosage form can be preservative-free, one or more preservatives may optionally be included in the printing fluid or powder blend. Suitable preservatives include antifungal or antimicrobial preservatives such as methylparaben and proprylparaben. In some embodiments, the printing fluid comprises 0.001 to 0.2% preservative.

[00104] One or more glidants can be included in the bulk powder. In some embodiments, the bulk powder comprises 0.1-2.0%, 0.25-1.5%, or 0.5-1.0% wt of glidant. Suitable glidants include fumed silica (colloidal silicon dioxide).

[00105] The matrix may also comprise glycerin (glycerol) introduced therein either by way of the bulk powder or the printing fluid. Glycerin can exhibit characteristics of a humectant, sweetener, preservative, lubricant, saponifier or solvent. The present inventors have discovered that glycerin unexpectedly behaves contrary to other excipients when included in a three-dimensionally printed dosage form. As noted above, increasing the amount of other excipients disclosed generally results in increased hardness with concomitantly increased disintegration time; however, increasing the amount of glycerin results in increased hardness but unexpectedly reduced disintegration time. The ability of glycerin to behave in this manner is particularly advantageous and has not been observed with any other material incorporated into a three-dimensionally printed orodispersible dosage form. Therefore, it is unexpected that one could achieve preparation of an

orodispersible matrix that disperses in 10 sec or less or 5 sec or less in a small volume of water.

[00106] In some embodiments, glycerin is included in the printing fluid. Accordingly, the invention provides a printing fluid for use in three-dimensional printing wherein the printing fluid comprises glycerin, water, and at least one organic solvent. The invention also provides a three-dimensional printing method comprising: a) depositing a printing fluid comprising glycerin, water and at least one organic solvent onto at least one layer of powder; and b) reducing the content of water and solvent in the at least one layer, thereby forming a three-dimensionally printed porous matrix. The invention also provides a three-dimensional printing system comprising: a) a layer-forming system that forms layers of powder; and b) a printing fluid deposition system that deposits printing fluid onto the layers of powder, wherein the printing fluid comprises glycerin, water and at least one organic solvent.

[00107] In some embodiments, the printing fluid comprises 1-10% wt, or 2-8 % wt or 3-5 % wt of glycerin. In some embodiments, the matrix comprises 0.05-5% wt, 0.25-2.0 % wt, 0.5-1.5% wt or 0.5-1.O% wt of glycerin.

[00108] In some embodiments, the process of the invention employs a printing fluid comprising at least one or combination of pharmaceutically acceptable solvent for at least one material in the bulk powder and/or in the printing fluid itself. The printing fluid may comprise: a) a solvent for a material in the bulk powder; b) a solvent for a material in the printing fluid; or c) a combination thereof.

[00109] Embodiments of the process of the invention include those wherein the printing fluid comprises a solvent for: a) LEV; b) a binder in the bulk powder; c) a binder in the printing fluid; d) LEV and a binder; or e) a combination thereof.

[00110] The printing fluid can comprise 55-95% wt, 60-85% wt or 65-75% wt of water or aqueous buffer.

[00111] The printing fluid can comprise 1-25% wt, 5-20% wt or 10-15% wt of at least one organic solvent. A suitable organic solvent is alcohol. Suitable alcohols include ethanol, methanol, propanol, isopropanol, or a combination thereof. In some embodiments, the alcohol is ethanol. In some embodiments, the solvent is isopropanol.

[00112] It should be understood, that compounds used in the art of pharmaceutics generally serve a variety of functions or purposes. Thus, if a compound

named herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that named purpose(s) or function(s).

[00113] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with tissues of human beings and animals and without excessive toxicity, irritation, allergic response, or any other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00114] As used herein a "derivative" is: a) a chemical substance that is related structurally to a first chemical substance and theoretically derivable from it; b) a compound that is formed from a similar first compound or a compound that can be imagined to arise from another first compound, if one atom of the first compound is replaced with another atom or group of atoms; c) a compound derived or obtained from a parent compound and containing essential elements of the parent compound; or d) a chemical compound that may be produced from first compound of similar structure in one or more steps.

[00115] The invention also provides a method of administering LEV to a subject in need thereof. The method comprises: (a) providing a rapidly dispersing, non-compressed matrix dosage form as described herein, and (b) inserting the dosage form into a moisture-containing body cavity, such as the mouth, of a subject in need thereof, the moisture being capable of dissolving the binder and dispersing the dosage form within a time period ranging from about one to about ninety seconds, thereby dispersing the dosage form in the body cavity. In some embodiments, the method further comprises the step of administering the dosage form to the subject with a sip (small volume) of fluid after the dosage form is placed in the mouth.

[00116] A study was conducted to determine whether or not the sip volume impacted the pharmacokinetic parameters of LEV following oral administration of a 3DP dosage form of the invention. Subjects were given the option to sip 30 ml or less of aqueous fluid when taking the 3DP dosage form. There was no correlation observed between sip volume and pharmacokinetic parameters observed. The sip volume ranged from 2-30 ml with an average of about 13 ml.

[00117] The invention also provides a method of treating a disease, disorder or condition that is therapeutically responsive to LEV, the method comprising: a)

administering to a subject in need thereof a three-dimensionally printed orodispersible matrix as described herein or as made by the process described herein. The matrix comprises LEV, a bulk powder, disintegrant and binder, and the matrix is dispersible in a small volume of fluid. The dosage and administration regimens detailed in the package inserts for FDA approved products containing LEV, e.g. KEPPRA®, or as described herein can be followed for administering the instant dosage form.

[00118] A study was conducted according to Example 7 to determine the bioabsorption of levetiracetam when administered orally in an orodispersible 3DP dosage form of the invention. It was found that the 3DP product of the invention is equivalent to the KEPPRA® reference product in terms of the bioavailability of LEV under fasting conditions. Moreover, the 3DP product only exhibits a food effect upon Cmax and Tmax but not upon overall systemic exposure, i.e. not upon AUC_{0-t} or AUC_{inf}. Based upon the KEPPRA® label, these results are consistent with the pharmacokinetics of KEPPRA® tablets administered in the fed state, whereby the extent of absorption is not affected but the Cmax is decreased by about 20% and the Tmax is extended by 1.5 hours

[00119] Dose efficiency (AUC/dose) is a measure of how well a drug is absorbed relative to the dose of drug administered. The 3DP dosage form of the invention provides efficient bioabsorption of LEV whether administered in the fed or fasting state. The 3DP dosage form provides the following pharmacokinetic parameters when administered orally to a subject.

3DP Dose (mg)	C_{max} (microg/ml)	T_{max} (hr)	AUC_{0-t} (microg-hr/ml)	AUC_{inf} (microg-hr/ml)
1000 (fasting)	23-43 or 13-53 or 10-60	0.15-1.0 or 0.15-1.5 or 0.12-1.7	227-340 or 170-397 or 160-425	235-351 or 176-410 or 160-450
1000 (Fed)	17-24 or 14-27 or 10-35	3-5 or 2-5 or 2-6	223-302 or 183-342 or 170-380	231-314 or 190-355 or 170-400
750 (fasting)	16-31 or 9-37 or 8-40	0.15-1.0 or 0.15-1.5 or 0.12-1.7	180-270 or 135-315 or 120-350	186-278 or 140-324 or 120-375
750 (Fed)	12-17 or 10-19 or 8-25	3-5 or 2-5 or 2-6	177-239 or 145-271 or 130-300	183-249 or 150-282 or 125-320
500 (fasting)	9-16 or 5-20 or 4-25	0.15-1.0 or 0.15-1.5 or 0.12-1.7	119-179 or 90-209 or 80-220	123-185 or 93-216 or 85-240
500	6-9 or	3-5 or	117-159 or	122-165 or

3DP Dose (mg)	C_{max} (microg/ml)	T_{max} (hr)	AUC_{0-t} (microg-hr/ml)	AUC_{inf} (microg-hr/ml)
(Fed)	5-10 or 4-15	2-5 or 2-6	96-180 or 85-200	100-187 or 87-220
250 (fasting)	6-11 or 3-14 or 3-18	0.15-1.0 or 0.15-1.5 or 0.12-1.7	72-108 or 54-127 or 45-150	75-112 or 56-131 or 47-160
250 (Fed)	4-6 or 4-7 or 3-10	3-5 or 2-5 or 2-6	71-96 or 58-109 or 47-125	74-100 or 60-113 or 50-140

[00120] The dosage form of the invention provides a fed/fasted ratio for Cmax in the range of 0.55 to 0.74 (or about 0.6-0.7), for Tmax in the range of 5 to 21 (or about 5-13 or 5-10), for AUC_{0-t} in the range of 0.89 to 0.98 and for AUC_{inf} in the range of 0.89 to 0.99.

[00121] The dosage form of the invention is substantially equivalent in rate and extent of absorption to the KEPPRA® tablet, as the latter is defined by New Drug Application No. N021035 (see above), in particular when administered under fasting conditions. The dosage form provides substantially linear dose proportionality for Cmax and AUC, such that a linear fit of Cmax or AUC versus the dose administered can be characterized as having a correlation coefficient, R^2, of 0.95 to 1.0. The Cmax and AUC for the orodispersible dosage form are within 80-125% of the values achieved by the KEPPRA® immediate release tablet product on an equivalent dose basis.

[00122] In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of embodiments of the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many embodiments contemplated by the present invention.

Example 1

Preparation of a three-dimensionally printed orodispersible dosage form

[00123] The following process is used to prepare a three-dimensionally printed orodispersible dosage form comprising a matrix comprising LEV. The ingredients for the printing fluid and the bulk powder are used in the amounts indicated below:

Printing fluid	I-A	I-B	I-C	I-D
Water (% wt)	68.99-70.7	68.47-69.12	66.89-67.95	66.5-71
Glycerin (% wt)	3.9-4	3.8-3.92	3.79-3.85	3.5-4
Isopropanol (% wt)	13.01-13.3	12.3-13.04	12.11-12.82	12-13.5
Tween 20 (% wt)	1.95-2	1.9-1.96	1.89-1.92	0.5-2
Povidone (% wt)	9.76-10	8.5-9.8	8.51-9.61	8.5-10
Sucralose (% wt)	2	2-5	4-6	0-3
Monoammonium glycyrrhizinate (% wt) Magnasweet 100			0.2-0.6	0-1
Spearmint Flavor HD45		0.01-0.03	0.01-0.05	0-1
Natural Peppermint Flavor HD29	0-0.38			0-1

Printing fluid	I-E	I-F	I-G	I-H
Water (% wt)	65-72	65-70		
Glycerin (% wt)	3.5-4	3.4-4.2		
Isopropanol (% wt)	12-13.5	11-13		
Tween 20 (% wt)	1-2	1.5-2.5		
Povidone (% wt)	8.5-10	8-10		
Sucralose (% wt)	>0-5	4-6		
Monoammonium glycyrrhizinate (% wt) Magnasweet 100	0-0.6	0.1-0.8		
Spearmint Flavor HD45	0-0.2	>0-0.1		
Natural Peppermint Flavor HD29	0-0.5			

Bulk powder:	II-A	II-B	II-C	II-D	II-E
LEV (% wt)	75	75	65	65	75-90

Avicel PH101 (% wt)	17.5	19.8	21.8	23.8	5-20
Mannitol (% wt)			12.5	10.5	
Povidone (PVP K29/32) (% wt)	4.5	4.5			5-10
Sucralose (% wt)	2				1-3
Monoammonium glycyrrhizinate (% wt)	0.5				0.5
Colloidal Silicon dioxide (% wt)	0.5	0.7	0.7	0.7	0.5

Bulk powder:	II-F	II-G	II-H
LEV (% wt)	65-75		
Avicel PH101 (% wt)	17.5-24		
Mannitol (% wt)	10.5-12.5		
Povidone (PVP K29/32) (% wt)	4-6		
Sucralose (% wt)	1-3		
Monoammonium glycyrrhizinate (% wt)	0.1-1		
Colloidal Silicon dioxide (% wt)	0.5-0.7		
Antioxidant (% wt)	0.1-7		

[00124] An incremental layer of bulk powder of predetermined thickness is spread onto a prior layer of powder, and printing fluid is applied to the incremental layer as droplets according to a predetermined saturation level, line spacing and printing fluid flowrate to bind the particles therein. This two step process is completed until a matrix comprising the target amount of printed incremental layers.

[00125] Any three dimensional printer equipment assembly, known or mentioned herein, can be used; however, these exemplary formulations can be made with a Coriolis Instrument (Dimatix/Spectra Technology Integration, model: Coriolis RP1). The printer is operated at a droplet size of 70-90 picoliter, and resolution of 200-400 dpi or about 300 dpi by 900-1500 dpi. Various different print patterns are used in the dosage form. The specified combination of printing fluid formulation and bulk powder formulation is used. A layer thickness of 0.008 to 0.011 inches or about 0.25 to about 0.265 mm is used. A resolution of 300 x 1200 dpi, 300 x 1000 dpi, 300 x 900 dpi, 400 x 900 dpi, 400 x 750 dpi, 400 x 675 dpi is used. The printing fluids I-A through I-D are

used. Many different combinations of the printing fluids and bulk powder formulations are used. Some of the resulting matrices comprise the following ingredients.

	III-A
LEV (% wt)	60-70
Avicel PH101 (% wt)	20-25
Mannitol (% wt)	9.5-11
Povidone (PVP K29/32) (% wt)	1-2
Sucralose (% wt)	0.5-1.5
Colloidal Silicon dioxide (% wt)	0.5-1
Moisture (% wt)	0.3-4
Glycerin (% wt)	0.1-1
Tween 20 (% wt)	0.1-0.5
Spearmint Flavor HD45	>0-0.2
Monoammonium glycyrrhizinate (% wt)	0.05-0.15

[00126] The printed matrix is separated from loose unprinted powder and the printed matrix is dried by any suitable means to reduce the amount of solvent and moisture to a desired level, thereby producing the final 3DP orodispersible dosage form.

[00127] The dispersion time, surface texture (smoothness) and hardness of the dosage form are then determined.

Example 2

Rapidly Dispersing Wafers with Varying Architecture in Different Incremental Layers

Preparation of a taste-masked three-dimensionally printed orodispersible dosage forms with varying architecture among incremental layers

[00128] The 3DP process described above is followed; however, it can be conducted in several different ways to prepare dosage forms of different architecture varying in hardness and composition of incremental layers. The following processes provide a wafer having greater hardness in the upper and lower surfaces as compared to the hardness of the interior portion of the wafer. This tactic helps create sections within a wafer with different mechanical properties. This approach is used to design wafers in which the composition of the top and bottom layers is different from the middle layers.

This design allows the wafers to have stronger top and bottom layers, thereby increasing hardness and reducing friability, and a large middle portion with lower hardness, which enables the wafer to disperse rapidly.

Method A:

[00129] In this process, the amount of binder deposited in different incremental layers or within different predefined regions within the same incremental layers is varied. The process of Example 3 is followed to prepare these wafers, except that the amount of binder, by way of the printing fluid, deposited onto the powder is varied among the incremental powder layers by using printing fluids differing in concentration of binder.

Method B:

[00130] The process of Example 3 is followed to prepare these wafers, except that the amount of printing fluid deposited onto the powder is varied among the incremental powder layers. The upper and lower incremental layers receive a higher amount of printing fluid and the incremental layers of the middle portion receive a lower amount of printing fluid.

Method C:

[00131] In this process, the printing pattern, employed for the upper and lower incremental layers of the dosage form, is a solid pattern (FIG. 3A). The printing pattern for the middle portion of incremental layers is a gray scale (FIG. 3 B). Gray scale printing can range from about 20 to about 90% or about 20 to about 80%.

Method D:

[00132] In this process, the printing pattern, employed for the upper and lower incremental layers of the dosage form, is a solid pattern (FIG. 3A). The printing pattern for the middle portion of incremental layers is an annular/hollow high saturation printing with no printing in the area surrounded by the annulus (FIG. 3C).

Method E:

[00133] In this process, the printing pattern, employed for the upper and lower incremental layers of the dosage form, is a solid pattern (FIG. 3A). The printing pattern for the middle portion of incremental layers is a combination of interior gray scale printing surrounded by an exterior high saturation printing (FIG. 3D).

Example 3

Characterization of Dosage Forms

[00134] The following procedures were used to characterize the three-dimensionally printed solid porous orodispersible matrices.

Friability

[00135] The matrices are analyzed for their resistance to breaking using the tablet friability test (USP protocol <1216>). The test employs a VanKel friabilator (model 45-2000, Varian, USA) equipped with a drum having the dimensions of 285 mm in diameter and 39 mm deep, which is rotated at 25 rpm for 100 revolutions. A minimum number of 10 wafers are tumbled at each revolution by a curved projection that extends from the middle of the drum to the outer wall. Thus, at each turn the tablets are caused to roll or slide and fall about 130 mm onto the drum or each other. All loose powder is removed from the tablets and they are weighted collectively before and after the 100 revolutions.

Surface Texture

[00136] The matrices are inspected visually with or without the aid of a microscope. The surface texture analyzed to determine if it is rough or smooth and whether the edges of indicia on the upper surface and the edges of the perimeter of the wafer are clean and sharp or rough and jagged.

[00137] The matrices exhibited smooth surfaces with clean and sharp edges.

Hardness

[00138] The matrices are analyzed for overall hardness as determined by a tablet breaking force assay according to USP <127> (31st edition) using a VK 200 tablet hardness tester (Varian, US). The strength or hardness of the wafers is measured by a fracture test. A wafer is centered between the jaws of the tester and force is applied until the wafer fractures. The load at fracture is returned in kiloponds (kp). A kilopond is a metric unit of force measurement with 1 kp being equivalent to 9.807 Newtons. A minimum number of 6 wafers are tested.

[00139] The hardness of the dosage forms ranges from about 0.7 to about 5.3 kp, about 1.7 to about 5.1 kp, about 2.1 to about 5.2 kp, about 3 to about 6 kp, about 1 to about 9 kp, or about 2.5 to about 5.3 kp.

Dispersion time

[00140] The matrices are analyzed for dispersion time in aqueous fluid as follows using a Texture Analyzer (TA HP, Texture Technologies, US) equipped with a 5 Kg load cell and a 1.0 inch diameter acrylic probe (Stable Micro Systems). The wafer is attached to the probe wit double-sided adhesive tape. Under a constant 50 g force (Dor et al. in *Pharm. Dev. Technol.* (2000), 5(4), 575-577; and El-Arini et al. in *Pharm. Dev. Technol.* (2002), 7(3), 361-371), the wafer is immersed in 3 ml of water at room temperature in a flat bottom aluminum weigh boat. The dispersion time test was conducted using the following parameters. A minimum of 5 wafers was tested.

Test mode	Compression
Pre-test speed (mm/sec)	5
Test speed (mm/sec)	8
Post-test speed (mm/sec)	10
Target mode	Force
Force (g)	50
Hold time (sec)	15
Trigger type	Auto (force)
Trigger force (g)	5
Water volume (ml)	3

[00141] The dispersion time observed for the dosage forms is about 10 sec or less or about 5 sec or less.

Bulk Density

[00142] The bulk density of the matrix is determined by measuring the weight of a wafer and dividing that value by the calculated volume of the wafer. The volume of a wafer is calculated by measuring its dimensions and using the proper mathematical formula according to the shape of the wafer. For example, for a cylindrical wafer, the volume of which is calculated using the form $\pi*r^2*H$, wherein r is the radius of the water and H is its height. A wafer weighing 0.5 g, having a height of 0.6 cm and a diameter of 1.1 cm, has a volume of about 0.57 cm^3, and a bulk density of about 0.877 g/cm^3, which is equivalent to about 877 mg/ml.

Dissolution of LEV

[00143] Dissolution testing is conducted according to the Guidance for Industry (Section 3.3.2; Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. August 2000. Section IIIc, p 7). The method of USP <711> was followed. Dissolution is performed using a USP Apparatus II (paddle) at 50 rpm using 900 mL of the following deaerated dissolution media: (1) 0.1N HCl ; (2) 0.05 M sodium acetate, pH 4.5 buffer and (3) 0.05M KH_2PO_4, pH 6.8 buffer at 37°C.

Example 4

In vivo evaluation of three-dimensionally printed orodispersible dosage forms

[00144] This method is used to establish efficacy of the dosage form. Single dosage forms comprising LEV are administered twice daily to a subject at 12-hour intervals. Administration is done by placing the dosage form in the mouth of the subject and optionally administering a sip (5-20 ml, or 2-30 ml) of fluid to the subject. Within a short period of time, the dosage form disperses in the subject's mouth. Alternatively, the dosage form is dispersed in a minimal amount of fluid and then administered to the subject orally. The total daily dose of LEV will typically range from about 500 to about 2000 mg divided over two doses. The subject's pharmacokinetic profile is determined using known methods in the art. The subject level of therapeutic response to the dosage form is determined using known methods in the art.

Example 5

HPLC/MS Analysis for LEV in Dosage Forms

[00145] The following procedures were used to analyze three-dimensionally printed solid porous orodispersible matrices and in support of drug-stability studies.

[00146] The following solutions were used.

