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(54) Title: RAPIDLY DISPERSIBLE DOSAGE FORM OF TOPIRAMATE

(57) Abstract: A taste-masked rapidly dispersible dosage form of topiramate is provided. Wax coated particles of topiramate are included within a porous bound matrix. The topiramate retains its taste-masked form after dispersion in the mouth of a subject even though the particles are not coated with a polymeric material. The dosage form disperses in saliva or water in less than 2 min even though it has a high content of wax. It can be used to treat diseases or disorders that are therapeutically responsive to topiramate or a derivative thereof.

RAPIDLY DISPERSIBLE DOSAGE FORM OF TOPIRAMATE

FIELD OF THE INVENTION

[001] The present invention concerns a taste-masked rapidly dispersing (orodispersible) solid oral dosage form of topiramate. In particular, the dosage form disperses within a period of less than about fifteen seconds when placed in the mouth of a subject and the topiramate maintains its taste masking. 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 topiramate. A process for preparing the dosage form is also provided.

BACKGROUND OF THE INVENTION

[002] Solid oral dosage forms containing Topiramate (TOP; 2,3:4,5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate; disclosed in EP 138441) are known (FDA Electronic Orange Book). Topiramate is an anticonvulsant indicated for treating partial onset or primary generalized tonic-clonic seizures in epilepsy, for adjunctive therapy in Lennox-Gaustat syndrome, and migraine. It has also been used to treat bipolar disorder, borderline personality disorder, adjuvant for anti-psychotics, post-traumatic stress disorder, antipsychotic-induced weight gain, and other conditions as is recognized in the relevant art.

[003] Topiramate is susceptible to heat and moisture. Degradation of topiramate is readily detected by changes in physical appearance i.e. discoloration to brown or black, and formation of sulfate ions, which can be measured by standard techniques. A typical solution to overcome this problem is to protect the drug by applying a coating which diminishes the contact of the outside environment with the active ingredient and to use volatile organic solvents while applying the coating.

[004] TOP is dosed at high levels such as 400 mg per day (two 200 mg doses) for the treatment of epilepsy. That upper dose is achieved by dose escalation over a period of 6 weeks. 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, and

only tablets or capsules (including a sprinkle capsule) have been approved in the U.S. to date.

[005] Given the high doses of TOP 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 have been disclosed.

[006] 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-compressed 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. U.S. 6,471,992, U.S. 2012-0207929 and U.S. 2003-0133975 disclose three-dimensionally printed rapidly dispersing dosage forms.

[007] Topiramate is known to have an extremely bitter taste, which is disadvantageous in orodispersible dosage forms. A major requirement of any such solid form is that it must be palatable to reduce the risk of a patient neglecting to take the medication. In cases where the active ingredient is particularly unpalatable and somewhat unstable, it is difficult to prepare such solid forms, and in addition show good stability and bioavailability.

[008] Taste-masked dosage forms for poorly tasting drugs have been developed. U.S. 6,767,557 to Ulrich suggests a reconstitutable powder containing drug encapsulated in a water insoluble enteric coating. U.S. 6,586,012 and U.S. 6,482,823 to Yu disclose a liquid formulation containing topiramate encapsulated in an acid soluble coating. U.S. 20120207836 to General suggests a film wafer formulation containing drug particles encapsulated in a cationic polyacrylate coating. U.S. 20120076858 to Kolter suggests a

rapidly dispersible formulation containing drug particles encapsulated in a cationic polyacrylate coating. U.S. 20120040001 to Koizumi suggests a rapidly dispersible compressed dosage form comprising drug, starch, binder and molding agent. U.S. 20110212171 to Venkatesh discloses an orodispersible dosage form comprising topiramate particles coated with a water insoluble polymer. U.S. 20100285130 to Sanghvi suggests a film formulation comprising a complex of drug and ion exchange resin coated with an ingestible polymer. U.S. 20100278901 and U.S. 20070092553 to Tengler suggests a rapidly dispersible compressed dosage form comprising drug complexed to a resin. U.S. 20070154550 to Arti discloses an acrylate or ethyl cellulose coated powdered form of topiramate. U.S. 20060182796 to Wu discloses an acrylate and enteric polymer coated powder form of topiramate. U.S. 20060159758 to Gandhi a taste-masked formulation containing an acrylate polymer in combination with another polymer. U.S. Pat. No. 6,106,861 discloses a rapidly disintegrable multiparticulate tablet which disintegrates in the mouth in less than 40 seconds and includes excipients selected from disintegrating agents, binding agents, and an active ingredient. The active ingredient is in the form of microcrystals coated with a taste masking coating that includes polymethacrylates and cellulose polymers such as hydroxypropyl-methyl cellulose, hydroxypropyl cellulose and cellulose acetophthalates. U.S. Pat. No. 6,136,347 describes flavor-masked pharmaceutical compositions that include microcapsules coated with water insoluble neutral methacrylic acid ester copolymers and triethylcitrate. PCT application WO 99/44581 discloses a process for taste masking of topiramate by coating the core with a taste masking coating mixture. The taste masking mixture includes cellulose acetate, cellulose acetate butyrate, methylcellulose, ethylcellulose or an Eudragit, and a disintegrant. U.S. 20060127479 to Kumaraperumal discloses a taste-masked drug coated with an acrylate polymer. U.S. 20060039981 to Murpani discloses a taste-masked drug coated with an acrylate polymer.

[009] Acceptable taste-masking in orodispersible dosage forms is difficult to achieve, especially with a drug such as TOP, since it is more difficult to mask the taste of a high-dose drug in such a dosage form. It is not possible to predict *a priori* which taste-masked form of TOP will be suitable for use in an orodispersible dosage form, since the process and components used to prepare the orodispersible dosage form would very likely alter the taste-masked TOP thereby forming unmasked TOP during preparation of the dosage form. Moreover, it is not possible to predict *a priori* whether a particular taste-

masked form of topiramate will retain its taste masking when incorporated into a three-dimensionally printed dosage form due to the use of various ingredients during printing and use of heat during drying.

[010] None of the above discloses a taste-masked rapidly dissolving solid oral dosage form containing TOP as described herein. It would be beneficial to provide a taste-masked rapidly-dispersing orodispersible solid oral dosage form containing TOP that exhibits sufficiently low friability and sufficient hardness to withstand storage and handling while at the same time exhibiting an extremely rapid disintegration rate and acceptable taste; however, no such suitable dosage form containing TOP has been disclosed in the art. In particular, no such three-dimensionally printed dosage form has been disclosed.

SUMMARY OF THE INVENTION

[011] 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 topiramate as the primary or sole active ingredient, wherein the dosage form comprises a bound matrix that disperses/disintegrates in 2 min or less in a volume of 15 ml or less of water or saliva and the topiramate remains taste-masked even after dispersion of the dosage in the mouth of a subject. The matrix disperses in the mouth of a subject to which it is administered, thereby facilitating swallowing and administration. In some embodiments, the disintegration time is determined according to USP <701>

[012] In some aspects, the invention provides a taste-masked rapidly dispersible, i.e. orodispersible, dosage form and administration thereof for the treatment of diseases, conditions or disorders that are therapeutically responsive to topiramate. The rapidly dispersible solid dosage form comprises a three-dimensionally printed matrix comprising TOP 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 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 taste, sufficient hardness, low friability and suitable dispersion time in a small volume of aqueous liquid.

[013] The topiramate is included in the matrix and bulk material as taste-masked particles comprising topiramate and at least one waxy material. In general, the weight percentage of topiramate does not exceed the total weight percentage of waxy material(s).

The weight ratio of topiramate to total waxy material is typically about 50:50 to about 20:80, about 50:50 to about 30:70, or about 50:50 to about 40:60.

[014] In some embodiments, prior to being coated with waxy material, topiramate (TOP) particles typically have an average or mean particle size in the range of about 30-50 microns (volume mean diameter, VMD), and/or have a D90 of less than about 200 microns, a D90 of less than about 150 microns, a D90 of less than about 125 microns, a D90 of less than about 100 microns, a D90 less than 65 microns, a D90 of about 50 to about 70 microns, and/or have a D50 of less than about 100 microns, a D50 of less than about 75 microns, a D50 of less than about 60 microns, a D50 of less than about 50 microns, a D50 of less than about 40 microns, a D50 of about 30 to about 50 microns, and/or have a D10 of less than about 50 microns, a D10 of less than about 40 microns, a D10 of less than about 30 microns, a D10 of less than about 20 microns, a D10 of about 5 to about 10 microns. After coating with waxy material, the coated particles typically have an average or mean particle size in the range of about 60 to about 250 microns, and/or have a D90 of less than 150 microns, a D90 of less than 125 micros, a D90 of less than 110 microns, and/or have a D50 of less than 120 microns, a D50 of less than 100 microns, a D50 of less than 75 microns, and/or have a D10 of less than 75 microns, a D10 of less than 50 microns, a D10 of less than 40 microns. TOP can be present as a mixture of two or more different native drug powders each having its own native particle size distribution and/or method of preparation.

[015] The taste-masked 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 taste-masked particles may have a D10 of 5-20 microns, a D50 from 30-60 microns and/or a D90 of 90-120 microns. The taste-masked particles can be present as a mixture of two or more different powders each having its own effective particle size distribution and/or method of preparation.

[016] In some embodiments, topiramate is present in crystalline form in the coated particles. All polymorphs of topiramate are contemplated. It can also be present in crystalline form prior to coating. The crystallinity of topiramate or any other material can be determined by differential scanning calorimetry (DSC) to determine the presence of amorphous material. In some embodiments, topiramate is present in amorphous form in the coated particles.

[017] The invention also provides a taste-masked orodispersible dosage form comprising a three-dimensionally printed matrix comprising bound particles of wax-coated topiramate, sweetener, binder, and surfactant, wherein the particles are bound by binder. The particles forming the matrix are not bound by topiramate. The printing fluid does not substantially dissolve topiramate during a three-dimensional printing process. The matrix optionally further comprises disintegrant.

[018] One aspect of the invention provides a taste-masked orodispersible three-dimensionally printed matrix comprising:

bound particles of taste-masked wax-coated topiramate, at least one sweetener, at least one binder, and optionally at least one disintegrant;

at least one surfactant, and at least one glidant; wherein

the particles are bound by binder;

the matrix is porous and non-compressed;

the matrix disperses in less than 90 sec in a volume of 15 ml of aqueous fluid; and

the weight ratio of topiramate to wax in the particles ranges from 20:80 to 50:50.

[019] Some embodiments of the invention include those wherein: a) the wax coated particles of topiramate are prepared by spray congealing a mixture comprising molten wax and particles of topiramate; b) the wax is not an ionic polymer or copolymer, an acrylate polymer or copolymer, a methacrylate polymer or copolymer, or an enteric polymer or copolymer; c) the wax coating comprises one or more, one, two, or three different waxes; d) the surfactant is present in an amount ranging from 0-2 % wt based upon the final weight of the dosage form; e) the total amount of wax coated particles ranges from 20-50% % wt based upon the final weight of the dosage form; f) the hardness of the matrix ranges up to about 1.0 kiloponds; g) binder is introduced into the matrix by way of printing fluid used to form the matrix; h) binder is introduced into the matrix by way of bulk powder used to form the matrix; i) the matrix comprises about 25 to about 200 mg of topiramate; j) the matrix comprises 10 to 40 printed incremental layers; k) the thickness (height) of an incremental layer ranges from 0.008 to 0.012 inches; l) the at least one sweetener is present in an amount range from 0-2% or >0 to about 2% based upon the final weight of the dosage form; m) the at least one binder is present in an amount range from >0 to about 20% based upon the final weight of the dosage form; n) the optional

disintegrant is present in an amount range from 0-30% based upon the final weight of the dosage form; o) the at least one glidant is present in an amount range from 0-2% based upon the final weight of the dosage form; and/or p) surfactant is present in the wax-coated topiramate particles..

[020] A method of treating a disease or disorder that is therapeutically responsive to topiramate is provided. The method comprises daily administering 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.

[021] A method of preparing a taste-masked orodispersible dosage form is also provided. The method comprises forming a porous matrix as described herein by forming incremental layers of powders and depositing printing fluid on each incremental layer to bind disintegrant, binder, surfactant, glidant, sweetener and wax coated particles of topiramate into a non-compressed porous matrix.

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

BRIEF DESCRIPTION OF THE FIGURES

[023] 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.

[024] 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.

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

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

[027] FIG. 4A depicts a sectional front elevation of an alternate embodiment of an orodispersible dosage form made from a three-dimensionally printed matrix.

[028] FIG. 4B depicts a perspective view of the dosage form of FIG. 4A

DETAILED DESCRIPTION OF THE INVENTION

[029] As used herein and unless otherwise specified, the term topiramate refers to the drug in underivatized or derivatized form. Topiramate also includes a topiramate derivative such as topiramate palmitate. Topiramate also includes novel salts of topiramate, and pharmaceutically acceptable polymorphs, solvates, hydrates, dehydrates, co-crystals, anhydrous, or amorphous forms thereof, as are described in U.S. Pat. No. 7,351,695, hereby incorporated by reference.

[030] The present invention provides a taste-masked orodispersible dosage form comprising particles of topiramate coated with one or more waxy materials. The dosage form comprises a non-compressed matrix of particles bound by binder. The matrix comprises wax-coated particles of topiramate, glycerin, binder, surfactant and optional disintegrant. The matrix is porous and disperses within less than 90 sec when placed in a minimal amount of water. The dosage form provides improved taste-masking and rapid dispersion as compared to other three-dimensionally printed dosage forms comprising polymer-coated particles of topiramate, cyclodextrin complex of topiramate, and others. The wax-coated particles are preferably prepared by spray-congealing, a melt comprising topiramate and at least one wax material.

[031] Various different three-dimensionally printed (3DP) dosage forms comprising coated particles of topiramate were prepared according to Example 3. Comparator coated particles had been prepared by ion exchange complexation, hot melt extrusion, roller compaction, supercritical fluid coating, complexation with cyclodextrin, or fluid bed coating. The resulting 3DP dosage forms were evaluated by several subjects for taste to determine which if any of the comparator coated particles provided sufficient taste-masking of topiramate. It was determined that none of the comparator formulations provided adequate taste-masking. It is believed that the printing fluid might be dissolving a part of the surface coating of the comparator coated particles during the printing and/or drying step of the 3DP process.

[032] On the other hand, the 3DP dosage forms of the invention which comprise spray-congealed wax coated particles of topiramate provided excellent taste-masking. Even after dispersion in the mouth, the bitter taste of topiramate was not apparent to the subjects. The inventors could not have predicted *a priori* which type of taste-masked coated particles would be suitable for preparation of a taste-masked orodispersible 3DP dosage form. Accordingly, the present inventors have discovered that one can achieve

acceptable taste-masking in a topiramate-containing 3DP dosage form without having to coat the topiramate with a polymeric material.

[033] The topiramate is coated with at least one waxy material, which is not an ionic polymer or copolymer, an acrylate polymer or copolymer, a methacrylate polymer or copolymer, or an enteric polymer. Inclusion of a waxy material in a 3DP matrix, however, presents substantial challenges in creating dosage forms that possess sufficient hardness. The wax tends to soften the matrix, especially when the matrix comprises a substantial weight percentage of coated particles. The wax also tends to increase the dispersion time of a 3DP orodispersible dosage form. As a result, the physical properties of the 3DP dosage form can be different that desired.

