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(71) Applicant *(for all designated States except US)*: **LATITUDE PHARMACEUTICALS INCORPORATED** [US/US]; 6364 Ferris Square, San Diego, California 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHEN, Hailiang** [CN/US]; 12638 Carmel Country Road, Unit 136, San Diego, California 92130 (US). **CHEN, Andrew Xian** [US/US]; 4646 Bryson Terrace, San Diego, California 92130 (US).

(74) Agents: **WILSON SONSINI GOODRICH & ROSATI** et al.; 650 Page Mill Road, Palo Alto, California 94304 (US).

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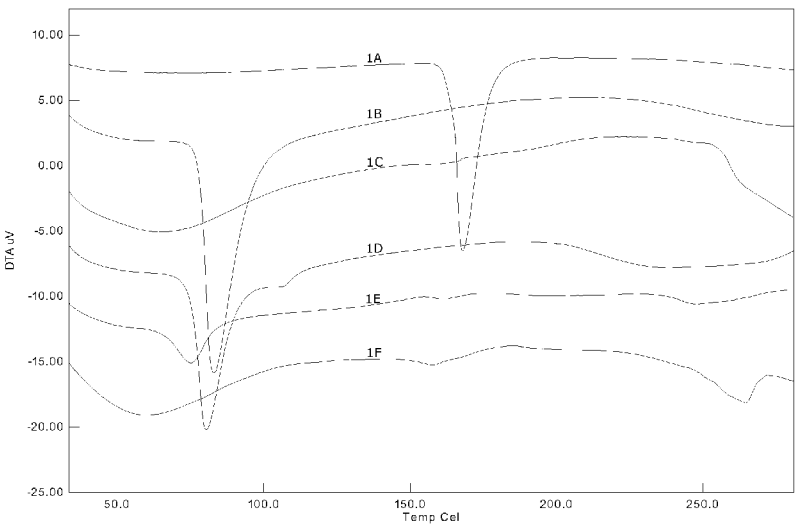
[Continued on next page]

(54) Title: COMPOSITIONS FOR DELIVERY OF INSOLUBLE AGENTS

FIGURE 1A-1F



(57) Abstract: Compositions and methods of making the same for improving the bioavailability of a substantially water-insoluble pharmacologically active agent are described. The composition includes a substantially water-insoluble pharmacologically active agent, and a substantially water-insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients, wherein the substantially water-insoluble pharmacologically active agent is dispersed in a solid matrix and wherein said pharmacologically active agent in said matrix is substantially free of the original crystalline form.

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COMPOSITIONS FOR DELIVERY OF INSOLUBLE AGENTS

CROSS-REFERENCE

[0001] This application claims priority to provisional U.S. Patent Application No. 61/236,865, filed August 25, 2009, which is incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The invention relates to compositions for delivery of substantially water-insoluble pharmacologically active agents, methods of making same and methods of delivery employing same.

BACKGROUND

[0003] Insoluble pharmacologically active agents, e.g., itraconazole, progesterone, cyclosporin, carbamazepine, fenofibrate, amphotericin B, naproxen, and glyburide, present oral absorption challenges due to their low solubility in aqueous medium. According to the Noyes-Whitney equation (Alfred Martin et al., Physical Pharmacy, 3rd ed, page 575), drug dissolution rate is directly proportional to its solubility, and hence an insoluble drug is intrinsically of slow dissolution. Many insoluble pharmacologically active agents are present in crystalline form that can be an additional energy barrier to drug dissolution.

SUMMARY

[0004] In accordance with the present invention, there are provided solid compositions for improving the bioavailability of a substantially water-insoluble pharmacologically active agent comprising: (1) a substantially water-insoluble pharmacologically active agent, and (2) a substantially water–insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients wherein the substantially water-insoluble pharmacologically active agent is dispersed in a solid matrix and wherein said pharmacologically active agent in said matrix is substantially free of the original crystalline form. In some embodiments, the compositions exhibit faster dissolution in an aqueous medium, relative to the water-insoluble pharmacologically active agent in the absence of said matrix forming material.

