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(71) Applicant: **W. R. GRACE & CO.-CONN.** [US/US]; 7500 Grace Drive, Columbia, Maryland 21044 (US).

(72) Inventor: **MONSUUR, Frederik, Hendrik**; Volderslaan 17, B-3500 Hasselt (BE).

(74) Agent: **ARTALE, Beverly**; 7500 Grace Drive, Columbia, Maryland 21044 (US).

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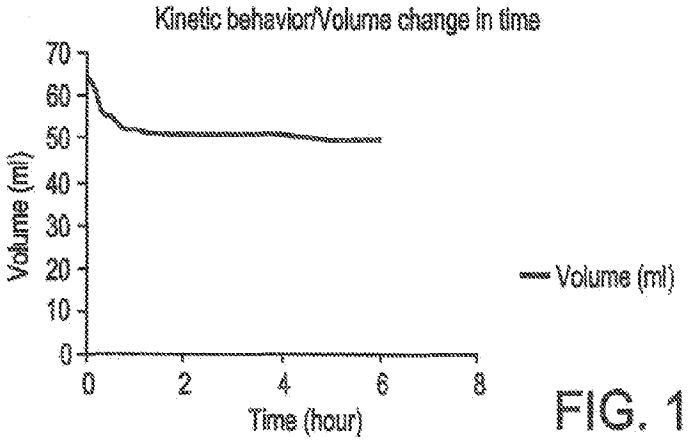


FIG. 1

(57) Abstract: Compositions containing a biologically active ingredient and an inorganic oxide material are disclosed. Methods of making and using compositions containing a biologically active ingredient and an inorganic oxide material are also disclosed. The present invention relates to compositions comprising inorganic oxide porous material containing a biologically active ingredient in liquid form, methods of making such compositions, and methods of using them.

POROUS SILICA GEL AS A CARRIER FOR LIQUID TECHNOLOGIES

TECHNICAL FIELD

[0001] The present invention relates to compositions comprising inorganic oxide porous material containing a biologically active ingredient in liquid form, methods of making such compositions, and methods of using them.

BACKGROUND

[0002] The oral route remains the preferred route of drug administration due to its convenience and good patient compliance. Major problems in oral drug formulations are the erratic and incomplete absorption throughout the gastro-intestinal (GI) tract, resulting in low and variable bioavailability and lack of dose proportionality. These problems mainly result from poor aqueous solubility of the active ingredient. It has been reported that an estimated 40% of existing pharmaceutical active ingredients and an even higher proportion of all newly developed drugs are poorly soluble or insoluble in water. This poses a major challenge to drug development, as there is a high need for producing suitable formulations to improve the solubility and bioavailability of such drugs.

[0003] Much research has been conducted into methods to cope with these problems. Methods that have been developed include the reduction of particle size of the drug by micronisation or nanonisation as to increase surface area, thereby increasing dissolution rate of the active ingredient. Further methods include solubilization in surfactant systems, water-soluble molecular complexes with cyclodextrins, converting the drug in amorphous form by lyophilization or formation of solid dispersions in hydrophilic carriers, microencapsuleation, and the release from porous carrier materials.

[0004] One technique for promoting dissolution properties and oral bioavailability of poorly water-soluble drugs is by using them in liquid phase by dissolution or emulsion in non-volatile oils/ lipids. Such systems have been referred to as lipid based drug delivery system (LBDDS). In these forms, the active ingredient is already in solution so that the drug is present on molecular level, avoiding the dissolution step from the crystalline state. The drugs in liquid phase are typically filled into soft gelatin capsulees. The latter give rise to drawbacks, such as complications in manufacturing, low manageability and portability, risks of leakage, limited shelf-life due to stability problems during storage caused by interactions between the components, oxidation of the lipid components, issues of compatibility of the

liquid formulation with the capsulee shell, criticality of storage temperature because of irreversible drugs/excipients precipitation at lower temperatures.

[0005] To overcome these problems, so-called liquisolid formulations have been developed, which are porous carrier materials wherein the drugs remain in liquid form. Liquisolid forms are obtained by conversion of drugs in liquid form into acceptably flowing non-adherent and compressible powder mixtures by blending with selected carriers and coating materials. These then are converted into solid dosage forms such as tablets, pellets, and capsulees.

[0006] Due to increased wetting and surface area for dissolution, liquisolid dosage forms of water insoluble drugs show improved dissolution properties and bioavailability. This technique was successfully applied for low dose water-insoluble drugs. However, as loadability and release of the drugs from the carriers used is limited, formulation of insoluble drugs at higher doses is one of the limitations of the liquisolid technique. Another problem associated with liquisolid formulations is their decreased flowability when loaded with higher amounts of drugs in liquid form. This causes these materials difficult to process in pharmaceutical manufacturing. In order to have acceptable flowability and compactability, high levels of carrier and coating materials have to be added thereby increasing the weight and volume of the resulting dosage forms.

[0007] One type of lipid based drug delivery systems are the self-emulsifying drug delivery systems (SEDDS). This type of emulsion-based drug formulations can be used in soft gelatin capsulees or as liquisolid formulations. SEDDS are isotropic and thermodynamically stable mixtures of drug, oil/lipid, surfactant/cosurfactant, that, in contact with aqueous fluids, spontaneously form oil-in-water emulsions of droplets, ranging in droplet size approximately between 100–300 nm. Systems forming emulsions with droplets of less than 50 nm are referred to as self-micro-emulsifying drug delivery systems (SMEDDS), and even smaller droplet sizes as self-nanoemulsifying drug delivery system (SNEDDS). Self-emulsifying formulations spread readily in the gastrointestinal (GI) tract, where the digestive motility of the stomach and the intestine provide the agitation necessary for selfemulsification. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDSs are physically stable formulations that are easy to manufacture. In particular for lipophilic drugs

that exhibit limited and distorted absorption, these systems offer an improvement in the rate and extent of absorption resulting in more reproducible bioavailability.

[0008] Given the advantages of solid dosage forms, SEDDS, SNEDDS and SMEDDS have also been converted into solid-SEDDS, solid-SNEDDS or solid-SMEDDS (S-SEDDS, S-SNEDDS or S-SMEDDS) using liquisolid solidification procedures similar as described above. The resulting solid formulations in turn can be worked into various solid or semi-solid dosage forms (tablets, pellets, capsules, creams, transdermal systems, etc.).

SUMMARY

[0009] It is an object of this invention to provide further carriers for use in the release of active ingredients of various nature. It is a further object of this invention to provide carriers that allow higher drug loading compared to known systems, showing desired dissolution release profiles and concomitant oral bioavailabilty characteristics. It is also an object of this invention to provide compact liquisolid dosage forms of high dose water-insoluble drugs, which are of acceptable size to patients. It is an object of this invention to provide liquisolid materials with optimum properties such as flow and bulk density. Still a further object concerns the provision of liquisolid formulations that have good flowability characteristics and can be easily processed in pharmaceutical manufacturing.

[0010] One or more of these objects and other advantages are attained by the various aspects and embodiments of the present invention.

[0011] In one embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein the inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, up to 2:1.

[0012] In another embodiment, the present invention relates to a pharmaceutical composition comprising at least one pharmaceutical dosage formulating ingredient and a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as

measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to inorganic oxide particles of at least 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, up to 2:1.

[0013] In an even further embodiment, the present invention relates to a method of making composition comprising porous inorganic oxide material containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, up to 2:1.

[0014] In another embodiment, the present invention concerns a method of making a pharmaceutical and/or cosmetic composition comprising at least one pharmaceutical dosage formulating ingredient and a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, or at least 2:1.

[0015] In a further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a pore size distribution having a relative span of about 1.5 or less, or about 1.4 or less, or about 1.3 or less, or about 1.2 or less, or about 1.1 or less, or about 1.0 or less.

[0016] In another embodiment, the present invention concerns a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a median pore size of 5 nm to 30 nm, wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to

inorganic oxide particles of at least 1:1, or 1.3, or 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, or at least 2:1.

[0017] In an even further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a median particle size of from 3 microns to 10 mm; wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to inorganic oxide particles of at least 1:1, or 1.3, or 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, or at least 2:1.

[0018] In another embodiment, the present invention concerns a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said composition, after mixing the inorganic oxide particles and liquid material, decreases in volume of at least about 15% after resting, or at least about 20%, or at least about 25%, or at least about 30%, or at least about 35%, or at least about 40% after resting.

[0019] In a further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said composition, after mixing the inorganic oxide particles and liquid material, increases in bulk density by at least about 15% after resting, or at least about 20%, or at least about 25%, or at least about 30%, or at least about 35%, or at least about 40% after resting.

[0020] In another embodiment, the present invention concerns a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein, after mixing the inorganic oxide particles and liquid material and then resting for at least 2 hours, at least about 400 mg of said

composition may be loaded into a zero size capsule. In another embodiment, at least about 410 mg, or at least about 420 mg, or at least about 430 mg of said composition may be loaded into a zero size capsule.

[0021] In an even further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a ratio of liquid material to inorganic oxide particles of at least 1:1; wherein at least 65% of the liquid material is desorbed from the particles upon desorption.

[0022] In one embodiment, the inorganic oxide material comprises porous particles comprising pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

[0023] In another embodiment, the porous inorganic oxide material containing a biologically active ingredient in a liquid material is in the form of particles, i.e. particles of porous inorganic oxide material containing a biologically active ingredient in liquid form. The average diameter of the particles of porous inorganic oxide material of the invention may be in the range of from about 3µm to about 5 mm.

[0024] The compositions of the invention may contain further liquid organic auxiliary materials such as oils, non-volatile solvents, and surfactants.

[0025] In one embodiment, the particles of porous inorganic oxide material containing a biologically active ingredient in a liquid material of the invention form a powder that is free-flowing. In a further embodiment, the powder has a Carr index of equal or lower than 25, or the powder has a Hausner index of about 1 to about 1.4. In one embodiment, the angle of repose of said powder is from about 30° to about 45°. These properties are measured before and after loading the biologically active ingredient on the porous inorganic oxide material.

[0026] In further embodiment, the composition comprising porous inorganic oxide material containing a biologically active ingredient in a liquid material has a bulk bulk density, after loading and resting during at least 2 hours, of at least 450 g/l.

[0027] Upon loading with a biologically active ingredient in a liquid material, the resulting loaded porous inorganic oxide material may show a limited (e.g. up to about 10%)

or no increase, but in particular shows a decrease in volume when compared to the unloaded inorganic oxide porous material. In one embodiment, the decrease is up to about 30%, or up to about 20%, or up to about 10% (each % in this paragraph being volume/volume or v/v). Each of the changes in volume and/or density mentioned herein are after loading and resting up to 2 hours depending upon the liquid, and even up to 24 or 48 hours. In one embodiment, upon loading the inorganic oxide porous material with biologically active ingredient in a liquid material, a decrease of the volume or increase in density, in particular the particular decreases of volume or increases in density mentioned herein, during a time period of about 3 hrs, in particular of about 2 hrs is observed, after which time period no further decrease occurs and the volume stays substantially constant.

[0028] The compositions of the present invention advantageously do not show the substantial increase of volume that is typically observed when loading art-known silicas with a biologically active ingredient in a liquid material. This allows the manufacture of more compact dosage forms, which in turn contributes to better processability during pharmaceutical manufacturing and to better acceptability of the dosage forms by patients.

[0029] In a further aspect, the present invention concerns a pharmaceutical composition comprising at least one pharmaceutical dosage formulating ingredient and a composition comprising porous inorganic oxide material containing a biologically active ingredient in a liquid material, wherein the inorganic oxide material has the oil adsorption, the pore volume, and BET surface area, as specified herein. In one embodiment, the said composition comprising inorganic oxide porous material containing a biologically active ingredient is in the form of particles.

[0030] The present invention is further directed to methods of making the disclosed compositions. In one embodiment, the method of making a composition of the present invention comprises incorporating at least one biologically active ingredient in a liquid material into the porous inorganic oxide material having the oil adsorption, the pore volume, and BET surface area, as specified herein.

[0031] In a further aspect, the present invention concerns a method of making a pharmaceutical composition comprising at least one pharmaceutical dosage formulating ingredient and a composition comprising porous inorganic oxide material containing a biologically active ingredient in a liquid material, wherein the inorganic oxide material has the oil adsorption, the pore volume, and BET surface area, as specified herein, said method

comprising combining said pharmaceutical dosage formulating ingredient with said composition.

[0032] The present invention is also directed to methods of using the disclosed compositions. In one embodiment, the method of using a composition of the present invention comprises administering a composition of the invention to a patient so as to deliver a biologically active material to the patient, wherein the composition comprises a porous inorganic oxide material containing a biologically active ingredient in a liquid material, wherein the inorganic oxide material has the oil adsorption, the pore volume, and BET surface area, as specified herein. The composition that is administered in particular is a pharmaceutical dosage form.

[0033] In one embodiment, the said inorganic oxide material is in the form of particles, in particular particles havin an average diameter as further specified herein.

[0034] These and other features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] The present invention is further described with reference to the appended figures, wherein:

[0036] **FIG. 1** graphically displays the kinetic behaviour or volume change over time of an exemplary composition of the present invention.

[0037] **FIG. 2** graphically displays capsule loading capacity change before and after resting of an exemplary composition of the present invention according to Example 4.

[0038] **FIG. 3** graphically displays a release profile of acetaminophen from an exemplary composition of the present invention according to Example 6.

[0039] **FIG. 4** graphically displays a release profile of ascorbic acid from an exemplary composition of the present invention according to Example 6.

[0040] **FIG. 5** graphically displays the release profile Gyburide from a solid SEDDS system of the present invention according to Example 8.

DETAILED DESCRIPTION

[0041] To promote an understanding of the principles of the present invention, descriptions of specific embodiments of the invention follow and specific language is used to describe the specific embodiments. It will nevertheless be understood that no limitation of the scope of the invention is intended by the use of specific language. Alterations, further modifications, and such further applications of the principles of the present invention discussed are contemplated as would normally occur to one ordinarily skilled in the art to which the invention pertains.

[0042] It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an oxide" includes a plurality of such oxides and reference to "oxide" includes reference to one or more oxides and equivalents thereof known to those skilled in the art, and so forth.

[0043] "About" modifying, for example, the quantity of an ingredient in a composition, concentrations, volumes, process temperatures, process times, recoveries or yields, flow rates, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that may occur, for example, through typical measuring and handling procedures; through inadvertent error in these procedures; through differences in the ingredients used to carry out the methods; and like proximate considerations. The term "about" also encompasses amounts that differ due to aging of a formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

[0044] As used herein, the term "biologically active ingredient" means an active pharmaceutical ingredient (API), which provides a pharmacological activity or otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in humans. Even though this includes poorly soluble material, it may also include materials that range in solubility, including those listed in the BCS (Biopharmaceutic Classification System), which is a classification approach where drugs (APIs) are divided into four classes based on the extent (high or low) of their aqueous solubility and permeability through the GI tract wall, in particular intestinal. In this regard, these four classes are: (Group I) High Solubility and High

Permeability drugs, (Group II) Low Solubility and High Permeability drugs, (Group III) High Solubility and Low Permeability drugs and, (Group IV) Low solubility and Low Permeability drugs.

[0045] As used herein, the term "bulk density" means the mass of particulate matter, such as a powder, divided by the total volume occupied by the matter, and includes intraparticle pore volume and interparticle void volume.

[0046] As used herein, the term "free flowing" means the ability of a group of particles or a powder to move when a force (e.g., gravity, or other external force) is applied to it. Commonly used tests for measuring powder flow include the Hausner ratio, compressibility index (Carr index) or angle of repose. The compressibility index (Carr index) and the Hausner ratio are determined by measuring both the bulk volume and the tapped volume of a powder.

[0047] As used herein, "inorganic oxides" is defined as binary oxygen compounds where the inorganic component is the cation and the oxide is the anion. The inorganic material includes metals may also include metalloids. Metals include those elements on the left of the diagonal line drawn from boron to polonium on the periodic table. Metalloids or semi-metals include those elements that are on the right of this line. Examples of inorganic oxides include silica, alumina, titania, zirconia, etc., and mixtures thereof.

[0048] As used herein, the term "intraparticle pore volume" means pore volume attributable to the spaces in the pore of the particles, as compared to interparticle pore volume, which is the pore volume attributable to the spaces between the particles (i.e., the interstitial space).

[0049] As used herein, the term "lipid material" or "lipid component" means organic materials comprising fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds. They include, but are not limited to, molecules that originate entirely or in part by carbanion-based condensations of thioesters (fatty acids, polyketides, etc.) and/or by carocation-based condensations of isoprene units (prenols, sterols, etc.).

[0050] As used herein, the term "ordered porous material" refers to porous particles that have an internal structural order such that they possess a low angle X-ray diffraction patterns according to Bragg's Law. Such materials include ordered mesoporous silica, for example, MCM-41, SBA-15, TUD-1, HMM-33 and FSM-16.

[0051] As used herein, the term "non-ordered porous material" refers to porous particles possessing an internal structure such that they do not have a low angle X-ray diffraction pattern according to Bragg's Law. Such materials may be formed via any known process including, but not limited to, a solution polymerization process such as for forming colloidal particles, a continuous flame hydrolysis technique such as for forming fused particles, a gel technique such as for forming gelled particles, and a precipitation technique such as for forming precipitated particles. The particles may be subsequently modified by autoclaving, flash drying, super critical fluid extracting, etching, or like processes. The particles may be composed of organic and/or inorganic materials and combinations thereof. In one exemplary embodiment the particles are composed of inorganic materials such as inorganic oxides, sulfides, hydroxides, carbonates, silicates, phosphates, etc, but are preferably inorganic oxides. The particles may be a variety of different symmetrical, asymmetrical or irregular shapes, including chain, rod or lath shape. The particles may have different structures including amorphous or crystalline, etc. The particles may include mixtures of particles comprising different compositions, sizes, shapes or physical structures, or that may be the same except for different surface treatments. Porosity of the particles may be intraparticle or interparticle in cases where smaller particles are agglomerated to form larger particles. In one exemplary embodiment the particles are composed of inorganic materials such as inorganic oxides, sulfides, hydroxides, carbonates, silicates, phosphates, etc, but are preferably inorganic oxides. Porous materials include organic and inorganic materials, or hybrids thereof, and may be in the form of particles, monoliths, membranes, coatings, and the like.

[0052] As used herein, the term "pore size distribution" means the relative abundance of each pore size in a representative volume of porous inorganic particles. As used herein "median pore size" is the pore diameter below which 50% of the intraparticle pore volume resides.

[0053] As used herein, the term "relative span" is defined as meaning a measure of the breadth of pore size distribution. The "span" is measured by subtracting the d_{10} pore size (i.e., the pore size/diameter below which 10% of the pore volume resides) from the d_{90} pore size (i.e., the pore size/diameter below which 90% by pore volume resides) as measured by mercury porosimetry. The term "relative span" is defined as the ratio of $(d_{90}-d_{10})/d_{50}$. The span and relative span are determined using nitrogen sorption (BJH method) of the cumulative pore volume.

[0054] As used herein the term "rested" or "after resting" is used to indicate a period of time wherein the porous inorganic oxide material is allowed to stand undisturbed after loading with a biologically active ingredient in a liquid material.

[0055] Whenever used herein in relation to a ratio or a percentage of components, w/w means weight/weight and w/v means weight/volume.

[0056] The present invention is directed to compositions comprising a biologically active material or ingredient and an inorganic oxide material, wherein the inorganic oxide material comprises porous particles. Efficient loading of biologically active materials in liquids or a liquid material onto vehicles for drug delivery is a concern for many biologically active materials and this invention relates to various embodiments that provide solutions to this problem. Applicants of the present invention have found that certain porous inorganic oxide materials having a specific sets of physical properties provide exceptional liquid loading and release of biologically active materials that are in various liquids or a liquid material.

[0057] In one embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein the inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, up to 2:1.

[0058] In an even further embodiment, the present invention relates to a method of making composition comprising porous inorganic oxide material containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, up to 2:1.

[0059] In another embodiment, the present invention concerns a method of making a pharmaceutical composition comprising at least one pharmaceutical dosage formulating ingredient and a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles

possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, or at least 2:1.

[0060] In another embodiment, the present invention concerns a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a median pore size of 5 nm to 30 nm, wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to inorganic oxide particles of at least 1:1, or 1.3, or 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, or at least 2:1.

[0061] In an even further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a median particle size of from 3 microns to 10 mm; wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to inorganic oxide particles of at least 1:1, or 1.3, or 1.5:1, or 1.6:1, or 1.7:1, or 1.8:1, or 1.9:1, or at least 2:1.

[0062] In a further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a pore size distribution where at least 0.5 cm^3/g of pore volume are from pores ranging from 10 nm to 30 nm, at least 0.5 cm^3/g, at least 0.6 cm^3/g , at least 0.8 cm^3/g, at least 1.0 cm^3/g, at least 1.2 cm^3/g, at least 1.4 cm^3/g, or at least 1.6 cm^3/g of pore volume are from pores ranging from 10 nm to 30 nm.

[0063] In a further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having a pore volume, as measured by nitrogen

porosimetry, of about 0.5 cm^3/g or greater; and (c) a pore size distribution having a relative span of about 1.5 or less, or about 1.4 or less, or about 1.3 or less, or about 1.2 or less, or about 1.1 or less, or about 1.0 or less.

[0064] The porous inorganic oxide material containing a biologically active ingredient in a liquid material may be in the form of particles, which may have a variety of different symmetrical, asymmetrical or irregular shapes, including chain, rod or lath shape. The particles may include mixtures of particles comprising different compositions, sizes, shapes or physical structures.

[0065] The average diameter of the particles of the porous inorganic oxide material of the invention may be in the range of from about 3μm to about 5 mm, preferably from about 50 μm (or about 44 μm) to about 500 μm; or from about 70 μm (or about 74 μm) to about 200 μm; or from about 50 μm (or about 44 μm) to about 150 μm (or about 149 μm); or from about 50 μm (or about 44 μm) to about 150 μm (or about 149 μm); or from about 100 μm (or about 105 μm) to about 120 μm (or about 125 μm), or from about 48 μm (or about 44 μm) to about 65 μm (or about 63 μm), or from about 90 μm to about 130 μm. The average diameters disclosed herein preferably are determined by Malvern instrumentation. The desired particle sizes can be obtained by milling and subsequent mesh sieving.

[0066] The porous inorganic oxide materials may be formed via any known process including a solution polymerization process such as for forming colloidal particles, a continuous flame hydrolysis technique such as for forming fused particles, a gel technique such as for forming gelled particles, and a precipitation technique such as for forming precipitated particles. The particles may be subsequently modified by autoclaving, flash drying, super critical fluid extracting, etching, or like processes. In one embodiment the particles are composed of inorganic materials such as inorganic oxides, sulfides, hydroxides, carbonates, silicates, phosphates, etc, but are preferably inorganic oxides. The particles may include mixtures of particles comprising different compositions, sizes, shapes or physical structures, or that may be the same except for different surface treatments.

[0067] Porous materials include organic and inorganic materials, or hybrids thereof, and may be in the form of particles, monoliths, membranes, coatings, and the like.

[0068] The porous particles may be in various forms, such as precipitates, gels, fumed, colloidal, etc, and combinations thereof, unmodified or modified by subsequent processes, such as autoclaving, super critical fluid extraction, flash drying, and the like. In

one embodiment, porous inorganic oxide material that is suitable for use in the present invention includes precipitated inorganic oxide particles and inorganic oxide gel particles. These inorganic oxides are referred to herein as "parent inorganic oxides", "parent particles", or "parent dispersions".

[0069] In another embodiment, the porous inorganic oxide materials are non-ordered, and may further possess random intraparticle porosity. Such materials have been found, when combined with the biologically active ingredient and liquid material, to provide beneficial adsorption and desorption (and dissolution) characteristics. Even though any inorganic oxide composition may be suitable for use in this invention (e.g., SiO_2, Al_2O_3, $AlPO_4$, MgO, TiO_2, ZrO_2, etc.), one embodiment of the present invention includes amorphous precipitated silica and silica gel. The inorganic oxides may also include mixed inorganic oxides such as $SiO_2.Al_2O_3$, $MgO.SiO_2.Al_2O_3$ and the like. Mixed inorganic oxides are prepared by conventional blending or cogelling procedures. In embodiments comprising gels, the dispersions are derived from porous inorganic oxide gels such as gels comprising SiO_2, Al_2O_3, $AlPO_4$, MgO, TiO_2, and ZrO_2. The gels can be hydrogels, aerogels, or xerogels.

[0070] In one embodiment, the inorganic oxide gels include a non-ordered porous silica gel that includes interparticle pore volume. Such a silica gel may be prepared by mixing an aqueous solution of an alkali metal silicate (e.g., sodium silicate) with a strong acid such as nitric or sulfuric acid, the mixing being done under suitable conditions of agitation to form a clear silica sol which sets into a hydrogel, i.e., macrogel, in less than about one-half hour. The resulting gel is then washed. The concentration of inorganic oxide, i.e., SiO_2, formed in the hydrogel is usually in the range of about 10 and about 50, or between about 20 and about 35, or between about 30 and about 35 weight percent, with the pH of that gel being from about 1 to about 9, or 1 to about 4. A wide range of mixing temperatures can be employed, this range being typically from about 20 to about 50° C. The newly formed hydrogels are washed simply by immersion in a continuously moving stream of water, which leaches out the undesirable salts, leaving about 99.5 weight percent or more pure inorganic oxide behind. The pH, temperature, and duration of the washing will influence the physical properties of the silica, such as surface area (SA) and pore volume (PV). Silica gel washed at 65-90° C. at pH's of 8-9 for 15-36 hours will usually have SA's of 250-400 and form aerogels with PV's of 1.4 to 1.7 cm^3/g.