Buffer:	20 mM ammonium acetate, pH 5.5
Mobile phase A (MPA):	95:5 Buffer : acetonitrile
Mobile phase B (MPB):	Acetonitrile
Diluent:	95:5 water : acetonitrile

[00147] The HPLC conditions were as follows:

Column: Alltima C18 4.6 x 150 mm, 5 μm

Mobile phase A (MPA): 95:5 Buffer : acetonitrile

Mobile phase B (MPB): Acetonitrile

UV detection: 205 nm

Column temperature: 25 °C

Injection volume: 10 μL

Flow rate: 0.9 mL/min

Autosampler temperature: 5 °C

[00148] Samples were prepared by transferring approximately 380 mg of sample to a 50-mL volumetric flask with 30 mL of Diluent. The sample was sonicated for 10 minutes then filled to volume with Diluent. A portion was filtered through a 0.22 μm nylon filter, discarding the first 3 – 5 mL.

[00149] Mass spectrophotometry was conducted by directly infusing a sodium formate solution into the mass spectrometer through the lock spray at 100 μL/min using a syringe pump. The sodium formate peak at m/z 158.9646126 was used for accurate mass analysis. The accurate masses were used for elemental composition analysis using the MassLynx software.

[00150] An impurity/degradant peak had a relative retention time (RRT) of 0.64 using the client provided method. The peak had an observed, protonated, mono-isotopic mass of 185.1 Da. Accurate mass analysis and elemental composition analysis of the peak were consistent with oxo-levetiracetam.

Example 6

Evaluation of LEV Stability in 3DP Dosage Forms

[00151] The following procedures were used to identify the preferred antioxidant(s) suitable stabilizing LEV against oxidative degradation.

[00152] A powder blend containing the following ingredients in the amounts indicated was prepared.

Ingredient	% (w/w)
Levetiracetam, USP	65.0
Colloidal silicon dioxide, NF	0.70
Microcrystalline cellulose, NF	23.8
Mannitol 50C, USP	10.5

[00153] A printing fluid containing the following ingredients in the amounts indicated was prepared.

Ingredient	% (w/w)	Function
Povidone K29/32, USP	8.51	Binder, viscosity modifier
Sucralose, NF	5.0	Sweetener
N&A Spearmint flavor HD45	0.03	Flavorant
Glycerin, USP	3.8	Humectant
Polysorbate 20, NF	1.9	Surfactant
Isopropyl alcohol, USP	12.3	Solvent
Purified water, USP	68.5	Solvent

[00154] The antioxidants evaluated are listed in the following table. Half of the amount of the IIG (Inactive Ingredient Guide) daily limit (mg) indicated in the table was used for each antioxidant since this would reach the limit when administered twice daily, which is the most common frequency of dosing immediate-release levetiracetam. For example, the amount of antioxidant would be "(IIG daily limit) / 2" for a 1000 mg tablet administered twice daily. It should be understood that IIG limits are periodically changed by regulatory agencies. Accordingly, the limits specified below should be considered approximations and not as absolute limits to the amount of antioxidant that can be included in a dosage form.

Antioxidant	IIG Daily Limit (mg)
Ascorbic acid	28.44
Butylated hydroxyanisole (BHA)	1
Butylated hydroxytoluene (BHT)	0.36
n-propyl gallate	2

Antioxidant	IIG Daily Limit (mg)
L-cysteine HCl	16.2
Sodium sulfite	0.65
Sodium bisulfite	0.65
Alpha-tocopherol (Vit E)	1.34
EDTA	100
Sodium metabisulfite	8
Methionine	5

[00155] The antioxidant was mixed with 6 mL of printing fluid. That mixture was then mixed with 30 g of powder blend to form a raw tablet composition, each of which was exposed to the following conditions: Condition 1- store composition at 70 C in tightly sealed glass jar; Condition 2- store composition at 50 C in loosely covered glass jar; and Condition 3- store composition at 40 C/ 75% RH in open glass jar.

[00156] The samples were subsequently analyzed by HPLC/MS and the identity of two key degradants was determined by comparison to standards. The key degradants were levetiracetam acid and oxo-levetiracetam. Moreover, some of the raw compositions became colored (yellowing) and others did not. The data indicate that sodium bisulfite, sodium sulfite, Vitamin E, methionine, BHA and BHT provide improved stability against oxidative degradation and against color formation. Sodium bisulfite, sodium sulfite, BHA and BHT provided the best results under the test conditions. Other antioxidants tested provided lesser degrees of protection or no protection against oxidative degradation and color formation.

Example 7

Determination of PK Parameters for LEV in Orodispersible 3DP Dosage Forms

[00157] The following procedures were used to determine the PK parameters of the orodispersible 3DP dosage form of the invention and to compare them to those of the commercial product KEPPRA film-coated tablets.

[00158] A single center, randomized, single dose, laboratory-blinded, 3-period, 3-sequence crossover study was conducted. Thirty-two male and female subjects 18-50 yr of age and in good health were included. The subjects were orally administered single doses of a 3DP dosage form containing 1000 mg of LEV or a KEPPRA® tablet containing

1000 mg of LEV. The single dose was administered once-a-week for three weeks as follows, thereby providing a 7-day wash-out period between doses:

- Group I: single dose of 3DP dosage form administered in the morning after a 10-hour overnight fast
- Group II: single dose of KEPPA® tablet administered in the morning after a 10-hour overnight fast
- Group III: single dose of 3DP dosage form administered in the morning after a 10-hour overnight fast and 30 min after the start of a high-fat, high calorie breakfast

[00159] The plasma concentration of LEV was determined prior to and after administration of each dose. The food effect was determined by comparing the C_{max}, T_{max}, AUC_{0-t} and AUC_{inf} obtained for the fasting and fed conditions. The following data provides a summary of the PK data.

Dosage Form	C_{max} (microg/ml)	T_{max} (hr)	AUC_{0-t} (microg-hr/ml)	AUC_{inf} (microg-hr/ml)
KEPPRA® (fasting)	Mean: 30.48 C.V.: 19.0	Mean:0.58 C.V.:69.9	Mean: 274.9 C.V.: 18.2	Mean: 284.3 C.V.: 18
3DP (fasting)	Mean: 33.27 C.V.: 30.1	Mean: 0.58 C.V.: 73.7	Mean: 283.69 C.V.: 20	Mean: 292.9 C.V.: 19.9
3DP (Fed)	Mean: 20.48 C.V.: 16.3	Mean: 4 C.V.: 21.6	Mean: 262.6 C.V.: 15.1	Mean: 272.6 C.V.: 15.2

[00160] It was found that the 3DP product of the invention is equivalent to the KEPPRA® reference product in terms of the bioavailability of LEV under fasting conditions. Moreover, the 3DP product only exhibits a food effect upon Cmax and Tmax but not upon overall systemic exposure, i.e. not upon AUC_{0-t} or AUC_{inf}. These results are consistent with the pharmacokinetics of KEPPRA® tablets administered in the fed state (KEPPRA® label, NDA 021035).

[00161] As used herein, the term "about" or "approximately" are taken to mean ±10%, ±5%, ±2.5% or ±1% of a specified valued. As used herein, the term "substantially" is taken to mean "to a large degree" or "at least a majority of" or "more than 50% of".

[00162] The above is a detailed description of particular embodiments of the invention. It will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made

without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims. All of the embodiments disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure.

Claims

1) A rapidly dispersible solid dosage form comprising levetiracetam in a bound matrix that disperses in about 15 sec or less in a volume of about 15 ml or less of water or saliva.

2) The dosage form of claim 1, wherein the matrix further comprises antioxidant.

3) A rapidly dispersible solid dosage form comprising a bound porous matrix that disperses in about 15 sec or less in a volume of about 15 ml or less of water or saliva, wherein the matrix comprises: levetiracetam; at least one antioxidant; at least one binder; and at least one disintegrant.

4) The dosage form of claim 1, 2 or 3, wherein the matrix comprises 0.1% or less of an oxidative degradant of LEV after being stored at 21° C for six months at 75% RH.

5) A rapidly dispersible solid dosage form comprising levetiracetam in a bound porous matrix that disperses in about 15 sec or less in a volume of about 15 ml or less of water or saliva, wherein the dosage form provides a Cmax within the ranges listed below when respective doses of levetiracetam are administered to a subject in the fasting state:

Dose (mg)	C_{max} (micrograms/ml)
1000	13-53
750	9-37
500	5-20
250	4-7.

6) The dosage form of claim 5, wherein the dosage form provides a Tmax within the range of 0.15-1.5 hours.

7) The dosage form of claim 5, wherein the dosage form provides an AUC_{0-t} and/or an AUC_{inf} within the ranges listed below:

3DP Dose (mg)	AUC_{0-t} (microg-hr/ml)	AUC_{inf} (microg-hr/ml)
1000	170-397	176-410
750	135-315	140-324
500	90-209	93-216
250	54-127	56-131.

8) A rapidly dispersible solid dosage form comprising levetiracetam in a bound porous matrix that disperses in about 15 sec or less in a volume of about 15 ml or less of water or saliva, wherein the dosage form provides a Cmax within the ranges listed below when respective doses of 1evetiracetam are administered to a subject in the fed state:

3DP Dose (mg)	C_{max} (microg/ml)
1000	14-27
750	10-19
500	5-10
250	4-7.

9) The dosage form of claim 8, wherein the dosage form provides a Tmax within the range of 2-5 hours.

10) The dosage form of claim 8, wherein the dosage form provides an AUC_{0-t} and/or an AUC_{inf} within the ranges listed below:

3DP Dose (mg)	AUC_{0-t} (microg-hr/ml)	AUC_{inf} (microg-hr/ml)
1000	183-342	190-355
750	145-271	150-282
500	96-180	100-187
250	58-109	60-113

11) A rapidly dispersible solid dosage form comprising levetiracetam in a bound porous matrix that disperses in about 15 sec or less in a volume of about 15 ml or less of

water or saliva, wherein the dosage form provides a fed/fasted ratio for Cmax in the range of 0.55 to 0.74 and for Tmax in the range of 5 to 21.

12) The dosage form of claim 11, wherein the dosage form provides a fed/fasted ratio, for AUC_{0-t} in the range of 0.89 to 0.98 and for AUC_{inf} in the range of 0.89 to 0.99.

13) The invention according to any one of the above claims, wherein the dosage form is equivalent in rate and extent of absorption to a KEPPRA® tablet, as defined by NDA No. N021035, in terms of C_{max}, AUC_{0-t} and/or AUC_{inf}.

14) The invention according to any one of the above claims, wherein: a) the dosage form is not compressed; b) the matrix is not compressed; c) the hardness of the exterior surfaces of the dosage form is greater than the hardness of an interior portion (one or more interior incremental printed layers thereof) of the dosage form, i.e. the exterior of the dosage form is harder than the interior; d) the dissolution time of LEV is slower than the dispersion time of the matrix when placed in an aqueous fluid; e) the matrix disperses in about 10 seconds or less when placed in a small volume of aqueous fluid; f) at least 75%, at least about 90, or at least about 95% of the LEV dissolves in about 2 minutes or less when placed in an aqueous fluid; g) LEV is present in a form selected from the group consisting of hydrate, hemi-hydrate, crystalline, amorphous, anhydrate or a combination thereof; h) the dosage form comprises not more than 10% wt and not less 0.1% moisture as determined by loss on drying at 120° C; i) the hardness of the matrix is substantially uniform; j) the dosage form comprises one or more other medicaments; k) the matrix further comprises glycerin; l) the content of glycerin in the dosage form ranges from about 0.05%-3%; and/or m) at least 95% of LEV is dissolved in 5 minutes or less in 900 ml of aqueous media at pH 1.2, 4.5 or 6.8 in a USP paddle apparatus operating at 50 RPM.

15) The invention according to any one of the above claims, wherein the matrix is a three-dimensionally printed matrix comprising LEV, disintegrant, one or more binders, one or more surfactants, one or more antioxidants, glycerin and optionally one or more of the following: one or more glidants (free-flow additive), one or more flavorants, one or more preservatives; wherein, the matrix comprises particles bound by binder and LEV; the matrix is porous and non-compressed; the matrix disperses in less than 15 sec in a volume of 10 ml of aqueous fluid; and the content of LEV in the matrix ranges from 50-80 % wt based upon the total weight of the matrix.

16) The invention according to any one of the above claims wherein: a) the at least one surfactant is present in an amount ranging from about 0.05 to about 1%, about 0.1 to about

0.8%, and about 0.2 to about 0.5 % wt based upon the final weight of the dosage form; b) the at least one antioxidant is present in an amount range from about 0.005 to about 5.0%, about 0.01 to about 1.0%, and about 0.08 to about 0.8% based upon the final weight of the dosage form; c) the at least one binder is present in an amount range from about 0.5 to about 20%, about 5 to about 15%, and about 7 to about 13% based upon the final weight of the dosage form; d) the at least one disintegrant is present in an amount range from about 3 to about 35%, about 10 to about 30%, and about 20 to about 26% based upon the final weight of the dosage form; e) the at least one glidant is present in an amount range from about 0.1 to about 2.0%, about 0.25 to about 1.5%, and about 0.5 to about 1.0% wt, based upon the final weight of the dosage form; and/or f) the matrix comprises about 250 to about 1000 mg, about 250 mg, about 500 mg, about 750 mg, about 1000 mg of LEV.

17) The invention according to any one of the above claims, wherein the dosage form has been prepared by a three-dimensional printing process.

18) The invention according to claim 17, wherein the dosage form has been prepared by a three-dimensional printing process employing any of the following printing fluid and a bulk powder compositions:

Printing fluid

Water (% wt)	68.99-70.7	68.47-69.12	66.89-67.95	66.5-71
Glycerin (% wt)	3.9-4	3.8-3.92	3.79-3.85	3.5-4
Isopropanol (% wt)	13.01-13.3	12.3-13.04	12.11-12.82	12-13.5
Tween 20 (% wt)	1.95-2	1.9-1.96	1.89-1.92	0.5-2
Povidone (% wt)	9.76-10	8.5-9.8	8.51-9.61	8.5-10
Sucralose (% wt)	2	2-5	4-6	0-3
Monoammonium glycyrrhizinate (% wt) Magnasweet 100			0.2-0.6	0-1
Spearmint Flavor HD45		0.01-0.03	0.01-0.05	0-1
Natural Peppermint Flavor HD29	0-0.38			0-1

Printing fluid		
Water (% wt)	65-72	65-70
Glycerin (% wt)	3.5-4	3.4-4.2
Isopropanol (% wt)	12-13.5	11-13
Tween 20 (% wt)	1-2	1.5-2.5
Povidone (% wt)	8.5-10	8-10
Sucralose (% wt)	>0-5	4-6
Monoammonium glycyrrhizinate (% wt) Magnasweet 100	0-0.6	0.1-0.8
Spearmint Flavor HD45	0-0.2	>0-0.1
Natural Peppermint Flavor HD29	0-0.5	

Bulk powder:					
LEV (% wt)	75	75	65	65	75-90
Avicel PH101 (% wt)	17.5	19.8	21.8	23.8	5-20
Mannitol (% wt)			12.5	10.5	
Povidone (PVP K29/32) (% wt)	4.5	4.5			5-10
Sucralose (% wt)	2				1-3
Monoammonium glycyrrhizinate (% wt)	0.5				0.5
Colloidal Silicon dioxide (% wt)	0.5	0.7	0.7	0.7	0.5

Bulk powder:	
LEV (% wt)	65-75
Avicel PH101 (% wt)	17.5-24
Mannitol (% wt)	10.5-12.5
Povidone (PVP K29/32) (% wt)	4-6
Sucralose (% wt)	1-3
Monoammonium glycyrrhizinate (% wt)	0.1-1
Colloidal Silicon dioxide (% wt)	0.5-0.7
Antioxidant (% wt)	0.1-7

19) The invention according to any one of the above claims, wherein the dosage form comprises the following ingredients:

LEV (% wt)	60-70
Disintegrant (% wt)	20-25
Binder (% wt)	10-15
Sweetener (% wt)	0.5-2
Glidant (% wt)	0.1-1.5
Glycerin (% wt)	0.1-5
Surfactant (% wt)	0.05-1.5
Flavor (% wt)	0-0.5

20) The invention according to clam 19, wherein the dosage form further comprises antioxidant.

21) The invention according to any one of the above claims, wherein: a) the hardness of the matrix ranges from about 1 to about 10 kp, about 2 to about 6 kp or about 3 to about 9 kp; b) the matrix disperses in 10 sec or less when placed in 15 ml of water or saliva; c) binder is introduced into the matrix by way of printing fluid used to form the matrix; d) binder is introduced into the matrix by way of bulk powder used to form the matrix; e) the matrix comprises about 250 mg to about 1000 mg of LEV; f) the matrix comprises 15 to 50 or 25 to 50 of printed incremental layers; g) the thickness (height) of an incremental layer ranges from 0.008 to 0.012 inches; and/or h) the matrix is porous and non-compressed.

22) A method of preparing a rapidly dispersible dosage form according to any one of the above claims, the method comprising:

a) providing an incremental layer of bulk powder comprising LEV, disintegrant, binder, antioxidant, optional flavorant, optional sweetener, and optional glidant;

b) according to a predetermined saturation level, applying a printing fluid to the layer of bulk powder to form an incremental printed layer, wherein the fluid comprises water, alcohol, binder, antioxidant, glycerin, surfactant (emulsifier), optional sweetener, optional preservative; and

c) repeating a) and b) at least two times, thereby forming the three-dimensionally printed orodispersible dosage form comprising at least three stacked incremental printed layers.

23) The invention according to any one of the above claims, wherein: a) the process further comprises forming an indicum or indicia on the surface of the dosage form in embossed (raised) or debossed (recessed) form during the 3DP process; b) the process further comprises removing water and alcohol from the dosage form to reduce its moisture content to within a range as described herein; c) the process further comprises separating the dosage form from bulk powder that has not been printed upon; d) a higher printing fluid saturation level is used for the upper and lower incremental layers of the dosage form than for the rest of the dosage form to provide, in the finished dosage form, increased hardness for the upper and lower incremental surfaces and reduced hardness for incremental layers there between; e) a higher printing fluid saturation level is used for the upper and lower incremental layers and for the periphery of the intermediate incremental layers of the dosage form than for the rest of the dosage form to provide, in the finished dosage form, increased hardness for its upper and lower incremental surfaces and for the periphery of its intermediate incremental layers and to provide reduced hardness for incremental layers there between; f) the process further comprises heating the dosage form to remove and reduce the amount of printing fluid therein; and/or g) the process further comprises preparing the bulk powder by mixing the ingredients thereof to form a mixture that is then sieved.

24) The invention according to any one of the above claims, wherein the dosage form is preservative free.

25) A method of treating a disease, condition or disorder that is therapeutically responsive to levetiracetam comprising administering a dosage form of any one of the above claims one to three times daily to a subject in need thereof throughout a treatment period.

26) A process for the manufacture of a medicament for the treatment of a disease, condition or disorder that is therapeutically responsive to levetiracetam comprising including the levetiracetam in a rapidly dispersible solid dosage form as described herein.

27) A medicament for the treatment of a disease, condition or disorder that is therapeutically responsive to levetiracetam comprising: levetiracetam in a rapidly dispersible solid dosage form as described herein.