[034] It has been determined that inclusion of a surfactant in the printing fluid aids in ensuring rapid dispersion of the 3DP dosage form without sacrificing taste-masking. Surfactant may also be included in the wax-coated topiramate particles. This result is unexpected as surfactants are typically used in cleaning compositions to dissolve waxes. Before evaluation of the surfactant employed herein, the inventors could not *a priori* predict whether or not the surfactant would interfere with taste-masking.

[035] The weight ratio of topiramate to waxy material can be varied; however, doing so will have an impact upon hardness, dispersion time, taste-masking, size and drug dose of the dosage form. If the waxy material content is too low, the taste-masking will be insufficient. If the waxy material content is too high, the hardness will be too low, the dispersion time will be too high, and the size of the dosage form would have to be increased substantially in order to include a suitable dose of topiramate therein.

[036] It has been determined that the waxy material should be present in at least equivalents amounts as topiramate and is preferably present in excess amounts over topiramate. In some embodiments, the weight ratio of topiramate to waxy material is in the range of 20:80 to 50:50, 30:70 to 50:50 or 40:60 to 50:50.

[037] The waxy coating can comprise one or more, one, two, or three different waxes.

[038] In some embodiments, the waxy material is selected from the group consisting of glyceryl dipalmitostearate (BIOGAPRESS VEGETAL), glyceryl distearate (glycerol distearate (PRECIROL®), glycerol palmitostearate, glyceryl dibehenate (COMPRITOL 888), mono and diglyceride mixture (GELEOL), glycerol monostearate,

beeswax, carrnuba wax, or cetyl esters wax. The waxy material is preferably glyceryl dipalmitostearate glyceryl or distearate.

[039] A surfactant aids in dispersion of the 3DP dosage form when placed in a minimal amount of water. The surfactant serves to enhance wetting of the waxy coated particles without reducing or eliminating taste-masking. The surfactant does not dissolve the coating to any substantial degree when the dosage form is administered to a subject. It 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. It may also negatively impact taste, due to the taste of the surfactant itself. In some embodiments, the surfactant is present in an amount ranging from 0.0-2.0%, 0.1%-1.0%, 0.2%-0.9% wt. based upon the weight of the finished dosage form.

[040] The rapidly dispersible dosage form can disperse (disintegrate) in less than about 3 min, less than about 2.5 min, less than about 2 min, less than about 1.5 min, less than about 60 seconds, less than about 30 seconds, 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 dispersion (disintegration) time is measured by swirling in a beaker with 15 ml of water. In some embodiments, the disintegration time is determined according to USP <701>.

[041] The small volume of aqueous fluid can be a sip such as a volume 50 ml or less, 40 ml or less, 30 ml or less, 20 ml or less, 10 ml or less, 5 ml or less, 2.5 ml or less or 1 ml or less. 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, 5 to 10 ml, 1 to 7.5 ml, 1 to 5 ml, 0.5 to 3 ml, or other such ranges. In a preferred embodiment, the sip may comprise about a tablespoon (15 ml) of water. 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).

[042] 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.

[043] In some embodiments, the overall hardness (as determined by a tablet breaking force assay according to USP <127>) of the matrix ranges from 0.5 kp to about 5 kp or from about 0.5 kp to about 2 kp. In some embodiments, the overall hardness is at least 0.5 kp, at least 1.0 kp or at least 1.5 kp. In some embodiments, the overall hardness is no more than 3.0 kp, no more than 2.0 kp or no more than 1.0 kp. In some embodiments, the dosage form is found to be adequate for handing and administration without providing a numerical result on a tablet hardness tester.

[044] The term friability is 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.

[045] 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.

[046] In some embodiments, the bulk density of the dosage form (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).

[047] 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.

[048] 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 wicking 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.

[049] 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.

[050] A particularly suitable printing assembly for three-dimensional printing of the instant dosage form 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.

[051] 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 and topiramate.

[052] 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) under conditions of handling, storage, and administration. The strength and extent of the particle binding depends on the proportion of the binding agent either in the powder layer or deposited by the printing fluid, 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 two or more of these different ways.

[053] 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.

[054] The binding agent can be a pharmaceutically acceptable binder. Including a "binder" as the binding agent in the printing fluid will result in a different internal microstructure of the dosage forms, particularly the pore size, than the internal microstructure of an otherwise same dosage form 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 dosage forms fabricated without binder in the printing fluid.

[055] The invention provides a process for the preparation of a rapidly dispersing solid dosage form comprising a three-dimensionally printed solid porous matrix comprising carrier, binder and drug, the process comprising: (a) providing a powdered mixture of one or more binders, one or more sweeteners, one or more humectants, one or

more glidants, optionally one or more disintegrants, and drug, 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.

[056] 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, donut, ring, tube, cube, spheroid, ellipsoid or rectangular box. In some embodiments, a donut shape may improve the dispersion time versus a shape of similar volume and composition but having no through-hole. In some instances of those embodiments, the dispersion or disintegration time may decrease by 50-80%.

[057] 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.

[058] 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.

[059] 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. 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. 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 recessed indicum in the surface of the final dosage form without pressing into the article as would be done with known techniques such as debossing or engraving.

[060] 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; j) plural layers of first solid print pattern, plural layers of combination annular and grayscale print pattern, and plural layers of indicum print pattern.

[061] 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; 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; e) plural layers of a first solid a first solid print pattern.

[062] The dosage form can also be shaped as a donut, ring or tube. FIG. 4A depicts an exemplary dosage form wherein the core of the dosage form about the vertical axis of the cylindrical shape has been left out or removed during manufacture of the dosage form. The diameter of the bore or hole can be in the range of 3-10 mm. In some embodiments, the hole is created via an unprinted zone within the dosage form and reaching at least one exterior surface such that unbound powder empties out. FIG. 4B depicts a perspective view of the dosage form of FIG. 4A.

[063] 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. Some of these variables were studied to determine which of those are result effective variables with respect to dosage form hardness, bulk density,

disintegration time, dissolution time, bioavailability, moisture content, taste, and friability. It was determined that the result effective variables include, at least, the amount of drug, amount of disintegrant, amount of binder, layer thickness, identity of some components, composition of the waxy material, and printing fluid saturation level.

[064] 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.

[065] 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.

[066] 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.

[067] 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.

[068] 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 (void volume basis) 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 is varied as needed to provide the target hardness and dispersion time. The saturation level can to a powder layer range from about 85% to about 120%, 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.

[069] 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 (uninterrupted series) of droplets while depositing printing fluid onto a powder layer. Continuous jet printheads may be used in conjunction with droplet deflection systems on order to select and control which droplets are deposited. 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. On some 3DP machines,

a printhead scans (moves across and selectively 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 printing fluid, an increase in the print speed from 1.0 m/s to 2.0 m/s reduces the total volume of printing fluid deposited in the dosage forms by half. As the print speed increases, the bulk density (theoretical, calculated from the weight and dimensions of the dosage form) decreases. A simultaneous decrease in the dimensions and weight of the dosage forms is also seen. This decrease is attributed to three factors: (i) a decrease in the total volume of droplets deposited onto the powder results in a decrease in the extent of printing fluid spreading in the powder; (ii) a decrease in the mass of nonvolatile components from the printing fluid that remain behind; (iii) a greater tendency for loss of material from the edges of more friable dosage forms during separation from the unprinted powder. Increasing the print speed also decreases the flash time and the hardness and increases the friability of the dosage forms. This result is obtained because the proportion of binding agent from the printing fluid (or the level of activation of binding agent in the powder) decreases in the dosage forms as the print speed increases. An increase in the print speed also increases the void volume inside the dosage forms, as illustrated by an increase in the percent volume of the dosage forms penetrated by mercury at 30 psi (% intrusion).

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

[071] The volume of individual droplets can be varied as desired. 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 rate. When using a continuous jet printhead, the size of the fluid droplets delivered by the printhead preferably ranges from about 10 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 20 μm to about 300 μm in diameter.

[072] The flow rate of the fluid delivered by the printhead can be varied as desired. Increasing the flow rate increases the saturation level and decreasing the flow rate

decreases the saturation level when comparing printing fluid deposition at a constant 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 preferably are about 55 to 75 μm.

[073] 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, preferably 15 to 25 layers. A matrix will typically comprise (consist essentially of or consist of) 20 to 50, 20 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, or 4 to 6 printed incremental layers. An end section with an indicum will typically comprise 2 to 10, 2 to 7, 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.

[074] Dosage forms produced by the 3DP process described herein vary in size according to the content of TOP and of excipients required to provide dosage forms exhibiting the desired properties. If the matrix comprises a higher dose of TOP, then a larger wafer is required as compared to another 3DP dosage form having the same percentage but lower dose of TOP. If a higher percentage of TOP is used, the dosage form weight can be decreased correspondingly and *vice versa*.

[075] 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, 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.

[076] 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.

[077] 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).

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

[079] 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. 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 0-20 % wt, 5-15 % wt or 8-12 % wt of binder. In some embodiments, the bulk powder comprises >0 to 10% wt, 1 to 5% wt, 0-30 % wt, 2-20 % wt or 5-15 % wt of binder. In some embodiments, the printed matrix comprises 0-30 % wt, 2-20 % wt or 5-15

% wt of binder. In some embodiments, binder is absent from the printing fluid or absent from the bulk material. Suitable binders include water-soluble synthetic polymer, polyvinlypyrrolidone, hydropropylmethylcellulose, copovidone (copolymer of vinyl acetate and vinyl acetate), partially or fully pre-gelatinized cornstarch, and hydroxypropylcellulose. A preferred binder is polyvinylpyrrolidone (povidone). In one preferred embodiment, the povidone (povidone K30) is characterized as exhibiting a k-value of approximately 27-32. In some embodiments, a water-soluble diluent aids binding of the matrix, with or without use of a traditional binder. Suitable diluents in this capacity include sugars and sugar-alcohols or polyols such as mannitol, sorbitol, xylitol, lactitol, erythritol. In this capacity, the diluent that aids binding may comprise 15-50%, or 30-45% of the printed matrix. In a preferred embodiment, the diluent that aids binding is mannitol.

[080] One or more disintegrants can optionally be included in the printed matrix. The disintegrant can be present in the bulk powder. In some embodiments, the bulk powder comprises 0 to 30% wt, 2 to 25% wt, 5 to 15% wt, or 5 to 10% wt of disintegrant. Suitable disintegrants include microcrystalline cellulose (MCC), crospovidone (cross-linked polyvinylpyrrolidone), or a combination thereof. In one preferred embodiment, the disintegrant is microcrystalline cellulose. Suitable grades of AVICEL® microcrystalline cellulose 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

Product Grades	Nominal Particle Size, μm	Moisture, %	LooseBulk Density, g/cc
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”.

[081] In another preferred embodiment, the disintegrant is crospovidone. When the disintegrant is crospovidone only, it may comprise 2-10% of the bulk powder. Crospovidone is a water-insoluble synthetic cross-linked homopolymer of N-vinyl-2-pyrrolidinone that is used as a superdisintegrant in conventional pharmaceutical processing, e.g., tableting. Several grades of crospovidone are available, including for example the product line offered by BASF that is distinguished by particle size for each grade: Kollidon® CL (110-130 microns), Kollidon® CL-F (20-40 microns), Kollidon® CL-SF (10-30 microns), and Kollidon® CL-M (3-10 microns).

[082] 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.

[083] 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. More efficient taste-masking is observed when at least one sweetener is present in at least the printing fluid. 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 printing fluid and the bulk powder each comprise sucralose or a glycyrrhizinic acid

derivative. In some embodiments, the printing fluid and the bulk powder each comprise sucralose, and the bulk powder further comprises a glycyrrhizinic acid derivative. 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% wt, >0 to 4% wt, >0 to 3% wt, >0 to 2% wt., 0.1 to 5% wt, 0.1 to 4% wt, 0.1 to 3% wt, 0.1 to 2% wt, 0.5 to 3% wt, or 1 to 3% wt sweetener.

[084] Suitable sweeteners are selected from the group consisting of glycyrrhizinic acid derivative, e.g. magnasweet (monoammonium glycyrrhizinate), sucralose, other natural or artificial sweeteners, and a combination thereof. The preferred sweetener in the printing fluid is sucralose. Sweetener is present in at least the printing fluid but may also be present in the bulk powder.

[085] Some ingredients that may be used for other purposes in the bulk powder may also contribute to sweetness. Examples of this are diluent powders such as mannitol, sorbitol, and xylitol.

[086] One or more optional flavorants can be included in the matrix. The flavorant can be present in the bulk powder and/or the printing fluid. If present in the printing fluid, the flavorant is preferably water soluble, aqueous fluid soluble, partially water soluble or partially aqueous fluid soluble. If present in the bulk powder, the flavorant is preferably present in a form applied to a carrier powder before preparation of the bulk powder. Suitable carrier powders may include starches, modified starches, celluloses, and other powder capable of absorbing, adsorbing, encasing, or encapsulating the flavorant. In some embodiments, the printing fluid comprises 0-5% % wt, 0.01-1.0 % wt or 0.05-0.5% wt of flavorant. In some embodiments, the bulk powder comprises 0.1 to 10% wt, or 1 to 10% wt, 2 to 8% wt, 3-7 % wt of flavorant-incorporated carrier powder. In some embodiments, the printed matrix comprises 0-10 % wt, 0.01- 10% wt of flavorant. In some embodiments, the flavorant is absent from the printing fluid or absent from the bulk material. Suitable flavorants include peppermint, spearmint, mint, vanilla, orange, lemon, citrus, lime, grape, cherry, strawberry, chocolate, coffee or a combination thereof.

[087] One or more surfactants can be included in the printing fluid and/or in the wax-coated topiramate particles. The surfactant is independently selected upon each occurrence. In some embodiments, the printing fluid comprises 0 to about 10%, >0 to about 7%, about 1 to about 5%wt of surfactant. In some embodiments, surfactant is

present in the wax coated at a range of 0.3 to 15]% wt, 1 to 12% wt, 1.5-9% wt, 2-6% wt. based upon the weight of wax coated particles included in the dosage form.

[088] 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).

[089] 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.

[090] One or more glidants can be included in the bulk powder. In some embodiments, the bulk powder comprises 0 to about 2%, >0 to about 1%wt of glidant. Suitable glidants include fumed silica (colloidal silicon dioxide).

[091] In some embodiments, the pharmaceutically acceptable excipient in the bulk powder is selected from the group consisting of spray dried lactose, fructose, sucrose, dextrose, sorbitol, mannitol, and xylitol. These might be considered as diluents or low affinity binders. They can be included in the powder in amounts ranging from 0 to about 70%, about 10 to about 60, or about 20 to about 50%.

[092] 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.

[093] 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.

[094] In some embodiments, the printing fluid comprises 0 to about 20% wt, >0 to about 15%, >0 to about 10% or >0 to about 5%wt of glycerin. In some embodiments, the matrix comprises 0 to about 2% or >0 to about 1% wt of glycerin.