[0005] In another aspect of the present invention, there are provided solid compositions comprising: (1) a substantially water-insoluble pharmacologically active agent, and (2) a substantially water–insoluble matrix forming material comprising enzyme digestible or bile

soluble nutrients wherein the substantially water-insoluble pharmacologically active agent is dispersed in a solid matrix and wherein said pharmacologically active agent in said matrix is substantially free of the original crystalline form and wherein the compositions have particle size less than about 500 micron in diameter In some embodiments, the solid compositions provide improved bioavailability of the substantially water-insoluble pharmacologically active agent relative to the pharmacologically active agent in the absence of the matrix forming material. In some embodiments, the solid compositions exhibit faster dissolution in an aqueous medium, relative to the water-insoluble pharmacologically active agent in the absence of the matrix forming material.

[0006] In yet another aspect, provided herein solid compositions comprising (1) a substantially water-insoluble pharmacologically active agent and (2) zein, alpha-tocopherol derivative, lecithin of high melting point, or a combination thereof, wherein the composition improves the bioavailability of said substantially water-insoluble pharmacologically active agent, and wherein said composition is in the form of a free-flowing, compressible and non-hygroscopic powder. In some embodiments, the solid compositions exhibit faster dissolution in an aqueous medium, relative to the water-insoluble pharmacologically active agent in the absence of the matrix forming material.

[0007] In yet another aspect, provided herein processes for preparing a solid matrix that include a substantially water-insoluble pharmacologically active agent dispersed in a substantially water-insoluble matrix forming material, the processes including: (a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and the substantially water-insoluble matrix forming material in one or more solvents, and (b) removing solvent(s) under suitable conditions.

[0008] In still another aspect, there are further provided processes for preparing a composition for in vivo delivery of a substantially water-insoluble pharmacologically active agent to a subject in need thereof, where the processes include (a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and a substantially water-insoluble matrix forming material in at least one or more solvents; and (b) removing said solvent(s) under suitable conditions.

[0009] The details of one or more embodiments are set forth in the accompanying drawings and description below. Other features, objects, and advantages will be apparent from the description and drawings.

BRIEF DESCRIPTION OF THE FIGURES

[0010] FIGS. 1A-1F illustrate the DSC profiles of itraconazole without formulation (FIG. 1A), alpha-tocopheryl succinate (FIG. 1B), zein (FIG. 1C), formulated itraconazole (alpha-tocopheryl succinate matrix) according to Example 1 (FIG. 1D), formulated itraconazole (alpha-tocopheryl succinate-zein matrix) according to Example 2 (FIG. 1E), and formulated itraconazole (zein matrix) according to Example 3 (FIG. 1F).

[0011] FIG. 2 illustrates in vitro dissolution profiles (n=3, +/- SD) of itraconazole without formulation (triangle), formulated itraconazole (alpha-tocopheryl succinate matrix) according to Example 1 (open square) and formulated itraconazole (alpha-tocopheryl succinate-zein matrix) according to Example 2 (diamond).

[0012] FIG. 3 illustrates a dynamic vapor sorption isotherm of formulated itraconazole (alpha-tocopheryl succinate-zein matrix) according to Example 2.

DETAILED DESCRIPTION

[0013] As the pharmacologically active agent (e.g., drug) moves through the human gastrointestinal tract after oral administration, its typical residence time in the stomach, intestines and colon is about 30 minutes, 3 hours and 30 hours, respectively. The pharmacologically active agent must dissolve in these time windows to allow for absorption. A pharmacologically active agent with a slow rate of dissolution, i.e., a significant portion of the agent fails to dissolve during its transit through the gastrointestinal tract, will simply not be entirely absorbed.

[0014] It is well understood that slow dissolution is a major reason for lack of oral absorption of insoluble pharmacologically active agents, and can cause an otherwise promising drug candidate compound to fail further drug development. Slow dissolution is also frequently related to high absorption variability among patients, high food effect on absorption and lack of dose-exposure relationship. Each of these can contribute to

suboptimal drug performance. It is estimated that 40-60% of discovered drug substances are insoluble and many of them suffer from the oral absorption problem.