FIG. 1

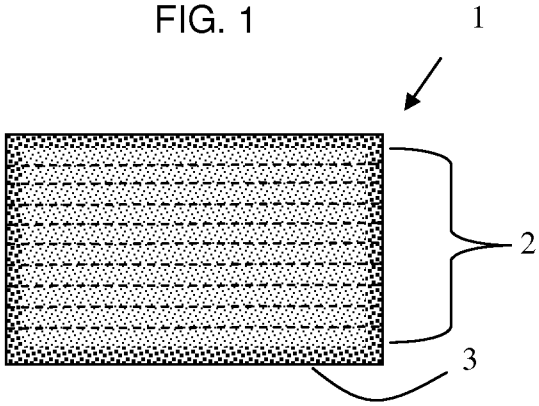


FIG. 2

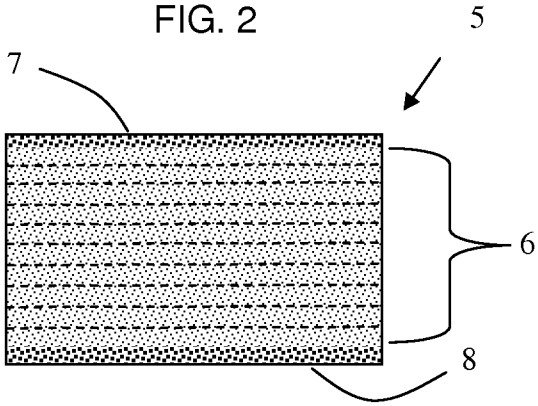


FIG. 3A

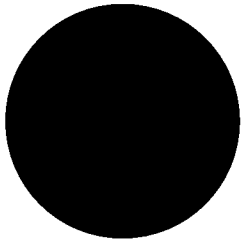


FIG. 3B

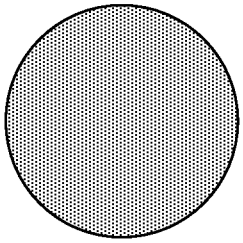


FIG. 3C

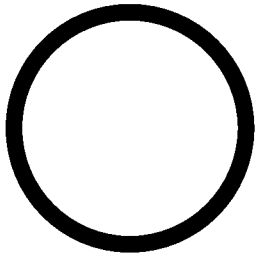


FIG. 3D

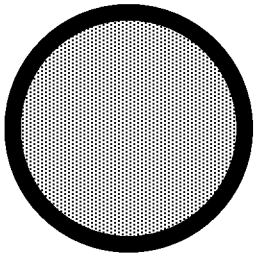
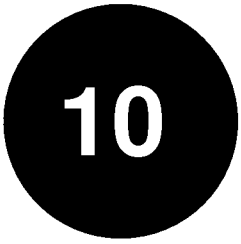


FIG. 3E



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/028954

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 25/08 (2014.01)
USPC - 424/469
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 9/52, 9/66, 47/38; A01N 43/36; A61P 25/00, 25/08 (2014.01)
USPC - 424/467, 469 472, 474; 514/424

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/4015, 9/1635, 9/2054, 9/2077, 9/2866 (2014.06)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, Google Patents, Pubmed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2011/0318390 A1 (FUISZ et al) 29 December 2011 (29.12.2011) entire document	1, 2 --- 5-12
X -- Y	US 2008/0069878 A1 (VENKATESH et al) 20 March 2008 (20.03.2008) entire document	3, 4
Y	US 2007/0212411 A1 (FAWZY et al) 13 September 20007 (13.09.2007) entire documnet	4
Y	STOCKIS et al. 'Assessment of Levetiracetam Bioavailability From Targeted Sites in the Human Intestine Using Remotely Activated Capsules and Gamma Scintigraphy: Open-Label, Single-Dose, Randomized, Four-Way Crossover Study in Healthy Male Volunteers'. Clinical Therapeutics. Volume 32, Number 10. Pages 1813-1821. September 2010. entire document	5-7
Y	JIANG et al. 'Single-dose pharmacokinetics of levetiracetam in healthy Chinese male subjects'. British Journal of Clinical Pharmacology. 63:5. Pages 614-617. 26 February 2007. entire document	7
Y	ROUTIS et al. 'Pharmacokinetics of levetiracetam XR 500mg tablets'. Epilepsy Research. Volume 84. Pages 224-231. 04 March 2009. entire document	8-12
A	US 7,863,316 B2 (KSHIRSAGAR et al) 04 January 2011 (04.01.2011) entire document	1-12

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 July 2014	28 JUL 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/028954

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 26, 27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 26 and 27 have been held as omnibus claims, as they refer to an invention "as described herein".

3. ☒ Claims Nos.: 13-25
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

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(71)申请人 阿普雷奇亚制药公司
地址 美国宾夕法尼亚州
(72)发明人 J·雅各布斯 N·夸勒
T·G·韦斯特 D·C·蒙克豪斯
H·L·苏尔普勒南 N·B·雅音
(74)专利代理机构 永新专利商标代理有限公司 72002
代理人 黄歆 过晓东
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权利要求书5页 说明书29页 附图1页
按照条约第19条修改的权利要求书6页
按照条约第19条修改的声明或说明2页

(54)发明名称

包含左乙拉西坦的快速分散剂型

(57)摘要

本发明公开一种高剂量快速分散三维打印剂型，其包含多孔基质中的高剂量左乙拉西坦，所述基质在水中于小于约10秒的时间段内分散。本发明还公开制备所述剂型的方法以及治疗对左乙拉西坦治疗上应答的疾病、疾病状况或病症的方法。本发明还提供制备所述剂型的方法。

CN 105188849 A

1. 一种快速分散固体剂型，所述剂型包含结合基质中的左乙拉西坦，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散。

2. 权利要求1的剂型，其中所述基质还包含抗氧化剂。

3. 一种快速分散固体剂型，所述剂型包含结合多孔基质，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散，其中所述基质包含左乙拉西坦、至少一种抗氧化剂、至少一种粘合剂和至少一种崩解剂。

4. 权利要求1、2或3的剂型，其中在75％ RH和21℃下存储6个月后，所述基质包含0.1％或更少的LEV的氧化降解物。

5. 一种快速分散固体剂型，所述剂型包含结合多孔基质中的左乙拉西坦，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散，其中在禁食状态下，向个体给药各自剂量的左乙拉西坦时，所述剂型提供下列范围内的Cmax：

剂量(mg)	C_{max}(微克/ml)
1000	13-53
750	9-37
500	5-20
250	4-7

。

6. 权利要求5的剂型，其中所述剂型提供0.15-1.5小时范围内的Tmax。

7. 权利要求5的剂型，其中所述剂型提供下列范围内的$AUC_{0\ t}$和/或AUC_{inf}：

3DP剂量(mg)	$AUC_{0\ t}$(微克-hr/ml)	AUC_{inf}(微克-hr/ml)
1000	170-397	176-410
750	135-315	140-324
500	90-209	93-216
250	54-127	56-131

。

8. 一种快速分散固体剂型，所述剂型包含结合多孔基质中的左乙拉西坦，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散，其中在进食状态下，向个体给药各自剂量的左乙拉西坦时，所述剂型提供下列范围内的Cmax：

3DP剂量(mg)	C_{max}(微克/ml)
1000	14-27

750	10-19
500	5-10
250	4-7

。

9. 权利要求 8 的剂型，其中所述剂型提供 2-5 小时范围内的 Tmax。

10. 权利要求 8 的剂型，其中所述剂型提供下列范围内的 $AUC_{0\ t}$ 和 / 或 AUC_{inf}：

3DP 剂量 (mg)	$AUC_{0\ t}$（微克 -hr/ml）	AUC_{inf}（微克 -hr/ml）
1000	183-342	190-355
750	145-271	150-282
500	96-180	100-187
250	58-109	60-113

。

11. 一种快速分散固体剂型，所述剂型包含结合多孔基质中的左乙拉西坦，所述基质在约 15ml 或更少体积的水或唾液中，于约 15 秒或更短的时间内分散，其中所述剂型提供的 Cmax 的进食 / 禁食比为 0.55-0.74，并且 Tmax 的进食 / 禁食比为 5-21。

12. 权利要求 11 的剂型，其中所述剂型提供的 $AUC_{0\ t}$ 的进食 / 禁食比为 0.89-0.98，并且 AUC_{inf} 的进食 / 禁食比为 0.89-0.99。

13. 前述权利要求中任一项的发明，其中如 NDA No.N021035 所定义的，对于 C_{max}、$AUC_{0\ t}$ 和 / 或 AUC_{inf}，所述剂型在吸收速率和程度上等同于 KEPPRA® 片剂。

14. 前述权利要求中任一项的发明，其中：

a) 所述剂型未被压制；b) 所述基质未被压制；c) 所述剂型的外表面的硬度大于所述剂型内部部分（其一个或多个内部增量打印层）的硬度；即所述剂型的外部比内部更硬；d) 当置于含水流体中时，LEV 的溶解时间慢于所述基质的分散时间；e) 当置于小体积的含水流体中时，所述基质在约 10 秒或更短的时间内分散；f) 当置于含水流体中时，至少 75%、至少约 90% 或至少约 95% 的 LEV 在约 2 分钟或更短的时间内溶解；g) LEV 以选自以下的形式存在：水合物、半水合物、晶体、无定形、无水物或其组合；h) 如通过 120℃下的干燥失重确定的，所述剂型包含不大于 10 重量% 并且不小于 0.1 重量% 的水分；i) 所述基质的硬度是基本上均匀的；j) 所述剂型包含一种或多种其他药物；k) 所述基质还包含甘油；l) 所述剂型中的甘油含量为约 0.05% -3%；和 / 或 m) 在以 50RPM 操作的 USP 桨装置中，在 pH1.2、4.5 或 6.8 下，于 900ml 含水介质中，至少 95% 的 LEV 在 5 分钟或更短的时间内溶解。

15. 前述权利要求中任一项的发明，其中所述基质是三维打印基质，所述基质包含 LEV、崩解剂、一种或多种粘合剂、一种或多种表面活性剂、一种或多种抗氧化剂、甘油以及任选存在的一种或多种以下成分：一种或多种助流剂（自由流动的添加剂）、一种或多种调味剂、一种或多种防腐剂；其中所述基质包含由粘合剂和 LEV 结合的颗粒；所述基质是多孔

的并且未被压制；所述基质在 10ml 体积的含水流体中于小于 15 秒的时间内分散；以及基于所述基质的总重量，所述基质中的 LEV 含量为 50-80 重量%。

16. 前述权利要求中任一项的发明，其中：

a) 基于所述剂型的最终重量，至少一种表面活性剂以约 0.05- 约 1 重量%、约 0.1- 约 0.8 重量%以及约 0.2- 约 0.5 重量%的量存在；b) 基于所述剂型的最终重量，至少一种抗氧化剂以约 0.005- 约 5.0 重量%、约 0.01- 约 1.0 重量%以及约 0.08- 约 0.8 重量%的量存在；c) 基于所述剂型的最终重量，至少一种粘合剂以约 0.5- 约 20 重量%、约 5- 约 15 重量%以及约 7- 约 13 重量%的量存在；d) 基于所述剂型的最终重量，至少一种崩解剂以约 3- 约 35 重量%、约 10- 约 30 重量%以及约 20- 约 26 重量%的量存在；e) 基于所述剂型的最终重量，至少一种助流剂以约 0.1- 约 2.0 重量%、约 0.25- 约 1.5 重量%以及约 0.5- 约 1.0 重量%的量存在；和 / 或 f) 所述基质包含约 250- 约 1000mg、约 250mg、约 500mg、约 750mg、约 1000mg 的 LEV。

17. 前述权利要求中任一项的发明，其中所述剂型通过三维打印方法制备。

18. 权利要求 17 的发明，其中所述剂型通过三维打印方法制备，所述方法使用以下打印流体和松散粉末组合物中的任一种：

打印流体

水(重量%)	68.99-70.7	68.47-69.12	66.89-67.95	66.5-71
甘油(重量%)	3.9-4	3.8-3.92	3.79-3.85	3.5-4
异丙醇(重量%)	13.01-13.3	12.3-13.04	12.11-12.82	12-13.5
吐温 20 (重量%)	1.95-2	1.9-1.96	1.89-1.92	0.5-2
聚维酮(重量%)	9.76-10	8.5-9.8	8.51-9.61	8.5-10
三氯蔗糖(重量%)	2	2-5	4-6	0-3
甘草酸单铵			0.2-0.6	0-1
(重量%)甘草甜 100				
留兰香香料 HD45		0.01-0.03	0.01-0.05	0-1
天然胡椒薄荷香料 HD29	0-0.38			0-1

打印流体

水(重量%)	65-72	65-70
甘油(重量%)	3.5-4	3.4-4.2

异丙醇(重量%)	12-13.5	11-13
吐温 20 (重量%)	1-2	1.5-2.5
聚维酮(重量%)	8.5-10	8-10
三氯蔗糖(重量%)	>0-5	4-6
甘草酸单铵 (重量%)甘草甜 100	0-0.6	0.1-0.8
留兰香香料 HD45	0-0.2	>0-0.1
天然胡椒薄荷香料 HD29	0-0.5	

松散粉末：

LEV (重量%)	75	75	65	65	75-90
Avicel PH101 (重量%)	17.5	19.8	21.8	23.8	5-20
甘露醇(重量%)			12.5	10.5	
聚维酮(PVP K29/32) (重量%)	4.5	4.5			5-10
三氯蔗糖(重量%)	2				1-3
甘草酸单铵 (重量%)	0.5				0.5
胶体二氧化硅(重量%)	0.5	0.7	0.7	0.7	0.5

松散粉末：

LEV (重量%)	65-75
Avicel PH101 (重量%)	17.5-24
甘露醇(重量%)	10.5-12.5
聚维酮(PVP K29/32) (重量%)	4-6
三氯蔗糖(重量%)	1-3
甘草酸单铵 (重量%)	0.1-1
胶体二氧化硅(重量%)	0.5-0.7
抗氧化剂(重量%)	0.1-7 。

19. 前述权利要求中任一项的发明，其中所述剂型包含以下成分：

LEV (重量%)	60-70
崩解剂(重量%)	20-25
粘合剂(重量%)	10-15
甜味剂(重量%)	0.5-2

助流剂(重量%)	0.1-1.5
甘油(重量%)	0.1-5
表面活性剂(重量%)	0.05-1.5
香料(重量%)	0-0.5

。

20. 权利要求 19 的发明，其中所述剂型还包含抗氧化剂。

21. 前述权利要求中任一项的发明，其中：

a) 所述基质的硬度为约 1- 约 10kp、约 2- 约 6kp 或者约 3- 约 9kp ；b) 当置于 15ml 水或唾液中时，所述基质在 10 秒或更短的时间内分散 ；c) 通过用于形成所述基质的打印流体将粘合剂引入所述基质 ；d) 通过用于形成所述基质的松散粉末将粘合剂引入所述基质 ；e) 所述基质包含约 250mg- 约 1000mg 的 LEV ；f) 所述基质包含 15-50 或 25-50 个打印增量层 ；g) 增量层的厚度（高度）为 0.008-0.012 英寸 ；和 / 或 h) 所述基质是多孔的并且未被压制。

22. 一种制备前述权利要求中任一项的快速分散剂型的方法，所述方法包括：

a) 提供松散粉末的增量层，其包含 LEV、崩解剂、粘合剂、抗氧化剂、任选存在的调味剂、任选存在的甜味剂以及任选存在的助流剂 ；

b) 根据预定的饱和水平，将打印流体施用于松散粉末的层以形成增量打印层，其中所述流体包含水、醇、粘合剂、抗氧化剂、甘油、表面活性剂（乳化剂）、任选存在的甜味剂、任选存在的防腐剂 ；以及

c) 重复 a) 和 b) 至少两次，从而形成三维打印的口分散剂型，所述剂型包含至少三个堆积的增量打印层。

23. 前述权利要求中任一项的发明，其中：

a) 所述方法还包括在 3DP 方法中，在所述剂型的表面上形成一个或多个凸起（突出）或凹入（嵌入）形式的标记 ；b) 所述方法还包括从所述剂型除去水和醇以将其水分减少至本文所述的范围内 ；c) 所述方法还包括分离所述剂型与未在其上打印的松散粉末 ；d) 所述剂型的上方和下方增量层所用的打印流体饱和水平高于所述剂型的其他部分，以在完成的剂型中为上方和下方的增量表面提供增加的硬度，并且为其之间的增量层提供降低的硬度 ；e) 所述剂型的上方和下方增量层以及中间增量层的外围所用的打印流体饱和水平高于所述剂型的其他部分，以在完成的剂型中为其上方和下方增量表面以及中间增量层的外围提供增加的硬度，并且为其之间的增量层提供降低的硬度 ；f) 所述方法还包括加热所述剂型以除去和降低其中的打印流体的量 ；和 / 或 g) 所述方法还包括通过混合其成分来制备松散粉末以形成随后进行筛分的混合物。

24. 前述权利要求中任一项的发明，其中所述剂型不含防腐剂。

25. 一种治疗对左乙拉西坦治疗上应答的疾病、疾病状况或病症的方法，所述方法包括在整个治疗期间向有此需要的个体每日给药前述权利要求中任一项的剂型 1-3 次。

26. 一种制备用于治疗对左乙拉西坦治疗上应答的疾病、疾病状况或病症的药物的方法，所述方法包括将所述左乙拉西坦包含于本文所述的快速分散固体剂型中。

27. 一种用于治疗对左乙拉西坦治疗上应答的疾病、疾病状况或病症的药物，其包含：本文所述的快速分散固体剂型中的左乙拉西坦。

包含左乙拉西坦的快速分散剂型

技术领域

[0001] 本发明涉及一种左乙拉西坦(levetiracetam)的快速分散(口分散)剂型。特别地,当置于个体的口中时,所述剂型在小于约15秒的时间段内分散。本发明还涉及所述剂型用于治疗对左乙拉西坦治疗上应答的疾病、病症或疾病状况的使用方法。本发明还提供一种用于制备所述剂型的方法。

背景技术

[0002] 包含左乙拉西坦(LEV;(S)-2-(2-氧代吡咯烷-1-基)丁酰胺;(-)-(S)-α-乙基-2-氧代-1-吡咯烷乙酰胺;描述于U.S.4,943,639)的固体口服剂型是已知的(FDA Electronic Orange Book)。固体片剂目前可以商品名KEPPRA®获得(NDA N021035,UCB,Inc.,批准日期1999年11月30日;包装内说明书见http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=9870)。这些片剂已知为包含250、500、750或1000mg的左乙拉西坦和以下赋形剂(无活性成分):胶体二氧化硅、交联羧甲基纤维素钠、硬脂酸镁、聚乙二醇3350、聚乙二醇6000、聚乙烯醇、滑石、二氧化钛,以及下列的额外物质:250mg片剂包含FD&C Blue#2/靛蓝铝色淀;500mg片剂包含氧化铁黄;750mg片剂包含FD&C黄#6/日落黄FCF铝色淀、氧化铁红。KEPPRA®口服溶液剂型也是可用的。

[0003] 左乙拉西坦极易溶于水(104.0g/100mL)。其易溶于氯仿(65.3g/100mL)和甲醇(53.6g/100mL),可溶于乙醇(16.5g/100mL),微溶于乙腈(5.7g/100mL),并且几乎不溶于正己烷。

[0004] 据发现,LEV在大范围的药物制剂中是化学上稳定的。LEV可商购的片剂中包含的成分包括玉米淀粉、交联羧甲基纤维素钠、聚维酮、胶体二氧化硅、滑石、硬脂酸镁、聚乙二醇、二氧化钛、氧化铁和聚乙烯醇等。然而,在压力(酸、碱、水、氧化、热或光照)的加速(60℃)条件下,据证实LEV发生明显降解(Shah,Der Pharmacia Sinica(2012),3(5),576-589)。Shah报道了氧化降解的速率常数小于酸性水解、碱性水解、水水解和UV光解。Prohotsky et al.(Am.J.Health Syst.Pharm.(2014),71(3),219-22)公开了左乙拉西坦的口服溶液的稳定性的研究结果。他们认为,溶液对于高达6个月的时间是稳定的。

[0005] Ensom et al.(Can.J.Hosp.Pharm.(2011),64(3),207-211)公开了ORA-SWEET和ORA-PLUS中的左乙拉西坦的临时混合溶液的稳定性的研究结果。他们报道了所有的样品在至少91天的时间段内没有发生变化。

[0006] LEV用于治疗癫痫,作为患有癫痫的成人和4岁及以上儿童的癫痫部分发作的辅助治疗,作为患有青少年肌阵挛性癫痫的成人和12岁及以上少年的肌阵挛发作治疗的辅助疗法,以及作为患有特发性全面性癫痫的成人和6岁及以上儿童的原发性全身性强直阵挛发作治疗的辅助疗法。已经提议用于改善表现出年龄相关的认知障碍或有这样风险的个体的认知功能,包括患有轻度认知障碍(MCI)、年龄相关的认知衰退(ARCD)或年龄相关的记忆障碍(AAMI)或者有轻度认知障碍(MCI)、年龄相关的认知衰退(ARCD)或年龄相关的记

忆障碍（AAMI）风险的个体。

[0007] 对于治疗癫痫和惊厥，LEV的高水平剂量为每片250-1000mg。治疗以1000mg/天的每日剂量开始，作为每天两次剂量给药（500mg BID）。可以给予额外的剂量增加（额外的1000mg/天，每两周）至3000mg的最大推荐每日剂量。在开放标记研究中已经使用大于3000mg/天的剂量达6个月及以上的时间。然而，年幼和年长患者通常难以吞咽包含如此之高剂量的固体口服剂型，特别是由于已知剂型中包含的大量赋形剂。吞咽困难导致较差的患者依从性。解决这一问题的尝试使得开发口服液体和可注射剂型。然而，这样的剂型仍然存在稳定性、污染和不精确的剂量给药问题。

[0008] 考虑到每片要求的高剂量的LEV，难以配制具有适合于存储和操作的足够硬度和脆性的快速分散固体口服剂型。公开了解决这样的问题的尝试。Karavas et al.的U.S.8,187,635公开的片剂包含磷酸二钙并且在约30分钟内崩解。UCB Pharma,S.A.的WO 2007/012439公开的片剂在约15-45分钟内崩解。Genpharm Inc.的WO 2006/102750公开的片剂通过制粒和流化床干燥制备，并且在约3-8分钟内崩解。这样的片剂并不满足口分散剂型的U.S.F.D.A.要求。

[0009] 口分散剂型在口中的最少量唾液或水中分散或崩解。这样的剂型容易吞咽，能够精确地剂量给药并且治疗作用起效快。Fu et al.的U.S.7,749,533公开的剂型包含颗粒，其含有药物、多孔塑性物质、水渗透增强剂、粘合剂和药物。颗粒必须进行压制以产生剂型。Gregory et al.的U.S.4,371,516和U.S.5,738,875公开了冷冻干燥剂型。Wehling et al.的U.S.5,178,878公开了软压制口分散剂型。不溶性微粒的泡腾剂型和快速释放包衣描述于U.S.5,578,322和5,607,697。冷冻干燥泡沫和液体描述于U.S.4,642,903和U.S.5,631,023。熔纺剂型描述于U.S.4,855,326、5,380,473和5,518,730。U.S.20070218129公开了速释可分散和口分散固体药物组合物，其具有分散入水时大小小于710μm的颗粒的形式，其中所述制剂通过湿法制粒来制备，但是崩解时间为53-60秒。