[095] 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.

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

[097] The printing fluid can comprise about 75% to about 95%, or about 80% to about 90% % wt of water.

[098] The printing fluid can comprise 0 to about 20%, >0 to about 20%, >0 to about 15%, >0 to about 10%, >0 to about 5%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.

[099] 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).

[0100] 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.

[0101] 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.

[0102] One or more of the components of the formulation can be present in its free base or pharmaceutically or analytically acceptable salt form. As used herein, "pharmaceutically or analytically acceptable salt" refers to a compound that has been modified by reacting it with an acid as needed to form an ionically bound pair. Examples of acceptable salts include conventional non-toxic salts formed, for example, from non-toxic inorganic or organic acids. Suitable non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and others known to those of ordinary skill in the art. The salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and others known to those of ordinary skill in the art. Lists of other suitable salts are found in *Remington´s Pharmaceutical Sciences*, 17th. ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the relevant disclosure of which is hereby incorporated by reference.

[0103] The invention also provides a method of administering topiramate 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.

[0104] The invention also provides a method of treating a disease, disorder or condition that is therapeutically responsive to topiramate, 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 topiramate, a bulk powder, and binder, and the matrix is dispersible in a small volume of fluid. The dosage and administration regimens detailed in the package insert for TOPAMAX® can be followed for administering the instant dosage form.

[0105] 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 coated particles

[0106] The following process is used to make particles of topiramate coated with a waxy material. The following ingredients in the amounts indicated are used.

INGREDIENT	**AMOUNT (% WT.)**	**AMOUNT (% WT.)**	**AMOUNT (% WT.)**	**AMOUNT (% WT.)**	**AMOUNT (% WT.)**	**AMOUNT (% WT.)**
Topiramate	50	40	50	50	50	30
GDPS	50	60	X	X	X	70
GELUCIRE	X	X	50	X	X	X
Vanillin	X	X	X	50	X	X
Poloxamer	X	X	X	X	50	X

[0107] The coated particles are made by spray congealing a molten mixture of the topiramate and waxy material. A modified lab scale spray dryer SD45 (Buchi, model B-290) can be used.

[0108] The feed suspensions/solutions are prepared by melting the excipient and then adding the topiramate while stirring. A spray congealing unit is operated in open cycle mode, i.e., without recirculation of the congealing nitrogen. The gas flowrate is controlled by a Coriolis flow meter (Model R025S) and its temperature was adjusted using a refrigerator containing ethanol and dry ice. Both feeding vessel and nozzle are thermo-controlled using hot water. In addition all the feeding pipes are heated by means of an electric tracing to avoid the cooling of the suspension inside the pipes that could lead to clogging.

[0109] Before initiating each batch, the spray congealing unit is stabilized with nitrogen to obtain the desired inlet temperature. After stabilization of the inlet temperature, the solution/suspension is fed into the spray congealing equipment and atomized at the nozzle's tip. The small droplets are then congealed in the spray congealing chamber by the co-current congealing nitrogen. The stream containing the frozen particles of product leaves the chamber and enters the cyclone, where most of the solids are separated and collected in the collecting vessel.

[0110] If needed, feeding of viscous solutions/suspensions can be improved by coupling a hot melt extruder (run at approximately 100-150° C) to the atomization system. The extruder forces a melt through the nozzle tip to cause atomization. A hot melt extrusion equipment assembly as described in U.S. 7,625,507, the entire disclosure of which is hereby incorporated by reference, can be used to prepare coated particles as described herein.

[0111] Approximately 50 to 100 g of molten material are charged into the spray congealing unit. Typical operating conditions include:

Congealing nitrogen temperature (° C): -45 to -25

Water temperature (° C): 75-95

Atomizing nitrogen height in rotameter (mm): 25-60

Inlet temperature (° C): -40 to -20

Outlet temperature (° C): -10 to -3

Gas flowrate (kg/h): 15 – 30

Feed (melt) flowrate (ml/min): 1 to 10 or about 5

Holt melt extruder (HME) temp (if present) (° C): 90-120

HME screw rotation (rpm): 50 – 100

[0112] Following atomization, the droplets of molten material congeal in the chamber to form coated particles comprising topiramate and excipient.

EXAMPLE 2

Determination of crystallinity

[0113] A differential scanning calorimeter is used to determine the level of crystallinity of materials before and after inclusion in coated particles. The following process for the temperature ramping profile was used.

1. Equilibrate at -10°C;
2. Ramp 10°C/min to 70°C;
3. Isothermal for 5 min;
4. Ramp 10°C/min to -20°C;
5. Equilibrate at -20°C;
6. Modulate ±0.8°C every 60s;
7. Isothermal for 2 min;
8. Ramp 5°C/min to 250°C;
9. Ramp 5°C/min to -10°C.

EXAMPLE 3

Preparation of a taste-masked three-dimensionally printed orodispersible dosage form

[0114] The following process is used to prepare a taste-masked three-dimensionally printed orodispersible dosage form comprising a matrix comprising bound coated particles of topiramate. 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	I-E
Water (% wt)	85	80	83	88	87
Glycerin (% wt)	5	5	5	0	5
Ethanol (% wt)	5	5	5	5	5
Tween 20 (% wt)	1	1	0	0	0
Tween 80 (% wt)	0	0	5	0	0
Sucralose (% wt)	2	2	2	2	2

Sodium lauryl sulfate (% wt)	2	2	0	0	0
PEG 400 (% wt)	0	5	0	0	0
Lutrol L44 (% wt)	0	0	0	5	0
Polysorbate (% wt)	0	0	0	0	1

Bulk powder:	II-A	II-B	II-C	II-D	II-E
Topiramate (coated particles) (% wt)	40	40	40	40	40
SLS (% wt)	1	1	1	1	1
Silica (colloidal silicon dioxide; % wt)	1	1	1	1	1
PVP K29/32 (% wt)	10	10	8	0	8
Mannitol 50 C (% wt)	24	24	30	30	30
Avicel PH101 (% wt)	24	24	0	0	0
HPC LH-22 (% wt) (hydroxypropylcellulose)	0	10	20	20	20
HPC-SL (%wt)	0	0	0	8	0
Kollidon CL-SF	0	0	0	0	0

	II-F	II-G	II-H	II-J	II-K
Topiramate (coated particles) (% wt)	40	40	20	20	30
SLS (% wt)	1	1	1	1	1
Silica (colloidal silicon dioxide; % wt)	1	1	1	1	1
PVP K29/32 (% wt)	8	8	8	8	0
Mannitol 50 C (% wt)	30	30	50	50	68
Avicel PH101 (% wt)	0	0	0	0	0
HPC LH-22 (% wt) (hydroxypropylcellulose)	20	20	20	20	20
HPC-SL (%wt)	0	0	0	0	0
Kollidon CL-SF	0	0	0	0	0

	II-L	II-M	II-N	II-O	II-P
Topiramate (coated particles) (% wt)	30	30	40	40	40
SLS (% wt)	1	1	1	1	0
Silica (colloidal silicon dioxide; % wt)	1	1	1	1	1

PVP K29/32 (% wt)	4	4	10	10	0
Mannitol 50 C (% wt)	64	64	24	24	44
Avicel PH101 (% wt)	0	0	24	24	0
HPC LH-22 (% wt) (hydroxypropylcellulose)	0	0	10	10	0
HPC-SL (%wt)	0	0	0	0	15
Kollidon CL-SF	0	0	0	0	0

	II-Q	II-R	II-S	II-T	II-U
Topiramate (coated particles) (% wt)	40	40	40	40	50
SLS (% wt)	0	0	0	0	0
Silica (colloidal silicon dioxide; % wt)	1	1	1	1	1
PVP K29/32 (% wt)	5	0	0	5	10
Mannitol 50 C (% wt)	49	51.5	46.5	49	29
Avicel PH101 (% wt)	0	0	0	0	0
HPC LH-22 (% wt) (hydroxypropylcellulose)	0	0	0	0	0
HPC-SL (%wt)	0	7.5	7.5	0	0
Kollidon CL-SF	5	0	5	5	10

[0115] Any three dimensional printer equipment assembly, known or mentioned herein, can be used. 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.

[0116] The following printing parameters are used on a Z-Corp lab scale printer (Model Z310). The printer is equipped with a HP-10 printhead and is operated at a droplet size of 35 μm and line spacing of 450-600 μm. A solid print pattern is used throughout the dosage form. The specified combination of printing fluid formulation and bulk powder formulation is used.

Printing Parameters:	III-A	III-B	III-C	III-D	III-E
Layer thickness (inches)	0.01	0.01	0.01	0.01	0.01
Saturation (%)	110	110	110	110	110
Printing fluid	I-A	I-A	I-A	I-A	I-B
Bulk Powder	II-A	II-B	II-C	II-D	II-E

Printing Parameters:	III-F	III-G	III-H	III-J	III-K
Layer thickness (inches)	0.01	0.008	0.01	0.008	0.01
Saturation (%)	116	145	116	145	116
Printing fluid	I-B	I-B	I-B	I-B	I-B
Bulk Powder	II-F	II-G	II-H	II-J	II-K

Printing Parameters:	III-L	III-M	III-N	III-O	III-P
Layer thickness (microns)	0.01	0.008	0.01	0.01	0.01
Saturation (%)	116	145	116	116	116
Printing fluid	I-B	I-B	I-C	I-D	I-D
Bulk Powder	II-L	II-M	II-N	II-O	II-P

Printing Parameters:	III-Q	III-R	III-S	III-T	III-U
Layer thickness (microns)	0.01	0.01	0.01	0.008	0.01
Saturation (%)	116	116	116	116	116
Printing fluid	I-D	I-D	I-D	I-D	I-D
Bulk Powder	II-Q	II-R	II-S	II-T	II-U

[0117] 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 taste-masked 3DP orodispersible dosage form. Dosage form weights ranged from 300 to 1200 mg or 330 to 1000 mg.

Final composition	IV-A	IV-B
Topiramate (% wt)	12-17	17-22
SLS (% wt)	2-3	2.5-3.5
Colloidal silicon dioxide (% wt)	0.5-1.5	0.5-1.5
PVP(% wt)	2-7	7-12

Kollidon (% wt)	2-7	7-12
Mannitol (% wt)	42-52	22-32
MCC (% wt)	0-15	0-10
HPC (% wt)	0-10	0-10

[0118] The dispersion time, hardness and acceptability of taste-masking of the dosage form are then determined.

EXAMPLE 4

Preparation of a taste-masked three-dimensionally printed orodispersible dosage form

[0119] The 3DP process described above is used to prepare a taste-masked three-dimensionally printed orodispersible dosage form comprising a matrix comprising bound coated particles of topiramate. The ingredients for the printing fluid and the bulk powder are used in the amounts indicated below:

Printing fluid	V-A	V-B
Water (% wt)	80-90	80-90
Glycerin (% wt)	0.05-20	1-8
Alcohol (% wt)	0.1-20	5-20
First Surfactant (% wt)	0.05 - 10	2-7
Sweetener (% wt)	0.1 – 5	1-3
Second Surfactant (% wt)	0 - 10	0-5

Bulk powder:	VI-A	VI-B
Topiramate (coated particles) (% wt) (35-45 % TOP in particles)	20-50	40-50
surfactant (% wt)	0 - 5	0-5
Silica (colloidal silicon dioxide; % wt)	>0 - 5	0.5-2
First Binder (% wt)	20 - 50	30-50
Second Binder (% wt)		5-10
Disintegrant(s) (% wt)	0-30	5-10

[0120] The printing fluid is applied to incremental layers of bulk powder by way of a 3DP process to prepare a taste-masked three-dimensionally printed orodispersible dosage form comprising a matrix comprising bound coated particles of topiramate.

Final composition	VII-A	VII-B
Weight of dosage form (mg)	335-365	
Topiramate (% wt)	15-20	
Wax (% wt)	20-30	
Surfactant (% wt)	2.5-3.5	
Colloidal silicon dioxide (% wt)	0.5-1.5	
PVP(% wt)	4.5-10	
Mannitol (% wt)	25-50	
Crospovidone (% wt)	4.5-10	
Sweetener (% wt)	1-2	

EXAMPLE 5

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

[0121] 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 dosage form having greater hardness in the upper and lower surfaces as compared to the hardness of the interior portion of the dosage form. This tactic helps create sections within a dosage form with different mechanical properties. This approach is used to design dosage forms in which the composition of the top and bottom layers is different from the middle layers. This design allows the dosage forms to have stronger top and bottom layers, thereby increasing hardness and reducing friability, and a large middle portion with lower hardness, which enables the dosage form to disperse rapidly.

Method A:

[0122] 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 dosage forms, 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:

[0123] The process of Example 3 is followed to prepare these dosage forms, 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:

[0124] 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).

Method D:

[0125] 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:

[0126] 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 6

Preparation of a non-taste-masked three-dimensionally printed orodispersible dosage form

[0127] The process above is followed to prepare a non-taste-masked three-dimensionally printed orodispersible dosage form comprising a matrix comprising bound uncoated particles of topiramate. The only difference is that the topiramate particles are uncoated and therefore smaller in size than the particles of Example 3. Since the uncoated particles are approximately half the weight of coated particles, the weight of topiramate is adjusted accordingly to provide substantially the same dosage strengths.

EXAMPLE 7

Characterization of Dosage Forms

[0128] The following procedures were used to characterize the three-dimensionally printed solid porous orodispersible matrices.

Friability

[0129] 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 dosage forms 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.

Hardness

[0130] 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 dosage forms is measured by a fracture test. A dosage form is centered between the jaws of the tester and force is applied until the dosage form 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 dosage forms are tested.

Dispersion time

[0131] 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 dosage form 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 dosage form 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 dosage forms 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

[0132] The dispersion time observed for some of the dosage forms is approximately as follows.

	III-H	III-J	III-K	III-L	III-M
Dispersion Time (s)	52	59	34	58	90

	III-N	III-O	III-Q	III-S	III-T	III-U
Dispersion Time (s)	80	40	42	65	52	66

Bulk Density

[0133] The bulk density of the matrix is determined by measuring the weight of a dosage form and dividing that value by the calculated volume of the dosage form. The volume of a dosage form is calculated by measuring its dimensions and using the proper mathematical formula according to the shape of the dosage form. For example, for a cylindrical dosage form, 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 dosage form 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 Topiramate

[0134] 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 8

In vivo evaluation of three-dimensionally printed orodispersible dosage forms

[0135] This method is used to establish efficacy of the dosage form. Single dosage forms comprising topiramate 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) 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 topiramate will typically be between 50 – 400 mg. 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.

[0136] If a dosage form is being evaluated for just its level of taste-masking, there is no need to determine a pharmacokinetic or therapeutic profile. The subject can merely comment on the taste of the dosage form as to whether or not it is acceptable.

[0137] 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".

[0138] 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 taste-masked rapidly dispersible dosage form comprising a solid porous non-compressed bound matrix comprising:

taste-masked wax-coated particles comprising topiramate and at least one waxy material present at a weight ratio ranging from 20:80 to 50:50, respectively;

binder; and

surfactant; wherein,

the dosage form disperses in less than 90 sec when placed in aqueous fluid.