[0015] Several approaches have been developed to improve solubility and/or dissolution rate of insoluble pharmacologically active agents. Common approaches include: converting an insoluble pharmacologically active agent into a more soluble salt or crystalline form including amorphous form; reducing the particle size of an insoluble pharmacologically active agent for faster dissolution; dissolving an insoluble pharmacologically active agent in a liquid medium comprising water-soluble components such as solvents and surfactants, etc., to form a "liquid formulation" (such as, for example, an emulsion); and dissolving or dispersing an insoluble pharmacologically active agent in a solid matrix comprising water-soluble or hydrophilic components, such as a solid polymer or lipids, to form a "solid dispersion formulation".

[0016] The above approaches have been applied in preparing or formulating some successful drug products. Insoluble naproxen was made soluble by forming a sodium salt, which is the active ingredient of the drug Naprosyn®. Size reduction by micronization has lead to drugs Prometrium® (micronized progesterone) and Micronase® (micronized glyburide). Dissolving the drug in a water-soluble liquid composition was the basis for drugs such as Sandimmune® (cyclosporin emulsion) and Neoral® (cyclosporin microemulsion). Dispersion of the insoluble griseofulvin in a solid dispersion matrix comprising water-soluble polymer propylene glycol (PEG) resulted in the drug Gris-PEG®.

[0017] The above approaches are based on the physical chemistry theories of drug solubility and dissolution. For example, a salt or an amorphous form of a pharmacologically active agent is commonly known to be more soluble and of faster dissolution than the unmodified pharmacologically active agent itself. Particle size reduction generates a greater surface area and a greater surface area leads to a faster dissolution rate as predicted by the Noyes-Whitney equation (Alfred Martin et al, Physical Pharmacy, 3rd ed, page 575). The liquid formulation first breaks up the crystals of the pharmacologically active agent by dissolving it in a water-soluble solvent and such water-liking solution can then readily be mixed into another aqueous environment such as gastric fluid, carrying the dissolved pharmacologically active agent to achieve a fast dissolution. Similarly, in a solid dispersion formulation, the insoluble pharmacologically active agent is

also first dissolved or dispersed in a solid matrix formed with a soluble ingredient, e.g. PEG or PVP, the matrix can then be readily mixed into the aqueous biological milieu providing a fast dissolution of the dissolved pharmacologically active agent, owing to the hydrophilic nature of the matrix-forming ingredient.

[0018] In essence, the liquid formulation and solid dispersion formulation are based on the same principle, i.e., (1) to dissolve the insoluble pharmacologically active agent in a water-soluble or hydrophilic matrix (liquid or solid) first to break the crystalline structure of the pharmacologically active agent, and (2) to render a fast mixing of the water-liking matrix with a biological aqueous milieu (gastric or intestinal fluid) with the already dissolved or dispersed pharmacologically active agent in it to allow for a fast dissolution.

[0019] In practice, these approaches suffer from several disadvantages. Some insoluble pharmacologically active agents cannot be converted to the more soluble salts or crystalline form, especially those that lack ionizable groups. Particle size reduction by micronization or nanonization presents processing and stability challenges, as well as dissolution limitations, since the micronized or nanosized pharmacologically active agent may still possess a high degree of crystallinity. Liquid formulations present drug precipitation and packaging challenges, due to solvent evaporation. Moreover, non-solid formulations are more prone to chemical instability and capsule-shell incompatibility, leading to the possibility of leakage upon storage. Solid dispersion formulations often suffer from re-crystallization of the insoluble pharmacologically active agent over time, resulting in decreased dissolution.

[0020] Solid dispersion formulations sometimes are called by different names depending upon their preparation processes. For example, a solid dispersion may be referred to as a "hot melt" formulation, if it is prepared by first dissolving the pharmacologically active agent in a molten polymer or lipid, and then cooling molten solution to form a semi-solid matrix. Water-soluble surfactants, e.g. vitamin E TPGS, or water-soluble or hydrophilic polymer, e.g. polyethylene glycol (PEG) of low melting point (<60 deg C) or mixture thereof, are commonly used in a hot melt formulation.