[0010] U.S.6,471,992、U.S.2012-0207929和U.S.2003-0133975公开了三维打印的快速分散剂型。即使如此，也没有提及包含LEV的口分散三维打印剂型。无法推理预测含有大量LEV的三维打印剂型可以制备为在最小量的含水流体中于15秒或更短、10秒或更短或者5秒或更短的时间内分散，同时保留足够的硬度以保证处理和存储。

[0011] 以上内容都没有公开包含左乙拉西坦的快速溶解固体口服剂型。Mahmut的WO 2011/136751公开了从包含LEV的颗粒制备的压制泡腾片剂，然而所述片剂在约5分钟或更短的时间内溶解。Beijing Yiling Bioengineering Co.Ltd.的CN102085194A公开了包含LEV、PEG 600、麦芽糖糊精和水解明胶的口服崩解冷冻干燥剂型。然而，冷冻干燥剂型在物理上非常不稳定，并且表现出非常高的脆性，因为它们并非坚硬的。

[0012] 在三维打印物品的制备中使用甘油公开于U.S.20080281019、U.S.20080187711、U.S.20070168815、U.S.20040187714、U.S.20030207959、U.S.20070146734、U.S.20050197431、U.S.20040056378、U.S.5,902,441、U.S.6,416,850和U.S.6,838,035。现有技术中并没有公开在三维打印的快速分散剂型的制备中使用甘油。

[0013] 应当有利地提供包含左乙拉西坦的快速分散口分散固体口服剂型，其表现出低脆性和足够的硬度以经受存储和处理，同时表现出非常快的崩解速率；然而现有技术中并没

有公开这样的包含 LEV 的合适剂型。

发明内容

[0014] 本发明意图克服现有技术中存在的一些或所有不足。如文本所述，本发明提供一种口分散固体剂型，其包含左乙拉西坦作为主要或唯一活性成分，其中所述剂型包含结合基质，所述基质在约 10ml 或更少体积的水或唾液中，于约 15 秒 (sec) 或更短的时间内分散。所述基质在给药的个体的口中分散，从而促进吞咽和给药。提供本文所述的口分散固体剂型对于现有技术是明显改进，所述剂型包含左乙拉西坦作为主要或唯一活性成分，其中所述剂型包含结合基质，所述基质在 5ml 或更少体积的水或唾液中于 20 秒或更短的时间内分散。所述基质在给药的个体的口中快速分散，从而促进吞咽和给药。

[0015] 所述剂型是自身防腐 (self-preserved) 的，并且不要求加入防腐剂，但是如果需要可以包含防腐剂。因此，本发明的一些实施方案提供一种不含防腐剂的 LEV 的快速口分散剂型。

[0016] 本发明人发现，左乙拉西坦在通过三维打印进行配制期间发生氧化降解，但是没有观察到对应于酸催化或碱催化的水解或光解或热降解的降解产物。这些结果是出人意料的，因为 (Shah，上文）教导了在加速条件下，LEV 的氧化降解速率比水解或光解慢得多。本发明人发现，在本发明的口分散剂型中包含抗氧化剂提供针对 3DP 口分散剂型的制备和存储期间 LEV 的氧化降解的保护。本发明人已经成功地制备包含 LEV 的 3DP 口分散剂型，其中基于所述剂型中 LEV 的重量，所述剂型中任何单独的氧化降解物的含量小于 0.1 重量%，其中所述剂型包含 LEV、抗氧化剂和水溶性粘合剂，所述粘合剂包含过氧化物作为杂质。即使在 75% RH 和 21℃下存储 6 个月后，任何单独的氧化降解物的含量保持为 0.1 重量%或低于 0.1 重量%。

[0017] 因此，本发明的一些实施方案提供一种稳定的快速口分散三维打印的固体多孔基质，所述基质包含 LEV、抗氧化剂、崩解剂和粘合剂，其中所述基质在 75% RH 和 21℃下存储 6 个月时对 LEV 的氧化降解是稳定的。本发明还提供一种稳定的快速口分散三维打印的固体多孔基质，所述基质包含 LEV、抗氧化剂、崩解剂和粘合剂，其中在 75% RH 和 21℃下存储 6 个月后，所述基质包含 0.1%或更少的 LEV 的氧化降解物。在一些实施方案中，抗氧化剂选自丁基羟基茴香醚 (BHA)、丁羟甲苯、亚硫酸钠、亚硫酸氢钠、甲硫氨酸、维生素 E 或其组合。

[0018] 在一些方面，本发明提供一种快速分散（即口分散）剂型及其给药，用于治疗对左乙拉西坦治疗上应答的疾病、疾病状况或病症。所述快速分散固体剂型包含三维打印的基质，所述基质包含 LEV、抗氧化剂和松散材料 (bulk material)。所述基质通过将打印流体沉积在粉末上形成，其中所述粉末的颗粒由 LEV 和 / 或粘合剂结合。所述基质是多孔的，具有限定的整体体密度、含水流体中的崩解（分散）时间、含水流体中的溶解时间以及水分含量。所述基质提供改善的化学稳定性、足够的硬度、低脆性以及小体积的含水液体中的非常快速的分散时间的平衡。

[0019] 增加 3DP 口分散剂型中许多不同类型的水溶性赋形剂的含量通常导致增加的硬度和增加的分散时间。例如，增加水溶性粘合剂和 LEV 的含量导致增加的硬度和分散时间。本发明人发现，增加 3DP 剂型中的甘油含量增加硬度，但是出人意料地减少分散时间。

[0020] 因此，本发明的另一方面提供包含甘油和至少一种药学可接受的溶剂的打印流体在制备快速分散剂型中的用途。本发明还提供一种三维打印系统，其包括含甘油的打印流体；并且提供一种三维打印口分散剂型的方法，所述方法包括：a) 将包含药物的粉末的增量层沉积在表面上；b) 将足量的打印流体沉积在所述增量层上以结合所述粉末中的颗粒，其中所述打印流体包含甘油和至少一种药学可接受的溶剂；以及 c) 重复 a) 和 b)，由此形成快速口分散剂型。

[0021] 本发明的一些实施方案包括这样的实施方案，其中 a) 所述药物是水溶性药物；b) 所述粉末和 / 或打印流体包含水溶性粘合剂；c) 所述打印流体中的甘油含量为 >0 重量％ -20 重量％或者约 0.05 重量％ - 约 10 重量％或者约 0.05 重量％ - 约 5 重量％；和 / 或 d) 基于所述剂型的最终重量，所述剂型中的甘油含量为约 0.05 重量％ -3 重量％或者约 0.1％ -2 重量％或 0.5 重量％ -1.0 重量％。

[0022] 本发明的一些方面提供一种口分散固体剂型，所述剂型包含三维打印的多孔基质，所述基质包含 LEV 和松散材料的结合颗粒，其中所述颗粒由 LEV 和 / 或粘合剂结合。本发明还提供一种口分散剂型，所述剂型包含三维打印基质，所述基质包含 LEV、崩解剂、粘合剂和抗氧化剂的结合颗粒，其中所述颗粒由 LEV 和 / 或粘合剂结合。

[0023] 在一些实施方案中，LEV 以晶体形式存在。涵盖其所有的多晶型物。LEV 或任何其他材料的结晶性可以通过差示扫描量热 (DSC) 确定来确定无定形材料的存在。在一些实施方案中，LEV 以松散粉末 (bulk powder) 或基质中的无定形形式存在。

[0024] 本发明的实施方案包括这样的实施方案，其中 a) 所述剂型未被压制；b) 所述基质未被压制；c) 所述剂型的外表面的硬度大于所述剂型内部部分 (其一个或多个内部增量打印层) 的硬度，即所述剂型的外部比内部更硬；d) 当置于含水流体中时，LEV 的溶解时间慢于基质的分散时间；e) 当置于小体积的含水流体中时，所述基质在约 10 秒或更短的时间内分散；f) 当置于含水流体中时，至少 75％、至少约 90％或至少约 95％的 LEV 在约 2 分钟或更短的时间内溶解；g)LEV 以选自以下的形式存在：水合物、半水合物、晶体、无定形、无水物或其组合；h) 如通过 120℃下的干燥失重确定的，所述剂型包含不大于 10 重量％并且不小于 0.1 重量％的水分；i) 所述基质的硬度是基本上均匀的；j) 所述剂型包含一种或多种其他药物；和 / 或 k) 以上的组合。

[0025] 本发明还提供一种三维打印的口分散剂型，所述剂型包含结合颗粒的三维打印的口分散基质，所述基质包含 LEV、崩解剂、一种或多种粘合剂、一种或多种表面活性剂、一种或多种抗氧化剂、甘油以及任选存在的一种或多种以下成分：一种或多种助流剂 (自由流动的添加剂)、一种或多种调味剂、一种或多种防腐剂；其中所述基质包含由粘合剂和 LEV 结合的颗粒；所述基质是多孔的并且未被压制；所述基质在 10ml 体积的含水流体中于小于 15 秒的时间内分散；并且基于所述基质的总重量，所述基质中的 LEV 含量为 50-80 重量％。当未置于含水流体中时，所述基质保持固定和刚性的三维结构，但是当置于小体积的含水流体 (如本文所定义) 中时，其在短时间段内 (如本文所定义) 分散。

[0026] 本发明的一些实施方案包括这样的实施方案，其中 a) 基于所述剂型的最终重量，至少一种表面活性剂以约 0.05- 约 1 重量％、约 0.1- 约 0.8 重量％以及约 0.2- 约 0.5 重量％的量存在；b) 基于所述剂型的最终重量，至少一种抗氧化剂以约 0.005- 约 5.0 重量％、约 0.01- 约 1.0 重量％以及约 0.08- 约 0.8 重量％的量存在；c) 基于所述剂型的最

终重量，至少一种粘合剂以约 0.5- 约 20 重量%、约 5- 约 15 重量%以及约 7- 约 13 重量%的量存在；d) 基于所述剂型的最终重量，至少一种崩解剂以约 3- 约 35 重量%、约 10- 约 30 重量%以及约 20- 约 26 重量%的量存在；和 / 或 e) 基于所述剂型的最终重量，至少一种助流剂以约 0.1- 约 2.0 重量%、约 0.25- 约 1.5 重量%以及约 0.5- 约 1.0 重量%的量存在。

[0027] LEV 颗粒的平均、中间或中值粒径为约 50- 约 400 微米、约 50- 约 300 微米、约 50- 约 250 微米、约 60- 约 250 微米、约 60- 约 100 微米或约 75- 约 250 微米。粒径可以表示为 VMD。在一些实施方案中，粒径范围定义为：a)Dv10 为约 20-60 微米，Dv50 为约 50-200 微米并且 Dv90 为约 100-500 微米；b)Dv10 为约 50-60 微米，Dv50 为约 150-200 微米并且 Dv90 为约 350-510 微米；c)Dv10 为约 20-30 微米，Dv50 为约 50-60 微米并且 Dv90 为约 100-120 微米；d)Dv10 为约 30-40 微米，Dv50 为约 70-80 微米并且 Dv90 为约 160-190 微米；或者 e)Dv10 为约 40-50 微米，Dv50 为约 125-150 微米并且 Dv90 为约 300-350 微米。在一些实施方案中，VMD 为约 60- 约 240 微米、50-70 微米、80-100 微米、150-175 微米、200-250 微米。

[0028] 本发明的一些实施方案包括这样的实施方案，其中所述基质包含约 250- 约 1000mg、约 250mg、约 500mg、约 750mg、约 1000mg 的 LEV。

[0029] 所述基质在少量的含水流体中快速分散（崩解）。本发明的一些实施方案包括这样的实施方案，其中当置于少量的含水流体中时，所述基质在约 30 秒或更短、约 20 秒或更短、约 15 秒或更短、约 10 秒或更短或者约 5 秒或更短的时间内分散。

[0030] 本发明的一些实施方案包括这样的实施方案，其中 a) 所述基质的硬度为约 1- 约 10kp、约 2- 约 6kp 或者约 3- 约 9kp；b) 当置于 15ml 水或唾液中时，所述基质在 10 秒或更短的时间内分散；c) 通过用于形成所述基质的打印流体将粘合剂引入所述基质；d) 通过用于形成所述基质的松散粉末将粘合剂引入所述基质；e) 所述基质包含约 250mg- 约 1000mg 的 LEV；f) 所述基质包含 15-50 或 25-50 个打印的增量层；g) 增量层的厚度（高度）为 0.008-0.012 英寸；和 / 或 h) 所述基质是多孔的并且未被压制。

[0031] 本发明还提供一种制备包含 LEV 的三维打印的口分散剂型的方法。所述方法包括：a) 提供松散粉末的增量层，其包含 LEV、崩解剂、粘合剂、抗氧化剂、任选存在的调味剂、任选存在的甜味剂以及任选存在的助流剂；b) 根据预定的饱和水平，将打印流体施用于松散粉末的层以形成增量打印层，其中所述流体包含水、醇、粘合剂、抗氧化剂、甘油、表面活性剂（乳化剂）、任选存在的甜味剂、任选存在的防腐剂；以及 c) 重复 a) 和 b) 至少两次，从而形成三维打印的口分散剂型，其包含至少三个堆积的增量打印层。抗氧化剂可以包含在粘合流体、粉末或者这两者中。

[0032] 本发明的一些实施方案包括这样的实施方案，其中：a) 所述方法还包括在 3DP 方法中，在所述剂型的表面上形成一个或多个凸起（突出）或凹入（嵌入）形式的标记 (indicum)；b) 所述方法还包括从所述剂型除去水和醇以将其水分减少至本文所述的范围内；c) 所述方法还包括分离所述剂型与未在其上打印的松散粉末；d) 所述剂型的上方和下方增量层的打印流体饱和水平高于所述剂型的其他部分，以在完成的剂型中为上方和下方的增量表面提供增加的硬度，并且为其之间的增量层提供降低的硬度；e) 所述剂型的上方和下方增量层和中间增量层外围的打印流体饱和水平高于所述剂型的其他部分，以在完成的剂型中为其上方和下方增量表面以及中间增量层的外围提供增加的硬度，并且为其之间的增量层提供降低的硬度；f) 所述方法还包括加热所述剂型以除去和降低其中的打印流

体的量；和/或g)所述方法还包括通过混合其成分来制备松散粉末以形成随后进行筛分的混合物。

[0033] 本发明的一些实施方案包括这样的实施方案，其中用于制备增量的打印层的打印流体饱和水平为40％-120％。

[0034] 本发明提供一种治疗对LEV治疗上应答的疾病或病症的方法。所述方法包括在治疗持续的数天、数周或数月内向有此需要的个体每日给药一种、两种或三种本发明的剂型，从而减少或消除所述疾病或病症的一种或多种症状。在一些实施方案中，本文所述的3DP剂型包含约250-约1000mg的剂量，在治疗时间段内每天给药两次。本发明还提供一种治疗癫痫或对LEV治疗上应答的其他疾病、病症或疾病状况的方法，所述方法包括向有此需要的个体给药如本文所述的包含LEV的三维打印的口分散剂型。

[0035] 本发明还提供一种制备口分散剂型的方法。所述方法包括通过形成粉末的增量层和在每个增量层上沉积打印流体以将崩解剂、粘合剂、表面活性剂、抗氧化剂、助流剂和LEV结合入快速口分散的未被压制的多孔基质来形成如本文所述的未被压制的多孔基质。

[0036] 本发明包括本文公开的本发明的方面、实施方案和子实施方案的所有组合。

附图说明

[0037] 以下附图构成说明书的一部分并且描述本发明的示例性实施方案。本领域技术人员参考这些附图和说明书能够实施本发明而无需过度实验。

[0038] 图1示出由三维打印的基质制成的口分散剂型的剖面正视图，所述基质包含结合松散材料的顺序形成的增量层。

[0039] 图2示出由三维打印基质制成的口分散剂型的替代实施方案的剖面正视图。

[0040] 图3A-3E示出各种不同的打印模式，其可以用于将打印流体施用于粉末的增量层。

具体实施方式

[0041] 如本文所用并且除非另外指明，术语左乙拉西坦(LEV)指药物((S)-2-(2-氧代吡咯烷-1-基)丁酰胺；(-)-(S)-α-乙基-2-氧代-1-吡咯烷乙酰胺，描述于U.S.4,943,639)的未衍生形式或衍生形式。左乙拉西坦可从TEVA(Jerusalem,Israel)和Hetero Labs(Hyderabad,India)、Esteve(Tarragona,Spain)、Aurobindo(Hyderabad,India)、Matrix Labs(Karachi,Pakistan)、Srini(Hyderabad,India)获得。LEV可以晶体或无定形形式存在。可以使用晶体LEV的所有多晶型物及其混合物。

[0042] 即使当置于小体积的含水流体如水、唾液、果汁、奶、饮料、体液、苏打或其组合中时，本发明的剂型发生其固体基质的立即且非常快速的崩解/分散，并且所述基质中的LEV和赋形剂发生快速的分散。分散(与崩解互换使用)通常但不是必需与溶解重叠。基质包含三维形状，其在组合物与至少小体积的含水流体接触时于期望的时间段内分散。

[0043] 本发明提供一种适合于向个体给药的药物组合物，所述组合物包含快速分散、未被压制的固体基质中包含的LEV，所述基质具有固定的三维形状并且包含松散材料和粘合剂，所述松散材料包含特定形式的药学可接受的化合物，并且所述粘合剂包含药学可接受

的、基本上水溶性的物质，其具有粘附并与松散材料的颗粒结合在一起的能力，从而在未置于含水流体中时维持所述基质的三维形状，并且使得所述组合物表现出适合于存储和处理的硬度和脆性特征。在一些实施方案中，所述基质包含 LEV、粘合剂、崩解剂、甘油和表面活性剂。

[0044] 包含所述基质的三维打印 (3DP) 剂型根据实施例 1 制备。评价所得的 3DP 剂型 (实施例 3) 的硬度、分散时间和脆性以确定提供合适的 3DP 口分散剂型的含药物颗粒哪些具有非常快速的分散时间、适当的硬度和最小的脆性。

[0045] 已经确定，当置于最少量的水中时，打印流体、松散粉末和含药物颗粒中包含表面活性剂有助于 3DP 剂型的快速分散。表面活性剂用于增强颗粒的润湿。与不含表面活性剂的其他 3DP 剂型相比，表面活性剂仅需要以足以增强分散的量存在。然而，如果表面活性剂以过高的量存在，其会不利地影响剂型的口感、性能和 / 或物理性质。表面活性剂可以包含在松散粉末和 / 或打印流体中。在一些实施方案中，基于打印流体的重量，打印流体中存在的表面活性剂的量为约 0.1- 约 4 重量%、约 1- 约 3 重量%或约 1.5- 约 2.5 重量%。

[0046] 当置于小体积的含水流体如唾液、胃液和 / 或一口水中时，快速分散剂型可以在约 20 秒或更短、约 15 秒或更短、约 10 秒或更短、约 5 秒或更短、约 4 秒或更短或者约 3.5 秒或更短的时间内分散 (崩解)。在一些实施方案中，分散 (崩解) 时间在 20ml 或更少、15ml 或更少、10ml 或更少、5ml 或更少、3ml 或更少以及至少 1ml 的小体积的含水流体中测量。在一些实施方案中，崩解时间根据 USP<701> 确定。

[0047] 小体积的含水流体可以是一口，例如小于 50ml、小于 40ml、小于 30ml、小于 20ml、小于 10ml、小于 5ml、小于 2.5ml 或小于 1ml 的体积。小体积可以是至少 0.1ml、至少 0.25ml、至少 0.5ml、至少 0.75ml、至少 1ml、至少 1.5ml 或至少 2ml。涵盖这些体积的所有可能组合。小体积的合适范围包括 0.1-50ml、0.1-40ml、0.1-30ml、0.1-20ml、0.1-10ml、0.2-10ml、0.3-10ml、0.5-10ml、1-10ml、1-7.5ml、1-5ml、0.5-3ml 或者其他这样的范围。优选地，一口为约 2- 约 30ml、约 10- 约 15ml(1 汤匙) 或者约 13ml 水 (流体)。

[0048] 在一些实施方案中，如通过 120℃下的干燥失重 (LOD) 所确定的，所述剂型包含不多于 10 重量%、不多于 7.5 重量%、不多于 5 重量%、不多于 4 重量%、不多于 3 重量%、不多于 2.5 重量%、不多于 2 重量%或不多于 1.5 重量%的水分。在一些实施方案中，如通过 120℃下的干燥失重所确定的，所述剂型包含至少 0.1 重量%、至少 0.2 重量%、至少 0.5 重量%、至少 0.75 重量%、至少 1 重量%、至少 1.5 重量%、至少 2 重量%、至少 2.5 重量%、至少 3 重量%、至少 4 重量%或至少 5 重量%的水分。在一些实施方案中，所述剂型包含 0.1-10 重量%、0.2-7.5 重量%、0.5-5 重量%、0.5-4 重量%或 1-3 重量%的水分。这些不同限制的所有组合都在本发明的范围内。