2) The dosage form of claim 1 further comprising one or more components selected from the group consisting of disintegrant, sweetener, diluent, glycerin and glidant.

3) The dosage form of any one of the above claims wherein: a) the wax coated particles of topiramate are prepared by spray congealing a mixture comprising molten wax and particles of topiramate; b) the wax is not an ionic polymer or copolymer, an acrylate polymer or copolymer, a methacrylate polymer or copolymer, or an enteric polymer or copolymer; c) the wax coating comprises one or more, one, two, or three different waxes; d) the surfactant is present in an amount ranging from 0-2 % wt based upon the final weight of the dosage form; e) the total amount of wax coated particles ranges from 20-50% % wt based upon the final weight of the dosage form; f) the hardness of the matrix ranges up to about 1.0 kiloponds; g) binder is introduced into the matrix by way of printing fluid used to form the matrix; h) binder is introduced into the matrix by way of bulk powder used to form the matrix; i) the matrix comprises about 25 mg, about 50 mg, about 100 mg, about 200 mg or from about 25 to about 200 mg of topiramate; j) the matrix comprises 10 to 40 printed incremental layers; k) the thickness (height) of an incremental layer ranges from 0.008 to 0.012 inches; l) the at least one sweetener is present in an amount range from 0-2% or >0 to about 2% based upon the final weight of the dosage form; m) the at least one binder is present in an amount range from >0 to about 20% based upon the final weight of the dosage form; n) the optional disintegrant is present in an amount range from 0-30% based upon the final weight of the dosage form; o) the at least one glidant is present in an amount range from 0-2% based upon the final weight of the dosage form; p) surfactant is present in the wax-coated topiramate particles; and/or q) surfactant is present in the wax coated at a range of 0.3 to 15]% wt, 1 to 12% wt, 1.5-9% wt, 2-6% wt. based upon the weight of wax coated particles included in the dosage form.

4) The dosage form of any one of the above claims wherein: a) the coated particles have an average or mean particle size in the range of about 60 to about 250 microns; b) topiramate particles in the wax-coated particles have an average or mean particle size in the range of about 30-50 microns; c) the matrix is a three-dimensionally printed matrix; d) the dosage form comprises not more than 10% wt moisture based upon the final weight of the dosage form; e) the hardness of the dosage form ranges from 0.5 to 3 kiloponds; f) the dosage form comprises 20 to 50 three-dimensionally printed incremental layers in stacked arrangement; and/or g) the average thickness of an incremental layer ranges from about 100 to about 400 microns.

5) The dosage form according to any one of the above claims, wherein the dosage form has been prepared by a three-dimensional printing process employing a printing fluid and a bulk powder of the following compositions:

Printing fluid:

Water (% wt)	80-90 or 80-90
Glycerin (% wt)	0.05-20 or 1-8
Alcohol (% wt)	0.1-20 or 5-20
First Surfactant (% wt)	0.05 – 10 or 2-7
Sweetener (% wt)	0.1 – 5 or 1-3
Second Surfactant (% wt)	0 – 10 or 0-5

Bulk powder:

Topiramate (coated particles) (% wt) (35-45 % wt TOP in particles)	20-50 or 40-50
surfactant (% wt)	0 – 5 or 0-5
Silica (colloidal silicon dioxide; % wt)	>0 – 5 or 0.5-2
First Binder (% wt)	20 – 50 or 30-50
Second Binder (% wt)	0-10 or 5-10
Disintegrant(s) (% wt)	0-30 or 5-10.

6) The dosage form according to any one of the above claims, wherein the dosage form has the following composition:

Topiramate (% wt)	15-20
Waxy material (% wt)	20-30
Surfactant (% wt)	2.5-3.5
Colloidal silicon dioxide (% wt)	0.5-1.5
PVP(% wt)	4.5-10
Mannitol (% wt)	25-50
Crospovidone (% wt)	4.5-10
Sweetener (% wt)	1-2

7) The invention according to any one of the above claims, wherein the dosage form is shaped as a wafer, cylinder, ring, donut, tube, cube, spheroid, ellipsoid or rectangular box.

8) A method of treating a disease, condition or disorder that is therapeutically responsive to topiramate 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.

FIG. 1

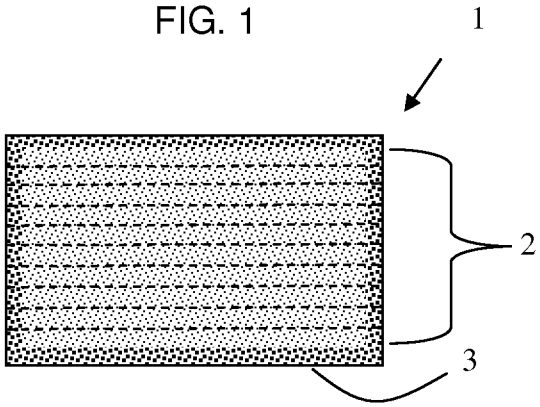


FIG. 2

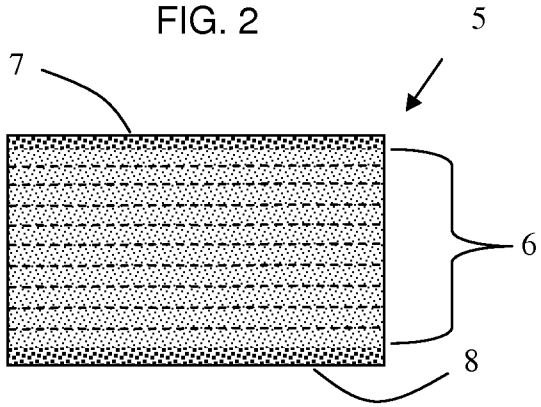


FIG. 3A

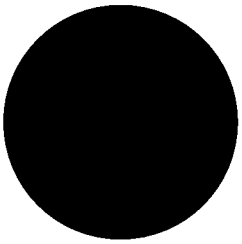


FIG. 3B

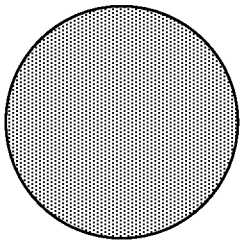


FIG. 3C

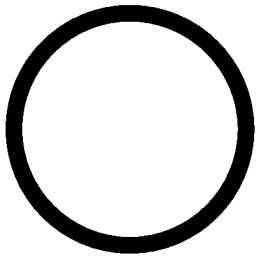


FIG. 3D

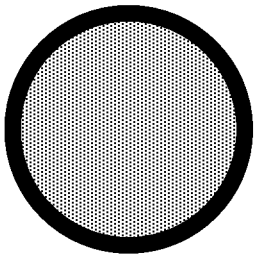


FIG. 3E

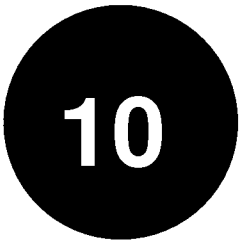


FIG. 4A

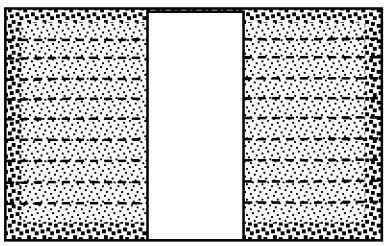
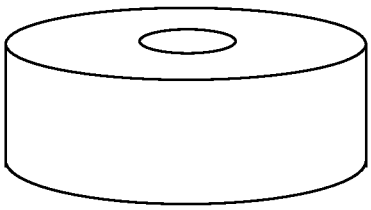


FIG. 4B



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K9/32 (2014.01)
USPC - 424/458
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 9/20, 9/28, 9/32, 9/50, 31/00; A61P 25/08 (2014.01)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 9/0056, 9/2077, 9/2806, 9/5005, 9/5084, 31/00; Y10S514/965, 977/906 (2014.06)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0207836 A1 (GENERAL et al) 16 August 2012 (16.08.2012) entire document	1-3
Y	US 2006/0099245 A1 (KUMAR et al) 11 May 2006 (11.05.2006) entire document	1-3
Y	US 2003/0143268 A1 (PRYCE LEWIS et al) 31 July 2003 (31.07.2003) entire document	1-3
A	US 2011/0212171 A1 (VENKATESH et al) 01 September 2011 (01.09.2011) entire document	1-3
A	WO 2009/106824 A2 (LULLA et al) 03 September 2009 (03.09.2009) entire document	1-3
A	US 2006/0039981 A1 (MURPANI et al) 23 February 2006 (23.02.2006) entire document	1-3

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

* Special categories of cited documents:
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"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
10 July 2014	30 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

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(54)发明名称

托吡酯的快速分散剂型

(57)摘要

本发明提供一种托吡酯的掩味的快速分散剂型。托吡酯的蜡包衣颗粒包含于多孔结合基质中。即使颗粒未用聚合材料包衣，托吡酯在个体的口中分散后仍然保持其掩味形式。虽然具有高含量的蜡，但是所述剂型在唾液或水中于小于2min的时间内分散。其可以用于治疗对托吡酯或其衍生物治疗上应答的疾病或病症。

CN 105050588 A

1. 一种掩味的快速分散剂型，其包含固体多孔未被压制的结合基质，所述基质包含：

掩味的蜡包衣颗粒，所述颗粒包含托吡酯和至少一种含蜡材料，所述托吡酯和含蜡材料分别以 20:80-50:50 的重量比存在；

粘合剂；以及

表面活性剂，

其中当置于含水流体中时，所述剂型在小于 90 秒的时间内分散。

2. 权利要求 1 的剂型，其还包含选自以下的一种或多种组分：崩解剂、甜味剂、稀释剂、甘油和助流剂。

3. 前述权利要求中任一项的剂型，其中：

a) 所述蜡包衣的托吡酯颗粒通过喷雾冷凝包含熔融蜡和托吡酯颗粒的混合物来制备；b) 所述蜡不是离子型聚合物或共聚物、丙烯酸酯聚合物或共聚物、甲基丙烯酸酯聚合物或共聚物、或者肠溶聚合物或共聚物；c) 所述蜡包衣包含一种或多种、一种、两种或三种不同的蜡；d) 基于所述剂型的最终重量，所述表面活性剂存在的量为 0-2 重量%；e) 基于所述剂型的最终重量，所述蜡包衣颗粒的总量为 20-50％重量%；f) 所述基质的硬度高达约 1.0 千克力；g) 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；h) 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；i) 所述基质包含约 25mg、约 50mg、约 100mg、约 200mg 或约 25- 约 200mg 的托吡酯；j) 所述基质包含 10-40 个打印的增量层；k) 增量层的厚度（高度）为 0.008-0.012 英寸；l) 基于所述剂型的最终重量，至少一种甜味剂存在的量为 0-2 重量%或 >0- 约 2 重量%；m) 基于所述剂型的最终重量，至少一种粘合剂存在的量为 >0- 约 20 重量%；n) 基于所述剂型的最终重量，任选存在的崩解剂的量为 0-30 重量%；o) 基于所述剂型的最终重量，至少一种助流剂存在的量为 0-2 重量%；p) 表面活性剂存在于所述蜡包衣的托吡酯颗粒中；和 / 或 q) 基于包含于所述剂型中的蜡包衣颗粒的重量，所述蜡包衣颗粒中存在的表面活性剂的量为 0.3-15 重量%、1-12 重量%、1.5-9 重量%、2-6 重量%。

4. 前述权利要求中任一项的剂型，其中：

a) 所述包衣颗粒的平均或中间粒径为约 60- 约 250 微米；b) 所述蜡包衣颗粒中的托吡酯颗粒的平均或中间粒径为约 30-50 微米；c) 所述基质为三维打印的基质；d) 基于所述剂型的最终重量，所述剂型包含不多于 10 重量%的水分；e) 所述剂型的硬度为 0.5-3 千克力；f) 所述剂型包含 20-50 个堆积排列的三维打印的增量层；和 / 或 g) 增量层的平均厚度为约 100- 约 400 微米。

5. 前述权利要求中任一项的剂型，其中所述剂型通过三维打印方法制备，所述方法使用以下组合物的打印流体和松散粉末：

打印流体：

水(重量%)	80-90	或	80-90
甘油(重量%)	0.05-20	或	1-8
醇(重量%)	0.1-20	或	5-20
第一表面活性剂(重量%)	0.05-10	或	2-7
甜味剂(重量%)	0.1-5	或	1-3
第二表面活性剂(重量%)	0-10	或	0-5

松散粉末：

托吡酯(包衣颗粒)(重量%) (颗粒中 35-45 重量%的 TOP)	20-50	或	40-50
表面活性剂(重量%)	0-5	或	0-5
二氧化硅(胶体二氧化硅；重量%)	>0-5	或	0.5-2
第一粘合剂(重量%)	20-50	或	30-50
第二粘合剂(重量%)	0-10	或	5-10
崩解剂(重量%)	0-30	或	5-10

。

6. 前述权利要求中任一项的剂型，其中所述剂型具有以下组成：

托吡酯(重量%)	15-20
含蜡材料(重量%)	20-30
表面活性剂(重量%)	2.5-3.5
胶体二氧化硅(重量%)	0.5-1.5
PVP(重量%)	4.5-10
甘露醇(重量%)	25-50
交聚维酮(重量%)	4.5-10
甜味剂(重量%)	1-2

。

7. 前述权利要求中任一项的发明，其中所述剂型的形状为薄片、圆柱体、环形物、圆环、管状物、立方体、球状体、椭圆体或矩形盒。

8. 一种治疗对托吡酯治疗上应答的疾病、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。

托吡酯的快速分散剂型

技术领域

[0001] 本发明涉及一种托吡酯(topiramate)的掩味的快速分散(口分散)固体口服剂型。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,并且托吡酯保持其掩味。本发明还涉及所述剂型用于治疗对托吡酯治疗上应答的疾病、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] 包含托吡酯(TOP;2,3:4,5-双-O-(1-甲基亚乙基)-β-D-吡喃果糖氨基磺酸酯;公开于EP 138441)的固体口服剂型是已知的(FDA Electronic Orange Book)。托吡酯是一种抗惊厥药,用于治疗癫痫中的部分发作或原发性全身性强直阵挛,用于Lennox-Gaustat综合征的辅助疗法和用于治疗偏头痛。其还用于治疗双相情感障碍,治疗边缘型人格障碍,用作抗精神病药的辅助药物,治疗创伤后应激障碍,治疗抗精神病药引起的体重增加,以及治疗相关领域认可的其他疾病状况。

[0003] 托吡酯对热和水分敏感。托吡酯的降解容易通过物理外观的改变(即变色为棕色或黑色)以及形成硫酸根离子来检测,这可以通过标准技术来测量。解决这一问题的常规方案是通过施加包衣以保护药物,这减少外部环境与活性成分的接触,以及在施加包衣时使用挥发性有机溶剂。

[0004] TOP以诸如400mg/天(两个200mg剂量)的高水平剂量给药来治疗癫痫。这样较高的剂量通过在6周的时间段内的剂量提高来实现。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制剂。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,并且目前为止美国仅批准了片剂或胶囊剂(包括撒布胶囊)。

[0005] 考虑到每片要求的高剂量的TOP,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。

[0006] 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。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。