[0071] Methods for preparing inorganic oxide gels such as alumina and mixed inorganic oxide gels such as silica/alumina cogels are also well known in the art, such as by conventional blending, co-gelation, co-precipitation, and the like. Methods for preparing such gels have been described in US 4,226,743. In general, alumina gels are prepared by mixing alkali metal aluminates and aluminum sulfate. Cogels are prepared by cogelling two or more metal oxides so that the gels are composited together. For example, silica alumina cogels can be prepared by gelling an alkali metal silicate with an acid or acid salt, and then adding alkali metal aluminate, aging the mixture and subsequently adding aluminum sulfate. The gel is then washed using conventional techniques. Another embodiment of this invention is derived from dispersions of certain precipitated inorganic oxides. Reinforced precipitated silica such as that described in US 4,157,920 can also be used to prepare the dispersion of this invention. For example, reinforced precipitated silicas can be prepared by first acidulating an alkali inorganic silicate to create an initial precipitate. The resulting precipitate is then reinforced or "post conditioned" by additional silicate and acid. The precipitate resulting from the second addition of silicate and acid comprises 10 to 70% by weight of the precipitate initially prepared. It is believed that the reinforced structure of this precipitate is more rigid than conventional precipitates as a result of the second precipitation. Once an inorganic oxide is selected for the parent dispersion, a liquid phase of the selected inorganic oxide is prepared. In general, the parent dispersion should be in a state that can be wet milled. The medium for the liquid phase can be aqueous or non-aqueous, e.g., organic. The liquid phase can be residual water in inorganic oxide gels which have been drained, but not yet dried, and to which additional water is added to reslurry the gel.

[0072] In another embodiment, dried inorganic oxides, e.g., xerogels, are dispersed in liquid medium. In some embodiments, the parent dispersion is then milled. The milling is conducted "wet", i.e., in liquid media. The general milling conditions can vary depending on the feed material, residence time, impeller speeds, and milling media particle size. The techniques for selecting and modifying these conditions to obtain the desired dispersions are known to those skilled in the art. The milling equipment used to mill the parent inorganic oxide particles should be of the type capable of severely milling and reducing materials to particles having the desired size, e.g., through mechanical action. Such mills are commercially available, with fluid energy mills, hammer mills, and sand mills being particularly suitable for this purpose. Hammer mills impart the necessary mechanical action through high speed metal blades, and sand mills impart the action through rapidly churning

media such as zirconia or sand beads. Impact mills can also be used. In other embodiments, milling is not needed, such as for air-set inorganic oxide gels. Such gels are formed by air-spraying an intimate mixture of an alkali metal solution (e.g., sodium silicate) with a suitable acid (e.g., sulfuric acid) at such a concentration so that mixture gels during flight, before being collected in a suitable medium, generally water. Any resulting dispersion or powder may also be further processed. For example, further processing is desirable if there is a need to prepare a relatively stable dispersion without the aid of dispersing agents, or if there is a significant population of particles that are larger than desired. Further processing may also be needed to insure that essentially all of the distribution of particles is below a certain size. In such a case, the dispersion or powder is processed to separate the smaller particles from the larger particles. This separation can be created by centrifuging the inorganic oxide particles into a supernatant phase, which comprises the smaller particles of the final product, and a settled phase which comprises the larger particles. The supernatant phase is then removed from the settled phase, e.g., by decanting. In some instances, it may be preferable to centrifuge the supernatant two, three or more times to further remove large particles remaining after the initial centrifuge. It is also contemplated that the larger particles of a milled dispersion can separate over time under normal gravity conditions, and the supernatant can be removed by decanting. Depending on the product particle size targets, the settled phase also can be regarded as particles of this invention. The dispersion of particles or powder also can be modified after milling to insure a stable dispersion. This can be accomplished through pH adjustment, e.g., adding alkaline material, or by the addition of conventional dispersants.

[0073] The inorganic oxide material in the compositions of the present invention may comprise two or more different and distinct types of porous particles. In one embodiment each type of porous particles provides a specific desorption and/or dissolution rate profile for the biologically active material in a liquid material so as to form a composite desorption and/or dissolution rate profile for the biologically active material.

[0074] In one embodiment, the surface of the inorganic oxide material, in particular the surface in the pores, has not been chemically modified. The pores in the inorganic oxide material are open so that the active ingredient in a liquid material can enter the pores and become adsorbed at the surface of the pores, or can leave the pores as to release the active ingredient.

[0075] The porous inorganic oxide material of the present invention has an oil adsorption of about 100 to about 600 ml/100 g, or of about 100 to about 500 ml/100 g, or of about 100 to about 450 ml/100 g, or of about 100 to about 400 ml/100 g, or of about 150 to about 400 ml/100 g, or of about 200 to about 400 ml/100 g . The oil adsorption values can be measured with standard methodology, in particular by titrating a predetermined quantity of the inorganic oxide material with an oil under constant mixing of the oil/ inorganic oxide material, until the mass shows excess of oil, such as done in ASTM D281.

[0076] The inorganic oxide material in the compositions of the present invention is porous. In one embodiment the pores have a mean pore diameter of greater than 5 nm, or from about 5 nm to about 30 nm; or from about 10 nm to about 30 nm. In a further embodiment, the mean pore diameter is about 20 to about 25 nm.

[0077] Desirably, the porous inorganic oxide material has a pore volume of about 0.5 cm^3/g or greater, or about 0.6 cm^3/g or greater, or about 0.7 cm^3/g or greater. In some embodiments, the upper limit of the pore volume is about 3.0 cm^3/g, or about 2.3 cm^3/g.

[0078] Desirably, the porous inorganic oxide material has a BET surface area, as measured by nitrogen adsorption, of about 10 m^2/g or greater, or about 100 m^2/g or greater, or of about 200 m^2/g or greater, or of about 300 m^2/g or greater. In some embodiments, the upper limit of the BET surface area is about 1000 m^2/g, or about 800 m^2/g, or of about 600 m^2/g. In other embodiments, the BET surface area may range from about 10 to about 1000 m^2/g, or about 100 to about 800 m^2/g, or about 150 to about 600 m^2/g, or about 200 to about 500 m^2/g, or about 250 to about 400 m^2/g.

[0079] In one embodiment, the porous inorganic oxide material has (i) a mean pore diameter of from about 5 nm to about 30 nm, (ii) a pore volume of about 0.7 cm^3/g or greater, and (iii) a surface area of about 20 to about 500 m^2/g, or greater. In another embodiment, this porous inorganic oxide material is in the form of particles, which may have a diameter from about 50 µm (or about 44 µm) to about 150 µm (or about 149 µm). In a further embodiment, this inorganic oxide porous material has an oil adsorption of about 100 to about 500 ml/100 g. Such materials are attractive due to their superior properties in terms of high loading, bulk density, flowability, desorption and dissolution charcteristics.

[0080] In the present invention, the measurements of pore volume are generated by N_2 porosity analysis and surface area are generated by the BET technique, which are art-known techniques.

[0081] The porous inorganic oxide material containing a biologically active ingredient in a liquid material may be obtained from porous inorganic oxide material that do not contain a biologically active ingredient in a liquid material, which biologically active ingredient in a liquid material subsequently is added so that it is adsorped by the porous inorganic oxide material . Or, alternatively, the biologically active ingredient in a liquid material may be added during one or more of the steps of the preparation of the porous inorganic oxide material.

[0082] In yet another embodiment, the inorganic oxide can be dispersed in a liquid compound, which is subsequently used as a reactant or solvent or medium, which forms the biologically active composition of the present invention.

[0083] The particles of porous inorganic oxide material of the invention may be free-flowing. In one embodiment said particles may have a Carr index of equal or lower than about 25, e.g. a Carr index of about 10 to about 25. In some embodiments the Carr index may be equal or lower than about 15, e.g. a Carr index of about 10 to about 15. The particles of porous inorganic oxide material of the invention may have a Hausner index of about 1 to about 1.4, in particular of about 1.2 to about 1.4. The particles of porous inorganic oxide material of the invention may have an angle of repose of about 30° to about 45°. In some embodiments, the Carr and Hausner index values and angles of repose mentioned herein apply to any of the particles of the invention having a w/w ratio of the biologically active ingredient in a liquid material to inorganic oxide inorganic oxide, as specified herein, and in particular where said w/w ratio is between about 0.5 : 1 to about 2 : 1. In some embodiments, the Carr and Hausner index values and angles of repose mentioned herein apply to any of the particles of the invention that are unloaded with biologically active ingredient in a liquid material.

[0084] The Carr index (C.I.) is an indication of the flowability and compressibility of a powdery material and is calculated by the formula $C = 100 \times (1-\rho_b/\rho_t)$, where ρ_b is the freely settled bulk bulk density of a powder, and ρ_t is the tapped bulk density of the powder. A Carr index greater than 25 is considered to be an indication of poor flowability. Materials having a Carr index equal to or lower than 25 show good flowability and can also be referred to as "free-flowing" materials. The Hausner index (H.I.) is calculated by the formula $H = \rho_t/\rho_b$.

[0085] In another embodiment, the present invention concerns a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said composition, after mixing the inorganic oxide particles and liquid material, decreases in volume of at least about 15% after resting, or at least about 20%, or at least about 25%, or at least about 30%, or at least about 35%, or at least about 40% after resting. Each of the changes in volume and/or density mentioned herein are after loading and resting up to 2 hours depending upon the liquid, and even up to 24 or 48 hours. In one embodiment, upon loading the inorganic oxide porous material with biologically active ingredient in a liquid material, a decrease of the volume or increase in density, in particular the particular decreases of volume or increases in density mentioned herein, during a time period of about 3 hrs, in particular of about 2 hrs is observed, after which time period no further decrease occurs and the volume stays substantially constant.

[0086] In a further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; and (b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein said composition, after mixing the inorganic oxide particles and liquid material, increases in bulk bulk density by at least about 15% after resting, or at least about 20%, or at least about 25%, or at least about 30%, or at least about 35%, or at least about 40% after resting. Each of the changes in volume and/or density mentioned herein are after loading and resting up to 2 hours depending upon the liquid, and even up to 24 or 48 hours. In one embodiment, upon loading the inorganic oxide porous material with biologically active ingredient in a liquid material, a decrease of the volume or increase in density, in particular the particular decreases of volume or increases in density mentioned herein, during a time period of about 3 hrs, in particular of about 2 hrs is observed, after which time period no further decrease occurs and the volume stays substantially constant.

[0087] In another embodiment, the present invention concerns a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about

100 to about 500 ml/100 g; and (b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; wherein, after mixing the inorganic oxide particles and liquid material and then resting for at least 2 hours, at least about 400 mg of the composition may be loaded into a zero size capsule. In another embodiment, at least about 410 mg, or at least about 420 mg, or at least about 430 mg of said composition may be loaded into a zero size capsule.

[0088] In an even further embodiment, the present invention relates to a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess (a) an oil adsorption of about 100 to about 500 ml/100 g; (b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and (c) a ratio of liquid material to inorganic oxide particles of at least 1:1; wherein at least 65% of the liquid material is desorbed from the particles upon desorption. In another embodiment, at least 70%, or at least 75%, or at least 80%, or at least 85% of the liquid material is desorbed from the particles upon desorption. The liquid material is desorbed under conditions that simulate desorption of liquid material in biological fluids. Such tests are performed by intense mixing in aqueous medium, as set forth in Example 7.

[0089] As used herein, the term "in liquid form" or "liquid material" in relation to biologically active ingredients refers to such ingredients that in themselves are liquids or to biologically active ingredients brought into liquid form by various techniques including, for example, desorption and/or dissolution or conversion into a self-emulsifying drug delivery system. Such materials may also include solid biologically active ingredients that are suspended, dispersed or incorporated with liquids.

[0090] The term "in liquid form" or "liquid material" refers to biologically active ingredients as such or brought into liquid form that are liquid at room tremperature or at physiological temperature, or are liquid at temperatures ranging from about 0°C to about 60°C, in partuclar about 10°C to about 50°C, or about 20°C to about 45°C. Such materials may be solid at certain conditions (e.g., temperature, concentration, etc.) and liquid under other conditions.

[0091] The porous inorganic oxide material in accordance with this invention contains a biologically active ingredient in liquid form. The term "contain" means that the porous inorganic oxide material is loaded with a biologically active ingredient, the term

"loaded" meaning that the active ingredient is adsorbed at the surface of the inorganic oxide material, including the surface within the pores of the inorganic oxide material. A major part of the active ingredient may be incorporated in the pores of the inorganic oxide material. Such inorganic oxide materials with adsorbed biologically active ingredient are referred as "loaded inorganic oxide materials". The terms "loaded" and "incorporated" in this context are meant to be equivalent.

[0092] In one embodiment, the w/w ratio of the biologically active ingredient in a liquid material (which comprises the biologically active ingredient itself as well as any added materials in the liquid) to inorganic oxide is in the range of about 0.5:1 to about 5:1, or of about 0.5:1 to about 3:1, or of about 0.5:1 to about 2:1, or of about 1:1 to about 2:1.

[0093] The composition comprising porous inorganic oxide material containing a biologically active ingredient in a liquid material may have a bulk density of at least 450 g/l. In some embodiments said bulk density is in the range of from 450 g/l to 750 g/l, in particular in the range of from 500 g/l to 700 g/l, or in the range of from 550 g/l to 650 g/l.

[0094] In one embodiment, the biologically active ingredient in a liquid material is a liquid lipid drug. Examples include vitamin A, vitamin E (dl-α-Tocopherol), paracetamol, ascorbic acid, sesame oil, miglyol, or combinations thereof.

[0095] In another embodiment the biologically active ingredient in a liquid material takes the form of a solution or dispersion of the biologically active ingredient in a non-volatile solvent, e.g. having a boiling point of above about 150°C. Examples include glycerin, propylene glycol, liquid polyethylene glycols such as polyethylene glycol 200 and 400, polysorbates such as polysorbate 80, or an oil. Oils that can be used include long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation; vegetable oils such as olive oil, sunflower oil, castor oil, linseed oil and the like; modified or hydrolyzed vegetable oils; semisynthetic medium-chain triglyceride oils having surfactant properties, for example Cremophor. In case of dispersions, the active ingredient is preferably in the form of micro- or of nanoparticles. In one embodiment, the concentration of the biologically active ingredient in the solution or dispersion is in the range of from 1 % to 90 %, or from ... (w/w).

[0096] In one embodiment, the biologically active ingredient in a liquid material is a self-emulsifying drug delivery system (SEDDS) comprising an oily/lipid component, a surfactant, cosolvent, and a biologically active ingredient.

[0097] The oily/lipid component is generally a fatty acid ester or a medium/long chain saturated, partially unsaturated or unsaturated hydrocarbon, in liquid, semisolid or solid form at room temperature (e.g., solid lipid nanoparticles, oily suspensions, submicron lipid emulsions, lipid implants, lipid microtubules, lipid microbubbles, or lipid microspheres, etc.). Examples include mineral oil, vegetable oil, modified or hydrolyzed vegetable oils, silicone oil, lanolin, liposomes, refined animal oil, fatty acids, fatty alcohols, and mono-/di-/tri-glycerides, including long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation and semisynthetic medium-chain triglyceride oils having surfactant properties. Further oily/lipid components include oils comprised of one or more medium chain fatty acids esters of propylene glycol such as propylene glycol monocaprate, propylene glycol dicaprate, propylene glycol dicaprylate/dicaprate, propylene glycol dipelargonate, and propylene glycol dilaurate, triacetin, fats and oils such as olive oil, sesame oil, soybean oil, corn oil, rape oil, castor oil, coconut oil, and eucalyptus oil; caprylic/capric acid triglyceride (Miglyol™ 812); a triglyceride such as tricaprylin and trilaurin; and polyglycerin fatty acid esters such as tetraglycerin polyricinoleate, hexaglycerin polyricinoleate, condensed polyricinoleate, and tetraglycerin mixed fatty acid esters . The term"medium chain fatty acid" is meant to refer to fatty acyl chains of between 6 and 14 carbons in length, more preferably between 8 and 12 carbons in length; "long chain fatty acid" is meant to refer to fatty acyl chains greater than 14 carbons in length; "short chain fatty acid" is meant to refer to fatty acyl chains less than 6 carbons in length.

[0098] The oil components may be used in the SEDDS formulations of the present invention in any effective concentration, including, for example, in a concentration range of 5% to 80% (w/v).

[0099] Preferred surfactants comprise non-ionic surfactants with a relatively high hydrophilic–lipophilic balance (HLB) value usually in concentration ranges between 30% and 60% (w/w).

[0100] The hydrophilic surfactant (HLB (hydrophile-lipophile balance) of 9.0 or higher that can be used include polyoxyethylene lauryl ethers (Laureth 2 (BL-2), Laureth 4.2 (BL-4.2), and Laureth 9 (BL-9), polyoxyethylene (20) sorbitan monococonut oil fatty acid ester ("Polysorbate 20"), Polysorbate 40, Polysorbate 80, Labrasol, D-α -tocopheryl polyethylene glycol 1000 succinate (Vitamin E TPGS NF), lauroyl polyoxyethylene glycerin (Gelucire 44/14), polyoxyethylene hydrogenated castor oil 40 , polyoxyethylene

hydrogenated castor oil 60 (HCO-60), polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, and polyoxyethylene sorbitan monooleate.

[0101] Any effective non-aqueous protic cosolvent, or combinations thereof, may be used in the SEDDS for use in the invention. Acceptable non-aqueous protic solvents include any pharmaceutically acceptable mono-, di-, tri-, or poly-hydroxy linear aliphatic and aromatic solvent, or combinations thereof. Examples of non-aqueous protic solvents include ethanol, propanol, benzyl alcohol, propylene glycol, liquid polyethylene glycols such as polyethylene glycol 200 and 400, and glycerol. The protic solvents may be used in the formulations of the present invention in any effective concentration, including, for example, in a concentration range of about 5% to about 50% (w/v).

[0102] Optionally, a chelating agent and/or a soluble antioxidant may be included in the SEDDS for use in the invention. Chelating agents may be added to enhance the stability of a hydrophobic drug in the SEDDS composition. Suitable optional chelating agents include any pharmaceutically acceptable chelating agent, such as citric acid, maleic acid, succinic acid, tartaric acid, EGTA (ethylene glycol-bis ((3-aminoethyl ether) tetraacetic acid, or egtazic acid) and EDTA (ethylene diamine tetraacetic acid, or edetic acid). Such chelating agents are available in various forms, e. g. , as sodium or potassium salts or as the free acids. Such chelating agents may be used in the formulations of the present invention in any effective concentration, including, for example, in a concentration range of between 0.01% and 10% (w/v).

[0103] For preparing an SEDDS formulation, for example, an absorption_promoter such as sodium salicylate, sodium deoxycholate, sodium myristate, or sodium dodecyl sulfate.

[0104] The SEDDS formulations may contain an auxiliary solvent such as ethanol, propylene glycol, polyethylene glycol, diethylenetriaminepentaacetic acid, diethanolamine, triethanolamine, ethylenediamine, monoethanolamine, or N,N-dimethylacetamide.

[0105] The SEDDS formulation may be prepared by dissolving the drug in a mix of oil, surfactant and cosolvent.

[0106] The biologically active material used in the compositions of the present invention may comprise any known biologically active material. The term "biologically active ingredient" is meant to cover any pharmaceutical or other active ingredient for administration to humans or animals, in particular to warm-blooded animals. The biologically

active material may be an active pharmaceutical ingredient (API), which comprises include natural, semi-synthetic or synthetic molecules. In some embodiments, the biologically active material comprises two or more active pharmaceutical ingredients (APIs) in combination with one another. Other biologically active ingredients include ingredients that have an effect on the general well-being or have an effect on the outer appearance (cosmetic) such as the skin, hair, lips, and eyes. Such ingredients include any agents for use in cleansing, beautifying, promoting attractiveness, or altering the appearance, for example moisturizers, oils, anti-wrinkle agents, fragrances, and the like. Also included are ingredients for nutritious applications (in particular the so-called "nutraceutical" ingredients). Such ingredients include food supplements such as, for example, dietary food supplements, vitamins, minerals, fiber, fatty acids, and amino acids. Examples of such ingredients are Vitamin C, omega-3 fatty acids, carotenes, and flavonoids. The term "biologically active" in relation to compositions for cosmetic or nutricious applications also includes activity relating to the improvement of the outer part of the body, in particular of the dermis, as well as the general well-being of an individual.

[0107] In one embodiment, the active ingredient has a molecular weight below about 1,000 (daltons), or below about 800, for example a molecular weight in the range of about 150 to about 1,000, or in the range of about 200 to about 800.

[0108] The active ingredient for use in the invention may be soluble or insoluble in water or aqueous media, in particular physiological aqueous media. According to generally accepted standards, any solvent solubility is defined as the amount of a solvent (g) required to dissolve 1 g of a compound, whereby the following solubility qualifications are defined: 10-30 g ("soluble"); 30-100 g ("sparingly soluble"); 100-1000 g ("slightly soluble"); 1000-10000 g ("very slightly soluble" or "poorly soluble") and more than 10000 g (practically insoluble).

[0109] In one embodiment, the active ingredient is soluble or insoluble in water or aqueous media, in particular physiological aqueous media. In one embodiment, the pharmaceutically active ingredient belongs to the so-called BCS classes I through IV. Classes I and III are the soluble drugs. The Biopharmaceutical Classification System (BCS) classifies drug substances based on their aqueous solubility and intestinal permeability into four classes: Class I--High Permeability, High Solubility; Class II--High Permeability, Low Solubility; Class III--Low Permeability, High Solubility; Class IV--Low Permeability, Low Solubility.

[0110] In one embodiment, the active ingredient has a partition coefficient (expressed as log P) that is in the range from 4 to 9, in the range from 3 and 8. In a further embodiment, the active ingredient has a pK_A that allows the molecule to be in neutral (non-ionic form) at about pH 5-8.

[0111] Exemplary APIs include, atorvastatin, amiodarone, candesartan-cilexetil, carvedilol, clopidogrel bisulfate, dipyridamole, eprosartan mesylate, epierenone, ezetimibe, felodipine, furosemide, isradipine, lovastatin, metolazone, nicardipine, nisoldipine, olmesartan medoxomil, propafenone HCl, qinapril, ramipril, simvastatin, telmisartan, trandolapril, valsartan and other cardio-vascular active drugs; acyclovir, adefovir, dipivoxil, amphotericin, Amprenavir, cefixime, ceftazidime, clarithromycin, clotrimazole, efavirenz, ganciclovir, itraconazole, norfloxacin, nystatin, ritonavir, saquinavir and other anti-infective drugs including anti-bacterial, anti-viral, anti-fungal and anti-parasitic drugs; cisplatin, carboplatin, docetaxel, etoposide, exemestane, idarubicin. irinotecan, melphalan, mercaptopurine, mitotane, paclitaxel, valrubicin, vincristine and other drugs used in oncology; azathioprine, tacrolimus, cyclosporin, pimecrolimus, sirolimus and other immonosupressive drugs; clozapine, entacapone, fluphenazine, imipramine, nefazodone, olanzapine, paroxetine, pimozide, sertraline, triazolam, zaleplon, ziprasidone, risperidone, carbamazepine and other drugs for CNS indications; danazol, dutasteride, medroxyprogesterone, estradiol, raloxifene, sildenafil, tadalafil, testosterone, vardenafil and other drugs used for reproductive health; celecoxib, dihydroergotamine mesylate, eletriptan, ergoloidmesylates, ergotamine tartrate, nabumetone, Ibuprofen, ketoprofen, triamcinolone, triamcinolone acetonide and other anti-inflammatory and analgesic drugs; bosentan, budesonide, desloratadine, fexofenadin, Fluticasone, loratadine, mometasone, salmeterol, xinafoate, triamcinolon acetonide, zafirlukast and other drugs for respiratory indications; and dronabinol, famotidine, glyburide, hyoscyamine, isotretinoin, megestrol, mesalamine, modafinil, mosapride, nimodipine, perphenazine, propofol, sucralfate, thalidomide, trizanidine hydrochloride and other drugs for various indications including in particular gastro-intestinal disorders, diabetes and dermatology indications. In further embodiments the APIs include ezetimimbe, glucoroniude, tadalafil, fenofibrate, danazol, itraconazole, carbamazepine, griseofulvin, nifedipin.

[0112] The active ingredients further include sugars, polysaccharides, vitamins, amino acids, peptides, prostaglandins, nucleic acids, nucleotides, nucleosides, as well as derivatives thereof. Also included are peptides, proteins, protein fragments, antibodies, small

antibody fragments, and the like. The latter include Fv" fragments, single-chain Fv (scFv) antibodies, antibody Fab fragments, antibody Fab' fragments, antibody fragments of heavy or light chain CDRs, or nanobodies. Also encompassed are small oligonucleic acid or peptide molecules such as aptamers, for example DNA aptamers, RNA aptamers or peptide aptamers.

[0113] In one embodiment, the biologically active ingredient in a liquid material when loaded in the inorganic oxide material shows an increased release compared to the active ingredient as such, or to formulations containing the active ingredient and ingredients that do not influence release. Increased release may for example be an increase of 10%, or of 20%, or of 30%, or of 50%, of the weight percentage of active ingredient released under physiological conditions (pH, temperature).

[0114] In a further embodiment, the biologically active ingredient in a liquid material when loaded in the inorganic oxide material shows immediate release from the compositions of the invention, the term "immediate release" meaning, for example, a release of at least 60% of the drug under physiological conditions (pH, temperature), such as within 60 minutes or less, such as within 30 or less, or within 20 minutes or less, or within 15 minutes or less.

[0115] In the methods of making a composition of the present invention, the step of incorporating the biologically active material into the inorganic oxide material typically comprises a variety of loading methods, including the solvent method and the incipient wetness method, which methods have been described in the prior art, or mere mixing without use of any solvent or other mixing aid.