[0021] In other cases, a solid dispersion is called a "spray-dried amorphous formulation" when prepared by first dissolving a pharmacologically active agent and a water-soluble or hydrophilic polymer, e.g. polyvinyl pyrrolidone or HPMC in a solvent (ethanol etc.), and

then spray drying the solution to obtain a solid dispersion. Alternatively, a solid dispersion is prepared by dissolving the pharmacologically active agent in a molten lipid or polymer and then spray-congealing to form particles. Despite the difference in their preparation process or names, solid dispersion formulations share the same composition features, i.e. an insoluble pharmacologically active agent dissolved or dispersed in a matrix formed by water-soluble ingredients, and the same concept of enhancing dissolution, i.e., an insoluble pharmacologically active agent is made fast dissolving by using a water-soluble or hydrophilic matrix-forming ingredient.

[0022] Although there was a great interest in solid dispersion systems during the past four decades as a means of increasing the dissolution rate and bioavailability of poorly water-soluble pharmacologically active agents, their commercial application has been very limited, primarily because of problems with manufacturing and drug stability. Solid dispersions of pharmacologically active agents were generally produced by the hot melt method. The materials, which were usually semisolid, were hardened by cooling. They were then pulverized, sieved, mixed with relatively large amounts of excipients, and encapsulated into hard gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. A solid dispersion formulation suffers from potential degradation of the pharmacologically active agent in the hot melt process, and a lack of free-flowing property prevents encapsulation or tablet compression using conventional capsule fillers or a tablet press. In addition, a "solid dispersion" or a "hot melt" is almost exclusively prepared using a synthetic polymer such as PEG, polyvinyl pyrrolidone (PVP), or polyvinyl pyrrolidone vinyl acetate copolymer (PVPVA) that melts at a temperature below 150 °C. Due to its safety limitations, the amount of such a polymer that can be dosed orally to a human subject can be very limited, thereby preventing its use in a product designated for human consumption, especially, for chronic use.

[0023] A substantially water-insoluble pharmacologically active agent can be made fast dissolving and/or imparted with improved bioavailability by employing a substantially water–insoluble matrix forming material instead of the water-soluble matrix materials used in conventional methods, which would seem counter-intuitive. Nevertheless, in accordance with the present invention, an enhanced dissolution and oral absorption of substantially water-insoluble pharmacologically active agents have been discovered to provide significantly broad utility.

[0024] For clarification, in some embodiments, the compositions are not necessarily directed to a slow release or sustained release formulation. Unlike formulations where water-insoluble matrix forming materials are used to slow down the dissolution of certain water-soluble drugs, compositions and methods described here are for achieving fast dissolution of substantially water-insoluble pharmacologically active agents by employing a substantially water–insoluble matrix forming material.

[0025] In some embodiments provide herein solid compositions for improving the bioavailability of a substantially water-insoluble pharmacologically active agent comprising: (1) a substantially water-insoluble pharmacologically active agent, and (2) a substantially water–insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients wherein the substantially water-insoluble pharmacologically active agent is dispersed in a solid matrix and wherein said pharmacologically active agent in said matrix is substantially free of the original crystalline form. In some embodiments, the compositions have particle size less than about 500 micron in diameter. In certain embodiments, the compositions have particle size less than about 200 micron in diameter. In certain embodiments, the compositions have particle size less than about 100 micron in diameter. In certain embodiments, the compositions have particle size less than about 50 micron in diameter. In some embodiments, the compositions exhibit faster dissolution in an aqueous medium, relative to the water-insoluble pharmacologically active agent in the absence of the matrix forming material.

[0026] In some embodiments provide herein solid compositions comprising: (1) a substantially water-insoluble pharmacologically active agent, and (2) a substantially water–insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients wherein the substantially water-insoluble pharmacologically active agent is dispersed in the solid matrix and wherein said pharmacologically active agent in said matrix is substantially free of the original crystalline form and wherein the compositions have particle size less than about 500 micron in diameter In certain embodiments, the compositions have particle size less than about 200 micron in diameter. In certain embodiments, the compositions have particle size less than about 100 micron in diameter. In certain embodiments, the compositions have particle size less than about 50 micron in diameter. In some embodiments, the compositions provide improved bioavailability of the substantially water-insoluble pharmacologically active agent relative to the pharmacologically active agent in

the absence of the matrix forming material. In some embodiments, the compositions exhibit faster dissolution in an aqueous medium, relative to the water-insoluble pharmacologically active agent in the absence of the matrix forming material.