[0049] 所述剂型是具有优异的整体硬度和脆性特征的快速分散剂型。基质的硬度可以在基质中是相同的 (均匀) 或者可以变化。在一些实施方案中，所述剂型 (或基质) 的外表面的硬度大于剂型 (或基质) 的内部的硬度，即剂型的外部比内部更硬。外部硬度可以是内部硬度的至少 1.05 倍、至少 1.1 倍、至少 1.2 倍、至少 1.3 倍、至少 1.4 倍、至少 1.5 倍、至少 1.75 倍、至少 2 倍、至少 2.5 倍、至少 3 倍、至少 5 倍、至少 7 倍或至少 10 倍。在一些实施方案中，上表面和下表面的硬度大于剂型内部部分 (一个或多个内部层)。实现基质的均匀硬度和变化硬度的方法在本文中讨论。在一些实施方案中，所述剂型的保质期为至少

6 个月或至少 1 年。

[0050] 在一些实施方案中，所述基质的整体硬度（如根据 USP<127> 的片剂破碎力测定所确定的）为 1kp- 约 20kp、约 1kp- 约 10kp、约 1kp- 约 7kp、约 3- 约 9kp、约 1- 约 3kp、约 4.5- 约 6kp、约 2.5- 约 6.5kp、约 3- 约 6kp 或约 1kp- 约 5kp。在一些实施方案中，整体硬度为至少 1kp、至少 2kp 或至少 3kp。在一些实施方案中，整体硬度不大于 10kp、不大于 8kp 或不大于 6kp。

[0051] 术语脆性指经受机械损伤时基质从其外边缘和表面丧失物质的趋势。脆性通过增加硬度而降低。在一些实施方案中，如通过 USP<1216> 所确定和下文进一步描述的，所述剂型的脆性小于约 25％，优选小于约 10％。

[0052] 在一些实施方案中，所述基质的孔隙率为剂型体积的约 10％ - 约 90％或约 30％ - 约 70％

[0053] 在一些实施方案中，所述基质的体密度（如通过测量和 / 或计算确定的）为 150(mg/mL)- 约 1300(mg/mL) 或者约 400(mg/mL)- 约 1000(mg/mL)。

[0054] 当置于含水流体中时，LEV 的溶解时间慢于所述剂型的基质的分散时间。本发明的一些实施方案包括这样的实施方案，其中当置于含水环境中时，所述剂型中存在的 LEV 的不少于 75 重量％（或者其中至少 75 重量％）在 20 分钟 (min) 或更短、10 分钟或更短、5 分钟或更短、4 分钟或更短、3 分钟或更短、2 分钟或更短或者 1 分钟或更短的时间内溶解。本发明的其他实施方案包括这样的实施方案，其中当置于含水环境或水中时，所述剂型中存在的 LEV 的不少于 95 重量％（或者其中至少 95 重量％）在 20 分钟或更短、10 分钟或更短、5 分钟或更短、4 分钟或更短、3 分钟或更短、2 分钟或更短或者 1 分钟或更短的时间内溶解。在一些实施方案中，以上溶解时间可以在特征在于 1.2 或 4.5 或 6.8 的 pH 含水环境中实现，并且可以在 50RPM 或 75RPM 或 100RPM 的 USP 桨装置中以及 900mL 或 950mL 或 1000mL 的体积下测试。

[0055] 本发明的快速分散剂型通过三维打印 (3DP) 方法来制备。用于物品的三维打印的合适设备组件可以商购或者已经在使用：Massachusetts Institute of Technology Three-Dimensional Printing Laboratory(Cambridge,MA)、Z Corporation's 3DP 和 HD3DP™系统 (Burlington,MA)、The Ex One Company,L.L.C.(Irwin,PA)、Soligen(Northridge,CA)、Specific Surface Corporation(Franklin,MA)、TDK Corporation(Chiba-ken,Japan)、Therics L.L.C.(Akron,OH, 现在是 Integra Lifesciences 的一部分)、Phoenix Analysis&Design Technologies(Tempe,AZ)、Stratasys,Inc.'s Dimension™系统 (Eden Prairie,MN)、Objet Geometries(Billerica,MA 或 Rehovot,Israel)、Xpress3D(Minneapolis,MN) 和 3D Systems' Invision™系统 (Valencia,CA)。其他合适的 3DP 系统公开于 U.S.No.20080281019、No.20080277823、No.20080275181、No.20080269940、No.20080269939、No.20080259434、No.20080241404、No.20080231645、No.20080229961、No.20080211132、No.20080192074、No.20080180509、No.20080138515、No.20080124464、No.20080121172、No.20080121130、No.20080118655、No.20080110395、No.20080105144、No.20080068416、No.20080062214、No.20080042321、No.20070289705、No.20070259010、No.20070252871、No.20070195150、No.20070188549、No.20070187508、No.20070182799、

No.20070182782、No.20060268057、No.20060268044、No.20060230970、No.20060141145、No.20060127153、No.20060111807、No.20060110443、No.20060099287、No.20060077241、No.20060035034、No.20060030964、No.20050247216、No.20050204939、No.20050179721、No.20050104241、No.20050069784、No.20050061241、No.20050059757、No.20040265413、No.20040262797、No.20040252174、No.20040243133、No.20040225398、No.20040183796、No.20040145781、No.20040145628、No.20040143359、No.20040141043、No.20040141030、No.20040141025、No.20040141024、No.20040118309、No.20040112523、No.20040012112、No.20040005360、No.20040005182、No.20040004653、No.20040004303、No.20040003741、No.20040003738、No.20030198677、No.20030143268、No.20020125592、No.20020114652、No.20020079601、No.20020064745、No.20020033548、No.20020015728、No.20010028471 和 No.20010017085；美国专利 No.5,490,962、No.5,204,055、No.5,121,329、No.5,127,037、No.5,252,264、No.5,340,656、No.5,387,380、No.5,490,882、No.5,518,680、No.5,717,599、No.5,851,465、No.5,869,170、No.5,879,489、No.5,934,343、No.5,940,674、No.6,007,318、No.6,146,567、No.6,165,406、No.6,193,923、No.6,200,508、No.6,213,168、No.6,336,480、No.6,363,606、No.6,375,874、No.6,508,971、No.6,530,958、No.6,547,994、No.6,596,224、No.6,772,026、No.6,850,334、No.6,905,645、No.6,945,638、No.6,989,115、No.7,220,380、No.7,291,002No.7,365,129、No.7,435,368、No.7,455,804、No.7,828,022、No.8,017,055；PCT 国际公开 No.WO 00/26026、No.WO 98/043762、No.WO 95/034468、No.WO 95/011007；以及欧洲专利 No.1,631,440，其由于结构而使用圆柱（放射或极性）基于坐标的系统。每个这些参考文献的整体公开援引加入本文。

[0056] 本文所述的 3DP 方法要求粉末分层系统，其形成粉末的层；以及打印系统，其根据预定的模式将打印流体施用于所述粉末的层，从而形成增量打印层。打印流体用于形成粉末的结合颗粒，即通过一种或多种药学赋形剂和 / 或一种或多种活性成分互相粘附的颗粒。在另一增量打印层的顶上形成增量打印层以垂直地构建本发明的剂型，从而形成包含多个增量打印层的剂型。重复铺展粉末和沉积小滴的过程直至剂型的期望数目的层完成。层由于打印流体从一层渗至相邻的另一层而互相粘附，从而一种或多种赋形剂和 / 或一种或多种活性成分粘附至相邻的两层。完成初始的三维结构后，通过干燥从所述剂型除去残留的打印流体或减少所述剂型中残留的打印流体。干燥过程期间溶剂的蒸发留下具有三维结构的基质，其包含由固化的粘合剂和 / 或其他组分结合的松散材料的颗粒，所述其他组分包括一种或多种活性成分和 / 或任何任选存在的药学可接受的赋形剂。

[0057] 三维打印过程通常在环境温度下进行。所述过程可以使用各种打印流体，包括生物相容的有机和含水溶剂。所述过程是加成的，由此逐层 (layer by layer) 加入微观特征，使得能在亚毫米尺度上精确地构建大范围的可能结构。利用三维打印来同时控制微观特征和宏观形状，获得本发明的独特药物递送系统。

[0058] 特别合适用于本发明的剂型的三维打印的打印组件描述于 2012 年 9 月 5 日提交的美国申请 No.61/696,839，其公开整体援引加入本文。所述组件包括构建模块，其具有分布于所述构建模块的空腔中的增量高度的可调节平台；粉末分层系统；打印系统；打印流体除去系统；以及剂型处理系统。

[0059] 通常，在用于制备快速分散剂型的基质的三维打印方法中使用至少两种组分。第一组分是包含在增量粉末层中的松散粉末材料。第二组分是打印流体（在一些情况下，流体还可以包含粘合剂），其通过打印头分配至粉末层上。在一些实施方案中，松散粉末包含一种或多种药学可接受的赋形剂、LEV、崩解剂、粘合剂和表面活性剂。

[0060] 所述基质的至少一种组分必须充当“粘合物质 (binding agent)”，其将完成的三维基质中的松散粉末的颗粒结合在一起。粘合物质产生松散粉末的颗粒之间的粘附。就是这种粘附使得剂型维持固定的形状（几何）并维持其适合允许处理和存储的硬度和脆性的特征。颗粒结合的强度和程度取决于粉末层中或溶于溶剂中的粘合物质的比例，并且是沉积的流体的量的函数。术语粘附表示松散材料的颗粒互相之间的键合或结合，或者与存在的其他材料如粘合剂或活性成分的颗粒的键合或结合。有若干种使得粘合物质包含于基质中的方式。本发明涵盖一种或两种或更多种这些不同方式的组合。

[0061] 在制备基质的方法的一些实施方案中，粘合物质存在于松散粉末、打印流体或者这两者中。打印流体中的粘合物质可以与松散粉末中的粘合物质相同或不同。

[0062] 粘合物质可以是粘合剂、LEV、另一药物赋形剂或其组合。在一些实施方案中，粘合物质为 a) 至少 LEV ；b) 至少粘合剂 ；或 c) 粘合剂和 LEV。在一些实施方案中，基质中存在两种或更多种粘合物质。在打印流体中包含“粘合剂”作为粘合物质会导致薄片 (wafer) 与相同但在粘合溶液中不含粘合剂的薄片的内部微观结构相比不同的内部微观结构，特别是孔径。在打印时，随着溶剂蒸发，粘合剂作为固体残留物保留，其占据诸如崩解剂或药物颗粒的粉末颗粒之间的空隙空间。所得的结构与在打印流体中不含粘合剂而制备的片剂相比具有更高的密度。

[0063] 本发明提供一种用于制备快速分散固体剂型的方法，所述剂型包含三维打印的固体多孔基质，所述基质包含松散粉末、粘合剂和 LEV，所述方法包括 ：(a) 提供一种或多种崩解剂、一种或多种粘合剂、一种或多种助流剂和 LEV 以及任何任选存在的药学可接受的赋形剂的粉状混合物 ；(b) 形成所述粉状混合物的增量层 ；(c) 根据预定的模式，向所述增量层施用打印流体的小滴以形成打印的增量层 ；(d) 重复 (b) 和 (c) 预定的次数，从而提供三维打印的湿润基质 ；以及 (e) 从所述湿润基质除去打印流体，从而提供三维打印的固体多孔基质，其具有本文所指定范围内的组成、水分含量、孔隙率、整体体密度、硬度、基质分散时间、体外药物溶解时间、体外分散行为、体内药物动力学行为、结构、增量层厚度、药物粒径、崩解剂粒径、药物含量和 / 或脆性。

[0064] 若需要，还可以将本发明的剂型进一步成形以促进其在个体口腔中的放置。一个这样的实施方案可以是薄片样的形状。

[0065] 图 1 示出由三维打印的基质制成的口分散剂型 (1) 的剖面正视图，所述基质包含结合的松散材料顺序形成的增量层 (2-3)。外表面 (3) 包括中间部分 (2)。外表面的硬度大于内部部分。这种剂型由三维打印的多个增量层制成。限定下表面的底部增量层和限定上表面的上部增量层以及环绕表面（中间部分的左和右）的硬度大于内部部分。通过利用更高的饱和水平、更高含量的粘合剂或者本文所述的其他方式来实现增加的硬度。中间部分的增量层外围增加的硬度通过增加外围的粘合剂的饱和水平和 / 或含量来实现，但是并不是各自的增量层的中间（非外围部分）。

[0066] 图 2 示出由三维打印基质制成的口分散剂型 (5) 的替代实施方案的剖面正视图。

限定下表面的底部增量层 (8) 和限定上表面的上部增量层 (7) 的硬度高于包含多个增量层的内部部分 (6)。剂型 (1) 和 (5) 的不同主要在于用于打印中间增量层的方法,(6) 的层不具有硬度增加的外围。

[0067] 图 3A-3E 示出可以用于制备本发明的 3DP 口分散基质的打印的增量层的三种不同打印模式的俯视图。虽然每个打印模式表示为圆形的,但是基本上可以使用任何几何形式,例如圆形、椭圆形、方形、矩形、拉长圆形 (oblong circle) 等。图 3A 示出第一实心 (solid) 打印模式,其中在整个打印区域使用基本上相同的完全、重或较高的饱和水平。图 3B 示出第二实心打印模式,其中在整个打印区域使用基本上相同的中等、低、轻或较低的饱和水平。这个第二实心模式称为灰度模式,因为其具有降低的饱和水平。当实心打印初始定义为 90-120％的饱和时,灰度打印定义为小于 90％的饱和,或者约 20-<90％或约 20- 约 85％或约 20- 约 80％、约 20％、约 35％、约 30％、约 35％、约 40％、约 45％、约 50％、约 55％、约 60％、约 65％、约 70％、约 75％、约 80％、约 85％的饱和,或者这些范围内的任何分数或整数增量。

[0068] 图 3C 示出环形 (中空) 打印模式,其中将打印流体施用于打印区域的外围,但不施用至打印区域的中心。图 3D 示出组合环形和灰度打印模式,其中将打印流体以较高的饱和水平施用于打印区域的外围,并且以灰度 (降低) 的饱和水平施用于打印区域的中心。图 3C 和 3D 中打印模式中外围环的径向厚度 (从圆心测量) 可以按需要变化。取决于剂型的直径,环厚度可以为约 0.05-10mm。其可以为约 0.1- 约 7mm、约 0.5- 约 7mm、约 1- 约 5mm 或约 1.5- 约 3.5mm。

[0069] 图 3E 示出标记打印模式,其中在整个打印区域使用基本上相同的饱和水平,除了标记区域,其中未施用打印流体,从而在最终剂型的表面上形成凹陷的标记。

[0070] 在一些实施方案中,所述剂型包含 (基本上由…组成或由…组成) 以下类型的打印增量层 :a) 第一实心打印模式的多层以及组合环形和灰度打印模式的多层 ;b) 第一实心打印模式的多层、环形打印模式的多层以及组合环形和灰度打印模式的多层 ;c) 第一实心打印模式的多层、环形打印模式的多层、组合环形和灰度打印模式的多层以及标记打印模式的多层 ;d) 第一打印模式的多层、环形打印模式的多层、组合环形和灰度打印模式的多层、第一实心打印模式的多层以及标记打印模式的多层 ;e) 第一实心打印模式的多层、灰度打印模式的多层以及第一实心打印模式的多层 ;f) 灰度打印模式的多层 ;g) 组合环形和灰度打印模式的多层 ;h) 第一实心打印模式的多层 ;i) 第一实心打印模式的多层以及环形打印模式的多层 ;或者 j) 第一实心打印模式的多层、组合环形和灰度打印模式的多层以及标记打印模式的多层。

[0071] 在一些实施方案中,所述剂型包含 (基本上由…组成或由…组成) 分类入剂型各自部分的以下类型的增量层 :a) 第一末端,其包含第一实心打印模式的多层 ;中间部分,其包含环形打印模式的多层以及组合环形和灰度打印模式的多层 ;以及第二末端,其包含标记打印模式的多层 ;b) 第一末端,其包含第一实心打印模式的多层 ;中间部分,其包含组合环形和灰度打印模式的多层 ;以及第二末端,其包含第一实心打印模式的多层和 / 或标记打印模式的多层 ;c) 第一末端,其包含第一实心打印模式的多层 ;中间部分,其包含环形打印模式的多层、组合环形和灰度打印模式的多层 ;以及第二末端,其包含第一实心打印模式的多层和 / 或标记打印模式的多层 ;或者 d) 第一末端,其包含第一实心打印模式的多层 ;

中间部分，其包含层的交替组，其中一组包含环形打印模式的多层，并且另一组包含组合环形和灰度打印模式的多层；以及第二末端，其包含第一实心打印模式的多层和/或标记打印模式的多层。

[0072] 所述剂型的物理性质可以通过改变以下来控制：增量粉末层厚度、粉末组成、打印流体组成、层上的打印流体饱和水平（打印密度）以及剂型中包含的赋形剂的性质和量，例如崩解剂、粘合剂、甜味剂、表面活性剂的性质和量。这些变量表现出对剂型硬度、体密度、崩解时间、溶解时间、生物利用度、水分含量、口感和脆性的不同影响水平。可以确定，最终(result)有效的变量至少包括药物的量、崩解剂的量、粘合剂的量、一些组分的性质以及含药物颗粒的组成。

[0073] 三维打印可以在三个不同的、通常是正交的方向的每一个上具有空间描述符。在三维打印中，流体可以以滴或类似滴的流体单元沉积。滴可以连续沉积，其形成对应于打印头的运动的线。这些滴之间的间隔为滴间(drop-to-drop)间隔。完成一排之后，另一排可以邻近较早沉积的排沉积，并且通过排间(line-to-line)间隔的距离与较早沉积的排分隔。完成在粉末的层上打印之后，可以沉积另一粉末层，并且每个粉末层具有层厚度。粉末层厚度是第三描述符。

[0074] 在一些情况下，小滴的间隔可以描述为打印系统的分辨率，通常表示为点每英寸(dpi)，这是小滴间隔的倒数。例如，300和600dpi的分辨率分别对应于约84.7微米和约42.3微米的小滴间隔。滴间间隔（一排内）或排间隔（一排与后一排的小滴的间隔）或者任何其他的小滴间隔可以描述为分辨率，表示为dpi。在一些情况下，用于制备剂型的叠层(layer-by-layer)指令可以由一系列的像素图像组成，该图像的特征在于两个正交线性方向的每一个的分辨率，其表示为点每英寸。在一些情况下，这些像素图像为1-比特(bit)单色图像，又称为二元或bi-水平图像，其中每个像素包含1个比特的信息(0或1)，其可以在荧幕上表示为黑或白。

[0075] 在一些情况下，剂型中局部区域中结合的相对量通过剂型设计中的“灰度”(即，使用灰度打印模式）来实现。在用于机器指令的1-比特单色图像的情况下，灰度通过改变剂型的所选区域，或者剂型的所选层，或者整个剂型中“黑”像素相对于“白”像素的数目来实现。通过利用全黑像素，任何其他区域可以是“实心”的。在一些实施方案中，剂型设计包括“实心”外部和“灰度”内部。在一些实施方案中，灰度可以通过等同地置于白像素中的黑像素来实现，以获得灰度区域中黑比白像素的整体比率。在其他实施方案中，灰度可以通过随机置于白像素中的黑像素来实现，以获得灰度区域中黑比白像素的整体比例。在其他的实施方案中，灰度可以白像素中的黑像素的所选模式（例如，平行线、散列模式、点模式）来实现，以获得灰度区域中黑比白像素的整体比例。

[0076] 在三维打印中，体素或单位体积可以通过以下来限定：快轴向运动方向中的一个滴间间隔，慢轴向运动方向中的一个排间间隔，以及垂直方向中的一个层厚度。这些单位体积中的一些被粉末颗粒占据，并且剩余的单位体积是空的空间，其整体上具有的体积为空隙体积。

[0077] 饱和水平（打印密度）描述这个单位体积中多少空隙体积被液体占据，所述液体分配于滴或流体单位中，其专用于该特定的体素。饱和水平是体素中分配的流体体积与空的空间体积的比率。通常，在三维打印中，饱和水平可以加以选择，以略微小于或大约等

于 1.0，其又表示为 100％。过低的饱和水平会趋向于导致不好的结构完整性。过高的饱和水平会趋向于导致液体从沉积该液体的地方过量渗出。在本发明的剂型中，在穿过剂型的聚集体中，或者在剂型的所选区域中，向粉末层施用打印流体的步骤中的饱和水平为约 10％－约 110％、约 15％－约 80％、约 20％－约 50％或约 15％－约 35％。