[0116] In the (slurry) solvent method the inorganic oxide material is loaded with an active ingredient by treatment with a solution of the active ingredient in a liquid material, after which the solvent is removed. The active ingredient in a liquid material thereby becomes adsorbed to the surface of the inorganic oxide material, including the surface within the pores of the inorganic oxide material. Appropriate organic solvents for use in this method include dichloromethane, 1,4-dioxane, tetrahydrofuran, 2-propanol, diethyl ether, ethyl acetate, acetonitrile, dimethylformamide, N-methyl-pyrrolidinone, hexane. For example, a solution containing about 50 mg of active ingredient per ml can be used for loading active ingredients in inorganic oxide material.

[0117] In the incipient wetness method, also referred to as capillary impregnation or dry impregnation the inorganic oxide material is wetted with the active ingredient in a liquid material or in a concentrated solution and is drawn into the pores by capillary action. The

porous inorganic oxide materials of the invention are particularly suited for this methodology as they show strong capillary action. In many instances, no or very little solvent needs to be used thereby avoiding the removal of the solvent after the loading step. This offers an additional advantage over known liquisolid formulations, which require additional ingredients needed to help adsorption, in particular solvents, involving methods of premixing the carrier or the drug in a liquid material (lipid or SEDDS) with a solvent to improve the adsorption. The presence of solvents in medicines and other products for human or animal use are critically scrutinized while many solvents are banned. Solvents also have environmental implications as they are considered an important source of pollution.

[0118] In another embodiment, the liquid material may be loaded onto the inorganic oxide material by spraying, or any other known method of liquid adsorption onto porous materials.

[0119] The biologically active ingredient in a liquid material either with or without solvent may have a viscosity that is selected such that it can be adequately adsorbed by the inorganic oxide material, in particular in terms of speed of adsorption, sufficient loading, and the like. It may for example have a viscosity below about 250 mPa.s, or below about 100 mPa.s, or below about 10 mPa.s, or below about 5 mPa.s, or below about 1 mPa.s. The lower limit of the viscosity may be about 0.1 mPa.s, or about 0.5 mPa.s.

[0120] The inorganic oxide materials of the invention are very efficient adsorbants of biologically active ingredient in liquid form. Contrary to known porous materials, where adsorption takes place in a very short time after being brought in contact with the liquid material, the inorganic oxide materials of the invention adsorp biologically active ingredient in liquid form during longer periods of time, in particular during several hours, for example up to about 2, 3, or 4 hours. It is believed that the decrease in volume after resting is related to capillary forces that continue to draw free liquid between the particles up into the pores of the particles. This attributes to the high loading capacity of the inorganic oxide materials of the invention.

[0121] The content of the active ingredient in the inorganic oxide material materials may be in the range of about 1% to about 50%, or about 10% to about 30%, or about 15% to about 25%, for example about 20%, relative to the total weight of the loaded silica material (all percentages herein being weight/weight).

[0122] The compositions of the present invention may in one or more additional steps formulated into a final dosage form, which may vary depending upon the manner in which it is administered to the patient. Preferred are solid or semisolid dosage forms for oral administration, in particular pills, tablets, and capsulees. Such dosage forms may be suitable for providing immediate or fast in vivo release of said biologically active species, or may be suitable for controlled release. This may include one or more pharmaceutically acceptable excipients

[0123] Regardless of the production method used to prepare the compositions containing a biologically active material and an inorganic oxide material in accordance with this invention, whether it is solvent-based or solventless, when the final dosage form comprises one or more pharmaceutically acceptable excipients, they may be introduced at any time during the process, including the step designed to load the biologically active material into the pores of the inorganic oxide material, or afterwards in a separate step.

[0124] The pharmaceutical compositions may also contain optional excipients. These may comprise any of the ingredients customarily employed in the art such as diluents, binding agents, granulating agents, glidants (flow aids), lubricants; disintegrants, sweeteners, flavors, and pigments to make the tablets visually attractive. Examples of such excipients include hydroxypropylmethyl cellulose, crospovidone, magnesium stearate, lactose, and talc.

[0125] The pharmaceutical compositions of the present invention may further comprise one or more pharmaceutically acceptable fillers selected, for example, from hydrocolloids (such as xanthan gum), binding agents, glidants, lubricants, surfactants and diluents.

[0126] These include for instance binding agents such as starch, gelatin, glucose, alginic acid, sodium and calcium alginates, water-soluble acrylic (co) polymers, polyvinyl-pyrrolidone, polyaminoacids, ethylene-vinyl acetate copolymers and the like; natural and synthetic mineral fillers or glidants such as silica, magnesium silicates such as talc, diatomaceous earth, aluminum silicate such as kaolinite, montmorillonite or mica, magnesium aluminum silicate such as attapulgite and vermiculite, carbon such as charcoal, sulphur and highly dispersed silicic acid polymers; water-soluble diluents such as lactose, sorbitol and the like.

[0127] The compositions of the present invention may also be formulated into forms suitable for topical application such as an ointment, a cream, a gel, a liniment or balm, etc...

[0128] The present invention is further directed to methods of using any of the herein disclosed compositions. In some embodiments, the compositions, in particular the pharmaceutical compositions, of the present invention may be used as medicaments, in particular may be used as medicaments via the oral route.

[0129] The present invention a method of administering a composition to a patient so as to deliver at least one biologically active material to the patient, wherein the composition comprises at least one pharmaceutical dosage formulating ingredient of a porous inorganic oxide material containing a biologically active ingredient in liquid form, wherein the inorganic oxide material has the oil adsorption, the intraparticle pore volume, and BET surface area, as specified herein. The compositions in this method are preferably administered by various means, including by oral, buccal, sublingual, periodontal, vaginal, intrauterine, rectal, pulmonary, nasal, inhalation, intraocular, ophthalmic, auricular, and topical means.

[0130] One of the reasons for improved release of the biologically active material from the compositions of the present invention is due to the improved desorption of the liquid material from the inorganic oxide material. The presence of pores within the inorganic oxide materials (i.e., intraparticle porosity) that have certain features allows for a substantial amount of the biologically active ingredient to be adsorbed and then released. For example, the pore size distribution of the present inorganic oxide material is narrow (i.e., a small relative span), which allows for a number of pores to readily adsorb and desorb the liquid material. This contrary to known porous materials where the biologically active ingredient is adsorbed into or released from interstitial voids between lumps or particles of the carrier material, the size and shape of which are more aleatory and offer less room for loading molecules. This causes not only less loading capacity, but also less regular release profiles. Other factors that influence release are viscosity of the active ingredient in liquid form and the isoelectric point (logP).

[0131] The compositions in accordance with the invention provide attractive drug delivery properties. They provide desirable desorption and/or dissolution rate profiles for a variety of biologically active materials (e.g., APIs). In some embodiments, the biologically active material exhibits a percent release desorption and/or dissolution rate of about 20 or greater within about 15 minutes of an initial time of contact with a dissolution medium. In some embodiments, the biologically active material exhibits a percent release dissolution rate

of about 25 or greater (or about 30 or greater; or about 35 or greater) within about 15 minutes of an initial time of contact with a dissolution medium.

[0132] Further, in some embodiments, the biologically active material exhibits a percent release dissolution rate of about 20 or greater about 30 minutes after an initial time of contact with a dissolution medium. In some embodiments, the biologically active material exhibits a percent release dissolution rate of about 30 or greater about 30 minutes after an initial time of contact with a dissolution medium.

[0133] In some embodiments, the biologically active material exhibits a percent release dissolution rate of about 10 or greater about 60 minutes after an initial time of contact with a dissolution medium. In some embodiments, the biologically active material exhibits a percent release dissolution rate of about 15 or greater (or about 20 or greater) about 60 minutes after an initial time of contact with a dissolution medium.

[0134] The compositions of the present invention in many instances show immediate release of the active ingredient but may be turned into controlled release compositions for example by coating the compositions with a suitable polymer. When mixing compositions with slected polymer coatings mixed release patterns can be obtained such as a combination of immediate and sustained release.

[0135] The inorganic oxide material may comprise two or more different and distinct types of porous particles with each distinct type of porous particles providing a specific desorption and/or dissolution rate profile for a single biologically active material (or two or more different biologically active materials) so as to form a composite desorption and/or dissolution rate profile.

[0136] A further aspect of this invention concerns particles of a inorganic oxide material, wherein the inorganic oxide material wherein the inorganic oxide material has the oil adsorption, the intraparticle pore volume, and BET surface area, as specified herein.

[0137] The compositions of the present invention not only show high loadability of drugs in liquid form, they moreover show higher bulk density compared to existing liquisolid systems. Further favorable properties include the excellent adsorptive capacity of the inorganic oxide material of the invention and the increased stability of the active ingredient. These advantages are in particular offered by the compositions of the invention in the form of particles.

[0138] The compositions of the present invention can also be used in dermatology and cosmetic applications because of their good skin-compatability and lack of unpleasant skin feel.

[0139] The following examples are meant to illustrate the present invention and should not be construed as a limitation of its scope.

Example 1

[0140] Sodium water glass with a Na content of 24.5% w/v and sulfuric acid of 45% w/v were mixed with a molar ratio of 0.85 to 0.99. After completion of the poly condensation the raw silica gel was crushed into pieces of several cm sizes. Then the by-product sodium sulfate was removed by washing the silica gel/sodium sulfate mixture with clear water. The aging of the silica by Oswald ripening took place in a water bath for 3-11 hours at 70-80°C and at pH between 8 and 9. After the liquid/solid separation the formed silica hydro gel was crushed down to a particle size of about 300 µm. The subsequent drying step controlled the formation of the pore volume. In order to achieve pore volumes of about 1.7 cm^3/g rapid drying for less than 4 seconds at a process air temperature of 180°C was needed and was conducted in a lab flash dryer type LABSPINFLASH (APV/Denmark). Silicas with pore volumes of < 1 cm^3/g were made by slow drying (packed bed drying) in a lab drying chamber at 100°C for 4h.

[0141] The following silica particles shown in **Table 1** below were used in the subsequent examples.

Table 1

Identification	S 1	S 2
Malvern		
D10 (μm)	75	23-41
D50 (μm)	102-120	48-65
D90 (μm)	174	76-96
Pore Size (nm) Desorption (BJH)	25	25
PV (ml/g)	1.6-1.95	1.6-1.95
Relative Span	0.71	0.71
BET SA (m^2/g)	280-355	280-355
APD (Calc) (Å)	250	250

[0142] The D10, D50 and D90 values indicate the 10^{th}, 50^{th} and 90^{th} percentiles of the weight of the particle diameter distribution. These values were obtained from a Malvern™ Mastersizer 2000 instrument available from Malvern Instruments Ltd. PV: pore volume; SA: surface area; APD: average pore diameter; BET SA: surface area; and Relative Span are determined using BJH nitrogen adsorption at a pressure of 0.995 using an ASAP 2420HV accelerated surface area and porosimetry system available from Micromeretics Instrument Corporation.

Example 2

[0143] Procedure: 2 to 5 g (based on bulk density) of the solid carrier material was placed in a 100 ml beaker and the oil or surfactant was added drop wise from a Burette, while mixing with spatula according to ASTM D281. The addition of oil or surfactant was continued until a thick paste-like mass formation. The addition of oil or surfactant was stopped when the mass appeared to contain excess oil. The Burette reading was recorded when the mass contained no excess oil or surfactant. The adsorption capacity was calculated using the below equation:

$$\text{Oil adsorption (g/100 g)} = \frac{\text{Volume of oil added (ml)} \cdot \text{SG of oil} \cdot 100}{\text{Weight of sample (g)}}$$

[0144] The following table lists oils and and their adsorption capacity on Sample S1 material as well as the specific gravity of the oils.

Table 2

No.	Name of the Oil	Specific gravity (g/mL)	Adsorption capacity (g/100g)
1	Raw linseed oil	0.930	294
2	Eucalyptus oil	0.915	328
3	Lemon grass oil	0.895	287
4	Peppermint oil	0.890	307
5	Castor oil	0.960	316
6	Sesame oil	0.923	298
7	Olive oil	0.920	305
8	Clove oil	1.045	390
9	Oleic acid	0.895	300
10	dl-α-Tocopherol	0.950	292
11	Captex 355	0.940	315
12	Labrafac PG	0.919	304
13	Miglyol 812	0.940	319
14	Capmul MCM	0.995	303

[0145] The following table lists surfactants and their adsorption capacity on Sample S1 material as well as the specific gravity of the surfactants.

Table 3

No.	Name of the Surfactant	Specific gravity (g/mL)	Oil adsorption S1 (g/100g)
1	Transcutol HP	0.987	295
2	Solutol HS 15	1.04	310
3	Cremophor EL	1.05	317
4	Labrasol	1.064	326
5	Labrafil M-1944CS	0.943	292
6	Capryol 90	0.942	300

[0146] In comparison, other carriers were tested for oil adsorption and following results were obtained.

Table 4

g. oil / 100g carrier	Oleic acid	Linseed oil	Tocopherol	Cremophor EL	Labrasol
Fujicalin	113	127	103	140	138
MCC PH 101	120	102	98	123	131
Galen IQ 721 (sugar based carrier)	63	69	57	67	69
Talc	62	57	54	70	67

Example 3

[0147] Following the procedure of Example 2, the Cremophor and Labrafil loaded materials were allowed to rest for 3 hours and then tested for free flowing properties. The results are shown in Tables 5 and 6.

Table 5

Flow parameters (Cremophor Loaded 1.5 :1)	S1 (250Å, 110μm)	S2 (250Å, 50μm)
Oil added (mL)	7.14	7.14
Carrier material (g)	5	5
B. Density	0.632	0.631
T. Density	0.702	0.742
C.I (USP rating)	10	15
	(Excellent)	(Good)
H.R (USP rating)	1.11	1.17
	(Excellent)	(Good)

Table 6

Flow parameters (Labrafil loaded 1.5:1)	S1	S2
Oil added (mL)	7.95	7.95
Carrier Material (g)	5	5
B. Density	0.615	0.616
T. Density	0.724	0.724
C.I (USP rating)	15	15
	(Good)	(Good)
H.R (USP rating)	1.17	1.17
	(Good)	(Good)

[0148] Bulk Density is measured by USP 616 Method 1 using a 250 ml graduated cylinder (USP30-NF25). Tapped density is measured by USP 616 Method 2 (250 taps per minute) using a 250 ml graduated cylinder, with an ETD-1020 Tap Density Tester available from Electrolab. USP rating is an observed measure of powder flow and is rated according to the following Table 7.

Table 7

Compressibility Index (%)	Flow Character	Hausner Ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Example 4

[0149] Following the procedure of Example 2, 10 grams of Sample S1 is loaded with 16.25 ml of sesame oil, which yield a 1:1.5 ratio of inorganic oxide material to oil. The volume of the mixture decreases from 65 ml to 50 ml over a period of 10 hours, which is a decrease in over 23% as shown in **FIG. 1**.

Example 5

[0150] The Cremophor and Labrafil loaded materials of Example 3 were loaded into zero size capsules manually using a casule filling tray, such as the Cap-M-Quick available from Empty Caps Company. As can be seen from **FIG. 2**, there is a significant difference between the filling amounts before and after resting of the material. The amounts of material loaded into the capsules are set forth in Tables 8 and 9.

Table 8

Flow parameters (Cremophor Loaded 1.5 :1)	S1 (250Å, 110µm)	S2 (250Å, 50µm)
Oil added (mL)	7.14	7.14
Carrier Material (g)	5	5
Filling Amount (mg) After resting	451	429
Filling Amount (mg) Before resting	357	357

Table 9

Flow parameters (Labrafil loaded 1.5:1)	S1	S2
Oil added (mL)	7.95	7.95
Carrier Material (g)	5	5
Filling Amount (mg) After resting	421	421
Filling Amount (mg) Before resting	366	366

Example 6

[0151] Following the procedure of Example 2, acetaminophen and ascorbic acid loaded material was obtained and labeled carriers S1 and S2, respectively The drug release from carriers S1 and S2 was determined as follows:

[0152] The acetaminophen loaded carrier (S1) was subjected to dissolution studies as per USP 30 for Acetaminophen Tablets for 30 min. Dissolution test conditions comprised of use of USP dissolution apparatus 2 (Paddle) operated at speed of 50 RPM for 30 minutes. Dissolution medium was 900 ml of pH 5.8 Phosphate Buffer at 37±0.5°C. For each carrier, 100 mg of the weighed amount of drug loaded carrier was used to dissolution studies. Aliquots (5 ml) were withdrawn at 10, 20, 30 minute time intervals, filtered and diluted with dissolution fluid. Absorbance of aliquots was determined spectrometrically at λmax 243nm.

The release profile is illustrated in **FIG. 3** The drug release from the both carriers S1 and S2 met the USP criteria (NLT 80% in 30 minutes).

[0153] The ascorbic acid loaded carrier (S1) was subjected to dissolution studies as per USP 30 for Ascorbic acid Tablets for 45 min. Dissolution test conditions comprised of use of USP dissolution apparatus 2 (Paddle) operated at speed of 50 RPM for 45 minutes. Dissolution medium was 900 ml of water at 37±0.5^{0}C. For each carrier, 100 mg of the weighed amount of drug loaded carrier was used to dissolution studies. Aliquots (5 ml) were withdrawn at 10, 20, 30 minute time intervals, filtered and diluted with water. Absorbance of aliquots was determined spectrometrically at λmax 266nm. The release profile is illustrated in **FIG. 4**. The drug release from the both carriers S1 and S2 met the USP criteria (NLT 75% in 45 minutes).

Example 7

[0154] Oil release or desorption: The carrier material used in the following trials was the material designated S1 prepared in Example 1. 2 grams of oil loaded carrier (1:1, w/w) prepared pursuant to method of Example 2 was mixed with 6 ml water in a beaker, vortexed during 1 hour, and centrifuged at 5000 RPM for 10 min in a Heraeus Multifuge 1S-R centrifuge available from Thermo Electron Corporation. The supernatant, i.e. oil + water, was transferred into a petry dish and dried in hot air oven up to constant weight.

[0155] The results, which are based upon the w/w % release obtained in the trials, are as follows. For sesame oil, 81% of the oil is released from the carrier material or inorganic oxide, and for Miglyol 812, 81.3% of the oil is released from the carrier material or inorganic oxide.

Example 8

[0156] Solid SEDDS System Loading and Release (or Desorption): The carrier materials used in the following trials was the materials designated as S1 and S2 in Example 1. A liquid SEDDS system was made up containing 0.6g of Glyburide as the API component, 15g of Capryol®90 as the oil/vehicle component, 54.4g of Trascutol® HP as a co-surfactant, and 30g of Tween® 20 as a surfactant. This liquid SEDDS system was loaded onto S1 and S2 by accurately weighing the required quantities of carrier and liquid SEDDS in the ratio of 1:1. Carrier and Liquid SEDDS were pre-heated at 60 ^{0}C for 15 min, prior to

mixing. Liquid SEDDS was added slowly to the carrier under stirring with metallic spatula. The prepared mixture was kept aside for around 24 hr to get free flowing powder.

[0157] The liquid SEDDS loaded carriers (S1) and (S2), as well as non-micronized Glyburide were subjected to dissolution studies as per USP<711> for 120 minutes. Dissolution test conditions comprised of use of USP dissolution apparatus 2 (paddle) operated at a speed of 75RPM. Dissolution medium was 500ml of pH 9.5 Borate Buffer (0.05M) at 37±1°C. For each carrier, a weighed amount of loaded carrier or API(non-micronized Gyburide) with an weight equivalent basis of 5mg Gyburide were used for the dissolution studies. 5ml Aliquots were withdrawn at 20, 30, 45, 60, and 120 minutes, filtered through 0.45 μ syringe filter and diluted with dissolution fluid. Samples were analyzed using HPLC (Waters Acquity H-class) using Grace Vision HT high load C18 column, Rocket Format, (53x7mm, 3μm) as stationary phase and Acetonitrile: o-phosphoric acid 0.4% in water (50:50) as mobile phase at flow rate of 1.5mL/min with injection volume of 50 μl . Samples were detected at λmax 226nm. The release profile is illustrated in **FIG.5**. The drug release from both carriers S1 and S2 met the USP criteria (NLT 70% drug release within 45 minutes, and NMT 3% relative SD).

[0158] To define the maximum amount of preloaded carrier in a tablet while maintaining optimum tabletting properties, the following experiments as shown in example 9 and 10 were performed:

Example 9

[0159] The carrier materials used in the following trials was the material designated S2 in Example 1. Cremophor® EL was the liquid lipid that was loaded on to the silica. Silica S2 was loaded pursuant to method of Example 8 and was used as the oil loaded carrier component in tablet formulations. To deliver oil in tablet dosage form, tablets were made with two different processes: direct compression (DC) and wet granulation (WG).

[0160] Direct compression tablets were obtained by accurately weighed the quantities of excipients for blend preparation. Diluent (MCC) and Oil loaded carriers were sieved through #40 mesh and mixed well for approximately 5 min. Binders and disintegrant were sieved through #40 mesh and added to the blend, then mixed well for approximately 5 min. Glidant was passed through #40 mesh and added to the blend and mixed well for 5 min.

Lubricant was sieved through # 60 mesh and added to the blend and mixed well for approximately 2min. This final blend was used for the compression of the tablets.

[0161] Wet granulation tablets were obtained by accurately weighed the quantities of excipients for blend preparation. Diluents (MCC) and Oil loaded carriers were sieved through #40 mesh and mixed well for approximately 5 min. Disintegrant was sieved through #40 mesh and added to the blend, then mixed well for approximately 5 min. Binder (starch/pregelatinized starch) was prepared in a water solution (5%). Granules were then prepared by mixing Prepared diluents/oil loaded carrier/disintegrant blend with the binder solution. Granules were dried at 50 ^{0}C to achieve LOD of 5-7%. Dried granules were passed through #20 mesh. Glidant was passed through #40 mesh and added to the blend and mixed well for 5 min. Lubricant (what material) was sieved through # 60 mesh and added to dried granules and mixed well for approximately 2min. This final blend was used for the compression of the tablets.

[0162] Tablets were prepared using a Parle Elizabeth tools Pvt Ltd, Eliza press 200 multi tooling single rotary tablet press operated at a Speed of 5 rpm, compresssion force of 20kN, ejection force <70N, and with a 12mm round bioconcave, D-tooling punch. The formulations tabletted are listed in Table 10 below.

Table 10

Formulation Identifier	DCA	DCB	DCC	DCD	DCE	WGA	WGB
Tabletting method (DC=Direct Compression; WG=Wet Granulation)	DC	DC	DC	DC	DC	WG	WG
Oil loaded Carrier S2 (wt%)	20	20	30	30	40	40	50
MCC PH102 (wt%)	70.5	70.5	60.5	60.5	45.5	50.5	40.5
PVPK30 (wt%)	5	5	5	5	0	0	0
Pregelatinized starch (wt%)	0	0	0	0	10	5	5
AcDiSol (wt%)	3	3	3	3	3	3	3
Syloid 244FP (wt%)	1	1	1	1	1	1	1
Mg St (wt%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Compression force (kN)	15	20	15	20	20	20	20
Weight (mg)	500	500	500	500	500	500	500

[0163] Tablet hardness for all formulations was measured with EH 01 tablet hardness tester (Electrolab, India). The hardness for tested formulations are listed in Table Y below.

Table 11

Formulation Identifier	DCA	DCB	DCC	DCD	DCE	WGA	WGB
Hardness (N)	83-93	83-97	68-76	84-91	60-70	80	30

[0164] In all cases the tablets met the USP specifications for Weight variation (NMT 5%), Firability(<1%), and disintegration time(<15min).

Example 10

[0165] High Concentration of Liquid Lipids Loaded onto Carrier and Compressed into Tablets: The carrier materials used in the following trials was the material designated S2 in Example 1. Tocopherol was the liquid lipid that was loaded on to the silica. Silica S2 was loaded with liquid lipid pursuant to method of Example 8 and was used as the oil loaded carrier component in tablet formulations. PVP30 was dispersed in ethanol (100mL) and added upon oil loaded carrier. Prepared blend was mixed thoroughly and allowed to dry at 50^{o}C. Additional excipients were added pursuant to the method in Example 9 to obtain a direct compression blend with the following composition : 70% Tocopherol loaded silica S2(1 :1 loaded), 12.5%MCCPH102, 14% PVP30, 2% AcDiSol, 1% SYLOID® 244FP, 0.5% Magnesium Stearate. Tablets were prepared using a Parle Elizabeth tools Pvt Ltd, Eliza press 200 multi tooling single rotary tablet press operated at a Speed of 5 rpm, compresssion force of 20kN, ejection force <70N, and with a 12mm round bioconcave, D-tooling punch.

[0166] Tablet hardness for all formulations was measured with EH 01 tablet hardness tester (Electrolab, India) at tablet weight of 500±5mg. Tablet hardenss results for these tablets was 40N. Friability was 0% and disintegration time was <1min.

Example 11

[0167] Oil Release (Tocopherol) from Tablets: The carrier materials used in the following trials was the material designated S2 in Example 1. Tocopherol was the liquid lipid that was loaded on to the silica. Silica S2 was loaded with liquid lipid pursuant to method of Example 8 and was used as the oil loaded carrier component in tablet. Tablets were prepared pursuant to the method in example 10. Tochopherol concentration in the tablet was 100mg.

[0168] Tablets prepared were subjected to dissolution studies pursuant to the method described in Example 8. An aliquot of 2 mL was withdrawn at predetermined time interval and filtered through 0.22 μ membrane filter. The dissolution samples were analyzed by using HPLC (Waters UPLC Wavelength: 294 nm Column: Rocket Format, 53x7mm, 3μ) Mobile Phase: 85% ACN: 10% MeOH: 5% H2O.)