[0007] 托吡酯已知为具有非常苦的味道，这对于口分散剂型是不利的。任何此类固体形式的主要要求是其必须可口以减少患者忽视服用药物的风险。当活性成分的味道非常难以接受并且有些不稳定时，难以制备这样的固体形式，并且还表现出良好的稳定性和生物利用度。

[0008] 对于味道不好的药物已经开发了掩味的剂型。Ulrich 的 U.S.6,767,557 提及了一种可复原粉末，其包含水不溶性肠溶包衣中封装的药物。Yu 的 U.S.6,586,012 和 U.S.6,482,823 公开了一种液体制剂，其包含封装于酸溶性包衣中的托吡酯。General 的 U.S.20120207836 提及了一种膜薄片制剂，其包含封装于阳离子聚丙烯酸酯包衣中的药物颗粒。Kolter 的 U.S.20120076858 提及了一种快速分散制剂，其包含封装于阳离子聚丙烯酸酯包衣中的药物颗粒。Koizumi 的 U.S.20120040001 提及了一种快速分散压制剂型，其包含药物、淀粉、粘合剂和成形剂。Venkatesh 的 U.S.20110212171 公开了一种口分散剂型，其包含用水不溶性聚合物包衣的托吡酯颗粒。Sanghvi 的 U.S.20100285130 提及了一种膜制剂，其包含用可吸收聚合包衣的药物和离子交换树脂的复合物。Tengler 的 U.S.20100278901 和 U.S.20070092553 提及了一种快速分散压制剂型，其包含与树脂复合的药物。Arti 的 U.S.20070154550 公开了一种丙烯酸酯或乙基纤维素包衣的托吡酯的粉末形式。Wu 的 U.S.20060182796 公开了一种丙烯酸酯和肠溶聚合物包衣的托吡酯的粉末形式。Gandhi 的 U.S.20060159758 公开了一种掩味的制剂，其包含丙烯酸酯聚合物联合其他聚合物。U.S.Pat.No.6,106,861 公开了一种快速崩解的多颗粒片剂，其在口中于小于 40 秒的时间内崩解并且包含选自崩解剂、粘合剂的赋形剂以及活性成分。活性成分为用掩味包衣包覆的微晶体形式，所述包衣包含聚甲基丙烯酸酯和纤维素聚合物如羟丙基甲基纤维素、羟丙基纤维素和纤维素乙酰基邻苯二甲酸酯。U.S.Pat.No.6,136,347 描述了遮味药物组合物，其包含用水不溶性中性甲基丙烯酸酯共聚物和柠檬酸三乙酯包衣的微胶囊。PCT 申请 WO 99/44581 公开了一种通过用掩味包衣混合物包衣核心来掩盖托吡酯的味道的方法。掩味混合物包含纤维素乙酸酯、纤维素乙酸丁酯、甲基纤维素、乙基纤维素或尤特奇 (Eudragit) 以及崩解剂。Kumaraperumal 的 U.S.20060127479 公开了一种用丙烯酸酯聚合物包衣的掩味药物。Murpani 的 U.S.20060039981 公开了一种用丙烯酸酯聚合物包衣的掩味药物。

[0009] 口分散剂型中可接受的掩味难以实现，特别是对于诸如 TOP 的药物，因为其更难以掩盖这样的剂型中高剂量药物的味道。现有技术无法预期 TOP 的何种掩味形式会适合用于口分散剂型，因为用于制备所述口分散剂型的方法和组分很可能会改变掩味的 TOP，从而在剂型的制备期间形成未掩味的 TOP。而且，现有技术无法预期托吡酯的特定掩味形式是否会在并入三维打印剂型中时保持其掩味，因为打印期间会使用各种成分并且在干燥期间会进行加热。

[0010] 以上都没有公开本文所述的包含 TOP 的掩味快速溶解固体口服剂型。应当有利地提供包含 TOP 的掩味快速分散口分散固体口服剂型，其表现出足够低的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和可接受的味道；然而现有技术中并没有公开这样的包含 TOP 的合适剂型。特别地，没有公开这样的三维打印的剂型。

发明内容

[0011] 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，其包含托吡酯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 15ml 或更少体积的水或唾液中，于 2min 或更短的时间内分散 / 崩解，并且即使所述剂型在个体的口中分散后，所述托吡酯保持掩味。所述基质在给药的个体的口中分散，从而促进吞咽和给药。在一些实施方案中，崩解时间根据 USP<701> 确定。

[0012] 在一些方面，本发明提供一种掩味的快速分散（即口分散）剂型及其给药，用于治疗对托吡酯治疗上应答的疾病、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 TOP 和松散材料 (bulk material)。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粘合剂结合。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。基质提供改善的味道、足够的硬度、低脆性和小体积含水液体中的合适分散时间的平衡。

[0013] 托吡酯以掩味颗粒的形式包含在基质和松散材料中，所述掩味颗粒包含托吡酯和至少一种含蜡材料。通常，托吡酯的重量百分比不超过含蜡材料的总重量百分比。托吡酯比总含蜡材料的重量比通常为约 50:50- 约 20:80、约 50:50- 约 30:70 或约 50:50- 约 40:60。

[0014] 在一些实施方案中，在用含蜡材料包衣之前，托吡酯 (TOP) 颗粒的平均或中间粒径通常为约 30-50 微米（体积平均直径，VMD)，和 / 或 D90 小于约 200 微米、D90 小于约 150 微米、D90 小于约 125 微米、D90 小于约 100 微米、D90 小于 65 微米、D90 为约 50- 约 70 微米，和 / 或 D50 小于约 100 微米、D50 小于约 75 微米、D50 小于约 60 微米、D50 小于约 50 微米、D50 小于约 40 微米、D50 为约 30- 约 50 微米，和 / 或 D10 小于约 50 微米、D10 小于约 40 微米、D10 小于约 30 微米、D10 小于约 20 微米、D10 为约 5- 约 10 微米。用含蜡材料包衣后，包衣颗粒的平均或中间粒径通常为约 60- 约 250 微米，和 / 或 D90 小于 150 微米、D90 小于 125 微米、D90 小于 110 微米，和 / 或 D50 小于 120 微米、D50 小于 100 微米、D50 小于 75 微米，和 / 或 D10 小于 75 微米、D10 小于 50 微米、D10 小于 40 微米。TOP 可以作为两种或更多种原始 (native) 药物粉末的混合物形式存在，所述粉末各自具有其自身的原始粒径分布和 / 或制备方法。

[0015] 掩味颗粒的平均、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。掩味颗粒的 D10 可以为 5-20 微米、D50 可以为 30-60 微米，和 / 或 D90 可以为 90-120 微米。掩味颗粒可以作为两种或更多种不同粉末的混合物存在，所述粉末各自具有其自身的有效粒径分布和 / 或制备方法。

[0016] 在一些实施方案中，托吡酯以包衣颗粒中的晶体形式存在，涵盖托吡酯所有的多晶型物。在包衣前，其还可以以晶体形式存在。托吡酯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，托吡酯以包衣颗粒中的无定形形式存在。

[0017] 本发明还提供一种掩味的口分散剂型，其包含三维打印的基质，所述基质包含蜡包衣的托吡酯的结合颗粒、甜味剂、粘合剂和表面活性剂，其中所述颗粒由粘合剂结合。形成基质的颗粒不被托吡酯结合。在三维打印过程中，打印流体基本上不溶解托吡酯。基质任选地还包含崩解剂。

[0018] 本发明的一方面提供一种掩味的口分散三维打印基质，其包含：

[0019] 掩味的蜡包衣的托吡酯的结合颗粒、至少一种甜味剂、至少一种粘合剂以及任选存在的至少一种崩解剂；

[0020] 至少一种表面活性剂和至少一种助流剂；

[0021] 其中

[0022] 所述颗粒由粘合剂结合；

[0023] 所述基质是多孔的并且未被压制；

[0024] 所述基质在 15ml 体积的含水流体中，于小于 90 秒 (sec) 的时间内分散；并且

[0025] 所述颗粒中托吡酯与蜡的重量比为 20:80-50:50。

[0026] 本发明的一些实施方案包括这样的实施方案，其中：a) 蜡包衣的托吡酯颗粒通过喷雾冷凝包含熔融蜡和托吡酯颗粒的混合物来制备；b) 蜡不是离子型聚合物或共聚物、丙烯酸酯聚合物或共聚物、甲基丙烯酸酯聚合物或共聚物、或者肠溶聚合物或共聚物；c) 蜡包衣包含一种或多种、一种、两种或三种不同的蜡；d) 基于剂型的最终重量，表面活性剂存在的量为 0-2 重量％；e) 基于剂型的最终重量，蜡包衣颗粒的总量为 20-50％重量％；f) 基质的硬度高达约 1.0 千克力；g) 通过用于形成基质的打印流体将粘合剂引入所述基质；h) 通过用于形成基质的松散粉末 (bulk powder) 将粘合剂引入所述基质；i) 基质包含约 25- 约 200mg 的托吡酯；j) 基质包含 10-40 个打印的增量层；k) 增量层的厚度 (高度) 为 0.008-0.012 英寸；l) 基于剂型的最终重量，至少一种甜味剂存在的量为 0-2 重量％或 >0- 约 2 重量％；m) 基于剂型的最终重量，至少一种粘合剂存在的量为 >0- 约 20 重量％；n) 基于剂型的最终重量，任选存在的崩解剂的量为 0-30 重量％；o) 基于剂型的最终重量，至少一种助流剂存在的量为 0-2 重量％；和 / 或 p) 表面活性剂存在于蜡包衣的托吡酯颗粒中。

[0027] 本发明提供一种治疗对托吡酯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。

[0028] 本发明还提供一种制备掩味的口分散剂型的方法。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、助流剂、甜味剂和蜡包衣的托吡酯颗粒结合入未被压制的多孔基质来形成如本文所述的多孔基质。

[0029] 本发明包括本文公开的方面、实施方案和子实施方案的所有组合。

附图说明

[0030] 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本文的说明书能够实施本发明而无需过度实验。

[0031] 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。

[0032] 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。

[0033] 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。

[0034] 图 4A 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。

[0035] 图 4B 示出图 4A 的剂型的透视图。

具体实施方式

[0036] 如本文所用并且除非另外指明，术语托吡酯指该药物未衍生或衍生形式。托吡酯还包括托吡酯衍生物如托吡酯棕榈酸酯 / 盐。托吡酯还包括托吡酯的新的盐及其药学可接受的多晶型物、溶剂化物、水合物、脱水物、共晶体、无水形式或者无定形形式，如 U.S.Pat.No.7,351,695 所述，其援引加入本文。

[0037] 本发明提供一种掩味的口分散剂型，其包含用一种或多种含蜡材料包衣的托吡酯颗粒。所述剂型包含由粘合剂结合的颗粒的未被压制的基质。所述基质包含蜡包衣的托吡酯颗粒、甘油、粘合剂、表面活性剂和任选存在的崩解剂。所述基质是多孔的，并且当置于最少量的水中时在少于 90 秒的时间内分散。与包含聚合物包衣的托吡酯颗粒、托吡酯的环糊精复合物等的其他三维打印的剂型相比，所述剂型提供改善的掩味以及快速的分散。蜡包衣颗粒优选地通过喷雾冷凝包含托吡酯和至少一种蜡材料的熔融物来制备。

[0038] 根据实施例 3 制备各种不同的包含托吡酯的包衣颗粒的三维打印 (3DP) 剂型。通过离子交换络合、热熔挤出、碾压成型、超临界流体包衣、用环糊精络合或流化床包衣来制备比较包衣颗粒。由若干个体评价所得的 3DP 剂型的味道，以确定是否任何比较包衣颗粒提供足够的托吡酯的掩味。可以确定，没有比较制剂提供充分的掩味。认为在 3DP 方法的打印和 / 或干燥步骤期间，打印流体可以溶解一部分比较包衣颗粒的表面包衣。

[0039] 在另一方面，本发明的 3DP 剂型提供优异的掩味，所述剂型包含喷雾冷凝的蜡包衣的托吡酯颗粒。即使在口中分散后，托吡酯的苦味对个体是不明显的。基于经验，发明人无法预测何种类型的掩味包衣颗粒适合于制备掩味的口分散 3DP 剂型。因此，本发明人发现，可以实现含托吡酯的 3DP 剂型中可接受的掩味，而无需用聚合材料包衣托吡酯。

[0040] 将托吡酯用至少一种含蜡材料包衣，所述含蜡材料不是离子型聚合物或共聚物、丙烯酸酯聚合物或共聚物、甲基丙烯酸酯聚合物或共聚物或者肠溶聚合物。然而，在 3DP 基质中包含含蜡材料代表制备具有足够硬度的剂型的明显挑战。蜡趋向于软化基质，特别是当基质包含大量的重量百分比的包衣颗粒时。蜡还趋向于增加 3DP 口分散剂型的分散时间。因此，3DP 剂型的物理性质会与期望的有所不同。

[0041] 已经确定，在打印流体中包含表面活性剂有助于确保 3DP 剂型的快速分散而无需牺牲掩味。表面活性剂还可以包含于蜡包衣的托吡酯颗粒中。这样的结果是无法预期的，因为表面活性剂通常用于清理组合物以溶解蜡。在评价本文所用的表面活性剂之前，根据经验，发明人无法预测表面活性剂是否会干扰掩味。

[0042] 托吡酯与含蜡材料的重量比可以变化，然而，这会影响剂型的硬度、分散时间、掩味、大小和药物剂量。如果含蜡材料含量过低，则掩味会不足。如果含蜡材料含量过高，则硬度会过低，分散时间会过长，并且剂型的大小必须明显增加以在其中包含合适剂量的托吡酯。

[0043] 已经确定，含蜡材料应当以托吡酯至少等同的量存在，并且优选比托吡酯过量的量存在。在一些实施方案中，托吡酯与含蜡材料的重量比为 20:80-50:50、30:70-50:50 或 40:60-50:50.