[0078] 合适的打印装置包括具有连续喷射打印头的装置，或者具有按需喷射 (drop-on-demand) 打印头的装置。连续喷射打印头提供小滴的连续喷射（喷施），同时将打印流体沉积在粉末层上。按需喷射打印头仅将打印流体的小滴沉积在粉末层上，如果其接收到这样进行的指令（命令、操作命令）。打印头从左至右以预定的速率如扫描速率扫描（将流体施用于）粉末层的表面，以形成小滴的排。当比较恒定的体积 / 单位时间的打印流体沉积时，高扫描速率会导致较低的饱和水平，而低扫描速率会导致较高的饱和水平。当考虑粘合剂存在于粘合溶液中的情况时，打印速度从 1.0m/s 增加至 2.0m/s 将片剂中沉积的粘合剂溶液的总体积减少一半。随着打印速度增加，体密度（从片剂的重量和大小理论计算）降低。还观察到片剂的大小和重量的同时降低。这种降低归因于沉积在粉末上的粘合剂小滴的总体积的降低引起粉末中粘合剂溶液铺展程度的降低。增加打印速度还降低闪断时间 (flash time) 和硬度并增加片剂的脆性。由于片剂中粘合剂的比例随打印速度增加而降低，而导致了这样的结果。如通过 30psi 下汞穿透的片剂的百分比体积（％侵入）增加所示例的，打印速度的增加还增加片剂中的空隙体积。

[0079] 当使用连续喷射打印头时，打印头扫描速率为约 0.5-3.0m/ 秒，并且最优选为约 1.75m/ 秒。当使用按需喷射打印头时，打印头扫描速率为 0.1-1m/ 秒，最优选为约 0.15- 约 0.5m/ 秒。

[0080] 单个小滴的体积可以按需要变化，例如通过选择不同的三维打印机，或者相同机器上的不同打印头组件，或者相同打印头和相同机器上的不同参数。当比较恒定扫描速率的打印流体沉积时，增加小滴体积会增加饱和水平，而降低小滴体积则会降低饱和水平。当使用连续喷射打印头时，优选地，通过打印头递送的流体小滴的大小的直径为约 15μm- 约 150μm。当使用按需喷射打印头时，优选地，通过打印头递送的流体小滴的大小的直径为约 50μm- 约 500μm。

[0081] 通过打印头递送的流体的流速可以按需要变化。当比较恒定扫描速率的打印流体沉积时，增加流速会增加饱和水平，而降低流速会降低饱和水平。如本文所讨论的，打印头沉积打印流体的小滴以形成粉末层中其平行的排。当使用连续喷射打印头时，排间隔为约 20- 约 1000μm、约 50- 约 500μm 或者优选约 100-200μm。当使用按需喷射打印头时，排间隔为约 20- 约 300μm、约 40- 约 100μm 或约 55-75μm。

[0082] 粉末分层系统和高度可调节的平台合作以在构建模块中形成粉末的薄增量层。剂型的总厚度（高度）是增量层的数目和厚度的函数。打印的增量层的数目通常为 5-50。在一些实施方案中，打印的增量层的数目为 10-50、15-45 或 20-40。基质通常包含（基本上由…组成或由…组成）20-50、20-40、25-40、30-40 或 30-35 个打印的增量层。剂型的“末端”部分通常包含 1-10、1-7、2-7、2-5 或 4-6 个打印的增量层。具有标记的末端部分通常包含 2-10、2-7、2-5 或 4-7 个打印的增量层。打印的增量层的平衡会包括剂型的相对于垂直高度的中间部分。中间部分通常包括 5-40、10-30、10-20 或 20-30 个打印的增量层。

[0083] 通过本文所述的 3DP 方法制备的薄片（基质，剂型）的大小随提供表现出期望性

质的剂型所需的LEV和赋形剂的含量而变化。如果基质包含较高剂量的LEV，则与具有相同百分比但较低剂量的LEV的其他3DP剂型相比，需要较大的薄片。如果使用较高百分比的LEV，则可以相应地降低剂型重量，反之亦然。本发明的薄片形剂型的直径为13-14mm（最低剂量）至约20-25mm（最高剂量），并且高度为约5-6mm（最低剂量）至约8-10mm（最高剂量）。

[0084] 增量层具有预定的高度（垂直厚度），其通常为0.005-0.015英寸、0.008-0.012英寸、0.009-0.011英寸、约0.01英寸、100-300μm、100-500μm、约200μm或约250μm。如果使用较厚的增量层，则必须在该层上沉积增加量的打印流体以确保所述层的平面和层与层的平面中的充分结合。相反地，对于较薄的增量层，必须沉积较少量打印流体以获得相同程度的结合。对于给定量的每层沉积的打印流体，使用较大的层厚度会降低（恶化）剂型的可操作性并降低（改进）分散时间。如果对于给定量的流体使用过厚的层，则可能形成片层缺陷，其使得剂型容易沿层的平面破裂（剥离），或者剂型自身可能完全不具有充分的操作强度。在一些实施方案中，增量层的厚度为100-400微米、150-300微米或200-250微米。在一优选实施方案中，层厚度为200微米。在另一优选实施方案中，层厚度为250微米。

[0085] 当包含于本发明的3DP剂型中时，LEV对氧化降解的稳定性通过将完成的剂型暴露于热来确定。如下文所详细描述的，通过HPLC/MS来观察和监测降解物的形成。每当不存在抗氧化剂且制剂包含氧化赋形剂如含过氧化物杂质的聚维酮或者含过氧化物杂质的二氧化硅时，能够确定LEV发生氧化降解以形成氧代左乙拉西坦。然而，聚维酮和二氧化硅是重要的功能成分。因此，本发明提供一种稳定的快速分散剂型，其包含LEV、氧化赋形剂、抗氧化剂、粘合剂和崩解剂，其中在21℃和75％ RH下存储6个月后，基质包含0.1重量％或更少的LEV的氧化降解物。

[0086] 本发明人确定，3DP剂型中常用的一些赋形剂可以包含氧化化合物（氧化剂），其可以得自制备过程或者赋形剂固有的不稳定性。认为一些氧化剂是过氧化物。可以确定，在存储期间赋形剂暴露于含氧气氛后，聚维酮中氧化剂的水平增加。无论氧化剂的来源，令人惊讶的是，如上文所引的现有技术中指出的，当包含于3DP剂型中而不是包含于其他剂型中时，左乙拉西坦对氧化剂是如此敏感。

[0087] 我们根据实施例6进行了稳定性研究。本发明人成功地鉴定和选择了一组优选的抗氧化剂，其使得左乙拉西坦对氧化稳定，所述氧化发生在升高温度下的存储和/或在制备本发明的剂型的3DP方法的干燥步骤期间暴露于升高温度下。合适的抗氧化剂包括亚硫酸钠、亚硫酸氢钠、维生素E、甲硫氨酸、BHA和BHT。优选的抗氧化剂包括亚硫酸氢钠、亚硫酸钠、BHA和BHT。

[0088] 一种或多种药学可接受的赋形剂可以包含于松散粉末材料和/或打印流体中。按需要，在每次出现时，每种赋形剂可以独立地选自水溶性、含水流体可溶性、部分水溶性、部分含水流体可溶性、水不溶性或含水流体不溶性赋形剂以提供打印基质中所需的颗粒与颗粒结合。

[0089] 可以使用大部分药学可接受的赋形剂，小分子和聚合物，其使得药学活性成分松散地包含于多孔结构（结合颗粒的基质）中，其在合适的含水流体如唾液的存在下发生快速分散。适合用于本发明的三维打印方法的这些赋形剂中的一些列于Handbook of

Pharmaceutical Excipients(Eds. A. Wade and P. J. Weller, Second edition, American Pharmaceutical Association, The Pharmaceutical Press, London, 1994)。

[0090] 合适类型的赋形剂包括粘合剂、崩解剂、分散剂、甜味剂、助流剂、调味剂、表面活性剂、湿润剂、防腐剂、抗氧化剂和稀释剂。虽然可以使用常规药学赋形剂，但是它们可能无法以传统药学加工相同的方式精确地发挥功能。

[0091] 一种或多种粘合剂可以包含于打印基质中。粘合剂可以包含于粉末材料或通过打印头分配的打印流体中。在每次出现时，粘合剂独立地加以选择。颗粒对粘合剂的粘附和/或由粘合剂粘附发生在当粘合剂通过打印头与打印流体接触时，或者当其存在于打印流体中时（即，可溶）。粘合剂优选是水溶性、含水流体可溶性、部分水溶性或部分含水流体可溶性。在一些实施方案中，打印流体包含 1-20 重量%、5-15 重量%或 8-12 重量%的粘合剂。在一些实施方案中，松散粉末包含 >0-10 重量%、5-15 重量%、0-15 重量%、8-14 重量%或 9-11 重量%的粘合剂。在一些实施方案中，打印基质包含 1-20 重量%、5-14 重量%或 8-12 重量%的粘合剂。在一些实施方案中，打印流体中不存在粘合剂或者松散材料中不存在粘合剂。

[0092] 合适的粘合剂包括水溶性合成聚合物、聚乙烯吡咯烷酮（聚维酮）、山梨醇、甘露醇、木糖醇、乳糖醇、赤藓醇、预胶凝淀粉、改性淀粉、羟丙基甲基纤维素和其他粘合剂。优选的粘合剂有聚乙烯吡咯烷酮如 PVP K30、改性淀粉（如辛烯基琥珀酸淀粉钠）、甘露醇或其组合。可以使用 K 值不同于 30 的 PVP，包括但不限于 PVP K25 和 PVP K90。

[0093] 以下材料视为粘合剂，虽然它们表现出低强度结合：喷雾干燥乳糖、果糖、蔗糖、葡萄糖、山梨醇、甘露醇或木糖醇。

[0094] 一种或多种崩解剂可以包含于打印基质中。崩解剂可以存在于松散粉末中。在每次出现时，崩解剂独立地加以选择。在一些实施方案中，松散粉末包含 5-30 重量%、10-25 重量%、15-25 重量%、18-24 重量%、18-23.7 重量%、1-30 重量%、10-25 重量%、20-25 重量%的崩解剂。

[0095] 合适的崩解剂包括微晶纤维素 (MCC)、交聚维酮（交联聚乙烯吡咯烷酮）、交联羧甲纤维素、羧甲基淀粉钠或其组合。优选的崩解剂有微晶纤维素。合适等级的 AVICEL® 总结于下表。所述剂型可以包含一种指定等级或者指定等级的组合。涵盖包含单个等级或等级的组合的所有这些实施方案。

[0096]

产品等级	标称粒径，μm	水分，%	松散体密度，g/cc
Avicel DG	45	NMT 5.0	0.25-0.40
Avicel PH-101	50	3.0-5.0	0.26-0.31
Avicel PH-102	100	3.0-5.0	0.28-0.33
Avicel HFE*-102	100	NMT 5.0	0.28-0.33
Avicel PH-102 SCG**	150	3.0-5.0	0.28-0.34
Avicel PH-105	20	NMT 5.0	0.20-0.30
Avicel PH-102 SCG	150	3.0-5.0	0.28-0.34
Avicel PH-200	180	2.0-5.0	0.29-0.36
Avicel PH-301	50	3.0-5.0	0.34-0.45
Avicel PH-302	100	3.0-5.0	0.35-0.46
Avicel PH-103	50	NMT 3	0.26-0.31
Avicel PH-113	50	NMT 2	0.27-0.34
Avicel PH-112	100	NMT 1.5	0.28-0.34
Avicel PH-200 LM	180	NMT 1.5	0.30-0.38
Avicel CE-15	75	NMT 8	N/A

[0097] NMT 表示“不多于”。

[0098] 粘合剂和崩解剂是用于控制基质的硬度、脆性和分散时间的关键成分。粘合剂的量越大，硬度越高，脆性越低，并且分散时间越慢。在另一方面，增加崩解剂的量提供较低的硬度、增加的脆性和较快的分散时间。因此，本发明的基质包含平衡量的粘合剂和崩解剂。

[0099] 一种或多种甜味剂可以包含于打印基质中。甜味剂可以存在于松散粉末和/或施用于松散粉末的打印流体中。当至少一种甜味剂存在于至少打印流体中时，观察到更好的掩味。在每次出现时，甜味剂独立地加以选择。打印流体和松散粉末可以具有至少一种共有的甜味剂，例如打印流体和松散粉末各自包含相同的甜味剂，并且松散粉末包含额外的甜味剂。在一些实施方案中，松散粉末包含 >0-5 重量%或 >0-2 重量%或 >0-1.5 重量%的甜味剂。在一些实施方案中，打印流体包含 >0-5 重量%或 0.5-4 重量%或 1-3 重量%的甜味剂。

[0100] 合适的甜味剂选自甘草酸衍生物如甘草甜 (magnasweet)(甘草酸单铵)、三氯蔗糖、阿司帕坦、乙酰舒泛钾、纽甜 (neotame) 及其组合。打印流体中优选的甜味剂有三氯蔗糖。甜味剂存在于至少打印流体中，并且也可以存在于松散粉末中。

[0101] 一种或多种调味剂可以包含于基质中。调味剂可以存在于松散粉末和/或打印流体中。在每次出现时，调味剂独立地加以选择。调味剂优选为水溶性、含水流体可溶性、部分水溶性或部分含水流体可溶性的。在一些实施方案中，打印流体包含0.01-5重量%、0.1-1重量%或0.2-0.5重量%的调味剂。在一些实施方案中，调味剂可以提供于粉状载体上。合适的载体可以选自淀粉、纤维素以及可以吸附、附着、封装或以其他方式装载调味剂的其他赋形剂。在一些实施方案中，松散粉末包含0.1-10重量%或1-9重量%或2-8重量%的装载调味剂的载体。在一些实施方案中，打印基质(printed matrix)包含0.1-10重量%或1-9重量%或2-8重量%的装载调味剂的载体。在一些实施方案中，打印流体不含调味剂或者松散材料不含调味剂。

[0102] 合适的调味剂包括留兰香、胡椒薄荷、薄荷、香草、橙子、柠檬、柑橘、酸橙、葡萄、樱桃、草莓、巧克力、咖啡或其组合。

[0103] 一种或多种表面活性剂可以包含于打印流体和/或松散粉末中。在每次出现时，表面活性剂独立地加以选择。在一些实施方案中，打印流体包含0.1-4重量%、1-3重量%或1.5-2.5重量%的表面活性剂。

[0104] 合适的表面活性剂包括聚山梨酯(用脂肪酸酯化的PEG-化脱水山梨醇(山梨醇的衍生物))、泊洛沙姆或其组合。合适的聚山梨酯包括聚山梨酯20(聚氧乙烯(20)脱水山梨醇单月桂酸酯)、聚山梨酯40(聚氧乙烯(20)脱水山梨醇单棕榈酸酯)、聚山梨酯60(聚氧乙烯(20)脱水山梨醇单硬脂酸酯)、聚山梨酯80(聚氧乙烯(20)脱水山梨醇单油酸酯)、十二烷基硫酸钠、泊洛沙姆(包括具有两条(聚(氧化乙烯)侧链的中心(聚(氧化乙烯)，如LUTROL)、低分子量聚乙二醇(如PEG 400)。合适的泊洛沙姆可以包括泊洛沙姆124、188、237、338或407。

[0105] 虽然所述剂型可以不含防腐剂，但是一种或多种防腐剂可以任选地包含在打印流体或粉末混合物(blend)中。合适的防腐剂包括抗真菌或抗微生物防腐剂，如对羟基苯甲酸甲酯(methylparaben)和对羟基苯甲酸丙酯(proprylparaben)。在一些实施方案中，打印流体包含0.001-0.2%的防腐剂。

[0106] 一种或多种助流剂可以包含于松散粉末中。在一些实施方案中，松散粉末包含0.1-2.0重量%、0.25-1.5重量%或0.5-1.0重量%的助流剂。合适的助流剂包括气相二氧化硅(胶体二氧化硅)。

[0107] 基质还可以包含通过松散粉末或打印流体引入其中的甘油(丙三醇)。甘油可以表现出湿润剂、甜味剂、防腐剂、润滑剂、皂化剂或溶剂的特征。本发明人发现，当包含于三维打印的剂型中时，甘油的行为与其他赋形剂出人意料地相反。如上文所述，增加所公开的其他赋形剂的量通常导致增加的硬度，并且伴有增加的崩解时间；然而，增加甘油的量导致增加的硬度，但是出人意料地导致减少的崩解时间。甘油这种方式的行为能力是特别有有利的，并且对于掺入三维打印的口分散剂型中的任何其他材料都没有观察到。因此，出人意料的是，可以实现口分散基质的制备，所述基质在小体积的水中于10秒或更短或者5秒或更短的时间内分散。

[0108] 在一些实施方案中，甘油包含于打印流体中。因此，本发明提供一种用于三维打印的打印流体，其中所述打印流体包含甘油、水和至少一种有机溶剂。本发明还提供一种三维打印方法，所述方法包括：a)将包含甘油、水和至少一种有机溶剂的打印流体沉积于至少

一个粉末的层上；和 b) 降低所述至少一个层中的水和溶剂的含量，从而形成三维打印的多孔基质。本发明还提供一种三维打印系统，其包括：a) 层形成系统，其形成粉末的层；和 b) 打印流体沉积系统，其将打印流体沉积于粉末的层上，其中所述打印流体包含甘油、水和至少一种有机溶剂。

[0109] 在一些实施方案中，打印流体包含 1-10 重量％或 2-8 重量％或 3-5 重量％的甘油。在一些实施方案中，基质包含 0.05-5 重量％、0.25-2.0 重量％、0.5-1.5 重量％或 0.5-1.0 重量％的甘油。

[0110] 在一些实施方案中，本发明的方法使用的打印流体包含松散粉末和 / 或打印流体自身中的至少一种材料的至少一种药学可接受的溶剂或者药学可接受的溶剂的组合。打印流体可以包含 a) 松散粉末中的材料的溶剂；b) 打印流体中的材料的溶剂；或 c) 它们的组合。

[0111] 本发明的方法的实施方案包括这样的实施方案，其中打印流体包含以下的溶剂：a)LEV；b) 松散粉末中的粘合剂；c) 打印流体中的粘合剂；d)LEV 和粘合剂；或者 e) 它们的组合。

[0112] 打印流体可以包含 55-95 重量％、60-85 重量％或 65-75 重量％的水或含水缓冲液。

[0113] 打印流体可以包含 1-25 重量％、5-20 重量％或 10-15 重量％的至少一种有机溶剂。合适的有机溶剂有醇。合适的醇包括乙醇、甲醇、丙醇、异丙醇或其组合。在一些实施方案中，醇为乙醇。在一些实施方案中，溶剂为异丙醇。

[0114] 应当理解，药学领域中所用的化合物通常用于各种功能或目的。因此，如果本文所指的化合物在本文中仅提及一次或者用于限定多于一个术语，则其目的或功能不应当理解为仅限于所指的目的或功能。

[0115] 本文所用的短语“药学可接受”表示这样的化合物、材料、组合物和 / 或剂型，其在合理的医疗判断范围内，适合用于与人和动物的组织接触，并且没有过度的毒性、刺激、过敏反应或者任何其他问题或并发症，具有合理的益处 / 风险比。

[0116] 本文所用的“衍生物”是：a) 化学物质，其结构上与第一化学物质相关并且理论上从其衍生；b) 化合物，其从类似的第一化合物形成，或者化合物，其可以设想为来自另外的第一化合物，如果第一化合物中的一个原子由另一原子或原子的集合代替；c) 化合物，其衍生或获得自母体化合物，并且包含该母体化合物的重要元素；或者 d) 化合物，其可以从具有类似结构的第一化合物在一个或多个步骤中制备。

[0117] 本发明还提供一种向有此需要的个体给药 LEV 的方法。所述方法包括：(a) 提供本文所述的快速分散、未被压制的基质剂型，和 (b) 将所述剂型插入有此需要的个体的含水分的体腔如口中，所述水分能够在约 1- 约 90 秒的时间段内溶解粘合剂并分散所述剂型，从而在所述体腔中分散所述剂型。在一些实施方案中，所述方还法包括以下步骤：在将剂型置于口中后，向个体给药所述剂型与一口（小体积）流体。

[0118] 进行研究以确定口服给药本发明的 3DP 剂型后，小口体积是否会影响 LEV 的药物动力学参数。使个体在服用 3DP 剂型时啜饮 30ml 或更少的含水流体。没有观察到啜饮体积与药物动力学参数之间的相关性。啜饮体积为 2-30ml，并且平均为约 13ml。

[0119] 本发明还提供一种治疗对 LEV 治疗上应答的疾病、病症或疾病状况的方法，所述

方法包括 :a) 向有此需要的个体给药本文所述的三维打印的口分散基质或者通过本文所述的方法制备的三维打印的口分散基质。所述基质包含 LEV、松散粉末、崩解剂和粘合剂，并且所述基质可分散于小体积流体中。FDA 批准的含 LEV 的产品如 KEPPRA® 的包装插页中详述的或本文所述的剂量和给药方案可以用于给药本发明的剂型。

[0120] 根据实施例 7 进行研究以确定在本发明的口分散 3DP 剂型口服给药时的左乙拉西坦的生物吸收。据发现，在禁食条件下，本发明的 3DP 产品对于 LEV 的生物利用度而言与 KEPPRA® 参考产品是等同的。而且，3DP 产品仅对 Cmax 和 Tmax 表现出食物效应，但是对整体全身暴露则没有，即对 $AUC_{0\ t}$ 或 AUC_{inf} 没有表现出这种效应。基于 KEPPRA® 标签，这些结果与进食状态中给药的 KEPPRA® 片剂的药物动力学是一致的，由此吸收程度未受影响，但是 Cmax 降低约 20％并且 Tmax 延长约 1.5 小时。