[0169] The Tocopherol release at 45 min was ≈100%.

[0170] While the invention has been described with a limited number of embodiments, these specific embodiments are not intended to limit the scope of the invention as otherwise described and claimed herein. It may be evident to those of ordinary skill in the art upon review of the exemplary embodiments herein that further modifications, equivalents, and variations are possible. All parts and percentages in the examples, as well as in the remainder of the specification, are by weight unless otherwise specified. Further, any range of numbers recited in the specification or claims, such as that representing a particular set of properties, units of measure, conditions, physical states or percentages, is intended to literally incorporate expressly herein by reference or otherwise, any number falling within such range, including any subset of numbers within any range so recited. For example, whenever a numerical range with a lower limit, R_L, and an upper limit R_U, is disclosed, any number R falling within the range is specifically disclosed. In particular, the following numbers R within the range are specifically disclosed: $R = R_L + k(R_U - R_L)$, where k is a variable ranging from 1% to 100% with a 1% increment, e.g., k is 1%, 2%, 3%, 4%, 5%. ... 50%, 51%, 52%. ... 95%, 96%, 97%, 98%, 99%, or 100%. Moreover, any numerical range represented by any two values of R, as calculated above is also specifically disclosed. Any modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims. All publications cited herein are incorporated by reference in their entirety.

Claims

1. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g; and

(b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater;

wherein said inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1.

2. The composition according to claim 1, wherein the inorganic oxide particles comprises pores having an intraparticle pore volume of about 0.5 cm^3/g or greater.

3. The composition according to claim 1, wherein the inorganic oxide particles comprises a BET surface area, as measured by nitrogen adsorption of about 20 m^2/g or greater.

4. The composition according to claim 1, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

5. The composition according to claim 1, wherein the porous inorganic oxide particles comprise a pore size distribution having a relative span of about 1.5 or less.

6. The composition according to claim 1, wherein the particles comprise a mean particle size of from about 3μm to about 5 mm.

7. The composition according to claim 1, wherein the liquid material comprises lipid materials, non-volatile solvents, and surfactants.

8. The composition according to claim 1, wherein said particles form a powder having a Carr index of equal or lower than 25.

9. The composition according to claim 1, wherein said porous inorganic oxide particles are non-ordered.

10. The composition according to claim 1, wherein the composition, after mixing the inorganic oxide particles and liquid material, decreases in bulk density of at least 15% after resting up to 24 hours.

11. The composition according to claim 1, wherein the biologically active ingredient is an active pharmaceutical ingredient.

12. The composition according to claim 1, wherein the biologically active ingredient is liquid.

13. The composition according to claim 1, wherein the biologically active ingredient is dissolved in a non-volatile solvent or a lipid material.

14. The composition according to claim 1, wherein the biologically active ingredient is formulated in a SEDDS.

15. A pharmaceutical composition comprising at least one pharmaceutical dosage formulating ingredient and a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g; and

(b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater;

wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to inorganic oxide particles of at least 1.5:1.

16. The composition according to claim 15, wherein the particles comprise a pore size distribution where at least 0.5 cc/g of pore volume are from pores ranging from 10 nm to 30 nm.

17. The composition according to claim 15, wherein the inorganic oxide particles comprises pores having an intraparticle pore volume of about 0.5 cm^3/g or greater.

18. The composition according to claim 15, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

19. The composition according to claim 15, wherein the inorganic oxide particles comprises a BET surface area, as measured by nitrogen adsorption of about 20 m^2/g or greater.

20. The composition according to claim 15, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

21. The composition according to claim 15, wherein the porous inorganic oxide particles comprise a pore size distribution having a relative span of about 1.5 or less.

22. The composition according to claim 15, wherein the particles comprise a mean particle siz of from about 3μm to about 5 mm.

23. The composition according to claim 15, wherein the liquid material comprises lipid materials, non-volatile solvents, and surfactants.

24. The composition according to claim 15, wherein said particles form a powder having a Carr index of equal or lower than 25.

25. The composition according to claim 15, wherein said porous inorganic oxide particles are non-ordered.

26. The composition according to claim 15, wherein the composition, after mixing the inorganic oxide particles and liquid material, decreases in bulk density of at least 15% after resting up to 24 hours.

27. The composition according to claim 15, wherein the biologically active ingredient is an active pharmaceutical ingredient.

28. The composition according to claim 15, wherein the biologically active ingredient is liquid.

29. The composition according to claim 15, wherein the biologically active ingredient is dissolved in a non-volatile solvent or a lipid material.

30. The composition according to claim 15, wherein the biologically active ingredient is formulated in a SEDDS.

31. A method of making composition comprising porous inorganic oxide material containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g; and

(b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater;

wherein said inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1.

32. A method of making a pharmaceutical composition comprising at least one pharmaceutical dosage formulating ingredient and a composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g; and

(b) pores having a pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater;

wherein said inorganic oxide particles remain free flowing at a weight ratio of liquid material to inorganic oxide particles of at least 1.5:1.

33. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g;

(b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and

(c) a pore size distribution having a relative span of about 1.5 or less.

34. The composition according to claim 33, wherein the inorganic oxide particles comprises pores having an intraparticle pore volume of about 0.5 cm^3/g or greater.

35. The composition according to claim 33, wherein the inorganic oxide particles comprises a BET surface area, as measured by nitrogen adsorption of about 20 m^2/g or greater.

36. The composition according to claim 33, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

37. The composition according to claim 33, wherein the porous inorganic oxide particles comprise a pore size distribution having a relative span of about 1.3 or less.

38. The composition according to claim 33, wherein the particles comprise a mean particle siz of from about 3μm to about 5 mm.

39. The composition according to claim 33, wherein the liquid material comprises lipid materials, non-volatile solvents, and surfactants.

40. The composition according to claim 33, wherein said particles form a powder having a Carr index of equal or lower than 25.

41. The composition according to claim 33, wherein said porous inorganic oxide particles are non-ordered.

42. The composition according to claim 33, wherein the composition, after mixing the inorganic oxide particles and liquid material, decreases in bulk density of at least 15% after resting up to 24 hours.

43. The composition according to claim 33, wherein the biologically active ingredient is an active pharmaceutical ingredient.

44. The composition according to claim 33, wherein the biologically active ingredient is liquid.

45. The composition according to claim 33, wherein the biologically active ingredient is dissolved in a non-volatile solvent or lipid material.

46. The composition according to claim 33, wherein the biologically active ingredient is formulated in a SEDDS.

47. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g;

(b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and

(c) a median pore size of 5 nm to 30 nm.

wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to inorganic oxide particles of at least 1:1.

48. The composition according to claim 47, wherein the inorganic oxide particles comprises pores having an intraparticle pore volume of about 0.5 cm^3/g or greater.

49. The composition according to claim 47, wherein the inorganic oxide particles comprises a BET surface area, as measured by nitrogen adsorption of about 20 m^2/g or greater.

50. The composition according to claim 47, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

51. The composition according to claim 47, wherein the porous inorganic oxide particles comprise a pore size distribution having a relative span of about 1.5 or less.

52. The composition according to claim 47, wherein the particles comprise a mean particle siz of from about 3μm to about 5 mm.

53. The composition according to claim 47, wherein the liquid material comprises lipid materials, non-volatile solvents, and surfactants.

54. The composition according to claim 47, wherein said particles form a powder having a Carr index of equal or lower than 25.

55. The composition according to claim 47, wherein said porous inorganic oxide particles are non-ordered.

56. The composition according to claim 47, wherein the composition, after mixing the inorganic oxide particles and liquid material, increases in bulk density of at least 15% after resting up to 24 hours.

57. The composition according to claim 47, wherein the biologically active ingredient is an active pharmaceutical ingredient.

58. The composition according to claim 47, wherein the biologically active ingredient is liquid.

59. The composition according to claim 47, wherein the biologically active ingredient is dissolved in a non-volatile solvent or a lipid material.

60. The composition according to claim 47, wherein the biologically active ingredient is formulated in a SEDDS.

61. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g;

(b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and

(c) a median particle size of from 3 microns to 300 microns;

wherein said inorganic oxide particles remain free flowing at a ratio of liquid material to inorganic oxide particles of at least 1:1.

62. The composition according to claim 61, wherein the inorganic oxide particles comprises pores having an intraparticle pore volume of about 0.5 cm^3/g or greater.

63. The composition according to claim 61, wherein the inorganic oxide particles comprises a BET surface area, as measured by nitrogen adsorption of about 20 m^2/g or greater.

64. The composition according to claim 61, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

65. The composition according to claim 61, wherein the porous inorganic oxide particles comprise a pore size distribution having a relative span of about 1.5 or less.

66. The composition according to claim 61, wherein the particles comprise a mean particle siz of from about 3μm to about 5 mm.

67. The composition according to claim 61, wherein the liquid material comprises lipid materials, non-volatile solvents, and surfactants.

68. The composition according to claim 61, wherein said particles form a powder having a Carr index of equal or lower than 25.

69. The composition according to claim 61, wherein said porous inorganic oxide particles are non-ordered.

70. The composition according to claim 61, wherein the composition, after mixing the inorganic oxide particles and liquid material, increases in bulk density of at least 15% after resting up to 24 hours.

71. The composition according to claim 61, wherein the biologically active ingredient is an active pharmaceutical ingredient.

72. The composition according to claim 61, wherein the biologically active ingredient is liquid.

73. The composition according to claim 61, wherein the biologically active ingredient is dissolved in a non-volatile solvent or a lipid material.

74. The composition according to claim 61, wherein the biologically active ingredient is formulated in a SEDDS.

75. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g; and

(b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater;

wherein said composition, after mixing the inorganic oxide particles and liquid material, decreases in volume of at least 15% after resting.

76. The composition according to claim 75, wherein the inorganic oxide particles comprises pores having an intraparticle pore volume of about 0.5 cm^3/g or greater.

77. The composition according to claim 75, wherein the inorganic oxide particles comprises a BET surface area, as measured by nitrogen adsorption of about 20 m^2/g or greater.

78. The composition according to claim 75, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

79. The composition according to claim 75, wherein the porous inorganic oxide particles comprise a pore size distribution having a relative span of about 1.5 or less.

80. The composition according to claim 75, wherein the particles comprise a mean particle siz of from about 3μm to about 5 mm.

81. The composition according to claim 75, wherein the liquid material comprises lipid materials, non-volatile solvents, and surfactants.

82. The composition according to claim 75, wherein said particles form a powder having a Carr index of equal or lower than 25.

83. The composition according to claim 75, wherein said porous inorganic oxide particles are non-ordered.

84. The composition according to claim 75, wherein the composition, after mixing the inorganic oxide particles and liquid material, increases in bulk density of at least 15% after resting up to 24 hours.

85. The composition according to claim 75, wherein the biologically active ingredient is an active pharmaceutical ingredient.

86. The composition according to claim 75, wherein the biologically active ingredient is liquid.

87. The composition according to claim 75, wherein the biologically active ingredient is dissolved in a non-volatile solvent or a lipid material.

88. The composition according to claim 75, wherein the biologically active ingredient is formulated in a SEDDS.

89. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g; and

(b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater;

wherein said composition, after mixing the inorganic oxide particles and liquid material, increases in bulk density by at least 15% after resting.

90. The composition according to claim 89, wherein the inorganic oxide particles comprises pores having an intraparticle pore volume of about 0.5 cm^3/g or greater.

91. The composition according to claim 89, wherein the inorganic oxide particles comprises a BET surface area, as measured by nitrogen adsorption of about 20 m^2/g or greater.

92. The composition according to claim 89, wherein the inorganic oxide particles comprises pores having a mean pore diameter in the range of about 5 nm to about 30 nm.

93. The composition according to claim 89, wherein the porous inorganic oxide particles comprise a pore size distribution having a relative span of about 1.5 or less.

94. The composition according to claim 89, wherein the particles comprise a mean particle siz of from about 3μm to about 5 mm.

95. The composition according to claim 89, wherein the liquid material comprises lipid materials, non-volatile solvents, and surfactants.

96. The composition according to claim 89, wherein said particles form a powder having a Carr index of equal or lower than 25.

97. The composition according to claim 89, wherein said porous inorganic oxide particles are non-ordered.

98. The composition according to claim 89, wherein the composition, after mixing the inorganic oxide particles and liquid material, increases in bulk density of at least 15% after resting up to 24 hours.

99. The composition according to claim 89, wherein the biologically active ingredient is an active pharmaceutical ingredient.

100. The composition according to claim 89, wherein the biologically active ingredient is liquid.

101. The composition according to claim 89, wherein the biologically active ingredient is dissolved in a non-volatile solvent or a lipid material.

102. The composition according to claim 89, wherein the biologically active ingredient is formulated in a SEDDS.

103. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

(a) an oil adsorption of about 100 to about 500 ml/100 g; and

(b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater;

wherein, after mixing the inorganic oxide particles and liquid material and then resting for at least 2 hours, at least about 400 mg of said composition may be loaded into a zero size capsule.

104. A composition comprising porous inorganic oxide particles containing a biologically active ingredient in a liquid material, wherein the inorganic oxide particles possess:

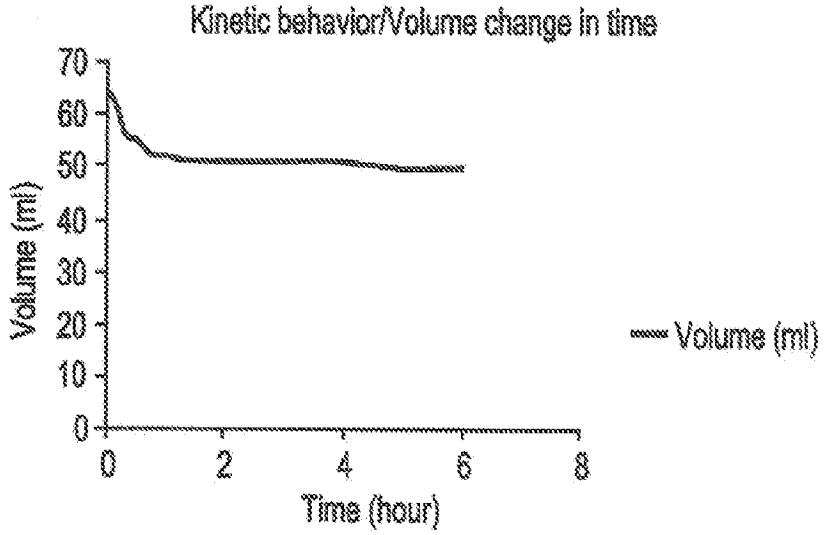
(a) an oil adsorption of about 100 to about 500 ml/100 g;

(b) pores having an pore volume, as measured by nitrogen porosimetry, of about 0.5 cm^3/g or greater; and

(c) a ratio of liquid material to inorganic oxide particles of at least 1:1;

wherein at least 65% of the liquid material is desorbed from the particles upon desorption.

FIG. 1


Kinetic behavior/Volume change in time
Volume (ml)
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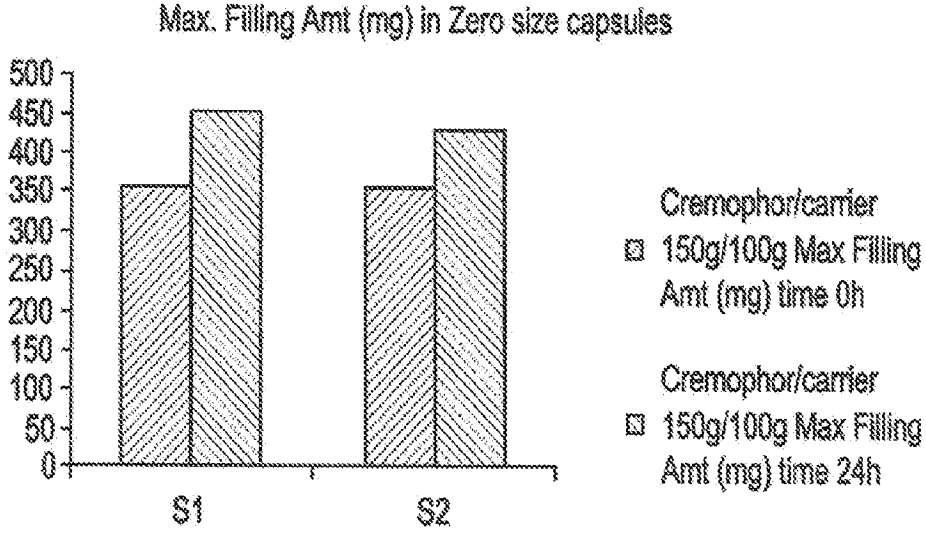
60
50
40
30
20
10
0
0
2
4
6
8
Time (hour)
Volume (ml)

FIG. 2


Max. Filling Amt (mg) in Zero size capsules
500
450
400
350
300
250
200
150
100
50
0
S1
S2
Cremophor/carrier
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Amt (mg) time 0h
Cremophor/carrier
150g/100g Max Filling
Amt (mg) time 24h

FIG. 3

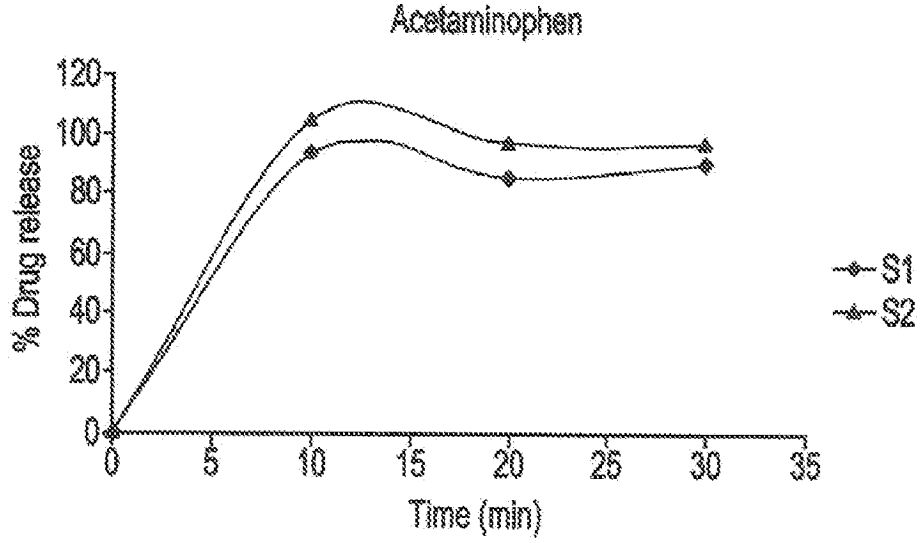

Acetaminophen
% Drug release
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Time (min)
S1
S2

FIG. 4

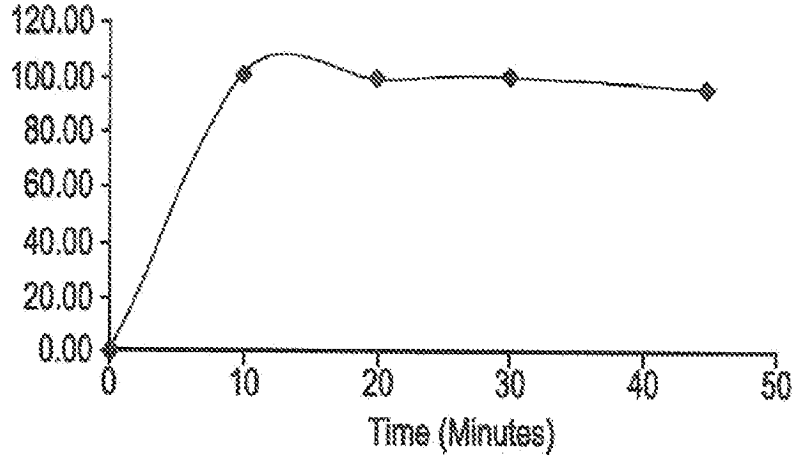
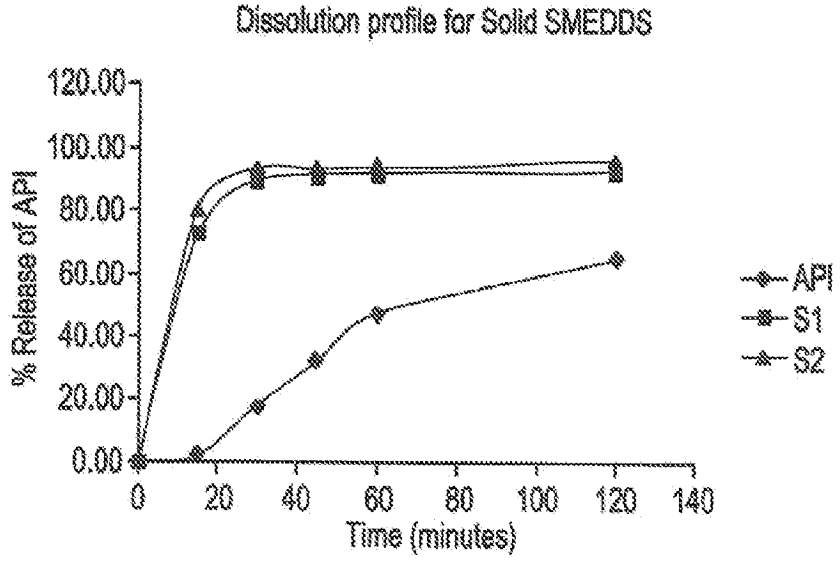

Ascorbic acid
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
10
20
30
40
50
Time (Minutes)

FIG. 5


Dissolution profile for Solid SMEDDS
% Release of API
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
20
40
60
80
100
120
140
Time (minutes)
API
S1
S2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/013848

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - B01J 20/10 (2014.01)
USPC - 502/408
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) - B01J 20/10; C01B 33/12 (2014.01)
USPC - 423/335, 339; 502/408

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - B01J 20/103; C01B 33/12 (2014.02)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
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 2009/0311159 A1 (GRAY) 17 December 2009 (17.12.2009) entire document	1-104
Y	US 2003/0152771 A1 (PRESTON et al) 14 August 2003 (14.08.2003) entire document	1-104
Y	US 2005/0112232 A1 (DOLLAT et al) 26 May 2005 (26.05.2005) entire document	8, 24, 40, 54, 68, 82, 96
Y	US 2012/0269792 A1 (KHAN et al) 25 October 2012 (25.10.2012) entire document	14, 30, 46, 60, 74, 88, 102
A	WO 2011/144346 A1 (KRETZSCHMAR et al) 24 November 2011 (24.11.2011) entire document	1-104

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
23 April 2014	07 MAY 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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(71)申请人 格雷斯公司
地址 美国马里兰州

(72)发明人 F.H. 蒙苏尔

(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 周李军 石克虎

(51)Int.Cl.
B01J 20/10(2006.01)

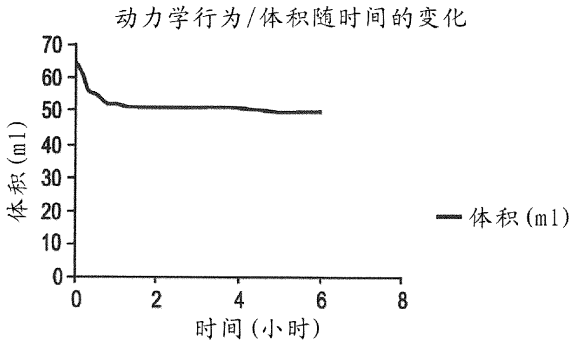
权利要求书6页 说明书25页 附图2页

(54)发明名称

作为用于液体技术的载体的多孔硅胶

(57)摘要

公开了含有生物活性成分和无机氧化物材料的组合物。还公开了制造和使用含有生物活性成分和无机氧化物材料的组合物的方法。本发明涉及包含含有呈液体形式的生物活性成分的无机氧化物多孔材料的组合物、制造此类组合物的方法、以及使用其的方法。



CN 105102117 A

1. 一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a)约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；以及

(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；

其中所述无机氧化物颗粒在至少 1.5:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

2. 根据权利要求 1 所述的组合物，其中所述无机氧化物颗粒包含具有约 0.5 cm^3/g 或更大的颗粒内孔体积的孔。

3. 根据权利要求 1 所述的组合物，其中所述无机氧化物颗粒包含如通过氮吸附法所测量的约 20 m^2/g 或更大的 BET 表面积。

4. 根据权利要求 1 所述的组合物，其中所述无机氧化物颗粒包含具有在约 5 nm 至约 30 nm 范围内的平均孔直径的孔。

5. 根据权利要求 1 所述的组合物，其中所述多孔无机氧化物颗粒包含具有约 1.5 或更小的相对跨度的孔大小分布。

6. 根据权利要求 1 所述的组合物，其中所述颗粒包含约 3 μm 至约 5 mm 的平均粒度。

7. 根据权利要求 1 所述的组合物，其中所述液体材料包含脂质材料、非挥发性溶剂以及表面活性剂。

8. 根据权利要求 1 所述的组合物，其中所述颗粒形成具有等于或低于 25 的卡尔指数的粉末。

9. 根据权利要求 1 所述的组合物，其中所述多孔无机氧化物颗粒是无序的。

10. 根据权利要求 1 所述的组合物，其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置直至 24 小时后堆积密度减小至少 15%。

11. 根据权利要求 1 所述的组合物，其中所述生物活性成分是活性医药成分。

12. 根据权利要求 1 所述的组合物，其中所述生物活性成分是液体。

13. 根据权利要求 1 所述的组合物，其中所述生物活性成分溶解于非挥发性溶剂或脂质材料中。

14. 根据权利要求 1 所述的组合物，其中所述生物活性成分配制于 SEDDS 中。

15. 一种包含至少一种医药剂量配制成分和包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物的医药组合物，其中所述无机氧化物颗粒具有：