[0044] 含蜡包衣可以包含一种或多种、一种、两种或三种不同的蜡。

[0045] 在一些实施方案中，含蜡材料选自二棕榈酸硬脂酸甘油酯 (BIOGAPRESS

VEGETAL)、二硬脂酸甘油酯（甘油二硬脂酸酯(PRECIROL®)、棕榈酸硬脂酸甘油酯、二山嵛酸甘油酯(COMPRITOL 888)、单和二甘油酯混合物(GELEOL)、单硬脂酸甘油酯、蜂蜡、巴西棕榈蜡(carrnuba wax)或十六烷基酯蜡。含蜡材料优选为二棕榈酸硬脂酸甘油酯或二硬脂酸甘油酯(glyceryl or distearate)。

[0046] 当置于最少量的水中时，表面活性剂有助于3DP剂型的分散。表面活性剂还增强蜡包衣颗粒的湿润而不会减少或消除掩味。当向个体给药剂型时，表面活性剂并不在任何明显的程度上溶解包衣。与不含表面活性剂的其他3DP剂型相比，其仅需以足以增强分散的量存在。然而，如果表面活性剂存在的量过高，其会不利地影响剂型的口感、性能和/或物理性质。由于表面活性剂自身的味道，其还可能不利地影响味道。在一些实施方案中，基于完成剂型的重量，表面活性剂存在的量为0.0-2.0重量%、0.1重量%-1.0重量%、0.2重量%-0.9重量%。

[0047] 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小于约3min、小于约2.5min、小于约2min、小于约1.5min、小于约60秒、小于约30秒、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，分散（崩解）时间通过在包含15ml水的烧杯中涡旋来测量。在一些实施方案中，崩解时间根据USP<701>确定。

[0048] 小体积的含水流体可以是一口，例如体积50ml或更少、40ml或更少、30ml或更少、20ml或更少、10ml或更少、5ml或更少、2.5ml或更少或者1ml或更少。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、5-10ml、1-7.5ml、1-5ml、0.5-3ml或者其他这样的范围。在优选的实施方案中，一口可以包括约一汤匙(15ml)的水。优选地，一口为约2-约30ml、约10-约15ml(1汤匙）或者约13ml水（流体）。

[0049] 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。

[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0.5kp-约5kp或约0.5kp-约2kp。在一些实施方案中，整体硬度为至少0.5kp、至少1.0kp或至少1.5kp。在一些实施方案中，整体硬度不大于3.0kp、不大于2.0kp或不大于1.0kp。在一些实施方案中，据发现，所述剂型对于处理和给药是足够的，无需在片剂硬度测试仪上提供数值结果。

[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，所述剂型的体密度（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] 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 and 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。

[0055] 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，从而形成增量的打印层。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。

[0056] 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。

[0057] 特别合适用于本发明的剂型的三维打印的打印组件包括构建模块，其各自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。

[0058] 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，松散粉末材料包含一种或多种药学可接受的赋形剂和托吡酯。

[0059] 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在处理、存储和给药条件下维持固定的形状（几何）。颗粒结合的强度和程度取决于粉末层中或通过打印流体沉积的粘合物质的比例，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的颗粒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。

[0060] 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。

[0061] 粘合物质可以是药学可接受的粘合剂。在打印流体中包含“粘合剂”作为粘合物质会导致剂型与相同但在粘合溶液中不含粘合剂的剂型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剂型相比具有更高的密度。

[0062] 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，所述基质包含载体、粘合剂和药物，所述方法包括：(a) 提供一种或多种粘合剂、一种或多种甜味剂、一种或多种湿润剂、一种或多种助流剂、任选存在的一种或多种崩解剂以及药物连同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。

[0063] 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 (wafer) 样形状、圆环 (donut)、环形物、管状物、立方体、球状体、椭圆体或矩形盒的形状。在一些实施方案中，与类似体积和组成但不具有贯穿的孔的形状相比，圆环状可以改进分散时间。在这些实施方案的一些实例中，分散或崩解时间可以减少 50-80％。

[0064] 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)。

[0065] 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。

[0066] 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。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 3E 示出标记 (indicum) 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，无需像诸如凹陷或雕刻的已知技术那样压制入物品。

[0067] 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、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 ;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。

[0068] 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 ;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 ;e) 第一实心打印模式的多层。

[0069] 所述剂型可以成形为圆环、环形物或管状物。图 4A 示出示例性剂型,其中所述剂型的核心的圆柱形垂直轴已经在所述剂型的制备期间取出或去除。孔或洞的直径可以为 3-10mm。在一些实施方案中,孔通过所述剂型中未打印的区域产生,并且到达至少一个外表面,从而排空未结合的粉末。图 4B 示出图 4A 的剂型的透视图。

[0070] 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。研究这些变量中的一些以确定哪些变量对剂型硬度、体密度、崩解时间、溶解时间、生物利用度、水分含量、口感和脆性是最终 (result) 有效的变量。可以确定,最终有效的变量至少包括药物的量、崩解剂的量、粘合剂的量、层厚度、一些组分的性质、含蜡材料的组成以及打印流体饱和水平。

[0071] 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。

[0072] 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，又称为二元或双水平图像，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。

[0073] 在一些情况下，剂型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 (solid)”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例。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，灰度可以通过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。

[0074] 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。

[0075] 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例。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（基于空隙体积），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，向粉末层施用打印流体的步骤中的饱和水平根据提供目标硬度和分散时间的需要加以变化。在穿过剂型的聚集体中，或者在剂型的所选区域中，向粉末层施加的饱和水平可以为约 85％－约 120％、约 10％－约 110％、约 15％－约 80％、约 20％－约 50％或约 15％－约 35％。

[0076] 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（不中断系列），同时将打印流体沉积在粉末层上。连续喷射打印头可以联合小滴偏转系统使用，以选择和控制要沉积的小滴。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）。在一些 3DP 机器上，打印头从左至右以预定的速率如扫描速率扫描（移动并选择性地将流体施用于）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打印流体中的情况时，打印速度从 1.0m/s 增加至 2.0m/s 将剂型中沉积的打印流体的总体积减少一半。随着打印速度增加，体密度（从剂型的重量和大小理论计算）降低。还观察到剂型的大小和重量的同时降低。这种降低归因于 3 个因素：(i) 沉积于粉末上的小滴总体积的降低导致铺展于粉末中的打印流体的程度降低；(ii) 来自打印流体的留下的不挥发性组分的质量降低；(iii) 在与未打印的粉末分离期间，从更脆的剂型边缘失去材料的更大趋势。增加打印速度还降低闪断时间 (flash

time）和硬度并增加剂型的脆性。由于剂型中粘合物质与打印流体的比例（或者粉末中粘合物质的活化水平）随打印速度增加而降低，而导致了这样的结果。如通过 30psi 下汞穿透的剂型的百分比体积（%侵入）增加所示例的，打印速度的增加还增加剂型中的空隙体积。

[0077] 当使用连续喷射打印头时，有效扫描速率为约 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，打印头的有效扫描速率为约 0.1-1m/ 秒，最优选为约 0.15- 约 0.5m/ 秒。

[0078] 单个小滴的体积可以按需要变化。当比较恒定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 10 μm- 约 150 μm。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 20 μm- 约 300 μm。

[0079] 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 1000 μm、约 50- 约 500 μm 或者优选约 100-200 μm。当使用按需喷射打印头时，排间隔为约 20- 约 300 μm、约 40- 约 100 μm 或者优选约 55-75 μm。

[0080] 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，优选 15-25 层。基质通常包含（基本上由…组成或由…组成）20-50、20-40、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 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 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。

[0081] 通过本文所述的 3DP 方法制备的剂型的大小随提供表现出期望性质的剂型所需的 TOP 和赋形剂的含量而变化。如果基质包含较高剂量的 TOP，则与具有相同百分比但较低剂量的 TOP 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 TOP，则可以相应地降低剂型重量，反之亦然。

[0082] 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、100-300 μm、100-500 μm、约 200 μm 或约 250 μm。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。

[0083] 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。

[0084] 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)。

[0085] 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，但是它们可能无法总是以传统药学加工相同的方式精确地发挥功能。

[0086] 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。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 0-20 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%、1-5 重量%、0-30 重量%、2-20 重量%或 5-15 重量%的粘合剂。在一些实施方案中，打印基质包含 0-30 重量%、2-20 重量%或 5-15 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。合适的粘合剂包括水溶性合成聚合物、聚乙烯吡咯烷酮、羟丙基甲基纤维素、交聚维酮（乙酸乙烯酯和乙酸乙烯酯的共聚物）、部分或完全预胶凝玉米淀粉以及羟丙基纤维素。优选的粘合剂有聚乙烯吡咯烷酮（聚维酮）。在一优选实施方案中，聚维酮（聚维酮 K30）的特征在于表现出约 27-32 的 k 值。在一些实施方案中，水溶性稀释剂辅助基质的结合，需要或不需要使用传统的粘合剂。这种范围内的合适稀释剂包括糖和糖醇或多羟基化合物，例如甘露醇、山梨醇、木糖醇、乳糖醇、赤藓醇。在这种范围内，辅助结合的稀释剂可以包含打印基质的 15-50％或 30-45％。在优选的实施方案中，辅助结合的稀释剂为甘露醇。

[0087] 一种或多种崩解剂可以任选地包含于打印基质中。崩解剂可以存在于松散粉末中。在一些实施方案中，松散粉末包含 0-30 重量%、2-25 重量%、5-15 重量%或 5-10 重量%的崩解剂。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）或其组合。在一优选的实施方案中，崩解剂为微晶纤维素。合适等级的 AVICEL® 微晶纤维素总结于下表。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。

[0088]

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

[0089] NMT 表示“不多于”。

[0090] 在另一优选实施方案中，崩解剂为交聚维酮。当崩解剂仅为交聚维酮时，其可以包含松散粉末的 2-10%。交聚维酮是 N- 乙烯基 -2- 吡咯烷酮的水不溶性合成交联均聚物，其在常规制药加工如压片中用作超崩解剂。若干等级的交聚维酮是可用的，包括例如 BASF 提供的产品线，其通过粒径来区分每个等级：Kollidon® CL(110-130 微米）、Kollidon® CL-F(20-40 微米）、Kollidon® CL-SF(10-30 微米）和 Kollidon® CL-M(3-10 微米）。

[0091] 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。

[0092] 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，观察到更有效的掩味。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，打印流体和松散粉末各自包含三氯蔗糖或甘草酸衍生物。在一些实施方案中，打印流体和松散粉末

各自包含三氯蔗糖，并且松散粉末还包含甘草酸衍生物。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%、>0-4 重量%、>0-3 重量%、>0-2 重量%、0.1-5 重量%、0.1-4 重量%、0.1-3 重量%、0.1-2 重量%、0.5-3 重量%或 1-3 重量%的甜味剂。

[0093] 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、其他天然或人工甜味剂及其组合。打印流体中优选的甜味剂有三氯蔗糖。甜味剂至少存在于打印流体中，但是也可以存在于松散粉末中。

[0094] 松散粉末中可以用于其他目的的一些成分也可以促进甜味。其实例有稀释剂粉末，如甘露醇、山梨醇和木糖醇。

[0095] 一种或多种任选存在的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。如果存在于打印流体中，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。如果存在于松散粉末中，调味剂优选以在制备松散粉末之前施用于载体粉末的形式存在。合适的载体粉末可以包括淀粉、改性淀粉、纤维素以及能够吸附、附着、包装或封装调味剂的其他粉末。在一些实施方案中，打印流体包含 0-5％重量％、0.01-1.0 重量％或 0.05-0.5 重量％的调味剂。在一些实施方案中，松散粉末包含 0.1-10 重量％或 1-10 重量％、2-8 重量％、3-7 重量％的并入调味剂的载体粉末。在一些实施方案中，打印基质包含 0-10 重量％、0.01-10 重量％的调味剂。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。合适的调味剂包括胡椒薄荷、留兰香、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。

[0096] 一种或多种表面活性剂可以包含于打印流体和 / 或蜡包衣的托吡酯颗粒中。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- 约 10 重量％、>0- 约 7 重量％、约 1- 约 5 重量％的表面活性剂。在一些实施方案中，基于剂型中包含的蜡包衣颗粒的重量，蜡包衣颗粒中存在的表面活性剂的范围为 0.3-15 重量％、1-12 重量％、1.5-9 重量％、2-6 重量％。

[0097] 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）。

[0098] 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。

[0099] 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- 约 2 重量％、>0- 约 1 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）。

[0100] 在一些实施方案中，松散粉末中药学可接受的赋形剂选自喷雾干燥乳糖、果糖、蔗糖、葡萄糖、山梨醇、甘露醇和木糖醇。这些物质可以视为稀释剂或低亲和力粘合剂。所述

粉末中可以包含的这些物质的量为0-约70%、约10-约60或约20-约50%。

[0101] 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。

[0102] 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。

[0103] 在一些实施方案中，打印流体包含0-约20重量%、>0-约15重量%、>0-约10重量%或>0-约5重量%的甘油。在一些实施方案中，基质包含0-约2重量%或>0-约1重量%的甘油。

[0104] 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。

[0105] 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）松散粉末中的粘合剂；b）打印流体中的粘合剂；或者c）它们的组合。

[0106] 打印流体可以包含约75重量%-约95重量%或约80重量%-约90重量%的水。

[0107] 打印流体可以包含0-约20重量%、>0-约20重量%、>0-约15重量%、>0-约10重量%、>0-约5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。

[0108] 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。

[0109] 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。

[0110] 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基团代替；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。

[0111] 所述制剂的一种或多种组分可以以其游离碱或者药学或分析可接受的盐形式存

在。如本文所用，“药学或分析可接受的盐”指这样的化合物，其通过按需要使其与酸反应以形成离子结合对而加以修饰。可接受的盐的实例包括常规无毒盐，其例如形成自无毒无机或有机酸。合适的无毒盐包括衍生自无机酸的那些盐，例如盐酸盐、氢溴酸盐、硫酸盐、磺酸盐、氨基磺酸盐、磷酸盐、硝酸盐以及本领域技术人员已知的其他盐。制备自有机酸的盐例如氨基酸、乙酸盐、丙酸盐、琥珀酸盐、乙醇酸盐、硬脂酸盐、乳酸盐、苹果酸盐、酒石酸盐、柠檬酸盐、抗坏血酸盐、扑酸盐、马来酸盐、羟基马来酸盐、苯乙酸盐、谷氨酸盐、苯甲酸盐、水杨酸盐、对氨基苯磺酸盐、2- 乙酰氧基苯甲酸盐、富马酸盐、甲苯磺酸盐、甲磺酸盐、乙二磺酸盐、草酸盐、羟乙磺酸盐以及本领域技术人员已知的其他盐。其他合适的盐的列表可见 Remington′ s Pharmaceutical Sciences, 17th. ed., Mack Publishing Company, Easton, PA, 1985, p. 1418，其相关公开援引加入本文。

[0112] 本发明还提供一种向有此需要的个体给药托吡酯的方法。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，所述方法还包括以下步骤：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。

[0113] 本发明还提供一种治疗对托吡酯治疗上应答的疾病、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。所述基质包含托吡酯、松散粉末和粘合剂，并且所述基质可分散于小体积流体中。可以根据TOPAMAX®的包装插页中详述的剂量和给药方案来给药本发明的剂型。

[0114] 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。

[0115] 实施例

[0116] 实施例 1 制备包衣颗粒

[0117] 以下方法用于制备用含蜡材料包衣的托吡酯颗粒。使用下文所示的量的成分。

[0118]

成分	量（重量%）	量（重量%）	量（重量%）	量（重量%）	量（重量%）	量（重量%）
托吡酯	50	40	50	50	50	30
GDPS	50	60	X	X	X	70
GELUCIRE	X	X	50	X	X	X
香兰素	X	X	X	50	X	X

泊洛沙姆	X	X	X	X	50	X

[0119] 通过喷雾冷凝托吡酯和含蜡材料的熔融混合物来制备包衣颗粒。可以使用改进的实验室规模的喷雾干燥仪 SD45(Buchi,型号 B-290)。

[0120] 通过熔化赋形剂然后在搅拌时加入托吡酯来制备进料悬浮液 / 溶液。喷雾冷凝单元以开放循环模式操作,即没有冷凝氮气的再循环。气体流速通过 Coriolis 流量计 (型号 R025S) 来控制,并且其温度利用包含乙醇和干冰的冰箱来调节。进料容器和喷嘴利用热水来控温。此外,所有的进料管通过电伴热 (electric tracing) 来加热,以避免可能导致堵塞的管中悬浮液的冷却。