[0121] 剂量效率 (AUC/ 剂量) 是吸收的药物相对于给药的药物剂量的程度的量度。无论在进食还是禁食状态给药，本发明的 3DP 剂型均提供 LEV 的有效生物吸收。当向个体口服给药时，3DP 剂型提供以下药物动力学参数。

[0122]

3DP 剂量 (mg)	C_{max} (微克(microg)/ml)	T_{max} (hr)	AUC_{0-t} (微克-hr/ml)	AUC_{inf} (微克-hr/ml)
1000 (禁食)	23-43 或 13-53 或 10-60	0.15-1.0 或 0.15-1.5 或 0.12-1.7	227-340 或 170-397 或 160-425	235-351 或 176-410 或 160-450
1000 (进食)	17-24 或 14-27 或 10-35	3-5 或 2-5 或 2-6	223-302 或 183-342 或 170-380	231-314 或 190-355 或 170-400
750 (禁食)	16-31 或 9-37 或 8-40	0.15-1.0 或 0.15-1.5 或 0.12-1.7	180-270 或 135-315 或 120-350	186-278 或 140-324 或 120-375
750 (进食)	12-17 或 10-19 或 8-25	3-5 或 2-5 或 2-6	177-239 或 145-271 或 130-300	183-249 或 150-282 或 125-320
500 (禁食)	9-16 或 5-20 或 4-25	0.15-1.0 或 0.15-1.5 或 0.12-1.7	119-179 或 90-209 或 80-220	123-185 或 93-216 或 85-240
500 (进食)	6-9 或 5-10 或 4-15	3-5 或 2-5 或 2-6	117-159 或 96-180 或 85-200	122-165 或 100-187 或 87-220
250 (禁食)	6-11 或 3-14 或 3-18	0.15-1.0 或 0.15-1.5 或 0.12-1.7	72-108 或 54-127 或 45-150	75-112 或 56-131 或 47-160
250 (进食)	4-6 或 4-7 或 3-10	3-5 或 2-5 或 2-6	71-96 或 58-109 或 47-125	74-100 或 60-113 或 50-140

[0123] 本发明的剂型提供的 Cmax 的进食 / 禁食比为 0.55-0.74(或约 0.6-0.7),Tmax 的进食 / 禁食比为 5-21(或约 5-13 或 5-10),$AUC_{0\ t}$的进食 / 禁食比为 0.89-0.98,并且 AUC_{inf} 的进食 / 禁食比为 0.89-0.99。

[0124] 本发明的剂型对吸收速率和程度而言与KEPPRA®片剂基本上等同,特别在禁食状态下给药时,后者是新药申请 No.N021035 所规定的(见上文)。所述剂型对 Cmax 和 AUC 提供基本上线性的剂量比例,从而 Cmax 或 AUC 比给药剂量的线性拟合的特征可以在于相关系数 R^2为 0.95-1.0。在等同剂量基础上,口分散剂型的 Cmax 和 AUC 在 KEPPRA®速释片剂产品实现的值的 80-125%内。

[0125] 根据上述说明书和以下实施例,本领域技术人员能够实施所要求保护的发明而无

需过度实验。参照详细描述本发明的实施方案的具体实施方法的以下实施例会更好地理解上文的内容。对这些实施例的所有参照用于示例目的。以下实施例不应理解为穷举的，而仅仅是示例本发明涵盖的许多实施方案中的一些。

[0126] 实施例

[0127] 实施例 1 制备三维打印的口分散剂型

[0128] 以下方法用于制备三维打印的口分散剂型，所述剂型包含基质，所述基质包含 LEV。打印流体和松散粉末的成分和所用的量如下：

[0129]

打印流体	I-A	I-B	I-C	I-D
水(重量%)	68.99-70.7	68.47-69.12	66.89-67.95	66.5-71
甘油(重量%)	3.9-4	3.8-3.92	3.79-3.85	3.5-4
异丙醇(重量%)	13.01-13.3	12.3-13.04	12.11-12.82	12-13.5
吐温 20 (重量%)	1.95-2	1.9-1.96	1.89-1.92	0.5-2
聚维酮(重量%)	9.76-10	8.5-9.8	8.51-9.61	8.5-10
三氯蔗糖(重量%)	2	2-5	4-6	0-3
甘草酸单铵 (重量%)甘草甜 100			0.2-0.6	0-1
留兰香香料 HD45		0.01-0.03	0.01-0.05	0-1
天然胡椒薄荷香料 HD29	0-0.38			0-1

打印流体	I-E	I-F	I-G	I-H
水(重量%)	65-72	65-70		
甘油(重量%)	3.5-4	3.4-4.2		
异丙醇(重量%)	12-13.5	11-13		
吐温 20 (重量%)	1-2	1.5-2.5		
聚维酮(重量%)	8.5-10	8-10		
三氯蔗糖(重量%)	>0-5	4-6		

[0130]

甘草酸单铵	0-0.6	0.1-0.8
(重量%)甘草甜 100		
留兰香香料 HD45	0-0.2	>0-0.1
天然胡椒薄荷香料 HD29	0-0.5	

松散粉末：	II-A	II-B	II-C	II-D	II-E
LEV (重量%)	75	75	65	65	75-90
Avicel PH101 (重量%)	17.5	19.8	21.8	23.8	5-20
甘露醇(重量%)			12.5	10.5	
聚维酮(PVP K29/32) (重量%)	4.5	4.5			5-10
三氯蔗糖(重量%)	2				1-3
甘草酸单铵	0.5				0.5
(重量%)					
胶体二氧化硅(重量%)	0.5	0.7	0.7	0.7	0.5

松散粉末：	II-F	II-G	II-H
LEV (重量%)	65-75		
Avicel PH101 (重量%)	17.5-24		
甘露醇(重量%)	10.5-12.5		
聚维酮(PVP K29/32) (重量%)	4-6		
三氯蔗糖(重量%)	1-3		
甘草酸单铵	0.1-1		
(重量%)			
胶体二氧化硅(重量%)	0.5-0.7		
抗氧化剂(重量%)	0.1-7		

[0131] 将预定厚度的松散粉末的增量层铺展于之前的粉末层上，并且将打印流体以小滴形式根据预定的饱和水平、排间隔和打印流体流速施用于增量层以结合其中的颗粒。完成这两个步骤过程直至获得包含目标量的打印的增量层的基质。

[0132] 可以使用已知或本文描述的任何三维打印机设备组件，但是这些示例性制剂可以用 Coriolis Instrument(Dimatix/Spectra Technology Integration, 型号:Coriolis RP1)来制备。打印机操作的小滴大小为 70-90 皮升 (picoliter)，并且分辨率为 200-400dpi 或约 300dpi 乘以 (by)900-1500dpi。所述剂型中使用各种不同的打印模式。使用打印流体配方和松散粉末配方的给定组合。使用的层厚度为 0.008-0.011 英寸或约 0.25- 约 0.265mm。使用的分辨率为 300x1200dpi、300x1000dpi、300x900dpi、400x900dpi、400x750dpi、400x675dpi。使用打印流体 I-A 至 I-D。使用打印流体和松散粉末配方的许多不同组合。一些所得的基质包含以下成分。

[0133]

III-A	
LEV (重量%)	60-70
Avicel PH101 (重量%)	20-25
甘露醇(重量%)	9.5-11
聚维酮(PVP K29/32) (重量%)	1-2
三氯蔗糖(重量%)	0.5-1.5
胶体二氧化硅(重量%)	0.5-1
水分(重量%)	0.3-4
甘油(重量%)	0.1-1
吐温 20 (重量%)	0.1-0.5
留兰香香料 HD45	>0-0.2
甘草酸单铵 (重量%)	0.05-0.15

[0134] 从松散的未打印粉末分离打印的基质并且通过任何合适的方式干燥打印的基质以将溶剂和水分的量降低至期望水平，由此制备最终的 3DP 口分散剂型。

[0135] 然后，确定剂型的分散时间、表面材质（光滑度）和硬度。

[0136] 实施例 2 不同的增量层中具有改变结构的快速分散薄片

[0137] 制备在增量层中具有改变结构的掩味的三维打印的口分散剂型

[0138] 根据上文所述的 3DP 方法，但是其可以以若干不同的方式进行以制备在硬度和增量层组成上改变的不同结构的剂型。以下方法提供的薄片的上表面和下表面的硬度与薄片的内部部分的硬度相比更大。这个策略有助于在具有不同机械性质的薄片中产生部分。这个方法用于设计这样的薄片，其中顶部和底部层的组成与中间层不同。这种设计使得薄片具有更强的顶部和底部层，从而增加硬度和降低脆性，并且具有硬度较低的大中间部分，这使得薄片快速地分散。

[0139] 方法 A:

[0140] 在这个方法中，沉积于不同增量层或相同增量层中不同预定区域内的粘合剂的量发生变化。根据实施例 3 的方法制备这些薄片，除了通过打印流体沉积在粉末上的粘合剂的量在通过粘合剂浓度变化的打印流体产生的增量粉末层中变化。

[0141] 方法 B:

[0142] 根据实施例 3 的方法制备这些薄片，除了沉积在粉末上的打印流体的量在增量粉末层中变化。上部和下部增量层接受较高量的打印流体，并且中间部分的增量层接受较低量的打印流体。

[0143] 方法 C:

[0144] 在这个方法中，用于剂型的上部和下部增量层的打印模式为实心模式（图 3A）。增量层的中间部分的打印模式为灰度（图 3B）。灰度打印可以为约 20- 约 90％或约 20- 约 80％。

[0145] 方法 D:

[0146] 在这个方法中，用于剂型的上部和下部增量层的打印模式为实心模式（图 3A）。增量层的中间部分的打印模式为环形 / 中空高饱和打印，被环形围绕的区域中没有打印（图 3C）。

[0147] 方法 E:

[0148] 在这个方法中，用于剂型的上部和下部增量层的打印模式为实心模式（图 3A）。增量层的中间部分的打印模式为外部高饱和打印围绕的内部灰度打印的组合（图 3D）。

[0149] 实施例 3 剂型的表征

[0150] 以下方法用于表征三维打印的固体多孔口分散基质。

[0151] 脆性

[0152] 利用片剂脆性测试 (USP 方法 <1216>) 分析基质对破裂的抗性。测试使用 VanKel 脆性测试器（型号 45-2000, Varian, USA），其装有直径 285mm 深 39mm 的大小的鼓，以 25rpm 旋转 100 圈。通过从鼓的中间延伸至外壁的弧形突起物在每圈落下最少 10 个薄片。因此，在每个翻转，使片剂滚动或滑动约 130mm 至鼓上或互相的片剂上。从片剂除去所有松散的粉末，并且在 100 圈之前和之后称重片剂。

[0153] 表面材质

[0154] 借助或不借助显微镜视觉检查基质。分析表面材质以确定其是粗糙或光华的，并且确定薄片的上表面上的标记边缘和周长边缘是清晰和锐利的或者粗糙和不整齐的。

[0155] 基质表现出光滑的表面，其具有清晰和锐利的边缘。

[0156] 硬度

[0157] 通过 USP<127>(31st版）的片剂破碎力测定所确定的，利用 VK 200 片剂硬度测试仪 (Varian, US) 分析基质的整体硬度。通过断裂测试测量薄片的强度或硬度。将薄片放置在测试仪的钳中间，并施加力直至薄片断裂。断裂的负载返回为千克力 (kp)。千克力是力的测量的公制单位，1kp 等于 9.807 牛顿。测试最少 6 个薄片。

[0158] 剂型的硬度为约 0.7- 约 5.3kp、约 1.7- 约 5.1kp、约 2.1- 约 5.2kp、约 3- 约 6kp、约 1- 约 9kp 或约 2.5- 约 5.3kp。

[0159] 分散时间

[0160] 如下利用质构仪 (Texture Analyzer, TA HP, Texture Technologies, US) 分析基质在含水流体中的分散时间，所述质构仪装有 5Kg 进样小室和 1.0 英寸直径的丙烯酸探针 (Stable Micro Systems)。使薄片通过双面胶带连接至探针。在室温下，在恒定的 50g 力下 (Dor et al. Pharm. Dev. Technol. (2000), 5(4), 575-577 和 El-Arini et al. Pharm. Dev. Technol. (2002), 7(3), 361-371)，在平底铝称量盘中，将薄片浸入 3ml 水中。利用以下参数进行分散时间测试。测试最少 5 个薄片。

[0161]

测试模式	压缩
测试前速度(mm/sec)	5
测试速度(mm/sec)	8
测试后速度(mm/sec)	10
目标模式	力
力(g)	50
维持时间(sec)	15
引发类型	自动(力)

[0162]

引发力(g)	5
水体积(ml)	3

[0163] 对剂型观察到的分散时间为约 10 秒或更短或者约 5 秒或更短。

[0164] 体密度

[0165] 基质的体密度通过测量薄片的重量并将该值除以薄片计算的体积来确定。薄片的体积通过测量其尺寸并根据薄片的形状利用合适的数学公式来计算。例如,对于圆柱形薄片,其体积利用公式 $\pi*r^2*H$ 来计算,其中 r 是薄片的半径并且 H 是其高度。重量为 0.5g,高度为 0.6cm 并且直径为 1.1cm 的薄片的体积为约 0.57cm^3,并且体密度为约 0.877g/cm^3,这等于约 877mg/ml。

[0166] LEV 的溶解

[0167] 溶解测试根据工业指南 (Guidance for Industry,3.3.2 章 ;Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.August2000.IIIc 章 , 第 7 页) 进行。使用 USP<711> 的方法。溶解利用 USP 装置 II(桨) 在 50rpm 下进行,其使用 900mL 以下脱气溶解介质 :(1)0.1N HCl ;(2)0.05M 乙酸钠,pH 4.5 缓冲液和 (3)0.05M KH_2PO_4,pH 6.8 缓冲液,37℃。实施例 4 三维打印的口分散剂型的体内评价

[0168] 这个方法用于确立剂型的效力。以 12 小时的间隔,向个体每天两次给药包含 LEV 的单剂型。给药通过将剂型置于个体的口中来完成,并且任选地向个体给药一小口 (5-20ml 或 2-30ml) 流体。在短时间段内,剂型在个体的口中分散。或者,将剂型在最小量的流体中分散,然后向个体口服给药。LEV 的总每日剂量通常为约 500- 约 2000mg,分成两个剂量。个体的药物动力学特征谱利用本领域中已知的方法确定。对剂型的治疗应答的个体水平利用本领域已知的方法确定。

[0169] 实施例 5 剂型中 LEV 的 HPLC/MS 分析

[0170] 以下方法用于分析三维打印的固体多孔口分散基质并用于支持药物稳定性研究。

[0171] 使用以下溶液 :

[0172]

缓冲液： 20 mM 乙酸铵，pH 5.5

流动相 A (MPA)： 95:5 缓冲液：乙腈

流动相 B (MPB)： 乙腈

稀释剂： 95:5 水：乙腈

[0173] HPLC 条件如下：

[0174]

柱：Alltima C18 4.6 x 150 mm, 5 μm

流动相 A (MPA)：95:5 缓冲液：乙腈

流动相 B (MPB)：乙腈

UV 检测：205 nm

柱温：25°C

进样体积：10 μL

流速：0.9 mL/分钟

自动取样温度：5°C

[0175] 样品通过将约 380mg 样品转入包含 30mL 稀释剂的 50-mL 容量瓶来制备。将样品超声处理 10 分钟，然后装入具有稀释剂的容器 (volume) 中。通过 0.22 μm 尼龙滤器过滤一部分样品，并弃去前面的 3-5mL。

[0176] 通过 100 μL/ 分钟的锁定喷雾 (lock spray)，利用注射泵，质谱分析通过直接将甲酸钠溶液注入质谱仪来进行。m/z 158.9646126 的甲酸钠峰用于精确的质量分析。利用 MassLynx 软件，精确质量用于元素组成分析。

[0177] 利用客户提供的方法，杂质 / 降解物峰的相对保留时间 (RRT) 为 0.64。该峰观察到的质子化单一同位素质量为 185.1Da。峰的精确质量分析和元素组成分析与氧代 - 左乙拉西坦一致。

[0178] 实施例 63DP 剂型中 LEV 稳定性的评价

[0179] 以下方法用于鉴定适合于稳定 LEV 避免氧化降解的优选抗氧化剂。

[0180] 制备包含以下指定量的成分的粉末混合物。

[0181]

成分	% (w/w)
左乙拉西坦，USP	65.0
胶体二氧化硅，NF	0.70
微晶纤维素，NF	23.8
甘露醇 50C, USP	10.5

[0182] 制备包含以下指定量的成分的打印流体。

[0183]

成分	% (w/w)	功能
聚维酮 K29/32,USP	8.51	粘合剂,粘度调节剂
三氯蔗糖 ,NF	5.0	甜味剂
N&A 留兰香香料 HD45	0.03	调味剂
甘油 ,USP	3.8	湿润剂
聚山梨酯 20,NF	1.9	表面活性剂
异丙醇 ,USP	12.3	溶剂
净化水 ,USP	68.5	溶剂

[0184] 评价的抗氧化剂如下表所列。将表中所列的 IIG(Inactive Ingredient Guide) 每日限制 (mg) 的一半的量用于每种抗氧化剂,因为当每日给药两次时这会达到限制,每日给药两次是速释左乙拉西坦的剂量给药最常用的频率。例如,对于每日两次给药的 1000mg 片剂,抗氧化剂的量是“(IIG 每日限制)/2”。应当理解, IIG 限制是定期由管理机构改变的。因此,下文所指的限制应当理解为近似,不是可以包含在剂型中的抗氧化剂的量的绝对限制。

[0185]

抗氧化剂	IIG 每日限制 (mg)
抗坏血酸	28.44
丁基羟基茴香醚 (BHA)	1
丁羟甲苯 (BHT)	0.36
没食子酸正丙酯	2
L- 半胱氨酸 HCl	16.2
亚硫酸钠	0.65
亚硫酸氢钠	0.65
α - 生育酚 (Vit E)	1.34
EDTA	100
焦亚硫酸钠	8

甲硫氨酸	5

[0186] 将抗氧化剂与6mL打印流体混合。然后将该混合物与30g粉末混合物混合以形成原始片剂组合物，将每一个组合物暴露于以下条件：条件1-将组合物在70C下存储于严格密封的玻璃罐中；条件2-将组合物在50C下存储于宽松覆盖的玻璃罐中；以及条件3-将组合物在40C/75％ RH下存储于敞口玻璃罐中。

[0187] 随后通过HPLC/MS分析样品，并通过与标准品比较来确定两种关键降解物的性质。关键的降解物是左乙拉西坦酸和氧代－左乙拉西坦。而且，一些原始组合物变为有色（发黄），而其他没有。数据表明，亚硫酸氢钠、亚硫酸钠、维生素E、甲硫氨酸、BHA和BHT提供改善的稳定性以避免氧化降解和颜色形成。在测试条件下，亚硫酸氢钠、亚硫酸钠、BHA和BHT提供最好的结果。测试的其他抗氧化剂提供针对氧化降解和颜色形成较差程度的保护或没有提供保护。

[0188] 实施例7口分散3DP剂型中LEV的PK参数的确定

[0189] 以下方法用于确定本发明的口分散3DP剂型的PK参数并与商业产品KEPPRA膜包衣片剂进行比较。

[0190] 进行单中心、随机、单剂量、实验室盲、3周期、3顺序交叉研究。包括18-50岁的32名健康状况良好的男性和女性个体。向个体口服给药单剂量的包含1000mg的LEV的3DP剂型或者包含1000mg的LEV的KEPPRA®片剂。如下每周一次给药单剂量，进行3周，剂量之间提供7天的清理期。

[0191] ●组I：10小时过夜禁食后，在早晨给药单剂量的3DP剂型

[0192] ●组II：10小时过夜禁食后，在早晨给药单剂量的KEPPA®片剂

[0193] ●组III：10小时过夜禁食后，并且在开始高脂肪、高热量早餐后30分钟，在早晨给药单剂量的3DP剂型

[0194] 在每个剂量给药之前和之后确定LEV的血浆浓度。食物效应通过对于禁食和进食条件比较获得的C_{max}、T_{max}、$AUC_{0\ t}$和$AUC_{\ inf}$来确定。以下数据提供PK数据的总结。

[0195]

剂型	C_{max} (微克/ml)	T_{max} (hr)	AUC_{0-t} (微克-hr/ml)	AUC_{inf} (微克-hr/ml)
KEPPRA® (禁食)	平均：30.48 C.V.：19.0	平均：0.58 C.V.:69.9	平均：274.9 C.V.：18.2	平均：284.3 C.V.：18
3DP (禁食)	平均：33.27 C.V.：30.1	平均：0.58 C.V.：73.7	平均：283.69 C.V.：20	平均：292.9 C.V.：19.9
3DP (进食)	平均：20.48 C.V.：16.3	平均：4 C.V.：21.6	平均：262.6 C.V.：15.1	平均：272.6 C.V.：15.2