(a)约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；以及

(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；

其中所述无机氧化物颗粒在至少 1.5:1 的液体材料与无机氧化物颗粒的比率下保持自由流动。

16. 根据权利要求 15 所述的组合物，其中所述颗粒包含至少 0.5 cc/g 的孔体积来自在 10 nm 至 30 nm 范围内的孔的孔大小分布。

17. 根据权利要求 15 所述的组合物，其中所述无机氧化物颗粒包含具有约 0.5 cm^3/g 或更大的颗粒内孔体积的孔。

18. 根据权利要求 15 所述的组合物，其中所述无机氧化物颗粒包含具有在约 5 nm 至约 30 nm 范围内的平均孔直径的孔。

19. 根据权利要求 15 所述的组合物，其中所述无机氧化物颗粒包含如通过氮吸附法所测量的约 20 m^2/g 或更大的 BET 表面积。

20. 根据权利要求 15 所述的组合物，其中所述无机氧化物颗粒包含具有在约 5 nm 至约 30 nm 范围内的平均孔直径的孔。

21. 根据权利要求 15 所述的组合物，其中所述多孔无机氧化物颗粒包含具有约 1.5 或更小的相对跨度的孔大小分布。

22. 根据权利要求 15 所述的组合物，其中所述颗粒包含约 3 μm 至约 5 mm 的平均粒度。

23. 根据权利要求 15 所述的组合物，其中所述液体材料包含脂质材料、非挥发性溶剂以及表面活性剂。

24. 根据权利要求 15 所述的组合物，其中所述颗粒形成具有等于或低于 25 的卡尔指数的粉末。

25. 根据权利要求 15 所述的组合物，其中所述多孔无机氧化物颗粒是无序的。

26. 根据权利要求 15 所述的组合物，其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置直至 24 小时后堆积密度减小至少 15%。

27. 根据权利要求 15 所述的组合物，其中所述生物活性成分是活性医药成分。

28. 根据权利要求 15 所述的组合物，其中所述生物活性成分是液体。

29. 根据权利要求 15 所述的组合物，其中所述生物活性成分溶解于非挥发性溶剂或脂质材料中。

30. 根据权利要求 15 所述的组合物，其中所述生物活性成分配制于 SEDDS 中。

31. 一种制造包含含有液体材料中的生物活性成分的多孔无机氧化物材料的组合物的方法，其中所述无机氧化物颗粒具有：

(a) 约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；以及

(b) 具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；

其中所述无机氧化物颗粒在至少 1.5:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

32. 一种制造包含至少一种医药剂量配制成分和包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物的医药组合物的方法，其中所述无机氧化物颗粒具有：

(a) 约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；以及

(b) 具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；

其中所述无机氧化物颗粒在至少 1.5:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

33. 一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a) 约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；

(b) 具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及

(c) 具有约 1.5 或更小的相对跨度的孔大小分布。

34. 根据权利要求 33 所述的组合物，其中所述无机氧化物颗粒包含具有约 0.5 cm^3/g 或更大的颗粒内孔体积的孔。

35. 根据权利要求 33 所述的组合物，其中所述无机氧化物颗粒包含如通过氮吸附法所测量的约 20 m^2/g 或更大的 BET 表面积。

36. 根据权利要求 33 所述的组合物，其中所述无机氧化物颗粒包含具有在约 5 nm 至约 30 nm 范围内的平均孔直径的孔。

37. 根据权利要求 33 所述的组合物，其中所述多孔无机氧化物颗粒包含具有约 1.3 或更小的相对跨度的孔大小分布。

38. 根据权利要求 33 所述的组合物，其中所述颗粒包含约 3 μm 至约 5 mm 的平均粒度。

39. 根据权利要求 33 所述的组合物，其中所述液体材料包含脂质材料、非挥发性溶剂以及表面活性剂。

40. 根据权利要求 33 所述的组合物，其中所述颗粒形成具有等于或低于 25 的卡尔指数的粉末。

41. 根据权利要求 33 所述的组合物，其中所述多孔无机氧化物颗粒是无序的。

42. 根据权利要求 33 所述的组合物，其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置直至 24 小时后堆积密度减小至少 15%。

43. 根据权利要求 33 所述的组合物，其中所述生物活性成分是活性医药成分。

44. 根据权利要求 33 所述的组合物，其中所述生物活性成分是液体。

45. 根据权利要求 33 所述的组合物，其中所述生物活性成分溶解于非挥发性溶剂或脂质材料中。

46. 根据权利要求 33 所述的组合物，其中所述生物活性成分配制于 SEDDS 中。

47. 一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a) 约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；

(b) 具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及

(c) 5 nm 至 30 nm 的中值孔大小，

其中所述无机氧化物颗粒在至少 1:1 的液体材料与无机氧化物颗粒的比率下保持自由流动。

48. 根据权利要求 47 所述的组合物，其中所述无机氧化物颗粒包含具有约 0.5 cm^3/g 或更大的颗粒内孔体积的孔。

49. 根据权利要求 47 所述的组合物，其中所述无机氧化物颗粒包含如通过氮吸附法所测量的约 20 m^2/g 或更大的 BET 表面积。

50. 根据权利要求 47 所述的组合物，其中所述无机氧化物颗粒包含具有在约 5 nm 至约 30 nm 范围内的平均孔直径的孔。

51. 根据权利要求 47 所述的组合物，其中所述多孔无机氧化物颗粒包含具有约 1.5 或更小的相对跨度的孔大小分布。

52. 根据权利要求 47 所述的组合物，其中所述颗粒包含约 3 μm 至约 5 mm 的平均粒度。

53. 根据权利要求 47 所述的组合物，其中所述液体材料包含脂质材料、非挥发性溶剂以及表面活性剂。

54.根据权利要求47所述的组合物，其中所述颗粒形成具有等于或低于25的卡尔指数的粉末。

55.根据权利要求47所述的组合物，其中所述多孔无机氧化物颗粒是无序的。

56.根据权利要求47所述的组合物，其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置直至24小时后堆积密度增加至少15%。

57.根据权利要求47所述的组合物，其中所述生物活性成分是活性医药成分。

58.根据权利要求47所述的组合物，其中所述生物活性成分是液体。

59.根据权利要求47所述的组合物，其中所述生物活性成分溶解于非挥发性溶剂或脂质材料中。

60.根据权利要求47所述的组合物，其中所述生物活性成分配制于SEDDS中。

61.一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a)约100 ml/100 g至约500 ml/100 g的油吸附值；

(b)具有如通过氮孔度测定法所测量的约0.5 cm^3/g或更大的孔体积的孔；以及

(c)3微米至300微米的粒度中值；

其中所述无机氧化物颗粒在至少1:1的液体材料与无机氧化物颗粒的比率下保持自由流动。

62. 根据权利要求61所述的组合物，其中所述无机氧化物颗粒包含具有约0.5 cm^3/g或更大的颗粒内孔体积的孔。

63. 根据权利要求61所述的组合物，其中所述无机氧化物颗粒包含如通过氮吸附法所测量的约20 m^2/g或更大的BET表面积。

64. 根据权利要求61所述的组合物，其中所述无机氧化物颗粒包含具有在约5 nm至约30 nm范围内的平均孔直径的孔。

65.根据权利要求61所述的组合物，其中所述多孔无机氧化物颗粒包含具有约1.5或更小的相对跨度的孔大小分布。

66. 根据权利要求61所述的组合物，其中所述颗粒包含约3 μm至约5 mm的平均粒度。

67.根据权利要求61所述的组合物，其中所述液体材料包含脂质材料、非挥发性溶剂以及表面活性剂。

68.根据权利要求61所述的组合物，其中所述颗粒形成具有等于或低于25的卡尔指数的粉末。

69.根据权利要求61所述的组合物，其中所述多孔无机氧化物颗粒是无序的。

70.根据权利要求61所述的组合物，其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置直至24小时后堆积密度增加至少15%。

71.根据权利要求61所述的组合物，其中所述生物活性成分是活性医药成分。

72.根据权利要求61所述的组合物，其中所述生物活性成分是液体。

73.根据权利要求61所述的组合物，其中所述生物活性成分溶解于非挥发性溶剂或脂质材料中。

74.根据权利要求61所述的组合物，其中所述生物活性成分配制于SEDDS中。

75. 一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a)约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；以及

(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；

其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置后体积减小至少 15%。

76. 根据权利要求 75 所述的组合物，其中所述无机氧化物颗粒包含具有约 0.5 cm^3/g 或更大的颗粒内孔体积的孔。

77. 根据权利要求 75 所述的组合物，其中所述无机氧化物颗粒包含如通过氮吸附法所测量的约 20 m^2/g 或更大的 BET 表面积。

78. 根据权利要求 75 所述的组合物，其中所述无机氧化物颗粒包含具有在约 5 nm 至约 30 nm 范围内的平均孔直径的孔。

79. 根据权利要求 75 所述的组合物，其中所述多孔无机氧化物颗粒包含具有约 1.5 或更小的相对跨度的孔大小分布。

80. 根据权利要求 75 所述的组合物，其中所述颗粒包含约 3 μm 至约 5 mm 的平均粒度。

81. 根据权利要求 75 所述的组合物，其中所述液体材料包含脂质材料、非挥发性溶剂以及表面活性剂。

82. 根据权利要求 75 所述的组合物，其中所述颗粒形成具有等于或低于 25 的卡尔指数的粉末。

83. 根据权利要求 75 所述的组合物，其中所述多孔无机氧化物颗粒是无序的。

84. 根据权利要求 75 所述的组合物，其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置直至 24 小时后堆积密度增加至少 15%。

85. 根据权利要求 75 所述的组合物，其中所述生物活性成分是活性医药成分。

86. 根据权利要求 75 所述的组合物，其中所述生物活性成分是液体。

87. 根据权利要求 75 所述的组合物，其中所述生物活性成分溶解于非挥发性溶剂或脂质材料中。

88. 根据权利要求 75 所述的组合物，其中所述生物活性成分配制于 SEDDS 中。

89. 一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a)约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；以及

(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；

其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置后堆积密度增加至少 15%。

90. 根据权利要求 89 所述的组合物，其中所述无机氧化物颗粒包含具有约 0.5 cm^3/g 或更大的颗粒内孔体积的孔。

91. 根据权利要求 89 所述的组合物，其中所述无机氧化物颗粒包含如通过氮吸附法所测量的约 20 m^2/g 或更大的 BET 表面积。

92. 根据权利要求 89 所述的组合物，其中所述无机氧化物颗粒包含具有在约 5 nm 至

约 30 nm 范围内的平均孔直径的孔。

93. 根据权利要求 89 所述的组合物，其中所述多孔无机氧化物颗粒包含具有约 1.5 或更小的相对跨度的孔大小分布。

94. 根据权利要求 89 所述的组合物，其中所述颗粒包含约 3 μm 至约 5 mm 的平均粒度。

95. 根据权利要求 89 所述的组合物，其中所述液体材料包含脂质材料、非挥发性溶剂以及表面活性剂。

96. 根据权利要求 89 所述的组合物，其中所述颗粒形成具有等于或低于 25 的卡尔指数的粉末。

97. 根据权利要求 89 所述的组合物，其中所述多孔无机氧化物颗粒是无序的。

98. 根据权利要求 89 所述的组合物，其中在混合所述无机氧化物颗粒与液体材料之后，所述组合物在静置直至 24 小时后堆积密度增加至少 15%。

99. 根据权利要求 89 所述的组合物，其中所述生物活性成分是活性医药成分。

100. 根据权利要求 89 所述的组合物，其中所述生物活性成分是液体。

101. 根据权利要求 89 所述的组合物，其中所述生物活性成分溶解于非挥发性溶剂或脂质材料中。

102. 根据权利要求 89 所述的组合物，其中所述生物活性成分配制于 SEDDS 中。

103. 一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a) 约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；以及

(b) 具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；

其中在混合所述无机氧化物颗粒与液体材料并且然后静置至少 2 小时后，可以将至少约 400 mg 的所述组合物装填至零号胶囊中。

104. 一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中所述无机氧化物颗粒具有：

(a) 约 100 ml/100 g 至约 500 ml/100 g 的油吸附值；

(b) 具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及

(c) 至少 1:1 的液体材料与无机氧化物颗粒的比率；

其中至少 65% 的所述液体材料在解吸附后从所述颗粒脱附。

作为用于液体技术的载体的多孔硅胶

技术领域

[0001] 本发明涉及包含含有呈液体形式的生物活性成分的无机氧化物多孔材料的组合物、制造此类组合物的方法、以及使用其的方法。

背景技术

[0002] 口服途径由于其便利性和良好的患者依从性而保持为优选的药物施用途径。口服药物制剂的主要问题是在整个胃肠(GI)道的不稳定和不完全吸收,从而产生低的和可变的生物利用度并且缺乏剂量比例性。这些问题主要是由于活性成分差的水溶性而引起。已经报道,据估计 40% 的现有医药活性成分和甚至更高比例的所有新开发的药物水溶性差或不溶于水。这对药物开发造成重大挑战,因为高度需要产生适合的制剂以改善此类药物的溶解度和生物利用度。

[0003] 已经对方法进行许多研究以解决这些问题。已经开发的方法包括通过微米化或纳米化以减小药物的粒度来增加表面积,从而增加活性成分的溶解速率。其它方法包括在表面活性剂系统中溶解,与环糊精形成水溶性分子复合物,通过冻干或在亲水性载体中形成固体分散体而使药物转变成非晶形式,微胶囊化,以及从多孔载体材料中释放。

[0004] 用于促进水溶性差的药物的溶解特性和口服生物利用度的一种技术是通过在非挥发性油 / 脂质中溶解或乳化而在液相中使用它们。此类系统已经被称作基于脂质的药物递送系统(LBDDS)。在这些形式中,活性成分已经处于溶液中以使得药物在分子水平上存在,避免了从结晶态的溶解步骤。通常将液相中的药物填充至软明胶胶囊中。后者产生弊端,诸如制造的复杂性、低的可处理性和可携带性、渗漏风险、因储存期间由组分之间的相互作用引起的稳定性问题所致的有限的存放期、脂质组分的氧化、液体制剂与胶囊外壳的相容性问题、由于在较低温度下不可逆的药物 / 赋形剂沉淀所致的储存温度的关键性。

[0005] 为了克服这些问题,已经开发了所谓的液固制剂,其为多孔载体材料,其中药物保持呈液体形式。液固形式是通过与所选的载体和包覆材料掺合而使呈液体形式的药物转变成可接受地流动的非粘附和可压缩粉末混合物。然后使这些转变成固体剂型,诸如片剂、丸剂以及胶囊。

[0006] 归因于湿润性和溶解表面积增加,不溶于水的药物的液固剂型显示改善的溶解特性和生物利用度。这种技术成功地应用于低剂量的不溶于水的药物。然而,由于药物的装填能力以及从所用载体中释放是有限的,所以更高剂量的不可溶药物的制剂是液固技术的限制之一。与液固制剂相关的另一个问题是当用较高量的呈液体形式的药物装填时其降低的流动性。这使得这些材料难以在医药制造中加工。为了具有可接受的可流动性和可压实性,必须添加高水平的载体和包覆材料,从而增加所得剂型的重量和体积。

[0007] 一种类型的基于脂质的药物递送系统是自乳化药物递送系统(SEDDS)。这种类型的基于乳液的药物制剂可以用于软明胶胶囊中或作为液固制剂。SEDDS 是药物、油 / 脂质、表面活性剂 / 助表面活性剂的各向同性和热力学稳定的混合物,其与水性流体接触,自发形成微滴的水包油乳液,微滴大小范围介于约 100 至 300 nm 之间。形成具有小于 50 nm 的

微滴的乳液的系统被称作自微乳化药物递送系统(SMEDDS),并且甚至更小的微滴大小被称作自纳米乳化药物递送系统(SNEDDS)。自乳化制剂容易在胃肠(GI)道中扩散,在胃肠道中胃和肠的消化运动性提供了自乳化所必需的搅动。这些系统有利地呈递呈溶解形式的药物并且小的微滴大小提供大界面面积用于药物吸收。当与呈敏感和亚稳定的分散形式的乳液相比较时,SEDDS 是易于制造的物理稳定制剂。特别是对于展现有限和扭曲的吸收的亲脂性药物,这些系统提供吸收速率和程度的改善,得到重现性更好的生物利用度。

[0008] 已知固体剂型的优点,使用类似于上文所描述的液固凝固程序还已经使 SEDDS、SNEDDS 以及 SMEDDS 转变成固体 -SEDDS、固体 -SNEDDS 或固体 -SMEDDS(S-SEDDS、S-SNEDDS 或 S-SMEDDS)。所得固体制剂继而可以被处理成各种固体或半固体剂型(片剂、丸剂、胶囊、乳膏、经皮系统,等等)。

[0009] 发明概述

本发明的一个目的在于提供用于释放各种性质的活性成分的其它载体。本发明的另一个目的在于提供相较于已知系统允许更高载药量,从而显示所需的溶解释放曲线和伴随的口服生物利用度特征的载体。本发明的一个目的也在于提供高剂量的不溶于水的药物的致密液固剂型,其具有对患者而言可接受的大小。本发明的一个目的在于提供具有最佳特性的液固材料,诸如流动和堆积密度。另一个目的涉及提供具有良好的可流动性特征并且可以在医药制造中容易地加工的液固制剂。

[0010] 这些目的和其它优点中的一个或多个通过本发明的各种方面和实施方案来达成。

[0011] 在一个实施方案中,本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;其中无机氧化物颗粒在至少 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、直至 2:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

[0012] 在另一个实施方案中,本发明涉及一种包含至少一种医药剂量配制成分和包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物的医药组合物,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;其中所述无机氧化物颗粒在至少 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、直至 2:1 的液体材料与无机氧化物颗粒的比率下保持自由流动。

[0013] 在另一个实施方案中,本发明涉及一种制造包含含有液体材料中的生物活性成分的多孔无机氧化物材料的组合物的方法,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;其中所述无机氧化物颗粒在至少 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、直至 2:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

[0014] 在另一个实施方案中,本发明涉及一种制造包含至少一种医药剂量配制成分和包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物的医药和 / 或化妆组合物的方法,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;其中所述无机氧化物颗粒在至少 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、或至少 2:1 的液体材料与无

机氧化物颗粒的重量比下保持自由流动。

[0015] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及(c)具有约 1.5 或更小、或约 1.4 或更小、或约 1.3 或更小、或约 1.2 或更小、或约 1.1 或更小、或约 1.0 或更小的相对跨度的孔大小分布。

[0016] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及(c)5 nm 至 30 nm 的中值孔大小，其中所述无机氧化物颗粒在至少 1:1、或 1.3、或 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、或至少 2:1 的液体材料与无机氧化物颗粒的比率下保持自由流动。

[0017] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及(c)3 微米至 10 毫米的中值粒度；其中所述无机氧化物颗粒在至少 1:1、或 1.3、或 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、或至少 2:1 的液体材料与无机氧化物颗粒的比率下保持自由流动。

[0018] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；其中在混合无机氧化物颗粒与液体材料之后，所述组合物在静置后体积减小至少约 15%，或在静置后减小至少约 20%、或至少约 25%、或至少约 30%、或至少约 35%、或至少约 40%。

[0019] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；其中在混合无机氧化物颗粒与液体材料之后，所述组合物在静置后堆积密度增加至少约 15%，或在静置后增加至少约 20%、或至少约 25%、或至少约 30%、或至少约 35%、或至少约 40%。

[0020] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；其中在混合无机氧化物颗粒与液体材料并且然后静置至少 2 小时后，可以将至少约 400 mg 的所述组合物装填至零号胶囊 (zero size capsule) 中。在另一个实施方案中，可以将至少约 410 mg、或至少约 420 mg、或至少约 430 mg 的所述组合物装填至零号胶囊中。

[0021] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及(c)至少 1:1 的液体材料与无机氧化物颗粒的比率；其中至少 65% 的液体材料在解吸附后

从颗粒脱附。

[0022] 在一个实施方案中，无机氧化物材料包含多孔颗粒，其包含具有在约 5 nm 至约 30 nm 范围内的平均孔直径的孔。

[0023] 在另一个实施方案中，含有液体材料中的生物活性成分的多孔无机氧化物材料呈颗粒形式，即，含有呈液体形式的生物活性成分的多孔无机氧化物材料的颗粒。本发明的多孔无机氧化物材料的颗粒的平均直径可以在约 3 μm 至约 5 mm 的范围内。

[0024] 本发明的组合物可以含有其它液体有机辅助材料，诸如油、非挥发性溶剂以及表面活性剂。

[0025] 在一个实施方案中，本发明的含有液体材料中的生物活性成分的多孔无机氧化物材料的颗粒形成自由流动的粉末。在另一个实施方案中，粉末具有等于或低于 25 的卡尔指数(Carr index)，或粉末具有约 1 至约 1.4 的豪斯纳指数(Hausner index)。在一个实施方案中，所述粉末的休止角为约 30° 至约 45° 。这些特性在装填生物活性成分于多孔无机氧化物材料上之前和之后测量。

[0026] 在另一个实施方案中，包含含有液体材料中的生物活性成分的多孔无机氧化物材料的组合物在至少 2 小时期间装填和静置后具有至少 450 g/l 的堆积密度。

[0027] 在用液体材料中的生物活性成分装填后，所得已装填的多孔无机氧化物材料当与未装填的无机氧化物多孔材料相比较时可以显示体积的有限增加(例如，至多约 10%)或不增加，但特别显示体积的减小。在一个实施方案中，减小为至多约 30%、或至多约 20%、或至多约 10% (在这一段中每个 % 是体积 / 体积或 v/v)。本文所提及的体积和 / 或密度变化中的每一个是在装填和静置直至 2 小时(取决于液体)并且甚至直至 24 或 48 小时后。在一个实施方案中，在用液体材料中的生物活性成分装填无机氧化物多孔材料后，在约 3 小时、特别是约 2 小时的时段期间，观测到体积的减小或密度的增加，特别是本文所提及的特定的体积减小或密度增加，在这个时段后不发生进一步减小并且体积保持基本上恒定。

[0028] 本发明的组合物有利地并不显示当用液体材料中的生物活性成分装填本领域已知的二氧化硅时通常观测到的体积的大量增加。这允许制造更致密的剂型，继而促成在医药制造期间更好的可加工性和患者对剂型更好的可接受性。

[0029] 在另一个方面，本发明涉及一种包含至少一种医药剂量配制成分和包含含有液体材料中的生物活性成分的多孔无机氧化物材料的组合物的医药组合物，其中无机氧化物材料具有如本文所指定的油吸附值、孔体积以及 BET 表面积。在一个实施例中，包含含有生物活性成分的无机氧化物多孔材料的所述组合物呈颗粒形式。

[0030] 本发明进一步涉及制造所公开的组合物的方法。在一个实施方案中，制造本发明的组合物的方法包括将至少一种液体材料中的生物活性成分并入具有如本文所指定的油吸附值、孔体积以及 BET 表面积的多孔无机氧化物材料中。

[0031] 在另一个方面，本发明涉及一种制造包含至少一种医药剂量配制成分和包含含有液体材料中的生物活性成分的多孔无机氧化物材料的组合物的医药组合物的方法，其中无机氧化物材料具有如本文所指定的油吸附值、孔体积以及 BET 表面积，所述方法包括组合所述医药剂量配制成分与所述组合物。

[0032] 本发明还涉及使用所公开的组合物的方法。在一个实施方案中，使用本发明的组合物的方法包括将本发明的组合物施用于患者以递送生物活性材料至患者，其中该组合物

包含含有液体材料中的生物活性成分的多孔无机氧化物材料，其中无机氧化物材料具有如本文所指定的油吸附值、孔体积以及 BET 表面积。所施用的组合物特别是医药剂型。

[0033] 在一个实施例中，所述无机氧化物材料呈颗粒形式，特别是具有如本文进一步指定的平均直径的颗粒。

[0034] 本发明的这些和其它特征以及优点将在审阅所公开的实施方案的以下详细描述和随附权利要求书之后变得显而易见。

[0035] 附图简述

本发明参考附图进一步描述，其中：

图 1用图形显示本发明的例示性组合物的动力学行为或体积随时间的变化。

[0036] 图 2用图形显示根据实施例 4 的本发明的例示性组合物在静置前后的胶囊载荷能力变化。

[0037] 图 3用图形显示醋氨酚（acetaminophen）从根据实施例 6 的本发明的例示性组合物中的释放曲线。

[0038] 图 4用图形显示抗坏血酸从根据实施例 6 的本发明的例示性组合物中的释放曲线。

[0039] 图 5用图形显示格布瑞德（Gyburide）从根据实施例 8 的本发明的固体 SEDDS 系统中的释放曲线。

[0040] 详述

为了促进对本发明的原理的理解，本发明的特定实施方案的描述如下并且特定语言用于描述特定实施方案。尽管如此，应了解，特定语言的使用并不意图限制本发明的范围。如本发明所属领域的一般技术人员将通常所想到，涵盖所论述的本发明的原理的变更、其它修改以及这类其它应用。

[0041] 须注意，除非上下文另有明确规定，否则如本文和随附权利要求书中所用的单数形式“一种”、“和”以及“这种”包括复数指示物。因此，举例来说，提及“一种氧化物”包括多种这类氧化物，并且提及“氧化物”包括提及本领域的技术人员已知的一种或多种氧化物和其等效物，等等。

[0042] 在描述本公开的实施方案中所采用的修饰例如组合物中成分的量、浓度、体积、加工温度、加工时间、回收率或产率、流动速率和类似值以及其范围的“约”指的是数值数量的变化，其可能因以下而发生：例如，经由典型的测量和处理程序；经由这些程序中的偶然误差；经由用于进行方法的成分的差异；以及类似的近似考虑因素。术语“约”还涵盖因具有特定初始浓度或混合物的制剂的老化而不同的量，以及因混合或加工具有特定初始浓度或混合物的制剂而不同的量。无论是否被术语“约”修饰，附加于此的权利要求书包括这些量的等效值。