[0121] 在开始每个批次之前,将喷雾冷凝单元用氮气稳定以获得期望的入口温度。入口温度稳定之后,将溶液 / 悬浮液加入喷雾冷凝设备并在喷嘴头处雾化。然后通过并流 (co-current) 的冷凝氮气在喷雾冷凝室中使小滴冷凝。包含冷冻的产物颗粒的流离开该室并进入旋风分离器,在那里将大部分固体分离并收集在收集容器中。

[0122] 若需要,可以通过将热熔挤出机 (在约 100-150℃下运行) 与雾化系统偶联来改进粘性溶液 / 悬浮液的进料。挤出机迫使熔融物通过喷嘴头以产生雾化。热熔挤出设备组件如 U.S.7,625,507 所述,并且可以用于制备本文所述的包衣颗粒,所述公开整体援引加入本文。

[0123] 将约 50-100g 熔融的材料装入喷雾冷凝单元。通常的操作条件包括 :

[0124] 冷凝氮气温度 (℃) :-45 至 -25

[0125] 水温 (℃) :75-95

[0126] 转子流量计中的雾化氮气高度 (mm) :25-60

[0127] 入口温度 (℃) :-40 至 -20

[0128] 出口温度 (℃) :-10 至 -3

[0129] 气体流速 (kg/h) :15-30

[0130] 进料 (熔融) 流速 (ml/min) :1-10 或约 5

[0131] 热熔挤出机 (HME) 温度 (如果存在)(℃) :90-120

[0132] HME 螺旋旋转 (rpm) :50-100

[0133] 雾化后,熔融材料的小滴在室中冷凝以形成包含托吡酯和赋形剂的包衣颗粒。

[0134] 实施例 2 确定结晶性

[0135] 差示扫描量热计用于确定包含于包衣颗粒中之前和之后的材料的结晶性水平。使用以下温度渐变 (ramping) 特征谱的方法。

[0136] 1. 在 -10℃下平衡 ;

[0137] 2. 以 10℃ /min 渐变至 70℃ ;

[0138] 3. 恒温 5min ;

[0139] 4. 以 10℃ /min 渐变至 -20℃ ;

[0140] 5. 在 -20℃下平衡 ;

[0141] 6. 每 60s 调节 ±0.8℃ ;

[0142] 7. 恒温 2min ;

[0143] 8. 以 5℃ /min 渐变至 250℃ ;

[0144] 9. 以 5℃ /min 渐变至 -10℃。

[0145] 实施例 3 制备掩味的三维打印口分散剂型

[0146] 以下方法用于制备掩味的三维打印口分散剂型，所述剂型包含基质，所述基质包含结合的托吡酯的包衣颗粒。所用的打印流体和松散粉末的成分的量如下所示：

[0147]

打印流体	I-A	I-B	I-C	I-D	I-E
水(重量%)	85	80	83	88	87
甘油(重量%)	5	5	5	0	5
乙醇(重量%)	5	5	5	5	5
吐温 20 (重量%)	1	1	0	0	0
吐温 80 (重量%)	0	0	5	0	0
三氯蔗糖(重量%)	2	2	2	2	2
十二烷基硫酸钠(重量%)	2	2	0	0	0
PEG 400 (重量%)	0	5	0	0	0
Lutrol L44 (重量%)	0	0	0	5	0
聚山梨酯(重量%)	0	0	0	0	1

[0148]

松散粉末：	II-A	II-B	II-C	II-D	II-E
托吡酯(包衣颗粒) (重量%)	40	40	40	40	40
SLS (重量%)	1	1	1	1	1
二氧化硅(胶体二氧化硅；重量%)	1	1	1	1	1
PVP K29/32 (重量%)	10	10	8	0	8
甘露醇 50 C (重量%)	24	24	30	30	30

[0149]

Avicel PH101 (重量%)	24	24	0	0	0
HPC LH-22 (重量%) (羟丙基纤维素)	0	10	20	20	20
HPC-SL (重量%)	0	0	0	8	0
Kollidon CL-SF	0	0	0	0	0

[0150]

	II-F	II-G	II-H	II-J	II-K
托吡酯(包衣颗粒) (重量%)	40	40	20	20	30
SLS (重量%)	1	1	1	1	1
二氧化硅(胶体二氧化硅；重量%)	1	1	1	1	1
PVP K29/32 (重量%)	8	8	8	8	0
甘露醇 50 C (重量%)	30	30	50	50	68
Avicel PH101 (重量%)	0	0	0	0	0
HPC LH-22 (重量%) (羟丙基纤维素)	20	20	20	20	20
HPC-SL (重量%)	0	0	0	0	0
Kollidon CL-SF	0	0	0	0	0

[0151]

	II-L	II-M	II-N	II-O	II-P
托吡酯(包衣颗粒) (重量%)	30	30	40	40	40
SLS (重量%)	1	1	1	1	0
二氧化硅(胶体二氧化硅；重量%)	1	1	1	1	1
PVP K29/32 (重量%)	4	4	10	10	0
甘露醇 50 C (重量%)	64	64	24	24	44
Avicel PH101 (重量%)	0	0	24	24	0
HPC LH-22 (重量%) (羟丙基纤维素)	0	0	10	10	0
HPC-SL (重量%)	0	0	0	0	15
Kollidon CL-SF	0	0	0	0	0

[0152]

	II-Q	II-R	II-S	II-T	II-U
托吡酯(包衣颗粒) (重量%)	40	40	40	40	50
SLS (重量%)	0	0	0	0	0
二氧化硅(胶体二氧化硅；重量%)	1	1	1	1	1
PVP K29/32 (重量%)	5	0	0	5	10

[0153]

甘露醇 50 C (重量%)	49	51.5	46.5	49	29
Avicel PH101 (重量%)	0	0	0	0	0
HPC LH-22 (重量%) (羟丙基纤维素)	0	0	0	0	0
HPC-SL (重量%)	0	7.5	7.5	0	0
Kollidon CL-SF	5	0	5	5	10

[0154] 可以使用已知或本文描述的任何三维打印机设备组件。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。

[0155] 在 Z-Corp 实验室规模打印机（型号 Z310）上使用以下打印参数。打印机配有 HP-10 打印头，以 35 μm 的小滴大小和 450-600 μm 的排间隔操作。整个剂型使用实心打印模式。使用打印流体配方和松散粉末配方的特定组合。

[0156]

打印参数：	III-A	III-B	III-C	III-D	III-E
层厚度(英寸)	0.01	0.01	0.01	0.01	0.01
饱和(%)	110	110	110	110	110
打印流体	I-A	I-A	I-A	I-A	I-B
松散粉末	II-A	II-B	II-C	II-D	II-E

[0157]

打印参数：	III-F	III-G	III-H	III-J	III-K
层厚度(英寸)	0.01	0.008	0.01	0.008	0.01
饱和(%)	116	145	116	145	116
打印流体	I-B	I-B	I-B	I-B	I-B
松散粉末	II-F	II-G	II-H	II-J	II-K

[0158]

打印参数：	III-L	III-M	III-N	III-O	III-P
层厚度(微米)	0.01	0.008	0.01	0.01	0.01
饱和(%)	116	145	116	116	116
打印流体	I-B	I-B	I-C	I-D	I-D
松散粉末	II-L	II-M	II-N	II-O	II-P

[0159]

打印参数：	III-Q	III-R	III-S	III-T	III-U
层厚度(微米)	0.01	0.01	0.01	0.008	0.01
饱和(%)	116	116	116	116	116
打印流体	I-D	I-D	I-D	I-D	I-D
松散粉末	II-Q	II-R	II-S	II-T	II-U

[0160] 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，由此制备最终的掩味的 3DP 口分散剂型。剂型重量为 300-1200mg 或 330-1000mg。

[0161]

最终组成	IV-A	IV-B
托吡酯(重量%)	12-17	17-22
SLS (重量%)	2-3	2.5-3.5
胶体二氧化硅(重量%)	0.5-1.5	0.5-1.5
PVP(重量%)	2-7	7-12
Kollidon (重量%)	2-7	7-12
甘露醇(重量%)	42-52	22-32
MCC (重量%)	0-15	0-10
HPC (重量%)	0-10	0-10

[0162] 然后，确定剂型的分散时间、硬度以及掩味的可接受性。

[0163] 实施例 4 制备掩味的三维打印口分散剂型

[0164] 上述 3DP 方法用于制备掩味的三维打印口分散剂型，所述剂型包含基质，所述基质包含结合的托吡酯的包衣颗粒。所用的打印流体和松散粉末的成分的量如下所示：

[0165]

打印流体	V-A	V-B
水(重量%)	80-90	80-90
甘油(重量%)	0.05-20	1-8
醇(重量%)	0.1-20	5-20
第一表面活性剂(重量%)	0.05 - 10	2-7
甜味剂(重量%)	0.1 – 5	1-3
第二表面活性剂(重量%)	0 - 10	0-5

[0166]

松散粉末：	VI-A	VI-B
托吡酯(包衣颗粒) (重量%)	20-50	40-50
(颗粒中 35-45 % TOP)		
表面活性剂(重量%)	0 - 5	0-5
二氧化硅(胶体二氧化硅；重量%)	>0 - 5	0.5-2
第一粘合剂(重量%)	20 - 50	30-50
第二粘合剂(重量%)		5-10
崩解剂(重量%)	0-30	5-10

[0167] 通过 3DP 方法将打印流体施用于松散粉末的增量层以制备掩味的三维打印口分散剂型，所述剂型包含基质，所述基质包含结合的托吡酯的包衣颗粒。

[0168]

最终组合物	VII-A	VII-B
剂型的重量(mg)	335-365	
托吡酯(重量%)	15-20	
蜡(重量%)	20-30	
表面活性剂(重量%)	2.5-3.5	
胶体二氧化硅(重量%)	0.5-1.5	
PVP(重量%)	4.5-10	
甘露醇(重量%)	25-50	
交聚维酮(重量%)	4.5-10	
甜味剂(重量%)	1-2	

[0169] 实施例 5 制备增量层中具有改变结构的掩味的三维打印口分散剂型

[0170] 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。以下方法提供的剂型的上表面和下表面的硬度与剂型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剂型中产生部分。这个方法用于设计这样的剂型，其中顶部和底部层的组成与中间层不同。这种设计使得剂型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，这使得剂型快速地分散。

[0171] 方法 A:

[0172] 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 的方法制备这些剂型，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。

[0173] 方法 B:

[0174] 根据实施例 3 的方法制备这些剂型，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。

[0175] 方法 C:

[0176] 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）。

[0177] 方法 D:

[0178] 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）。

[0179] 方法 E:

[0180] 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）。

[0181] 实施例 6 制备非掩味的三维打印口分散剂型

[0182] 根据上述方法制备非掩味三维打印口分散剂型，所述剂型包含基质，所述基质包含结合的托吡酯的未包衣颗粒。唯一的差异在于托吡酯颗粒是未包衣的，因此比实施例 3 的颗粒更小。由于未包衣颗粒重量约为包衣颗粒的一半，因此相应地调整托吡酯的重量以提供基本上相同的剂量强度。

[0183] 实施例 7 剂型的表征

[0184] 以下方法用于表征三维打印的固体多孔口分散基质。

[0185] 脆性

[0186] 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 个剂型。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。

[0187] 硬度

[0188] 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。通过断裂测试测量剂型的强度或硬度。将剂型放置在测试仪的钳中间，并施加力直至剂型断裂。断裂的负载返回为千克力 (kp)。千克力是力测量的公制单位，1kp 等于 9.807 牛顿。测试最少 6 个剂型。

[0189] 分散时间

[0190] 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)。使剂型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，将剂型浸入 3ml 水中。利用以下参数进行分散时间测试。测试最少 5 个剂型。

[0191]

测试模式	压缩
测试前速度(mm/秒)	5
测试速度(mm/秒)	8
测试后速度(mm/秒)	10
目标模式	力
力(g)	50
维持时间(秒)	15
引发类型	自动(力)
引发力(g)	5
水体积(ml)	3

[0192] 对一些剂型观察到的分散时间大约如下。

[0193]

	III-H	III-J	III-K	III-L	III-M
分散时间(s)	52	59	34	58	90

	III-N	III-O	III-Q	III-S	III-T	III-U
分散时间(s)	80	40	42	65	52	66

[0194] 体密度

[0195] 基质的体密度通过测量剂型的重量并将该值除以剂型计算的体积来确定。剂型的体积通过测量其尺寸并根据剂型的形状利用合适的数学公式来计算。例如,对于圆柱形剂型,其体积利用公式 $\pi*r^2*H$ 来计算,其中 r 是剂型的半径并且 H 是其高度。重量为 0.5g,高度为 0.6cm 并且直径为 1.1cm 的剂型的体积为约 0.57cm^3,并且体密度为约 0.877g/cm^3,这等于约 877mg/ml。

[0196] 托吡酯的溶解

[0197] 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℃。

[0198] 实施例 8 三维打印的口分散剂型的体内评价

[0199] 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托吡酯的单剂型。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) 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。托吡酯的总每日剂量通常为 50-400mg。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。