[0196] 据发现，在禁食条件下，本发明的3DP产品对于LEV的生物利用度而言等同于KEPPRA®参考产品。而且，3DP产品仅对Cmax和Tmax表现出食物效应，但是对整体全

身暴露则没有，即对 $AUC_{0\ t}$ 或 AUC_{inf} 没有表现出这种效应。这些结果与进食状态中给药的 KEPPRA® 片剂的药物动力学（KEPPRA® 标签，NDA 021035）是一致的。

[0197] 本文所用的术语“约”或“大约”应当理解为指定值的 ±10%、±5%、±2.5% 或 ±1%。本文所用的术语“基本上”应当理解为表示“大程度”或“至少多数”或“大于 50%”。

[0198] 上文是本发明的特定实施方案的详细描述。应当理解，虽然本文为了示例目的描述了本发明的具体实施方案，但是可以进行各种修饰而不偏离本发明的精神和范围。因此，本发明仅受所附的权利要求的限制。根据本文的公开，可以进行所有公开且要求保护的实施方案而无需过度实验。

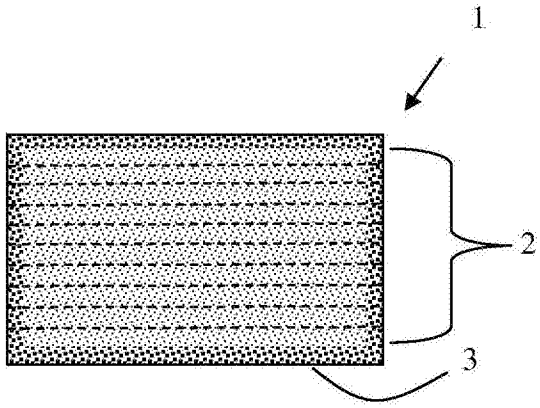

图 1

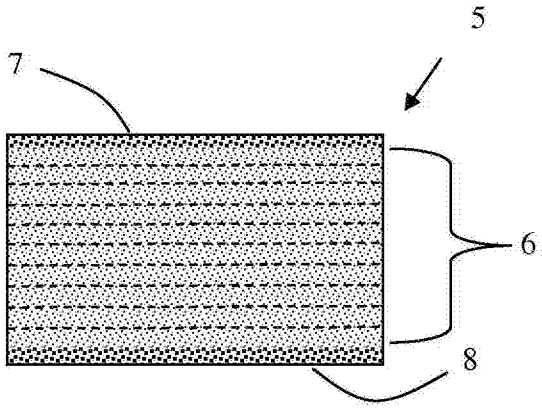

图 2

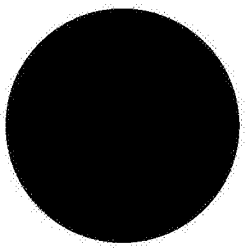

图 3A

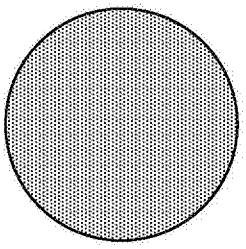

图 3B

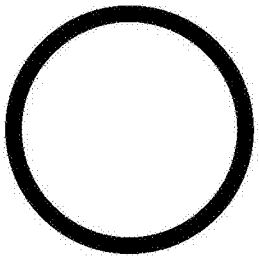

图 3C

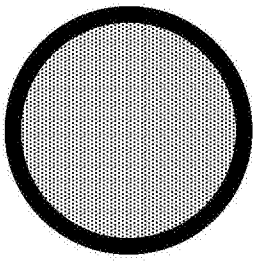

图 3D

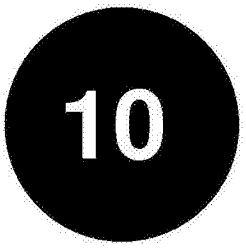

图 3E

1.一种快速分散固体剂型，所述剂型包含结合基质中的左乙拉西坦，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散。

2.权利要求1的剂型，其中所述基质还包含抗氧化剂。

3.一种快速分散固体剂型，所述剂型包含结合多孔基质，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散，其中所述基质包含左乙拉西坦、至少一种抗氧化剂、至少一种粘合剂和至少一种崩解剂。

4.权利要求1、2或3的剂型，其中在75％ RH和21℃下存储6个月后，所述基质包含0.1％或更少的LEV的氧化降解物。

5.一种快速分散固体剂型，所述剂型包含结合多孔基质中的左乙拉西坦，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散，其中在禁食状态下，向个体给药各自剂量的左乙拉西坦时，所述剂型提供下列范围内的Cmax：

剂量(mg)	C_{max}(微克/ml)
1000	13-53
750	9-37
500	5-20
250	4-7

。

6.权利要求5的剂型，其中所述剂型提供0.15-1.5小时范围内的Tmax。

7.权利要求5的剂型，其中所述剂型提供下列范围内的$AUC_{0\ t}$和/或AUC_{inf}：

3DP剂量(mg)	$AUC_{0\ t}$(微克-hr/ml)	AUC_{inf}(微克-hr/ml)
1000	170-397	176-410
750	135-315	140-324
500	90-209	93-216
250	54-127	56-131

。

8.一种快速分散固体剂型，所述剂型包含结合多孔基质中的左乙拉西坦，所述基质在约15ml或更少体积的水或唾液中，于约15秒或更短的时间内分散，其中在进食状态下，向个体给药各自剂量的左乙拉西坦时，所述剂型提供下列范围内的Cmax：

3DP剂量(mg)	C_{max}(微克/ml)
1000	14-27

3DP 剂量 (mg)	C_{max} (微克 /ml)
750	10-19
500	5-10
250	4-7

。

9. 权利要求 8 的剂型，其中所述剂型提供 2-5 小时范围内的 Tmax。

10. 权利要求 8 的剂型，其中所述剂型提供下列范围内的 $AUC_{0\ t}$ 和 / 或 AUC_{inf}：

3DP 剂量 (mg)	$AUC_{0\ t}$ (微克 -hr/ml)	AUC_{inf} (微克 -hr/ml)
1000	183-342	190-355
750	145-271	150-282
500	96-180	100-187
250	58-109	60-113

。

11. 一种快速分散固体剂型，所述剂型包含结合多孔基质中的左乙拉西坦，所述基质在约 15ml 或更少体积的水或唾液中，于约 15 秒或更短的时间内分散，其中所述剂型提供的 Cmax 的进食 / 禁食比为 0.55-0.74，并且 Tmax 的进食 / 禁食比为 5-21。

12. 权利要求 11 的剂型，其中所述剂型提供的 $AUC_{0\ t}$ 的进食 / 禁食比为 0.89-0.98，并且 AUC_{inf} 的进食 / 禁食比为 0.89-0.99。

13. 权利要求 1、3、5、8 或 11 中任一项的发明，其中如 NDA No.N021035 所定义的，对于 C_{max}、$AUC_{0\ t}$ 和 / 或 AUC_{inf}，所述剂型在吸收速率和程度上等同于 KEPPRA® 片剂。

14. 权利要求 1、3、5、8 或 11 中任一项的发明，其中：

a) 所述剂型未被压制；b) 所述基质未被压制；c) 所述剂型的外表面的硬度大于所述剂型内部部分 (其一个或多个内部增量打印层) 的硬度；即所述剂型的外部比内部更硬；d) 当置于含水流体中时，LEV 的溶解时间慢于所述基质的分散时间；e) 当置于小体积的含水流体中时，所述基质在约 10 秒或更短的时间内分散；f) 当置于含水流体中时，至少 75%、至少约 90% 或至少约 95% 的 LEV 在约 2 分钟或更短的时间内溶解；g)LEV 以选自以下的形式存在：水合物、半水合物、晶体、无定形、无水物或其组合；h) 如通过 120℃下的干燥失重确定的，所述剂型包含不大于 10 重量% 并且不小于 0.1 重量% 的水分；i) 所述基质的硬度是基本上均匀的；j) 所述剂型包含一种或多种其他药物；k) 所述基质还包含甘油；l) 所述剂型中的甘油含量为约 0.05% -3%；和 / 或 m) 在以 50RPM 操作的 USP 桨装置中，在 pH1.2、4.5 或 6.8 下，于 900ml 含水介质中，至少 95% 的 LEV 在 5 分钟或更短的时间内溶解。

15. 权利要求 1、3、5、8 或 11 中任一项的发明，其中所述基质是三维打印基质，所述基质包含 LEV、崩解剂、一种或多种粘合剂、一种或多种表面活性剂、一种或多种抗氧化剂、甘油

以及任选存在的一种或多种以下成分：一种或多种助流剂（自由流动的添加剂）、一种或多种调味剂、一种或多种防腐剂；其中所述基质包含由粘合剂和 LEV 结合的颗粒；所述基质是多孔的并且未被压制；所述基质在 10ml 体积的含水流体中于小于 15 秒的时间内分散；以及基于所述基质的总重量，所述基质中的 LEV 含量为 50-80 重量%。

16. 权利要求 15 的发明，其中：

a) 基于所述剂型的最终重量，至少一种表面活性剂以约 0.05- 约 1 重量%、约 0.1- 约 0.8 重量%以及约 0.2- 约 0.5 重量%的量存在；b) 基于所述剂型的最终重量，至少一种抗氧化剂以约 0.005- 约 5.0 重量%、约 0.01- 约 1.0 重量%以及约 0.08- 约 0.8 重量%的量存在；c) 基于所述剂型的最终重量，至少一种粘合剂以约 0.5- 约 20 重量%、约 5- 约 15 重量%以及约 7- 约 13 重量%的量存在；d) 基于所述剂型的最终重量，至少一种崩解剂以约 3- 约 35 重量%、约 10- 约 30 重量%以及约 20- 约 26 重量%的量存在；e) 基于所述剂型的最终重量，至少一种助流剂以约 0.1- 约 2.0 重量%、约 0.25- 约 1.5 重量%以及约 0.5- 约 1.0 重量%的量存在；和 / 或 f) 所述基质包含约 250- 约 1000mg、约 250mg、约 500mg、约 750mg、约 1000mg 的 LEV。

17. 权利要求 1、3、5、8 或 11 中任一项的发明，其中所述剂型通过三维打印方法制备。

18. 权利要求 17 的发明，其中所述剂型通过三维打印方法制备，所述方法使用以下打印流体和松散粉末组合物中的任一种：

打印流体

水(重量%)	68.99-70.7	68.47-69.12	66.89-67.95	66.5-71
甘油(重量%)	3.9-4	3.8-3.92	3.79-3.85	3.5-4
异丙醇(重量%)	13.01-13.3	12.3-13.04	12.11-12.82	12-13.5
吐温 20 (重量%)	1.95-2	1.9-1.96	1.89-1.92	0.5-2
聚维酮(重量%)	9.76-10	8.5-9.8	8.51-9.61	8.5-10
三氯蔗糖(重量%)	2	2-5	4-6	0-3
甘草酸单铵			0.2-0.6	0-1
(重量%)甘草甜 100				
留兰香香料 HD45		0.01-0.03	0.01-0.05	0-1
天然胡椒薄荷香料 HD29	0-0.38			0-1

打印流体

水(重量%)	65-72	65-70
甘油(重量%)	3.5-4	3.4-4.2

异丙醇(重量%)	12-13.5	11-13
吐温 20 (重量%)	1-2	1.5-2.5
聚维酮(重量%)	8.5-10	8-10
三氯蔗糖(重量%)	>0-5	4-6
甘草酸单铵 (重量%)甘草甜 100	0-0.6	0.1-0.8
留兰香香料 HD45	0-0.2	>0-0.1
天然胡椒薄荷香料 HD29	0-0.5	

松散粉末：

LEV (重量%)	75	75	65	65	75-90
Avicel PH101 (重量%)	17.5	19.8	21.8	23.8	5-20
甘露醇(重量%)			12.5	10.5	
聚维酮(PVP K29/32) (重量%)	4.5	4.5			5-10
三氯蔗糖(重量%)	2				1-3
甘草酸单铵 (重量%)	0.5				0.5
胶体二氧化硅(重量%)	0.5	0.7	0.7	0.7	0.5

松散粉末：

LEV (重量%)	65-75
Avicel PH101 (重量%)	17.5-24
甘露醇(重量%)	10.5-12.5
聚维酮(PVP K29/32) (重量%)	4-6
三氯蔗糖(重量%)	1-3
甘草酸单铵 (重量%)	0.1-1
胶体二氧化硅(重量%)	0.5-0.7
抗氧化剂(重量%)	0.1-7 。

19. 权利要求 1、3、5、8 或 11 中任一项的发明，其中所述剂型包含以下成分：

LEV (重量%)	60-70
崩解剂(重量%)	20-25

粘合剂(重量%)	10-15
甜味剂(重量%)	0.5-2
助流剂(重量%)	0.1-1.5
甘油(重量%)	0.1-5
表面活性剂(重量%)	0.05-1.5
香料(重量%)	0-0.5

。

20. 权利要求 19 的发明，其中所述剂型还包含抗氧化剂。

21. 权利要求 1、3、5、8 或 11 中任一项的发明，其中：

a) 所述基质的硬度为约 1- 约 10kp、约 2- 约 6kp 或者约 3- 约 9kp ；b) 当置于 15ml 水或唾液中时，所述基质在 10 秒或更短的时间内分散 ；c) 通过用于形成所述基质的打印流体将粘合剂引入所述基质 ；d) 通过用于形成所述基质的松散粉末将粘合剂引入所述基质 ；e) 所述基质包含约 250mg- 约 1000mg 的 LEV ；f) 所述基质包含 15-50 或 25-50 个打印增量层 ；g) 增量层的厚度（高度）为 0.008-0.012 英寸 ；和 / 或 h) 所述基质是多孔的并且未被压制。

22. 一种制备权利要求 1、3、5、8 或 11 中任一项的快速分散剂型的方法，所述方法包括：

a) 提供松散粉末的增量层，其包含 LEV、崩解剂、粘合剂、抗氧化剂、任选存在的调味剂、任选存在的甜味剂以及任选存在的助流剂 ；

b) 根据预定的饱和水平，将打印流体施用于松散粉末的层以形成增量打印层，其中所述流体包含水、醇、粘合剂、抗氧化剂、甘油、表面活性剂（乳化剂）、任选存在的甜味剂、任选存在的防腐剂 ；以及

c) 重复 a) 和 b) 至少两次，从而形成三维打印的口分散剂型，所述剂型包含至少三个堆积的增量打印层。

23. 权利要求 22 的发明，其中：

a) 所述方法还包括在 3DP 方法中，在所述剂型的表面上形成一个或多个凸起（突出）或凹入（嵌入）形式的标记 ；b) 所述方法还包括从所述剂型除去水和醇以将其水分减少至本文所述的范围内 ；c) 所述方法还包括分离所述剂型与未在其上打印的松散粉末 ；d) 所述剂型的上方和下方增量层所用的打印流体饱和水平高于所述剂型的其他部分，以在完成的剂型中为上方和下方的增量表面提供增加的硬度，并且为其之间的增量层提供降低的硬度 ；e) 所述剂型的上方和下方增量层以及中间增量层的外围所用的打印流体饱和水平高于所述剂型的其他部分，以在完成的剂型中为其上方和下方增量表面以及中间增量层的外围提供增加的硬度，并且为其之间的增量层提供降低的硬度 ；f) 所述方法还包括加热所述剂型以除去和降低其中的打印流体的量 ；和 / 或 g) 所述方法还包括通过混合其成分来制备松散粉末以形成随后进行筛分的混合物。

24. 权利要求 1、3、5、8 或 11 中任一项的发明，其中所述剂型不含防腐剂。

25. 一种治疗对左乙拉西坦治疗上应答的疾病、疾病状况或病症的方法，所述方法包括在整个治疗期间向有此需要的个体每日给药权利要求 1、3、5、8 或 11 中任一项的剂型 1-3 次。

26. 删除

27. 删除

28. 一种快速口分散三维打印的固体多孔基质，所述基质包含 LEV、抗氧化剂、崩解剂和粘合剂，其中在 75% RH 和 21℃下存储 6 个月后，所述基质包含 0.1%或更少的 LEV 的氧化降解物。

29. 权利要求 28 的发明，其中所述基质在约 15ml 或更少体积的水或唾液中，于约 15 秒或更短的时间内分散。

30. 权利要求 3、28 或 29 的发明，其中所述粘合剂为水溶性粘合剂，并且包含过氧化物作为杂质。

[0001] 修改

[0002] 本次修改中保留了权利要求 1-25 和 28-30，修改了权利要求 13-17、19 和 21-25，引入了新的权利要求 28-30 并且删除了权利要求 26-27。

[0003] 说明

[0004] 权利要求 1-2 和对比文件 1：对比文件 1(US 2011/0318390A1) 的“快速溶解片剂”具有“快速释放包衣”RRC，其在 10 秒内溶解，但是片剂的剩余部分并非如此（参见摘要，第 [0004]、[0007]、[0009] 和 [0017] 段以及实施例 A)。其必须具有在 10 秒内溶解的外部 RRC。然而，对比文件 1 并没有公开整个片剂在 10 秒内溶解。其也不能实现这一效果，而仍然提供预期的充分掩味效果。对比文件 1 设计 RRC 在内部组分之前溶解来提供改变 pH 的效果，从而实现掩味。

[0005] 权利要求 3 和对比文件 2：虽然对比文件 2(US 2008/0069878A1) 教导了在 ODT 剂型中包含定时脉冲释放 TPR 珠（第 [0021]-[0022] 段），但是这样的公开仅仅是泛泛而论的（第 [0067]-[0070] 段，特别是第 [0071] 段，其指出了 30 或 60 秒）。然而并没有提示或教导表明，对比文件 2 可以实现 <15 秒的溶解。

[0006] 权利要求 4 和对比文件 2/ 对比文件 3：审查员认为对比文件 3(US 2007/0212411A1)（第 [0047]、[0054] 和 [0068] 段）公开了左乙拉西坦剂型表现出所声称的纯度水平 (0.1％或更少的 LEV 氧化降解物）。对比文件 2 没有表明 <15 的降解时间。对比文件 3 没有公开对于任何药物，特别是左乙拉西坦，如何实现所声称的纯度水平。本申请说明书（第 [0016]、[0017] 和 [0085]-[0087] 段）则表明，当包含于 3DP 剂型中时，与常规压制片剂相比，赋形剂对 LEV 的氧化具有出人意料的效果，其没有表现出氧化不稳定性。

[0007] 权利要求 5-7 和对比文件 1/ 对比文件 4(Assessment of levetiracetam bioavailability from targeted sites in the human intestine using remotely activated capsules and gamma scintigraphy:Open-label,single-dose,randomized,four-way crossover study in healthy male volunteers,Clin Ther.2010 Sep;32(10):1813-1821)：审查员所指出的数据涉及胶囊的口服给药，其将药物递送至近端小肠（表 I，星号，栏的开始部分）。IR 片剂（将药物递送至胃）提供的 Cmax 为 8.4 微克 /ml(不在 4-7 微克 /ml 的范围内）。审查员的意见仅表明通过 250mg 的 LEV 的单一口服剂量（与权利要求 5-7 不同），ODT 片剂（对比文件 1) 表现出 30-60 秒的崩解时间，并且提供 8.4 微克 /ml 的 Cmax。因此，对比文件 1/ 对比文件 4 并没有提示如何制备所声称的快速分散剂型 (RDDF)。

[0008] 权利要求 8-10 和对比文件 1/ 对比文件 6：对比文件 6(Pharmacokinetics of levetiracetam XR 500mg tablets,Epilepsy Res.2009 Apr;84(2-3):224-231) 公开了控释 (XR)，而不是 RDDF，因此这些文献的组合是不合适的。而且，审查员看起来忽视了对比文件 6 的治疗方案，即比较 XR 片剂与 IR 片剂（治疗 1-3)。对比文件 6 公开了每天给药 500mg 剂量 IR 片剂两次，以及每天 b.i.d 给药一次。IR 剂量仅在禁食状态下给药。相反地，两个 500mg 剂量 XR 片剂在禁食或进食状态下每天给药 1 次。对比文件 6 最相关的剂量给药方案是 IR 片剂的第二个方案。即使如此，对比文件 6 的 IR 剂型也不是 RDDF，其在 <15 秒的时间内分散。审查员还提及了表 2-3（对 XR剂型的 PK 的食物效应）。但是对比文件 6 并没有公

开对 IR剂型的 PK 的食物效应。

[0009] 权利要求 11-12 和对比文件 6/ 对比文件 1 :对比文件 6 公开了 XR 比 IR 剂型的不同 PK 特征谱。但是无法预期对比文件 6/ 对比文件 1 是否会提供具有所声称的崩解和 PK 的 RDDR。而且对比文件 6/ 对比文件 1 也没有教导提供具有 0.55-0.74 的 Cmax 进食 / 禁食比和 5-21 的 Tmax 的 RDDR。

Abstract

A high dose rapidly dispersing three-dimensionally printed dosage form comprising a high dose of levetiracetam in a porous matrix that disperses in water within a period of less than about 10 seconds is disclosed. Also disclosed are methods of preparing the dosage form and of treating a condition, disease or disorder that is therapeutically responsive to levetiracetam. A process for preparing the dosage form is also provided.