[0043] 如本文所用的术语“生物活性成分”意指活性医药成分（API），其提供药理活性或以其它方式在疾病的诊断、治愈、缓解、治疗或预防方面具有直接作用，或在恢复、校正或改进在人类中的生理功能方面具有直接作用。尽管这包括溶解性差的材料，但其还可以包括在一定溶解度范围内的材料，包括 BCS（生物药剂学分类系统）中所列出的那些，BCS 是将药物（API）基于其水溶性和通过 GI 道壁（特别是肠）的渗透性的程度（高或低）而分成四类的分类方法。在这方面，这四类是：（第 I 组）高溶解度和高渗透性药物、（第 II 组）低溶解度

和高渗透性药物、(第 III 组)高溶解度和低渗透性药物,以及(第 IV 组)低溶解度和低渗透性药物。

[0044] 如本文所用的术语“堆积密度”意指微粒物质(诸如粉末)的质量除以这种物质所占据的总体积,并且包括颗粒内孔体积和颗粒间空隙体积。

[0045] 如本文所用的术语“自由流动”意指颗粒或粉末组当对其施加力(例如,重力或其它外力)时移动的能力。用于测量粉末流动的常用测试包括豪斯纳比(Hausner ratio)、可压缩性指数(卡尔指数)或休止角。可压缩性指数(卡尔指数)和豪斯纳比通过测量粉末的堆积体积与振实体积两者来确定。

[0046] 如本文所用的“无机氧化物”被定义为二元含氧化合物,其中无机组分是阳离子并且氧化物是阴离子。无机材料包括金属,还可以包括类金属。金属包括在周期表上从硼至钋所绘制的对角线左侧的那些元素。类金属或半金属包括在这条线右侧的那些元素。无机氧化物的实例包括二氧化硅、氧化铝、二氧化钛、氧化锆等,以及其混合物。

[0047] 如本文所用的术语“颗粒内孔体积”意指可归因于颗粒孔中的空间的孔体积,与颗粒间孔体积对照,颗粒间孔体积是可归因于颗粒之间的空间的孔体积(即,间隙空间)。

[0048] 如本文所用的术语“脂质材料”或“脂质组分”意指包含脂肪酸和其衍生物的有机材料,以及在生物合成或功能方面与这些化合物有关的物质。其包括(但不限于)完全或部分通过硫酯的基于碳阴离子的缩合(脂肪酸、聚酮等)和/或通过异戊二烯单元的基于碳阳离子的缩合(异戊烯醇、固醇等)而产生的分子。

[0049] 如本文所用的术语“有序多孔材料”指的是具有内部结构次序以使得其根据布拉格定律(Bragg's Law)具有低角 X 射线衍射图案的多孔颗粒。这类材料包括有序介孔二氧化硅,例如,MCM-41、SBA-15、TUD-1、HMM-33 以及 FSM-16。

[0050] 如本文所用的术语“无序多孔材料”指的是具有一定内部结构以使得其根据布拉格定律不具有低角 X 射线衍射图案的多孔颗粒。这类材料可以经由任何已知的工艺形成,包括(但不限于)溶液聚合工艺,诸如用于形成胶态颗粒;连续火焰水解技术,诸如用于形成熔融颗粒;凝胶技术,诸如用于形成凝胶态颗粒;以及沉淀技术,诸如用于形成沉淀颗粒。颗粒可以随后通过压热、急骤干燥、超临界流体萃取、蚀刻或类似工艺来改进。颗粒可以由有机和/或无机材料以及其组合组成。在一个例示性实施方案中,颗粒由无机材料组成,诸如无机氧化物、硫化物、氢氧化物、碳酸盐、硅酸盐、磷酸盐等,但优选无机氧化物。颗粒可以具有多种不同的对称、不对称或不规则形状,包括链、棒或板条形状。颗粒可以具有不同的结构,包括非晶或结晶等。颗粒可以包括颗粒的混合物,这些颗粒包含不同的组成、大小、形状或物理结构,或除了不同表面处理之外可以是相同的。颗粒的孔隙度可以是颗粒内的或颗粒间的(在较小颗粒聚结形成较大颗粒的情况下)。在一个例示性实施方案中,颗粒由无机材料组成,诸如无机氧化物、硫化物、氢氧化物、碳酸盐、硅酸盐、磷酸盐等,但优选无机氧化物。多孔材料包括有机和无机材料或其杂合物,并且可以呈颗粒、单块、膜、包衣等形式。

[0051] 如本文所用的术语“孔大小分布”意指在多孔无机颗粒的代表性体积中每个孔大小的相对丰度。如本文所用的“中值孔大小”是 50% 的颗粒内孔体积处于其之下的孔直径。

[0052] 如本文所用的术语“相对跨度”被定义为意指孔大小分布的宽度的量度。“跨度”通过从如通过水银孔度测定法所测量的 d_{90} 孔大小(即,90% 的孔体积处于其之下的孔大小/直径)减去 d_{10} 孔大小(即,10% 的孔体积处于其之下的孔大小/直径)来测量。术语“相对

跨度”被定义为 $(d_{90}-d_{10})/d_{50}$的比率。跨度和相对跨度是使用累积孔体积的氮吸附(BJH 方法)来测定。

[0053] 如本文所用的术语“已静置”或“静置后”用于指示一定时段,其中允许多孔无机氧化物材料在用液体材料中的生物活性成分装填后保持无扰动。

[0054] 每当在本文中关于组分的比率或百分比使用时,w/w 意指重量 / 重量并且 w/v 意指重量 / 体积。

[0055] 本发明涉及包含生物活性材料或成分和无机氧化物材料的组合物,其中无机氧化物材料包含多孔颗粒。于液体或液体材料中的生物活性材料至用于药物递送的媒介物上的有效装填是许多生物活性材料所关注的问题,并且本发明涉及提供这一问题的解决方案的各种实施方案。本发明的申请者已经发现,具有一组特定的物理特性的某些多孔无机氧化物材料提供各种液体或液体材料中的生物活性材料的极佳液体装填和释放。

[0056] 在一个实施方案中,本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;其中无机氧化物颗粒在至少 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、直至 2:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

[0057] 在另一个实施方案中,本发明涉及一种制造包含含有液体材料中的生物活性成分的多孔无机氧化物材料的组合物的方法,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;其中所述无机氧化物颗粒在至少 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、直至 2:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

[0058] 在另一个实施方案中,本发明涉及一种制造包含至少一种医药剂量配制成分和包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物的医药组合物的方法,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;其中所述无机氧化物颗粒在至少 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、或至少 2:1 的液体材料与无机氧化物颗粒的重量比下保持自由流动。

[0059] 在另一个实施方案中,本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;以及(c)5 nm 至 30 nm 的中值孔大小,其中所述无机氧化物颗粒在至少 1:1、或 1.3、或 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、或至少 2:1 的液体材料与无机氧化物颗粒的比率下保持自由流动。

[0060] 在另一个实施方案中,本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物,其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值 ;(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔 ;以及(c)3 微米至 10 毫米的中值粒度 ;其中所述无机氧化物颗粒在至少 1:1、或 1.3、或 1.5:1、或 1.6:1、或 1.7:1、或 1.8:1、或 1.9:1、或至少 2:1 的液体材料与无机氧化物颗粒的比率下保持自由流动。

[0061] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及(c)其中至少 0.5 cm^3/g 的孔体积来自在 10 nm 至 30 nm 范围内的孔，至少 0.5 cm^3/g、至少 0.6 cm^3/g、至少 0.8 cm^3/g、至少 1.0 cm^3/g、至少 1.2 cm^3/g、至少 1.4 cm^3/g、或至少 1.6 cm^3/g 的孔体积来自在 10 nm 至 30 nm 范围内的孔的孔大小分布。

[0062] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及(c)具有约 1.5 或更小、或约 1.4 或更小、或约 1.3 或更小、或约 1.2 或更小、或约 1.1 或更小、或约 1.0 或更小的相对跨度的孔大小分布。

[0063] 含有液体材料中的生物活性成分的多孔无机氧化物材料可以呈颗粒形式，其可以具有多种不同的对称、不对称或不规则形状，包括链、棒或板条形状。颗粒可以包括颗粒的混合物，这些颗粒包含不同的组成、大小、形状或物理结构。

[0064] 本发明的多孔无机氧化物材料的颗粒的平均直径可以在约 3 μm 至约 5 mm 的范围内，优选地约 50 μm (或约 44 μm)至约 500 μm；或约 70 μm (或约 74 μm)至约 200 μm；或约 50 μm (或约 44 μm)至约 150 μm (或约 149 μm)；或约 50 μm (或约 44 μm)至约 150 μm (或约 149 μm)；或约 100 μm (或约 105 μm)至约 120 μm (或约 125 μm)；或约 48 μm (或约 44 μm)至约 65 μm (或约 63 μm)；或约 90 μm 至约 130 μm。本文所公开的平均直径优选地用 Malvern 仪器测定。所需粒度可以通过研磨和后续网筛而获得。

[0065] 多孔无机氧化物材料可以经由任何已知的工艺形成，包括溶液聚合工艺，诸如用于形成胶态颗粒；连续火焰水解技术，诸如用于形成熔融颗粒；凝胶技术，诸如用于形成凝胶态颗粒；以及沉淀技术，诸如用于形成沉淀颗粒。颗粒可以随后通过压热、急骤干燥、超临界流体萃取、蚀刻或类似工艺来改性。在一个实施方案中，颗粒由无机材料组成，诸如无机氧化物、硫化物、氢氧化物、碳酸盐、硅酸盐、磷酸盐等，但优选无机氧化物。颗粒可以包括颗粒的混合物，这些颗粒包含不同的组成、大小、形状或物理结构，或除了不同表面处理之外可以是相同的。

[0066] 多孔材料包括有机和无机材料或其杂合物，并且可以呈颗粒、单块、膜、包衣等形式。

[0067] 多孔颗粒可以呈各种形式，诸如沉淀物、凝胶、烟雾状、胶态等，以及其组合，未改性或通过后续工艺以改性，诸如压热、超临界流体萃取、急骤干燥，等等。在一个实施方案中，适合用于本发明的多孔无机氧化物材料包括沉淀无机氧化物颗粒和无机氧化物凝胶颗粒。这些无机氧化物在本文中被称作“母体无机氧化物”、“母体颗粒”或“母体分散体”。

[0068] 在另一个实施方案中，多孔无机氧化物材料是无序的，并且可以进一步具有无规颗粒内孔隙度。已经发现这类材料当与生物活性成分和液体材料组合时，提供有利的吸附和解吸附(以及溶解)特征。尽管任何无机氧化物组成可以适合用于本发明中(例如，SiO_2、Al_2O_3、$AlPO_4$、MgO、TiO_2、ZrO_2等)，但本发明的一个实施方案包括非晶沉淀二氧化硅和硅胶。无机氧化物还可以包括混合无机氧化物，诸如 $SiO_2.Al_2O_3$、$MgO.SiO_2.Al_2O_3$等。混合无机氧

化物通过常规的掺合或共胶凝程序来制备。在包含凝胶的实施方案中，分散体来源于多孔无机氧化物凝胶，诸如包含 SiO_2、Al_2O_3、$AlPO_4$、MgO、TiO_2以及 ZrO_2的凝胶。凝胶可以是水凝胶、气凝胶或干凝胶。

[0069] 在一个实施方案中，无机氧化物凝胶包括无序多孔硅胶，其包括颗粒间孔体积。这样的硅胶可以通过混合碱金属硅酸盐(例如，硅酸钠)的水溶液与诸如硝酸或硫酸的强酸来制备，混合是在适合的搅动条件下进行以形成清澈的硅溶胶，其在小于约一个半小时内沉降为水凝胶，即，大粒凝胶。然后洗涤所得凝胶。在水凝胶中形成的无机氧化物(即，SiO_2)的浓度通常在约 10 与约 50 重量％的范围内，或介于约 20 与约 35 重量％之间，或介于约 30 与约 35 重量％之间，那种凝胶的 pH 为约 1 至约 9、或 1 至约 4。可以采用大范围的混合温度，这个范围通常为约 20℃至约 50℃。新形成的水凝胶通过浸入连续运动的水流中来简单地洗涤，水流滤去不需要的盐，留下约 99.5 重量％或更纯的无机氧化物。洗涤的 pH、温度以及持续时间将影响二氧化硅的物理特性，诸如表面积(SA)和孔体积(PV)。在 65-90℃下、在 8-9 的 pH 下洗涤 15-36 小时的硅胶将通常具有 250-400 的 SA 并且形成具有 1.4 至 1.7 cm^3/g 的 PV 的气凝胶。

[0070] 制备无机氧化物凝胶(诸如氧化铝)和混合无机氧化物凝胶(诸如二氧化硅 / 氧化铝共凝胶)的方法在本领域中也是众所周知的，诸如通过常规掺合、共胶凝、共沉淀，等等。制备这类凝胶的方法已经描述于 US 4,226,743 中。一般来说，氧化铝凝胶通过混合碱金属铝酸盐与硫酸铝来制备。共凝胶通过共胶凝两种或更多种金属氧化物以使得凝胶复合在一起来制备。举例来说，二氧化硅氧化铝共凝胶可以通过胶凝碱金属硅酸盐与酸或酸盐，并且然后添加碱金属铝酸盐，使混合物老化并且随后添加硫酸铝来制备。然后使用常规技术洗涤凝胶。本发明的另一个实施方案来源于某些沉淀无机氧化物的分散体。强化的沉淀二氧化硅，诸如 US 4,157,920 中所描述，可以用于制备本发明的分散体。举例来说，强化的沉淀二氧化硅可以通过首先酸化碱性无机硅酸盐以形成初始沉淀物来制备。然后用额外的硅酸盐和酸来强化或“后调节”所得沉淀物。由第二次添加硅酸盐和酸产生的沉淀物包含 10 至 70 重量％的初始制备的沉淀物。据信，这种沉淀物的强化结构由于第二次沉淀而比常规沉淀物更硬。一旦选择无机氧化物用于母体分散体，就制备所选无机氧化物的液相。一般来说，母体分散体应处于可以湿磨的状态。液相的介质可以是水性或非水性的，例如，有机的。液相可以是已经排水、但尚未干燥的无机氧化物凝胶中的残余水，并且向其中添加额外的水以使凝胶再浆化。

[0071] 在另一个实施方案中，使干燥的无机氧化物，例如干凝胶，分散于液体介质中。在一些实施方案中，然后研磨母体分散体。研磨“湿式”进行，即，在液体介质中。一般研磨条件可以有变化，这取决于进料、停留时间、叶轮速度以及研磨介质粒度。用于选择和修改这些条件以获得所需分散体的技术为本领域的技术人员所知。用于研磨母体无机氧化物颗粒的研磨设备应为能够例如通过机械作用严格地研磨并减小材料至具有所需大小的颗粒的类型。这类研磨机可商购，其中流体能研磨机、锤式研磨机以及砂磨机特别适合于这个目的。锤式研磨机经由高速金属刀片赋予必需的机械作用，并且砂磨机经由快速搅拌介质(诸如氧化锆或砂珠)赋予作用。也可以使用冲击式研磨机。在其它实施方案中，不需要研磨，诸如对于空气硬化的无机氧化物凝胶。这类凝胶通过以下方式形成：空气喷射一定浓度的碱金属溶液(例如，硅酸钠)与适合的酸(例如，硫酸)的紧密混合物以使得混合物凝胶在飞

行期间胶凝，随后收集于适合的介质中，一般是水。还可以进一步加工任何所得分散体或粉末。举例来说，如果需要在没有分散剂的帮助下制备相对稳定的分散体，或如果存在大于所需的大量颗粒群体，那么需要进一步加工。还可能需要进一步加工以确保基本上所有的颗粒分布低于一定大小。在这样的情况下，加工分散体或粉末以分离较小颗粒与较大颗粒。这种分离可以通过将无机氧化物颗粒离心为包含最终产物的较小颗粒的上清液相和包含较大颗粒的沉降相来达成。然后从沉降相去除上清液相，例如，通过倾析。在一些情况下，可能优选地离心上清液两次、三次或更多次以进一步去除在初始离心后残留的大颗粒。还预期，研磨过的分散体的较大颗粒可以在正常重力条件下随着时间而分离，并且可以通过倾析去除上清液。取决于产物粒度目标，沉降相也可以被视为本发明的颗粒。还可以在研磨后改性颗粒或粉末的分散体以确保稳定的分散体。这可以通过 pH 调节来实现，例如，添加碱性材料，或通过添加常规分散剂。

[0072] 本发明的组合物中的无机氧化物材料可以包含两种或更多种不同和独特类型的多孔颗粒。在一个实施方案中，每种类型的多孔颗粒提供液体材料中的生物活性材料的特定解吸附和 / 或溶解速率曲线以形成生物活性材料的复合解吸附和 / 或溶解速率曲线。

[0073] 在一个实施方案中，无机氧化物材料的表面，特别是孔中的表面，尚未经过化学改性。无机氧化物材料中的孔是开放的以使得液体材料中的活性成分可以进入孔并且变得被吸附在孔的表面处，或可以留着孔以释放活性成分。

[0074] 本发明的多孔无机氧化物材料具有约 100 至约 600 ml/100 g、或约 100 至约 500 ml/100 g、或约 100 至约 450 ml/100 g、或约 100 至约 400 ml/100 g、或约 150 至约 400 ml/100 g、或约 200 至约 400 ml/100 g 的油吸附值。油吸附值可以用标准方法测量，特别是通过在油 / 无机氧化物材料的恒定混合下用油滴定预定量的无机氧化物材料直至质量显示过量的油，诸如在 ASTM D281 中完成。

[0075] 本发明的组合物中的无机氧化物材料是多孔的。在一个实施方案中，孔具有大于 5 nm、或约 5 nm 至约 30 nm、或约 10 nm 至约 30 nm 的平均孔直径。在另一个实施方案中，平均孔直径为约 20 至约 25 nm。

[0076] 理想地，多孔无机氧化物材料具有约 0.5 cm^3/g 或更大、或约 0.6 cm^3/g 或更大、或约 0.7 cm^3/g 或更大的孔体积。在一些实施方案中，孔体积的上限为约 3.0 cm^3/g 或约 2.3 cm^3/g。

[0077] 理想地，多孔无机氧化物材料具有如通过氮吸附法所测量的约 10 m^2/g 或更大、或约 100 m^2/g 或更大、或约 200 m^2/g 或更大、或约 300 m^2/g 或更大的 BET 表面积。在一些实施方案中，BET 表面积的上限为约 1000 m^2/g、或约 800 m^2/g、或约 600 m^2/g。在其它实施方案中，BET 表面积可以在约 10 至约 1000 m^2/g、或约 100 至约 800 m^2/g、或约 150 至约 600 m^2/g、或约 200 至约 500 m^2/g、或约 250 至约 400 m^2/g 的范围内。

[0078] 在一个实施方案中，多孔无机氧化物材料具有（i）约 5 nm 至约 30 nm 的平均孔直径，（ii）约 0.7 cm^3/g 或更大的孔体积，以及（iii）约 20 至约 500 m^2/g 或更大的表面积。在另一个实施方案中，这种多孔无机氧化物材料呈颗粒形式，其可以具有约 50 μm（或约 44 μm）至约 150 μm（或约 149 μm）的直径。在另一个实施方案中，这种无机氧化物多孔材料具有约 100 至约 500 ml/100 g 的油吸附值。这类材料由于其在高载荷、堆积密度、可流动性、解吸附以及溶解特征方面的优良特性而有吸引力。

[0079] 在本发明中，孔体积的测量值通过 N_2 孔隙度分析生成，并且表面积通过 BET 技术生成，这些是本领域已知的技术。

[0080] 含有液体材料中的生物活性成分的多孔无机氧化物材料可以获自不含液体材料中的生物活性成分的多孔无机氧化物材料，随后添加液体材料中的生物活性成分以使得其被多孔无机氧化物材料吸附。或者，可以在制备多孔无机氧化物材料的一个或多个步骤期间添加液体材料中的生物活性成分。

[0081] 在另一个实施方案中，可以使无机氧化物分散于液体化合物中，其随后用作形成本发明的生物活性组合物的反应物或溶剂或介质。

[0082] 本发明的多孔无机氧化物材料的颗粒可以是自由流动的。在一个实施方案中，所述颗粒可以具有等于或低于约 25 的卡尔指数，例如，约 10 至约 25 的卡尔指数。在一些实施方案中，卡尔指数可以等于或低于约 15，例如，约 10 至约 15 的卡尔指数。本发明的多孔无机氧化物材料的颗粒可以具有约 1 至约 1.4、特别为约 1.2 至约 1.4 的豪斯纳指数。本发明的多孔无机氧化物材料的颗粒可以具有约 30° 至约 45° 的休止角。在一些实施方案中，本文所提及的卡尔和豪斯纳指数值以及休止角适用于具有如本文所指定的液体材料中的生物活性成分与无机氧化物无机氧化物的 w/w 比的本发明的任何颗粒，并且特别是所述 w/w 比介于约 0.5:1 至约 2:1 之间。在一些实施方案中，本文所提及的卡尔和豪斯纳指数值以及休止角适用于放空液体材料中的生物活性成分的本发明的任何颗粒。

[0083] 卡尔指数(C.I.)是粉末状材料的可流动性和可压缩性的指示并且由公式 $C = 100 \times (1-\rho_b/\rho_t)$ 计算，其中 ρ_b 是粉末的自由沉降堆积密度，并且 p_t 是粉末的振实堆积密度。大于 25 的卡尔指数被认为是差的可流动性的指示。具有等于或低于 25 的卡尔指数的材料显示良好的可流动性并且也可以被称作“自由流动”材料。豪斯纳指数(H.I.)由公式 $H = p_t/\rho_b$ 计算。

[0084] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；其中在混合无机氧化物颗粒与液体材料之后，所述组合物在静置后体积减小至少约 15%，或在静置后减小至少约 20%、或至少约 25%、或至少约 30%、或至少约 35%、或至少约 40%。本文所提及的体积和 / 或密度变化中的每一个是在装填和静置直至 2 小时(取决于液体)并且甚至直至 24 或 48 小时后。在一个实施方案中，在用液体材料中的生物活性成分装填无机氧化物多孔材料后，在约 3 小时、特别是约 2 小时的时段期间，观测到体积的减小或密度的增加，特别是本文所提及的特定的体积减小或密度增加，在这个时段后不发生进一步减小并且体积保持基本上恒定。

[0085] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；其中在混合无机氧化物颗粒与液体材料之后，所述组合物在静置后堆积密度增加至少约 15%，或在静置后增加至少约 20%、或至少约 25%、或至少约 30%、或至少约 35%、或至少约 40%。本文所提及的体积和 / 或密度变化中的每一个是在装填和静置直至 2 小时(取决于液体)并且甚至直至 24 或 48 小时后。在一个实施方案中，在用液体材料中的生物活性成分装

填无机氧化物多孔材料后，在约 3 小时、特别是约 2 小时的时段期间，观测到体积的减小或密度的增加，特别是本文所提及的体积的特定减小或密度的增加，在这个时段后不发生进一步减小并且体积保持基本上恒定。

[0086] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；以及(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；其中在混合无机氧化物颗粒与液体材料并且然后静置至少 2 小时后，可以将至少约 400 mg 的组合物装填至零号胶囊中。在另一个实施方案中，可以将至少约 410 mg、或至少约 420 mg、或至少约 430 mg 的所述组合物装填至零号胶囊中。

[0087] 在另一个实施方案中，本发明涉及一种包含含有液体材料中的生物活性成分的多孔无机氧化物颗粒的组合物，其中无机氧化物颗粒具有(a)约 100 至约 500 ml/100 g 的油吸附值；(b)具有如通过氮孔隙度测定法所测量的约 0.5 cm^3/g 或更大的孔体积的孔；以及(c)至少 1:1 的液体材料与无机氧化物颗粒的比率；其中至少 65% 的液体材料在解吸附后从颗粒脱附。在另一个实施方案中，至少 70%、或至少 75%、或至少 80%、或至少 85% 的液体材料在解吸附后从颗粒脱附。液体材料在模拟液体材料在生物流体中解吸附的条件下脱附。这类测试通过如实施例 7 中所陈述，在水性介质中强烈混合来进行。

[0088] 如本文所用的关于生物活性成分的术语“呈液体形式”或“液体材料”指的是本身是液体的那些成分，或指的是通过各种技术变成液体形式的生物活性成分，这些技术包括例如解吸附和 / 或溶解或转变成自乳化药物递送系统。这类材料还可以包括用液体悬浮、分散或合并的固体生物活性成分。

[0089] 术语“呈液体形式”或“液体材料”指的是按原样或变成液体形式的生物活性成分，其在室温下或在生理温度下是液体，或在约 0℃至约 60℃、特别为约 10℃至约 50℃、或约 20℃至约 45℃范围内的温度下是液体。这类材料可能在某些条件(例如，温度、浓度等)下是固体并且在其它条件下是液体。

[0090] 根据本发明的多孔无机氧化物材料含有呈液体形式的生物活性成分。术语“含有”意指多孔无机氧化物材料装填有生物活性成分，术语“装填”意指活性成分被吸附在无机氧化物材料的表面处，包括在无机氧化物材料的孔内的表面。活性成分的主要部分可以并入无机氧化物材料的孔中。吸附有生物活性成分的这类无机氧化物材料被称作“已装填的无机氧化物材料”。术语“已装填”和“已并入”在这个背景下意味着是等效的。

[0091] 在一个实施方案中，于液体材料(其包含生物活性成分本身以及液体中任何添加的材料)中的生物活性成分与无机氧化物的 w/w 比在约 0.5:1 至约 5:1、或约 0.5:1 至约 3:1、或约 0.5:1 至约 2:1、或约 1:1 至约 2:1 的范围内。