[0200] 如果仅评价剂型的掩味水平，则无需确定药物动力学或治疗特征谱。个体可以仅对剂型的味道评论其是否是可接受的。

[0201] 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%”。

[0202] 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。

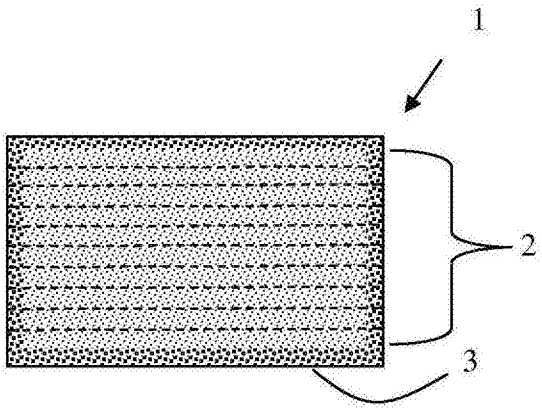

图 1

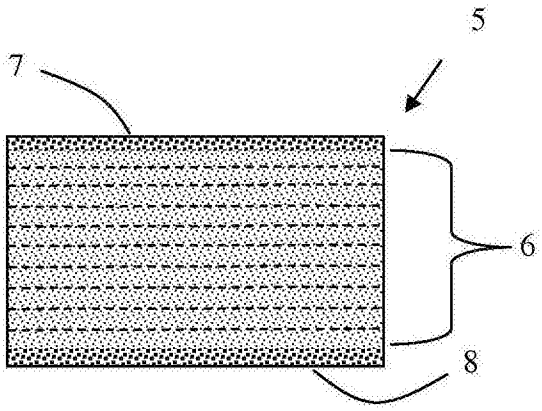

图 2

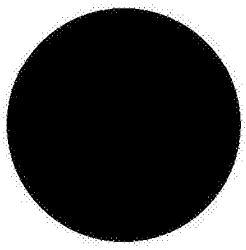

图 3A

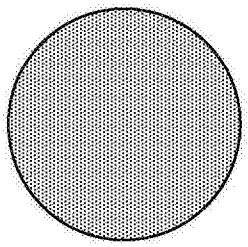

图 3B

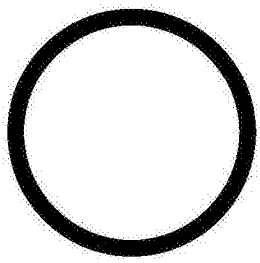

图 3C

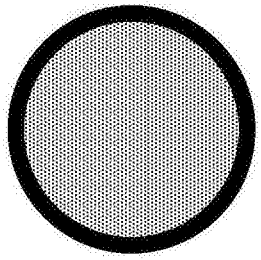

图 3D

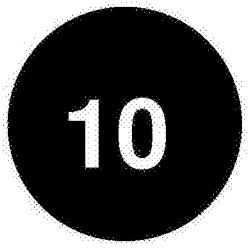

图 3E

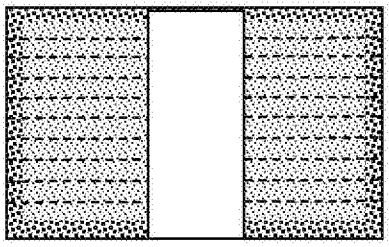

图 4A

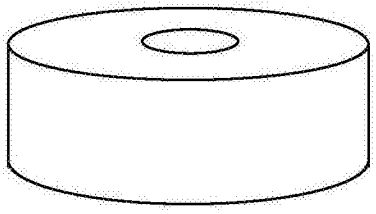

图 4B

1. 一种掩味的快速分散剂型，其包含三维打印的固体多孔未被压制的结合基质，所述基质包含：

掩味的蜡包衣颗粒，所述颗粒包含托吡酯和至少一种含蜡材料，所述托吡酯和含蜡材料分别以 20:80-50:50 的重量比存在；

粘合剂；以及

表面活性剂，

其中当置于含水流体中时，所述剂型在小于 90 秒的时间内分散。

2. 权利要求 1 的剂型，其还包含选自以下的一种或多种组分：崩解剂、甜味剂、稀释剂、甘油和助流剂。

3. 前述权利要求中任一项的剂型，其中：

a) 所述蜡包衣的托吡酯颗粒通过喷雾冷凝包含熔融蜡和托吡酯颗粒的混合物来制备；b) 所述蜡不是离子型聚合物或共聚物、丙烯酸酯聚合物或共聚物、甲基丙烯酸酯聚合物或共聚物、或者肠溶聚合物或共聚物；c) 所述蜡包衣包含一种或多种、一种、两种或三种不同的蜡；d) 基于所述剂型的最终重量，所述表面活性剂存在的量多达 2 重量%；e) 基于所述剂型的最终重量，所述蜡包衣颗粒的总量为 20-50％重量%；f) 所述基质的硬度高达约 1.0 千克力；g) 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；h) 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；i) 所述基质包含约 25mg、约 50mg、约 100mg、约 200mg 或约 25- 约 200mg 的托吡酯；j) 所述基质包含 10-40 个打印的增量层；k) 基于所述剂型的最终重量，至少一种甜味剂存在的量为 >0- 约 2 重量%；l) 基于所述剂型的最终重量，至少一种粘合剂存在的量为 >0- 约 20 重量%；m) 基于所述剂型的最终重量，所述崩解剂存在的量多达 30 重量%；n) 基于所述剂型的最终重量，至少一种助流剂存在的量多达 2 重量%；o) 表面活性剂存在于所述蜡包衣的托吡酯颗粒中；和 / 或 p) 基于包含于所述剂型中的蜡包衣颗粒的重量，所述蜡包衣颗粒中存在的表面活性剂的量为 0.3-15 重量%、1-12 重量%、1.5-9 重量%、2-6 重量%。

4. 权利要求 1 或 2 的剂型，其中：

a) 所述包衣颗粒的平均或中间粒径为约 60- 约 250 微米；b) 所述蜡包衣颗粒中的托吡酯颗粒的平均或中间粒径为约 30-50 微米；c) 基于所述剂型的最终重量，所述剂型包含不多于 10 重量%的水分；d) 所述剂型的硬度为 0.5-3 千克力；和 / 或 e) 所述剂型包含 20-50 个堆积排列的三维打印的增量层。

5. 权利要求中 1 或 2 的剂型，其中所述剂型通过三维打印方法制备，所述方法使用以下组合物的打印流体和松散粉末：

打印流体：

水(重量%)	80-90	或	80-90
甘油(重量%)	0.05-20	或	1-8
醇(重量%)	0.1-20	或	5-20
第一表面活性剂(重量%)	0.05-10	或	2-7
甜味剂(重量%)	0.1-5	或	1-3
第二表面活性剂(重量%)	0-10	或	0-5

松散粉末：

托吡酯(包衣颗粒)(重量%)	20-50	或	40-50
(颗粒中 35-45 重量%的 TOP)			
表面活性剂(重量%)	0-5	或	0-5
二氧化硅(胶体二氧化硅；重量%)	>0-5	或	0.5-2
第一粘合剂(重量%)	20-50	或	30-50
第二粘合剂(重量%)	0-10	或	5-10
崩解剂(重量%)	0-30	或	5-10 。

6. 权利要求 1 或 2 的剂型，其中所述剂型具有以下组成：

托吡酯(重量%)	15-20
含蜡材料(重量%)	20-30
表面活性剂(重量%)	2.5-3.5
胶体二氧化硅(重量%)	0.5-1.5
PVP(重量%)	4.5-10
甘露醇(重量%)	25-50
交聚维酮(重量%)	4.5-10
甜味剂(重量%)	1-2 。

7. 权利要求 1 或 2 的发明，其中所述剂型的形状为薄片、圆柱体、环形物、圆环、管状物、立方体、球状体、椭圆体或矩形盒。

8. 一种治疗对托吡酯治疗上应答的疾病、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 或 2 的剂型 1-3 次。

9. 权利要求 3 的剂型，其中所述增量层的厚度（高度）为 0.008-0.012 英寸。

10. 权利要求 4 的剂型，其中所述增量层的平均厚度为约 100- 约 400 微米。

11. 一种掩味的口分散三维打印基质，其包含：

掩味的蜡包衣的托吡酯颗粒，其中所述颗粒中托吡酯与蜡的重量比为 20:80-50:50，并且基于所述基质的最终重量，所述颗粒存在的量为 20-50 重量%；

至少一种粘合剂，基于所述基质的最终重量，其存在的量为 >0-20 重量%；和

至少一种表面活性剂，基于所述基质的最终重量，其存在的量多达 2 重量%；

其中所述颗粒与所述至少一种粘合剂通过三维打印结合；并且

所述三维打印基质是多孔的且未被压制的，并且在 15ml 体积的含水流体中于小于 90 秒的时间内分散。

12. 权利要求 11 的基质，其在所述蜡包衣的托吡酯颗粒中还包含表面活性剂。

13. 权利要求 12 的基质，其中基于包含于所述剂型中的蜡包衣颗粒的重量，所述蜡包衣颗粒中存在的表面活性剂的量为 0.3-15 重量%、1-12 重量%、1.5-9 重量%、2-6 重量%。

14. 权利要求 11 的基质，其还包含：

a) 至少一种甜味剂，基于所述基质的最终重量，其存在的量为 >0- 约 2%；b) 至少一种崩解剂，基于所述基质的最终重量，其存在的量为 0-30%；c) 至少一种助流剂，基于所述基

质的最终重量，其存在的量为0-2％；d）所述蜡包衣的托吡酯颗粒中存在至少一种表面活性剂；和/或e）基于所述剂型中包含的蜡包衣颗粒的重量，所述蜡包衣颗粒中存在的至少一种表面活性剂的量为0.3-15重量％、1-12重量％、1.5-9重量％、2-6重量％。

15.权利要求11的基质，其中所述包衣颗粒的平均或中间粒径为约60-约250微米，并且所述基质中的托吡酯颗粒的平均或中间粒径为约30-50微米。

16.权利要求11的基质，其中

a）所述基质的硬度高达约1.0千克力；b）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；c）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；和/或d）所述基质包含10-40个三维打印的增量层。

17.一种掩味的快速分散剂型，其包含固体多孔未被压制的三维打印的结合基质，所述基质包含：

喷雾冷凝的掩味的蜡包衣颗粒，所述颗粒包含托吡酯和至少一种含蜡材料，所述托吡酯和含蜡材料分别以20:80-50:50的重量比存在，其中所述蜡包衣的托吡酯颗粒通过喷雾冷凝包含熔融蜡和托吡酯颗粒的混合物来制备；

至少一种粘合剂；和

至少一种表面活性剂，

其中当置于含水流体中时，所述剂型在小于90秒的时间内分散，

基于所述剂型的最终重量，所述蜡包衣颗粒的总量为20-50％重量％，

所述包衣颗粒的平均或中间粒径为约60-约250微米；以及

托吡酯颗粒的平均或中间粒径为约30-50微米。

18.权利要求17的剂型，其中：

a）基于所述剂型的最终重量，至少一种甜味剂存在的量为>0-约2重量％；b）基于所述剂型的最终重量，至少一种粘合剂存在的量为>0-约20重量％；c）基于所述剂型的最终重量，至少一种崩解剂存在的量为0-30重量％；d）基于所述剂型的最终重量，至少一种助流剂存在的量为0-2重量％；e）至少一种表面活性剂存在于所述蜡包衣的托吡酯颗粒中；和/或f）基于包含于所述剂型中的蜡包衣颗粒的重量，所述蜡包衣颗粒中存在的至少一种表面活性剂的量为0.3-15重量％、1-12重量％、1.5-9重量％、2-6重量％。

19.权利要求11或17的发明，其中托吡酯存在的量为约25-约200mg。

20.权利要求11或17的发明，其中：

a）所述蜡不是离子型聚合物或共聚物、丙烯酸酯聚合物或共聚物、甲基丙烯酸酯聚合物或共聚物、或者肠溶聚合物或共聚物；b）所述蜡包衣包含一种或多种、一种、两种或三种不同的蜡；c）基于所述剂型或基质的最终重量，所述表面活性剂存在的量为0-2重量％。

21.权利要求11或17的发明，其中：

a）所述基质的硬度高达约1.0千克力；b）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；c）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；d）所述基质包含10-40或20-50个堆积排列的三维打印的增量层；和/或e）所述剂型的硬度为0.5-3千克力。

22.权利要求21的发明，其中所述增量层的厚度（高度）为0.008-0.012英寸或约100-约400微米。

23. 权利要求 11 或 17 的发明，其中基于所述剂型的最终重量，所述基质包含不多于 10 重量％的水分。

24. 一种松散粉末，按重量％计，其包含：

蜡包衣的托吡酯颗粒 20-50

所述颗粒中包含 35-45 重量％的托吡酯；

表面活性剂	0-5；
胶体二氧化硅	>0-5；
第一粘合剂	20-50；
第二粘合剂	0-10；以及
崩解剂	0-30 。

25. 一种松散粉末，按重量％计，其包含：

蜡包衣的托吡酯颗粒 40-50

所述颗粒中包含 35-45 重量％的托吡酯；

表面活性剂	0-5；
胶体二氧化硅	0.5-2；
第一粘合剂	30-50；
第二粘合剂	5-10；以及
崩解剂	5-10 。

[0001] 审查员对现有技术的组合的理解并不正确。审查员组合溶剂模铸的薄膜（对比文件 1(US2012/0207836 A1)，在小于 3min的时间内分散，并且可以包含蜡包衣的药物颗粒）与压制的包衣片剂（对比文件 2(US 2006/0099245 A1)，IR 包衣在 10-30min内分散，并且 CR 核心提供药物在数小时内的控释），以及未压制的 3DP 剂型（对比文件 3(US 2003/0143268 A1)）。然而，这些现有技术都没有提示在 <90 秒的时间内释放药物的快速分散剂型 / 基质 (RDDF)。

[0002] 审查员承认对比文件 1 没有明确公开所要求保护的 RDDF 在 <90 秒的时间内分散，但是认为本领域技术人员能够明显地改进对比文件 1 以提供 <90 秒的分散时间，因为“崩解剂型在口中典型的保留时间通常低于 3 分钟”。将崩解时间降低至 <90 秒的启示是缺乏的，因为对比文件 <3 分钟在对比文件 1 中是可接受的。

[0003] 对比文件 1 公开了薄膜（厚度≤ 300 微米 ;第 [0142] 段）可以包含托吡酯（包含于数百种药物和药物类别的列表中）。对比文件 1 仅仅提示剂型应当在其施用后，于 3 分钟内完全崩解（第 [0070]-[0071] 段）。然而，对比文件 1 并没有提供任何可行手段来改进薄膜使得提供 <90 秒的崩解。对比文件 1 也没有提供任何启示，来使用 3DP 固体多孔非压制剂型代替溶剂模铸薄膜。对比文件 1 教导了要求特定的粒径范围（第 [0085] 段）。对比文件 1 的粒径限制低于本发明的优选范围（“约 60- 约 250 微米”，权利要求 4）。对比文件 1 也没有公开活性成分的粒径（“蜡包衣颗粒中的托吡酯颗粒的平均或中间粒径为约 30-50 微米”，权利要求 4）。

[0004] 对比文件 2 公开胃内滞留双相释放 (IR/CR) 剂型，其可以为“团粒（多微粒或单一单位剂型）、珠、颗粒、胶囊或片剂”（摘要、第 [0041]、[0042] 和 [0044] 段），但并没有涉及薄膜。对比文件 2 描述了剂型的性能并且定义了术语双相释放（第 [0051]-[0052] 段）。IR 部分在 10-30 分钟内释放药物，但是 CR部分保留完整并在胃液中浮游 数小时以提供持续释放。该剂型并不是 RDDF。因此对比文件 1/2 的组合对于不同剂型是不合适的。

[0005] 比文件 1/2 的组合仅仅提示双相释放剂型，其包含薄膜，该薄膜在 <3-30 分钟内释放第一部分的药物，并且 CR 部分在胃中保持完整数小时以提供药物的 CR。可见，这并不是 RDDF。

[0006] 对比文件 3 公开了单轴向压制和未压制的 3DP 剂型，然而这都不是 RDDF。对比文件 1/3 的组合是不合适的。对比文件 1 涉及溶剂模铸的薄膜，而对比文件 3 则涉及 3DP 剂型，其通过将溶剂，任选地连同粘合剂，喷施在颗粒上来结合所述颗粒从而形成固体多孔基质。对比文件 1-3 的方法以及由此制备的剂型是完全不同的。

[0007] 相比之下，本申请则提供实现 <90 秒的崩解的证据，这并不是显而易见的。

Abstract

A taste-masked rapidly dispersible dosage form of topiramate is provided. Wax coated particles of topiramate are included within a porous bound matrix. The topiramate retains its taste-masked form after dispersion in the mouth of a subject even though the particles are not coated with a polymeric material. The dosage form disperses in saliva or water in less than 2 min even though it has a high content of wax. It can be used to treat diseases or disorders that are therapeutically responsive to topiramate or a derivative thereof.