[0092] 包含含有液体材料中的生物活性成分的多孔无机氧化物材料的组合物可以具有至少 450 g/l 的堆积密度。在一些实施方案中，所述堆积密度在 450 g/l 至 750 g/l 的范围内，特别是在 500 g/l 至 700 g/l 的范围内，或在 550 g/l 至 650 g/l 的范围内。

[0093] 在一个实施方案中，液体材料中的生物活性成分是液体脂质药物。实例包括维生素 A、维生素 E (dl-α-生育酚)、对乙酰氨基酚(paracetamol)、抗坏血酸、芝麻油、米格列醇(miglyol)，或其组合。

[0094] 在另一个实施方案中，液体材料中的生物活性成分采用生物活性成分于非挥发性

溶剂中的溶液或分散体的形式，例如，具有高于约 150℃的沸点。实例包括甘油；丙二醇；液体聚乙二醇，诸如聚乙二醇 200 和 400；聚山梨醇酯，诸如聚山梨醇酯 80；或油。可以使用的油包括具有不同饱和度的长链甘油三酯和中链甘油三酯油；植物油，诸如橄榄油、葵花油、蓖麻油、亚麻籽油等；改性或水解植物油；具有表面活性剂特性的半合成中链甘油三酯油，例如 Cremophor。在分散体方面，活性成分优选地呈微米颗粒或纳米颗粒的形式。在一个实施方案中，溶液或分散体中生物活性成分的浓度在 1% 或 90% 的范围内，或从 ..... （w/w）。

[0095] 在一个实施方案中，液体材料中的生物活性成分是包含油 / 脂质组分、表面活性剂、助溶剂以及生物活性成分的自乳化药物递送系统（SEDDS）。

[0096] 油 / 脂质组分一般是在室温下呈液体、半固体或固体形式的脂肪酸酯或中链 / 长链饱和、部分不饱和或不饱和烃（例如，固体脂质纳米颗粒、油性悬浮液、亚微米脂质乳液、脂质植入物、脂质微管、脂质微泡或脂质微球等）。实例包括矿物油、植物油、改性或水解植物油、硅酮油、羊毛脂、脂质体、精炼动物油、脂肪酸、脂肪醇以及甘油单酯 / 甘油二酯 / 甘油三酯，包括具有不同饱和度的长链甘油三酯和中链甘油三酯油以及具有表面活性剂特性的半合成中链甘油三酯油。其它油 / 脂质组分包括由一种或多种丙二醇中链脂肪酸酯组成的油，诸如丙二醇单癸酸酯、丙二醇二癸酸酯、丙二醇二辛酸酯 / 二癸酸酯、丙二醇二壬酸酯以及丙二醇二月桂酸酯；三醋精；脂肪和油，诸如橄榄油、芝麻油、大豆油、玉米油、菜油、蓖麻油、椰子油以及桉叶油；辛酸 / 癸酸甘油三酯（米格列醇™ 812）；甘油三酯，诸如三辛酸甘油酯和三月桂酸甘油酯；以及聚甘油脂肪酸酯，诸如四甘油聚蓖麻油酸酯、六甘油聚蓖麻油酸酯、缩合聚蓖麻油酸酯，以及四甘油混合脂肪酸酯。术语“中链脂肪酸”意图指代长度介于 6 个与 14 个碳之间、更优选长度介于 8 个与 12 个碳之间的脂肪酰基链；“长链脂肪酸”意图指代长度大于 14 个碳的脂肪酰基链；“短链脂肪酸”意图指代长度小于 6 个碳的脂肪酰基链。

[0097] 油组分可以按任何有效的浓度用于本发明的 SEDDS 制剂中，包括例如在 5% 至 80%（w/v）的浓度范围内。

[0098] 优选的表面活性剂包含具有通常在介于 30% 与 60%（w/w）之间的浓度范围内的相对高的亲水 - 亲脂平衡（HLB）值的非离子性表面活性剂。

[0099] 可以使用的亲水性表面活性剂（9.0 或更高的 HLB（亲水 - 亲脂平衡））包括聚氧乙烯月桂基醚（Laureth 2（BL-2）、Laureth 4.2（BL-4.2）以及 Laureth 9（BL-9））、聚氧乙烯 (20) 脱水山梨糖醇单椰子油脂肪酸酯（“聚山梨醇酯 20”）、聚山梨醇酯 40、聚山梨醇酯 80、Labrasol、D-α - 生育酚聚乙二醇 1000 琥珀酸酯（维生素 E TPGS NE）、月桂酰基聚氧乙烯甘油（Gelucire 44/14）、聚氧乙烯氢化蓖麻油 40、聚氧乙烯氢化蓖麻油 60（HCO-60）、聚氧乙烯脱水山梨糖醇单月桂酸酯、聚氧乙烯脱水山梨糖醇单棕榈酸酯以及聚氧乙烯脱水山梨糖醇单油酸酯。

[0100] 在用于本发明的 SEDDS 中可以使用任何有效的非水性质子性助溶剂或其组合。可接受的非水性质子性溶剂包括任何医药学上可接受的单羟基、二羟基、三羟基或多羟基线性脂肪族和芳香族溶剂或其组合。非水性质子性溶剂的实例包括乙醇、丙醇、苯甲醇、丙二醇、液体聚乙二醇（诸如聚乙二醇 200 和 400）以及甘油。质子性溶剂可以按任何有效的浓度用于本发明的制剂中，包括例如在约 5% 至约 50%（w/v）的浓度范围内。

[0101] 任选地，在用于本发明的SEDDS中可以包括螯合剂和/或可溶性抗氧化剂。可以添加螯合剂以增强疏水性药物在SEDDS组合物中的稳定性。适合的任选螯合剂包括任何医药学上可接受的螯合剂，诸如柠檬酸、马来酸、琥珀酸、酒石酸、EGTA(乙二醇双(3-氨基乙醚)四乙酸，或依他酸(egtazic acid))以及EDTA(乙二胺四乙酸，或依地酸(edetic acid))。这类螯合剂以各种形式可用，例如，呈钠或钾盐形式或呈游离酸形式。这类螯合剂可以按任何有效的浓度用于本发明的制剂中，包括例如在介于0.01%与10%(w/v)之间的浓度范围内。

[0102] 为了制备SEDDS制剂，例如，吸收促进剂，诸如水杨酸钠、脱氧胆酸钠、肉豆蔻酸钠或十二烷基硫酸钠。

[0103] SEDDS制剂可以含有辅助溶剂，诸如乙醇、丙二醇、聚乙二醇、二乙烯三胺五乙酸、二乙醇胺、三乙醇胺、乙二胺、单乙醇胺或N,N-二甲基乙酰胺。

[0104] SEDDS制剂可以通过将药物溶解于油、表面活性剂以及助溶剂的混合物中来制备。

[0105] 用于本发明的组合物中的生物活性材料可以包含任何已知的生物活性材料。术语“生物活性成分”意图涵盖任何医药或其它活性成分以供施用于人类或动物，特别是温血动物。生物活性材料可以是活性医药成分(API)，其包含天然、半合成或合成分子。在一些实施方案中，生物活性材料包含两种或更多种彼此组合的活性医药成分(API)。其它生物活性成分包括对一般健康状况有影响，或对诸如皮肤、头发、嘴唇以及眼睛的外貌有影响(化妆)的成分。这类成分包括用于清洁、美化、促进吸引力，或改变外貌的任何试剂，例如，保湿霜、油、抗皱剂、香精，等等。还包括用于营养应用的成分(特别是所谓的“营养”成分)。这类成分包括食品补充剂，诸如膳食补充剂、维生素、矿物、纤维、脂肪酸以及氨基酸。这类成分的实例是维生素C、ω-3脂肪酸、胡萝卜素(carotene)以及类黄酮(flavonoid)。关于用于化妆或营养应用的组合物的术语“生物活性”还包括涉及改善身体的外部分、特别是皮肤，以及个体的一般健康状况的活性。

[0106] 在一个实施方案中，活性成分具有低于约1,000(道尔顿)或低于约800的分子量，例如，在约150至约1,000范围内或在约200至约800范围内的分子量。

[0107] 用于本发明的活性成分可以可溶或不溶于水或水性介质，特别是生理水性介质。根据普遍接受的标准，任何溶剂溶解度被定义为溶解1 g化合物所需的溶剂量(g)，借此定义以下溶解度限制条件：10-30 g(“可溶”)；30-100 g(“难溶”)；100-1000 g(“微溶”)；1000-10000 g(“极微溶”或“溶解性差”)；以及大于10000 g(“几乎不溶”)。

[0108] 在一个实施方案中，活性成分可溶或不溶于水或水性介质，特别是生理水性介质。在一个实施方案中，医药活性成分属于所谓的BCS I类至IV类。I类和III类是可溶性药物。生物药剂学分类系统(BCS)将原料药基于其水溶性和肠渗透性而分成四类：I类-高渗透性、高溶解度；II类-高渗透性、低溶解度；III类-低渗透性、高溶解度；IV类-低渗透性、低溶解度。

[0109] 在一个实施方案中，活性成分具有在4至9范围内、在3与8范围内的分配系数(用log P表示)。在另一个实施方案中，活性成分具有使分子在约pH 5-8下呈中性(非离子形式)的pK_A。

[0110] 例示性API包括阿托伐他汀(atorvastatin)、胺碘酮(amiodarone)、坎地沙坦西酯(candesartan-cilexetil)、卡维地洛(carvedilol)、硫酸氢氯吡格雷

(clopidogrel bisulfate)、双嘧达莫(dipyridamole)、甲磺酸依普罗沙坦(eprosartan mesylate)、依普利酮(epierenone)、依泽替米贝(ezetimibe)、非洛地平(felodipine)、呋塞米(furosemide)、伊拉地平(isradipine)、洛伐他汀(lovastatin)、美托拉宗(metolazone)、尼卡地平(nicardipine)、尼索地平(nisoldipine)、奥美沙坦美索酯(olmesartan medoxomil)、盐酸普罗帕酮(propafenone HCl)、喹那普利(qinapril)、雷米普利(ramipril)、辛伐他汀(simvastatin)、替米沙坦(telmisartan)、群多普利(trandolapril)、缬沙坦(valsartan),以及其它心血管活性药物;阿昔洛韦(acyclovir)、阿德福韦(adefovir)、双吡呋酯(dipivoxil)、两性霉素(amphotericin)、安普那韦(Amprenavir)、头孢克肟(cefixime)、头孢他啶(ceftazidime)、克拉霉素(clarithromycin)、克霉唑(clotrimazole)、依法韦仑(efavirenz)、更昔洛韦(ganciclovir)、伊曲康唑(itraconazole)、诺氟沙星(norfloxacin)、制霉菌素(nystatin)、利托那韦(ritonavir)、沙奎那韦(saquinavir),以及其它抗感染药物,包括抗细菌、抗病毒、抗真菌以及抗寄生虫药物;顺铂(cisplatin)、卡铂(carboplatin)、多烯紫杉醇(docetaxel)、依托泊苷(etoposide)、依西美坦(exemestane)、伊达比星(idarubicin)、伊立替康(irinotecan)、美法仑(melphalan)、巯基嘌呤(mercaptopurine)、米托坦(mitotane)、太平洋紫杉醇(paclitaxel)、戊柔比星(valrubicin)、长春新碱(vincristine),以及肿瘤学中所用的其它药物;硫唑嘌呤(azathioprine)、他克莫司(tacrolimus)、环孢菌素(cyclosporin)、吡美莫司(pimecrolimus)、西罗莫司(sirolimus),以及其它免疫抑制药物;氯氮平(clozapine)、恩他卡朋(entacapone)、氟奋乃静(fluphenazine)、丙咪嗪(imipramine)、萘法唑酮(nefazodone)、奥氮平(olanzapine)、帕罗西汀(paroxetine)、匹莫齐特(pimozide)、舍曲林(sertraline)、三唑仑(triazolam)、扎来普隆(zaleplon)、齐拉西酮(ziprasidone)、利培酮(risperidone)、卡马西平(carbamazepine),以及用于CNS适应症的其它药物;达那唑(danazol)、度他雄胺(dutasteride)、甲羟孕酮(medroxyprogesterone)、雌二醇(estradiol)、雷洛昔芬(raloxifene)、西地那非(sildenafil)、他达拉非(tadalafil)、睾酮(testosterone)、伐地那非(vardenafil),以及用于生殖健康的其它药物;塞来昔布(celecoxib)、甲磺酸双氢麦角胺(dihydroergotamine mesylate)、依来曲普坦(eletriptan)、甲磺酸双氢麦角碱(ergololdmesylate)、酒石酸麦角胺(ergotamine tartrate)、萘丁美酮(nabumetone)、布洛芬(Ibuprofen)、酮洛芬(ketoprofen)、曲安奈德(triamcinolone)、醋酸曲安奈德(triamcinolone acetonide),以及其它消炎和止痛药;波生坦(bosentan)、布地奈德(budesonide)、地洛他定(desloratadine)、非索非那定(fexofenadin)、氟替卡松(Fluticasone)、氯雷他定(loratadine)、莫米松(mometasone)、沙美特罗(salmeterol)、昔萘酸(xinafoate)、醋酸曲安奈德(triamcinolon acetonide)、扎鲁司特(zafirlukast),以及用于呼吸适应症的其它药物;以及屈大麻酚(dronabinol)、法莫替丁(famotidine)、格列本脲(glyburide)、莨菪碱(hyoscyamine)、异维甲酸(isotretinoin)、甲地孕酮(megestrol)、美沙拉嗪(mesalamine)、莫达非尼(modafinil)、莫沙必利(mosapride)、尼莫地平(nimodipine)、奋乃静(perphenazine)、异丙酚(propofol)、硫糖铝(sucralfate)、沙利度胺(thalidomide)、盐酸替扎尼定(trizanidine hydrochloride),以及用于各种适应症的其它药物,特别包括胃肠病症、糖尿病以及

皮肤病适应症。在其它实施方案中，API 包括依泽替米贝(ezetimimbe)、格鲁康德(glucoroniude)、他达拉非、非诺贝特(fenofibrate)、达那唑、伊曲康唑、卡马西平、灰黄霉素(griseofulvin)、硝苯地平(nifedipin)。

[0111] 活性成分进一步包括糖、多糖、维生素、氨基酸、肽、前列腺素、核酸、核苷酸、核苷以及其衍生物。还包括肽、蛋白质、蛋白质片段、抗体、小抗体片段，等等。后者包括 Fv″片段、单链 Fv （scFv)抗体、抗体 Fab 片段、抗体 Fab’片段、重链或轻链 CDR 的抗体片段，或纳米抗体。还涵盖小寡核酸或肽分子，诸如适体，例如 DNA 适体、RNA 适体或肽适体。

[0112] 在一个实施方案中，液体材料中的生物活性成分当装填于无机氧化物材料中时，与按原样的活性成分或含有活性成分和不影响释放的成分的制剂相比显示增加的释放。增加的释放可以为例如增加在生理条件(pH、温度)下释放的活性成分的重量百分比的 10%、或 20%、或 30%、或 50%。

[0113] 在另一个实施方案中，液体材料中的生物活性成分当装填于无机氧化物材料中时，显示从本发明的组合物中立即释放，术语“立即释放”意指例如在诸如 60 分钟或更短时间内、诸如 30 分钟或更短时间内、或在 20 分钟或更短时间内、或 15 分钟或更短时间内，在生理条件(pH、温度）下释放至少 60% 的药物。

[0114] 在制造本发明的组合物的方法中，将生物活性材料并入无机氧化物材料中的步骤通常包括多种装填方法，包括溶剂法和初湿含浸法，这些方法已经描述于现有技术中，或在不使用任何溶剂或其它混合助剂的情况下单一混合。

[0115] 在(浆液）溶剂法中，无机氧化物材料通过用液体材料中的活性成分的溶液处理而装填有活性成分，之后去除溶剂。液体材料中的活性成分从而变得被吸附至无机氧化物材料的表面，包括在无机氧化物材料的孔内的表面。用于这种方法的适当有机溶剂包括二氯甲烷、1,4- 二噁烷、四氢呋喃、2- 丙醇、二乙醚、乙酸乙酯、乙腈、二甲基甲酰胺、N- 甲基 - 吡咯烷酮、己烷。举例来说，每毫升含有约 50 mg 活性成分的溶液可以用于将活性成分装填于无机氧化物材料中。

[0116] 在初湿含浸法，也被称作毛细浸渍或干式浸渍中，用液体材料中或于浓缩溶液中的活性成分湿润无机氧化物材料并且通过毛细作用吸引至孔中。本发明的多孔无机氧化物材料特别适于这种方法，因为其显示强的毛细作用。在许多情况下，不需要使用溶剂或使用极少溶剂，从而避免在装填步骤之后去除溶剂。这提供了优于已知的液固制剂的额外优点，液固制剂需要帮助吸附所需的额外成分，特别是溶剂，这涉及预混合于液体材料(脂质或 SEDDS）中的载体或药物与溶剂以改善吸附的方法。严格地审查供人类或动物使用的药品和其它产品中溶剂的存在，而许多溶剂被禁用。溶剂还具有环境影响，因为其被认为是重要的污染来源。

[0117] 在另一个实施方案中，可以通过喷射、或液体吸附至多孔材料上的任何其它已知方法将液体材料装填至无机氧化物材料上。

[0118] 在存在或不存在溶剂的情况下液体材料中的生物活性成分可以具有所选的粘度以使得其可以被无机氧化物材料充分地吸收，特别是在吸附速度、足量装填等方面。其可以例如具有低于约 250 mPa.s、或低于约 100 mPa.s、或低于约 10 mPa.s、或低于约 5 mPa.s、或低于约 1 mPa.s 的粘度。粘度的下限可以为约 0.1 mPa.s 或约 0.5 mPa.s。

[0119] 本发明的无机氧化物材料是呈液体形式的生物活性成分的极有效的吸附剂。与在

与液体材料接触之后的极短时间内发生吸附的已知多孔材料相反，本发明的无机氧化物材料在较长时段内、特别是在几小时内，例如长达约 2、3 或 4 小时内吸附呈液体形式的生物活性成分。据信，在静置后体积的减小与毛细力有关，毛细力继续将颗粒之间的游离液体吸引至颗粒的孔中。这归因于本发明的无机氧化物材料的高装填能力。

[0120] 无机氧化物材料中活性成分的含量相对于已装填的二氧化硅材料的总重量可以在约 1% 至约 50%、或约 10% 至约 30%、或约 15% 至约 25% 的范围内，例如约 20%（本文中的所有百分比都是重量 / 重量）。

[0121] 本发明的组合物可以在一个或多个额外步骤中配制成最终剂型，最终剂型可以取决于其施用于患者的方式而变化。优选的是用于口服施用的固体或半固体剂型，特别是药丸、片剂以及胶囊。这类剂型可以适合于提供所述生物活性物质的立即或快速体内释放，或可以适合于控制释放。这可以包括一种或多种医药学上可接受的赋形剂。

[0122] 与用于制备根据本发明的含有生物活性材料和无机氧化物材料的组合物的生产方法无关，无论这种方法是基于溶剂的或无溶剂的，当最终剂型包含一种或多种医药学上可接受的赋形剂时，其可以在工艺期间的任何时间引入，包括设计用于将生物活性材料装填至无机氧化物材料的孔中的步骤，或之后在独立的步骤中。

[0123] 医药组合物还可以含有任选的赋形剂。这些可以包含本领域中通常所采用的任何成分，诸如稀释剂、粘合剂、成粒剂、助流剂（流动助剂）、润滑剂、崩解剂、甜味剂、香料以及颜料以使片剂视觉上有吸引力。这类赋形剂的实例包括羟丙基甲基纤维素、交联聚维酮（crospovidone）、硬脂酸镁、乳糖以及滑石。

[0124] 本发明的医药组合物可以进一步包含一种或多种医药学上可接受的填充剂，其选自例如水状胶体（诸如黄原胶）、粘合剂、助流剂、润滑剂、表面活性剂以及稀释剂。

[0125] 这些包括例如粘合剂，诸如淀粉、明胶、葡萄糖、海藻酸、海藻酸钠和海藻酸钙、水溶性丙烯酸类聚合物（共聚物）、聚乙烯吡咯烷酮、聚氨基酸、乙烯 - 乙酸乙烯酯共聚物等；天然和合成矿物填充剂或助流剂，诸如二氧化硅；硅酸镁，诸如滑石；硅藻土；硅酸铝，诸如高岭石、蒙脱石或云母；硅酸镁铝，诸如绿坡缕石和蛭石；碳，诸如木炭；硫以及高度分散的硅酸聚合物；水溶性稀释剂，诸如乳糖、山梨糖醇等。

[0126] 本发明的组合物还可以配制成适合于局部施加的形式，诸如软膏、乳膏、凝胶、擦剂或香膏，等等。

[0127] 本发明进一步涉及使用本文所公开的组合物中的任一种的方法。在一些实施方案中，本发明的组合物，特别是医药组合物可以用作药剂，特别可以用作经由口服途径的药剂。

[0128] 本发明涉及一种将组合物施用于患者以递送至少一种生物活性材料至患者的方法，其中这种组合物包含含有呈液体形式的生物活性成分的多孔无机氧化物材料的至少一种医药剂量配制成分，其中无机氧化物材料具有如本文所指定的油吸附值、颗粒内孔体积以及 BET 表面积。这种方法中的组合物优选地通过各种方式施用，包括通过口服、经颊、舌下、牙周、经阴道、子宫内、经直肠、经肺、经鼻、吸入、眼内、经眼、经耳以及局部方式。

[0129] 生物活性材料从本发明的组合物中的释放改善的一个原因是归因于液体材料从无机氧化物材料的解吸附有所改善。在具有某些特征的无机氧化物材料（即，颗粒内孔度）内孔的存在允许吸附并且然后释放大量的生物活性成分。举例来说，本发明的无机氧化物

材料的孔大小分布是窄的(即,小的相对跨度),其允许许多孔容易地吸附和脱附液体材料。这与生物活性成分被吸附至载体材料的团块或颗粒之间的间隙孔中或从间隙孔释放的已知多孔材料相反,这些团块或颗粒的大小和形状更加随机并且提供更少的空间用于装填分子。这不仅导致更小的载荷能力,而且导致更不规则的释放曲线。影响释放的其它因素是呈液体形式的活性成分的粘度和等电点(logP)。

[0130] 根据本发明的组合物提供有吸引力的药物递送特性。其提供多种生物活性材料(例如 API)的所需解吸附和 / 或溶解速率曲线。在一些实施方案中,生物活性材料在与溶解介质接触的初始时间的约 15 分钟内展现约 20 或更大的释放解吸附和 / 或溶解速率百分比。在一些实施方案中,生物活性材料在与溶解介质接触的初始时间的约 15 分钟内展现约 25 或更大(或约 30 或更大 ;或约 35 或更大)的释放溶解速率百分比。

[0131] 此外,在一些实施方案中,生物活性材料在与溶解介质接触的初始时间之后约 30 分钟展现约 20 或更大的释放溶解速率百分比。在一些实施方案中,生物活性材料在与溶解介质接触的初始时间之后约 30 分钟展现约 30 或更大的释放溶解速率百分比。

[0132] 在一些实施方案中,生物活性材料在与溶解介质接触的初始时间之后约 60 分钟展现约 10 或更大的释放溶解速率百分比。在一些实施方案中,生物活性材料在与溶解介质接触的初始时间之后约 60 分钟展现约 15 或更大(或约 20 或更大)的释放溶解速率百分比。

[0133] 本发明的组合物在许多情况下显示活性成分的立即释放,但可以例如通过用适合的聚合物包覆组合物而转变成控制释放组合物。当混合组合物与所选的聚合物包衣时,可以获得混合释放模式,诸如立即释放和持续释放的组合。

[0134] 无机氧化物材料可以包含两种或更多种不同和独特类型的多孔颗粒,其中每种独特类型的多孔颗粒提供单一生物活性材料(或两种或更多种不同生物活性材料)的特定解吸附和 / 或溶解速率曲线以形成复合解吸附和 / 或溶解速率曲线。

[0135] 本发明的另一个方面涉及无机氧化物材料的颗粒,其中无机氧化物材料具有如本文所指定的油吸附值、颗粒内孔体积以及 BET 表面积。

[0136] 本发明的组合物不仅显示呈液体形式的药物的高装填能力,此外其与现有液固系统相比显示更高的堆积密度。其它有利的特性包括本发明的无机氧化物材料的极佳吸附能力和活性成分的增加的稳定性。这些优点特别由呈颗粒形式的本发明的组合物提供。

[0137] 本发明的组合物还可以用于皮肤病学和化妆应用中,这是由于其良好的皮肤相容性并且没有不合意的皮肤感觉。

[0138] 以下实施例意图说明本发明并且不应被解释为限制其范围。

[0139] 实施例 1

将具有 24.5% w/v 的 Na 含量和 45% w/v 的硫酸的钠水玻璃以 0.85 至 0.99 的摩尔比混合。在完成缩聚之后,将原硅胶压碎成几厘米大小的块。然后,通过用清水洗涤硅胶 / 硫酸钠混合物来去除副产物硫酸钠。通过奥斯瓦尔德熟化(Oswald ripening)使二氧化硅在 70-80℃下并且在 8 与 9 之间的 pH 下在水浴中进行老化 3-11 小时。在液 / 固分离之后,将所形成的二氧化硅水凝胶压碎缩减至约 300 μm的粒度。后续干燥步骤控制孔体积的形成。为了达到约 1.7 cm^3/g 的孔体积,需要在 180℃的工艺空气温度下小于 4 秒的快速干燥并且在实验室急骤干燥器 LABSPINFLASH 型(APV/Denmark)中进行。具有 < 1 cm^3/g 的孔体积的二氧化硅通过在 100℃下在实验室干燥室中缓慢干燥(填充床干燥)4 小时而制成。

[0140] 表 1中所示的以下二氧化硅颗粒用于后续实施例中。

表 1

标识	S1	S2
Malvern		
D10（μm）	75	23-41
D50（μm）	102-120	48-65
D90（μm）	174	76-96
孔大小（nm）解吸附（BJH）	25	25
PV（ml/g）	1.6-1.95	1.6-1.95
相对跨度	0.71	0.71
BET SA（m^2/g）	280-355	280-355
APD（计算值）（Å）	250	250

[0141] D10、D50 以及 D90 值指示颗粒直径分布的加权的第 10、第 50 以及第 90 百分位数。这些值从可获自 Malvern Instruments Ltd 的 Malvern™ Mastersizer 2000 仪器获得。PV :孔体积 ;SA :表面积 ;APD :平均孔直径 ;BET SA :表面积 ;并且相对跨度是使用BJH氮吸附法,在 0.995 的压力下,使用可获自 Micromeretics Instrument Corporation 的 ASAP 2420HV 加速表面积和孔隙度测定系统来测定。

[0142] 实施例 2

程序 :将 2 至 5 g (基于堆积密度)的固体载体材料放置于 100 ml 烧杯中,并且从滴管逐滴添加油或表面活性剂,同时根据 ASTM D281 用刮刀混合。继续添加油或表面活性剂直至形成稠的膏状块体。当块体看似含有过量油时,停止添加油或表面活性剂。当块体不含过量油或表面活性剂时,记录滴管读数。使用以下等式计算吸附能力 :

$$\text{油吸附值 (g/100 g)} = \frac{\text{所添加的油体积 (ml)} \cdot \text{油的SG} \cdot 100}{\text{样品重量 (g)}}$$

下表列出了油和其在样品 S1 材料上的吸附能力以及油的比重。

[0143] 表 2

编号	油名称	比重(g/mL)	吸附能力(g/100g)
1	生亚麻籽油	0.930	294
2	桉叶油	0.915	328
3	柠檬草油	0.895	287
4	薄荷油	0.890	307
5	蓖麻油	0.960	316
6	芝麻油	0.923	298
7	橄榄油	0.920	305
8	丁香油	1.045	390

9	油酸	0.895	300
10	dl-α-生育酚	0.950	292
11	Captex 355	0.940	315
12	Labrafac PG	0.919	304
13	米格列醇 812	0.940	319
14	Capmul MCM	0.995	303

下表列出了表面活性剂和其在样品 S1 材料上的吸附能力以及表面活性剂的比重。

[0144] 表 3

编号	表面活性剂名称	比重(g/mL)	油吸附值 S1 (g/100 g)
1	Transcutol HP	0.987	295
2	Solutol HS 15	1.04	310
3	Cremophor EL	1.05	317
4	Labrasol	1.064	326
5	Labrafil M-1944CS	0.943	292
6	Capryol 90	0.942	300

与之相比较,测试其它载体的油吸附值并且获得以下结果。

表 4

g 油/100 g 载体	油酸	亚麻籽油	生育酚	Cremophor EL	Labrasol
Fujicalin	113	127	103	140	138
MCC PH 101	120	102	98	123	131
Galen IQ 721 (糖基载体)	63	69	57	67	69
滑石	62	57	54	70	67

[0145] 实施例 3

遵循实施例 2 的程序,使 Cremophor 和 Labrafil 装填的材料静置 3 小时并且然后测试自由流动特性。结果示于表 5 和表 6 中。

表 5

流动参数（Cremophor 装填，1.5:1）	S1（250 Å，110 μm）	S2（250 Å，50 μm）
所添加的油（mL）	7.14	7.14
载体材料（g）	5	5
堆积密度	0.632	0.631
振实密度	0.702	0.742
C.I（USP 等级）	10	15
	（极佳）	（良好）
H.R（USP 等级）	1.11	1.17
	（极佳）	（良好）

表 6

流动参数（Labrafil 装填，1.5:1）	S1	S2
所添加的油（mL）	7.95	7.95
载体材料（g）	5	5
堆积密度	0.615	0.616
振实密度	0.724	0.724
C.I（USP 等级）	15	15
	（良好）	（良好）
H.R（USP 等级）	1.17	1.17
	（良好）	（良好）

[0146] 堆积密度通过 USP 616 方法 1 使用 250 ml 刻度量筒（USP30-NF25）来测量。振实密度通过 USP 616 方法 2（每分钟振实 250 下）使用 250 ml 刻度量筒来测量，其中 ETD-1020 振实密度测试仪可获自 Electrolab。USP 等级是粉末流动的观测量度并且根据下表 7 来评级。

[0147] 表 7

可压缩性指数（%）	流动特征	豪斯纳比
<10	极佳	1.00-1.11
11-15	良好	1.12-1.18
16-20	一般	1.19-1.25
21-25	尚可	1.26-1.34
26-31	差	1.35-1.45
32-37	很差	1.46-1.59
>38	极差	>1.60

实施例 4

遵循实施例 2 的程序，用 16.25 ml 芝麻油装填 10 克样品 S1，其得到无机氧化物材料与油的 1:1.5 比率。混合物的体积经过 10 小时的时段从 65 ml 减小至 50 ml，如图 1中所示减小超过 23%。

[0148] 实施例 5

使用胶囊填充托盘，诸如可获自 Empty Caps Company 的 Cap-M-Quick，手动地将实施例 3 的 Cremophor 和 Labrafil 装填的材料装填至零号胶囊中。如从图 2可见，在材料静置前后的填充量之间存在显著差异。装填至胶囊中的材料量陈述于表 8 和表 9 中。

[0149] 表 8

流动参数(Cremophor装填,1.5:1)	S1（250 Å,110 μm）	S2（250 Å,50 μm）
所添加的油(mL)	7.14	7.14
载体材料(g)	5	5
静置后的填充量(mg)	451	429
静置前的填充量(mg)	357	357

表 9

流动参数(Labrafil 装填,1.5:1)	S1	S2
所添加的油(mL)	7.95	7.95
载体材料(g)	5	5
静置后的填充量(mg)	421	421
静置前的填充量(mg)	366	366

实施例 6

遵循实施例 2 的程序，获得醋氨酚和抗坏血酸装填的材料并且分别标记为载体 S1 和 S2。药物从载体 S1 和 S2 中的释放如下测定：

按照用于醋氨酚片剂的 USP 30 对醋氨酚装填的载体(S1)进行溶解研究，持续 30 分钟。溶解测试条件由以下组成：使用在 50 RPM 的速度下操作的 USP 溶解装置 2 (桨叶)，持续 30 分钟。溶解介质是在 37 ± 0.5℃下的 900 ml pH 5.8 磷酸盐缓冲液。对于每种载体，将 100 mg 称重量的药物装填的载体用于溶解研究。以 10、20、30 分钟时间间隔抽出等分试样(5 ml)，过滤并且用溶解流体稀释。在 λmax 243 nm 下以光谱测定法来测定等分试样的吸光度。释放曲线示于图 3中。药物从载体 S1 与 S2 两者中的释放都符合 USP 准则(在 30 分钟内 NLT 80%)。

[0150] 按照用于抗坏血酸片剂的 USP 30 对抗坏血酸装填的载体(S1)进行溶解研究，持续 45 分钟。溶解测试条件由以下组成：使用在 50 RPM 的速度下操作的 USP 溶解装置 2(桨叶)，持续 45 分钟。溶解介质是在 37 ± 0.5℃下的 900 ml 水。对于每种载体，将 100 mg 称重量的药物装填的载体用于溶解研究。以 10、20、30 分钟时间间隔抽出等分试样(5 ml)，过滤并且用水稀释。在 λmax 266 nm 下以光谱测定法来测定等分试样的吸光度。释放曲线示于图 4中。药物从载体 S1 与 S2 两者中的释放都符合 USP 准则(在 45 分钟内 NLT 75%)。

[0151] 实施例 7

油释放或解吸附：以下试验中所用的载体材料是实施例 1 中所制备的指定为 S1 的材料。将依照实施例 2 的方法所制备的 2 克油装填的载体(1:1，w/w)在烧杯中与 6 ml 水混合，在 1 小时内涡旋，并且在可获自 Thermo Electron Corporation 的 Heraeus Multifuge 1S-R 离心机中以 5000 RPM 离心 10 分钟。将上清液，即，油 + 水，转移至培养皿中并且在热空气烘箱中干燥直至恒重。

[0152] 基于试验中所获得的释放 w/w % 的结果如下。对于芝麻油，81% 的油从载体材料或无机氧化物中释放，并且对于米格列醇 812，81.3% 的油从载体材料或无机氧化物中释放。

[0153] 实施例 8

固体 SEDDS 系统装填和释放（或解吸附）：以下试验中所用的载体材料是实施例 1 中指定为 S1 和 S2 的材料。所制成的液体 SEDDS 系统含有 0.6 g 格列本脲作为 API 组分、15 g Capryol®90 作为油 / 媒介物组分、54.4 g Trascutol® HP 作为助表面活性剂，以及 30 g Tween® 20 作为表面活性剂。通过以 1:1 的比率精确地称重所需量的载体和液体 SEDDS 将这种液体 SEDDS 系统装填至 S1 和 S2 上。在 60℃下预热载体和液体 SEDDS 持续 15 分钟，随后混合。在用金属刮刀搅拌下将液体 SEDDS 缓慢地添加至载体中。将所制备的混合物搁置约 24 小时以得到自由流动粉末。

[0154] 按照 USP<711> 对液体 SEDDS 装填的载体（S1）和（S2）以及非微米化的格列本脲进行溶解研究，持续 120 分钟。溶解测试条件由以下组成：使用在 75 RPM 的速度下操作的 USP 溶解装置 2（桨叶）。溶解介质是在 37 ± 1℃下的 500 ml pH 9.5 硼酸盐缓冲液（0.05 M）。对于每种载体，将具有以重量当量计 5 mg 格布瑞德的称重量的已装填的载体或 API（非微米化的格列本脲）用于溶解研究。在 20、30、45、60 以及 120 分钟抽出 5 ml 等分试样，经由 0.45 μ 针筒过滤器过滤并且用溶解流体稀释。使用 HPLC（Waters Acquity H-class），使用 Grace Vision HT 高载荷 C18 柱、Rocket Format（53 × 7 mm，3 μm）作为固定相以及乙腈：水中的正磷酸 0.4%（50:50）作为流动相、1.5 mL/min 的流动速率、50 μl 的注射体积来分析样品。在 λmax 226 nm 下检测样品。释放曲线示于图 5 中。药物从载体 S1 与 S2 两者中的释放都符合 USP 准则（在 45 分钟内 NLT 70% 药物释放，以及 NMT 3% 相对 SD）。

[0155] 为了定义片剂中预装填的载体的最大量，同时维持最佳压片特性，进行如实施例 9 和 10 中所示的以下实验：

实施例 9

以下试验中所用的载体材料是实施例 1 中指定为 S2 的材料。Cremophor® EL 是装填至二氧化硅上的液体脂质。依照实施例 8 的方法装填二氧化硅 S2 并且用作片剂制剂中的油装填的载体组分。为了递送呈片剂剂型的油，使用两种不同工艺制成片剂：直接压缩（DC）和湿式制粒（WG）。

[0156] 通过精确地称重用于掺合物制备的赋形剂量来获得直接压缩片剂。经由 40 号筛网筛分稀释剂（MCC）和油装填的载体并且充分混合约 5 分钟。经由 40 号筛网筛分粘合剂和崩解剂并且添加至掺合物中，然后充分混合约 5 分钟。使助流剂通过 40 号筛网并且添加至掺合物中，并且充分混合 5 分钟。经由 60 号筛网筛分润滑剂并且添加至掺合物中，并且充分混合约 2 分钟。这种最终掺合物用于片剂压缩。

[0157] 通过精确地称重用于掺合物制备的赋形剂量来获得湿式制粒片剂。经由 40 号筛网筛分稀释剂（MCC）和油装填的载体并且充分混合约 5 分钟。经由 40 号筛网筛分崩解剂并且添加至掺合物中，然后充分混合约 5 分钟。制备粘合剂（淀粉 / 预胶凝淀粉）的水溶液（5%）。然后通过混合所制备的稀释剂 / 油装填的载体 / 崩解剂掺合物与粘合剂溶液来制备颗粒。在 50℃下干燥颗粒以达到 5-7% 的 LOD。使干燥的颗粒通过 20 号筛网。使助流剂通过 40 号筛网并且添加至掺合物中，并且充分混合 5 分钟。经由 60 号筛网筛分润滑剂（何种材料）并且添加至干燥的颗粒中，并且充分混合约 2 分钟。这种最终掺合物用于片剂压缩。

[0158] 使用在 5 rpm 的速度、20 kN 的压缩力、<70 N 的顶出力下并且使用 12 mm 圆形双凹面、D- 加工冲头操作的 Parle Elizabeth tools Pvt Ltd 的 Eliza 压机 200 多工具单一旋转式压片机来制备片剂。压片的制剂列于下表 10 中。

[0159] 表 10

制剂标识符	DCA	DCB	DCC	DCD	DCE	WGA	WGB
压片方法(DC= 直接压缩 ;WG= 湿式制粒)	DC	DC	DC	DC	DC	WG	WG
油装填的载体 S2 (wt%)	20	20	30	30	40	40	50
MCC PH102 (wt%)	70.5	70.5	60.5	60.5	45.5	50.5	40.5
PVPK30 (wt%)	5	5	5	5	0	0	0
预胶凝淀粉(wt%)	0	0	0	0	10	5	5
AcDiSol (wt%)	3	3	3	3	3	3	3
Syloid 244FP (wt%)	1	1	1	1	1	1	1
Mg St (wt%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
压缩力(kN)	15	20	15	20	20	20	20
重量(mg)	500	500	5 00	500	500	500	500

用 EH01 片剂硬度测试仪(Electrolab, India)测量所有制剂的片剂硬度。所测试的制剂的硬度列于下表 Y。

[0160] 表 11

制剂标识符	DCA	DCB	DCC	DCD	DCE	WGA	WGB
硬度(N)	83-93	83-97	68-76	84-91	60-70	80	30

在所有情况下,片剂对于重量变化(NMT 5%)、脆度(<1%)以及崩解时间(<15 分钟)而言符合 USP 规格。

[0161] 实施例 10

高浓度的液体脂质装填至载体上并且压缩成片剂 :以下试验中所用的载体材料是实施例 1 中指定为 S2 的材料。生育酚是装填至二氧化硅上的液体脂质。依照实施例 8 的方法用液体脂质装填二氧化硅 S2 并且用作片剂制剂中的油装填的载体组分。使 PVP30 分散于乙醇(100 mL)中并且添加于油装填的载体上。将所制备的掺合物充分混合并且使其在 50℃下干燥。依照实施例 9 中的方法添加额外赋形剂以获得具有以下组成的直接压缩掺合物 :70% 生育酚装填的二氧化硅 S2 (1:1 装填)、12.5% MCCPH102、14% PVP30、2% AcDiSol、1% SYLOID® 244FP、0.5% 硬脂酸镁。使用在 5 rpm 的速度、20 kN 的压缩力、<70 N 的顶出力下并且使用 12 mm 圆形双凹面、D- 加工冲头操作的 Parle Elizabeth tools Pvt Ltd 的 Eliza 压机 200 多工具单一旋转式压片机来制备片剂。

[0162] 用 EH 01 片剂硬度测试仪(Electrolab, India)在 500 ± 5 mg 的片剂重量下测量所有制剂的片剂硬度。这些片剂的片剂硬度结果是 40 N,脆度是 0% 并且崩解时间 <1 分钟。

[0163] 实施例 11

油从片剂中的释放(生育酚):以下试验中所用的载体材料是实施例 1 中指定为 S2 的材料。生育酚是装填至二氧化硅上的液体脂质。依照实施例 8 的方法用液体脂质装填二氧化硅 S2 并且用作片剂中的油装填的载体组分。依照实施例 10 中的方法制备片剂。片剂中的生育酚浓度为 100 mg。

[0164] 依照实施例 8 中所描述的方法对所制备的片剂进行溶解研究。以预定时间间隔抽出 2 mL 等分试样并且经由 0.22 μ 膜滤器过滤。通过使用 HPLC (Waters UPLC 波长 :294 nm ;柱 :Rocket Format (53 × 7 mm,3 μ);流动相 :85% ACN:10% MeOH:5% H_2O) 分析溶解

样品。

[0165] 在 45 分钟时生育酚释放≈ 100%。

[0166] 虽然本发明已经采用有限数量的实施方案来描述，但这些特定实施方案并不意图限制如本文中以其它方式描述和主张的本发明的范围。本领域的一般技术人员在查阅本文中的例示性实施方案后可以显而易见的是，其它修改、等效物以及变更是可能的。除非另有规定，否则实施例中以及说明书的其余部分中的所有份数和百分比都以重量计。此外，说明书或权利要求书中所叙述的任何数值范围，诸如代表特性、测量单位、条件、物理状态或百分比的特定集合的数值范围，意图通过引用或以其它方式在本文中明确地按字面意义并入处于这类范围内的任何数值，包括在如此叙述的任何范围内的数值的任何子集。举例来说，每当公开具有下限 R_L 和上限 R_U 的数值范围时，特定地公开处于这个范围内的任何数值 R。具体地说，特定地公开在这个范围内的以下数值 R：$R = R_L + k(R_U - R_L)$，其中 k 为以 1% 增量在 1% 至 100% 范围内的变量，例如，k 为 1%、2%、3%、4%、5%...50%、51%、52%...95%、96%、97%、98%、99% 或 100%。此外，还特定地公开由如上文所计算的任何两个 R 值代表的任何数值范围。除了本文示出和描述的那些之外，本发明的任何修改将为本领域的技术人员从前述描述和附图变得显而易见。这类修改意图处于所附权利要求书的范围内。本文所引用的所有出版物以全文引用的方式并入。

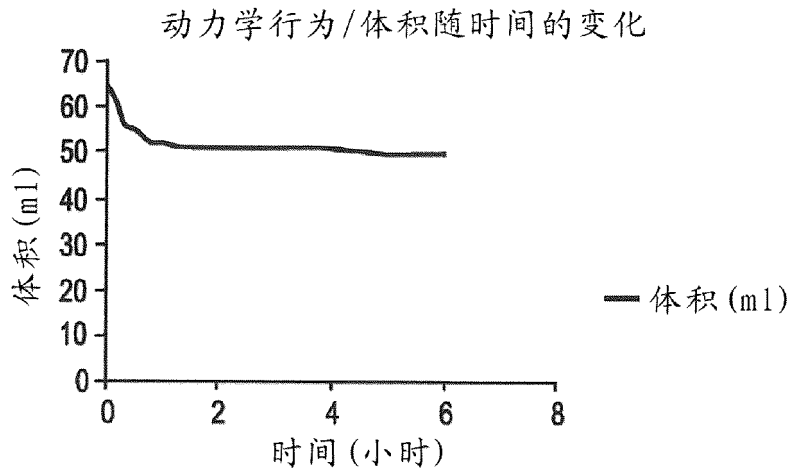

动力学行为/体积随时间的变化
体积(ml)
70
60
50
40
30
20
10
0
0
2
4
6
8
时间(小时)
体积(ml)

图 1

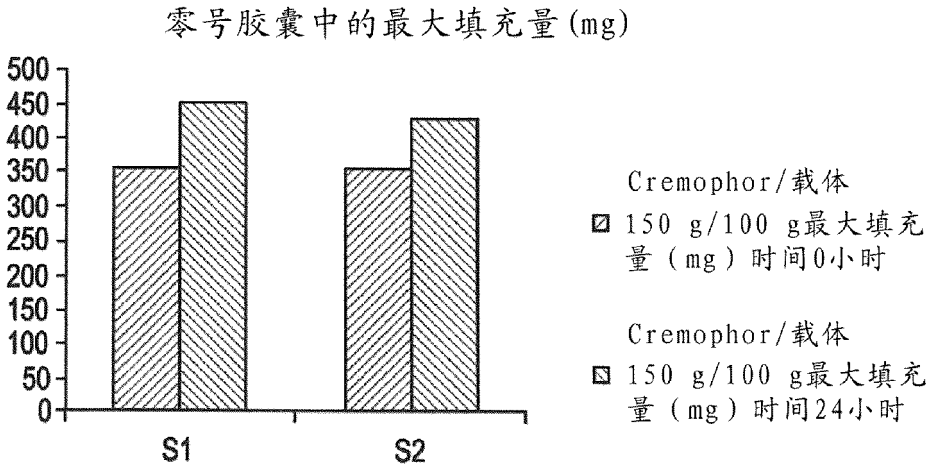

零号胶囊中的最大填充量(mg)
500
450
400
350
300
250
200
150
100
50
0
S1
S2
Cremophor/载体
150 g/100 g最大填充量（mg）时间0小时
Cremophor/载体
150 g/100 g最大填充量（mg）时间24小时

图 2

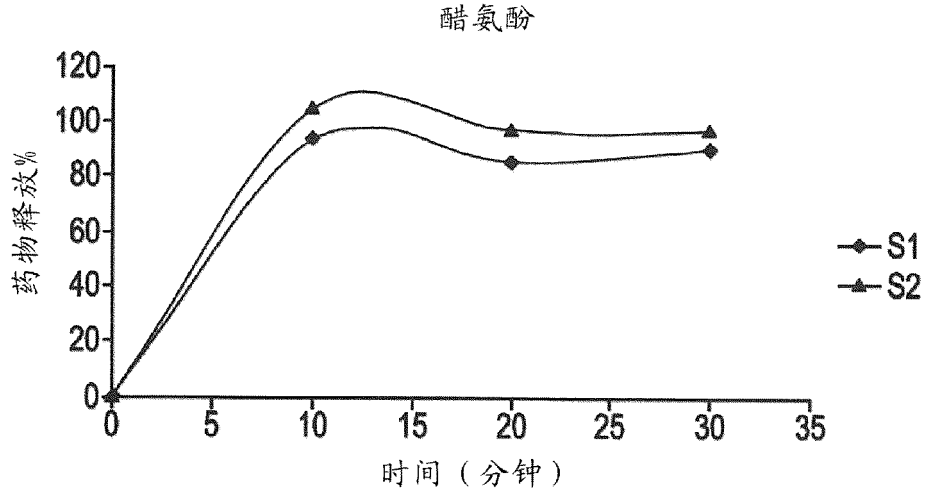

醋氨酚
药物释放%
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
时间（分钟）
S1
S2

图 3

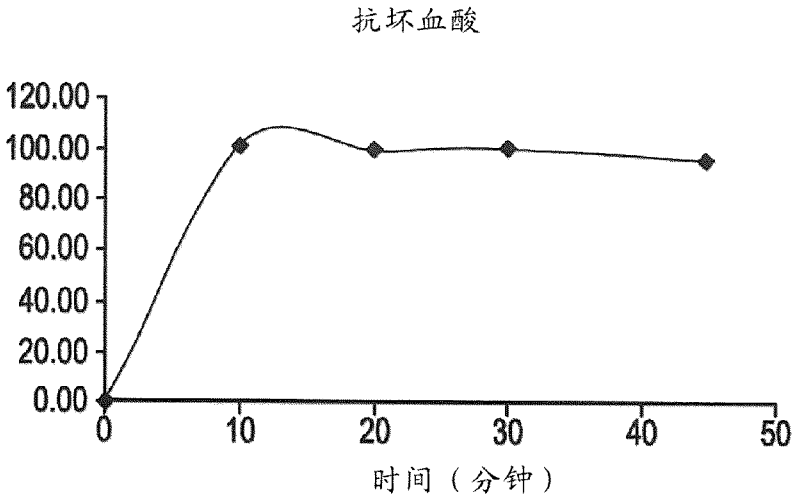

抗坏血酸
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
10
20
30
40
50
时间（分钟）

图 4

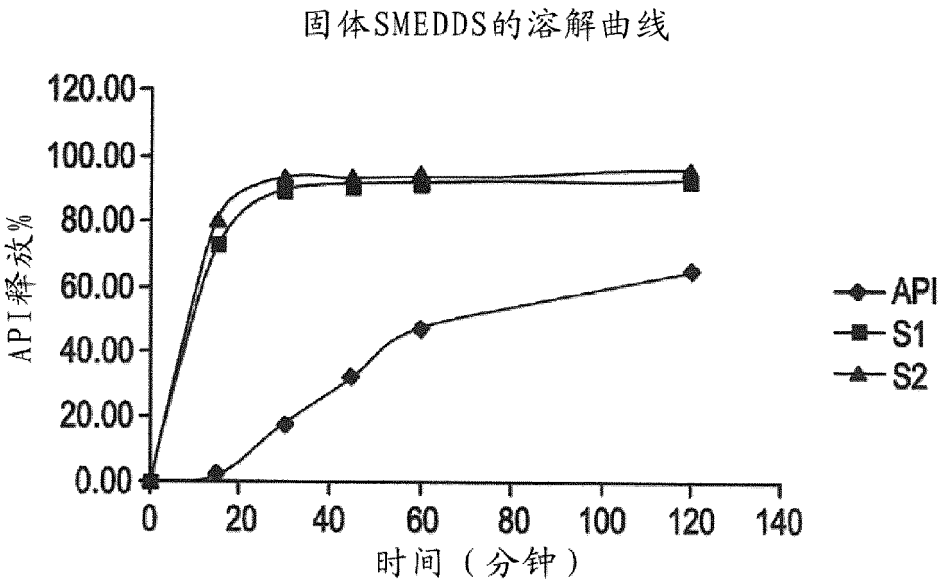

固体SMEDDS的溶解曲线
API释放%
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
20
40
60
80
100
120
140
时间（分钟）
API
S1
S2

图 5