[0027] As used herein, the term "water-insoluble" refers to the limited solubility of a pharmacologically active agent in aqueous solutions (such as water, physiological saline, injectable dextrose solutions, etc). The United States Pharmacoepia/National Formulary (USP/NF) generally expresses solubility in terms of the volume of solvent required to dissolve 1 gram of the pharmacologically active agent at a specified temperature (e.g., 1 g aspirin in 300 mL water or 5 mL ethanol at 25 °C.). Other references may use more subjective terms to describe solubility, such as those given in the following table from *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa., by Joseph Remington and Alfonso Gennaro: Mack Publishing, 1995,

[0037] Table 1

Descriptive terms	Parts of solvent needed for 1 part solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble or insoluble	>10,000

Thus, as used herein, "water-insoluble pharmacologically active agents" include the pharmacologically active agents in the last four solubility categories, i.e., "sparingly soluble," "slightly soluble," "very slightly soluble," and "practically insoluble or insoluble," when water is used as the solvent. Thus, the phrase "substantially water-insoluble active agents" means those agents that are sparingly, slightly, or very slightly soluble, or practically insoluble according to the definitions for solubility provided in Table 1 above.

[0028] As used herein, the term "water-insoluble" may be used interchangeably with hydrophobic, lipophilic, oleophilic, and similar terms.

[0029] The substantially water-insoluble pharmacologically active agents contemplated here are not limited by therapeutic category, and can be, for example, analgesics, anti-

inflammatory agents, antihelminthics, anti-arrhythmic agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-epileptics, anti-fungal agent, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, erectile dysfunction improvement agents, immunosuppresants, anti-protozoal agents, anti-thyroid agents, anxiolytic agents, sedatives, hypnotics, neuroleptics, .beta.-blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine receptor antagonists, keratolytics, lipid regulating agents, anti-anginal agents, Cox-2 inhibitors, leukotriene inhibitors, macrolides, muscle relaxants, anti-osteoporosis agents, anti-obesity agents, cognition enhancers, anti-urinary incontinence agents, nutritional oils, anti-benign prostate hypertrophy agents, essential fatty acids, non-essential fatty acids, and the like, as well as mixtures thereof.

[0030] Exemplary, non-limiting substantially water-insoluble pharmacologically active agents are: abyssomicin, acetohexamide, acetretin, albendazole, albuterol, aminoglutethimide, amiodarone, amlodipine, amphetamine, amphotericin B, anthraquinones, apigenin, atorvastatin, atovaquone, atrop-abyssomicin, azaspiracid-1, azithromycin, baclofen, bactrim, BE-43472B, beclomethasone, benezepril, benzathine, benzonatate, benzylpenicillin, betamethasone, bicalutanide, biyouyanagin, budesonide, bupropion, busulfan, butamben, butenafine, butoconazole, butyl aminobenzoate, calcifediol, calcipotriene, calcitriol, camptothecin, candesartan, capsaicin, carbamezepine, carbendazim, carbothione, carotenes, celecoxib, cerivastatin, cervinomycin, cetirizine, cholecalciferol, chlorpheniramine, chloramphenicol, cilostazol, cimetidine, cinnarizine, ciprofloxacin, cisapride, 13-cisretinoic acid, clarithromycin, clemastine, clomiphene, clomipramine, clopidogrel, clortrimazole, codeine, coenzyme Q10, cyclobenzaprine, cyclopenthiazide, cyclosporin, danazol, dantrolene, desflurane, desmethoxyrapamycin, dexamethazone palmitate, dexchlorpheniramine, diacetyl dapsone, diazepam, diclofenac, dicoumarol, difenoxin, digoxin, diphenoxylate, dehydroepiandrosterone, desonide, dihydroergotamine, dihydrotachysterol, dirithromycin, donezepil, endrin, efavirenz, eplevenone, eprosartan, ergocalciferol, ergotamine, essential fatty acid sources, estrogen, etodolac, etoposide, ezetimibe, famotidine, felodipine, fenbendazole, fenofibrate, fentanyl, fexofenadine, finasteride, fluconazole, fludarabine, flurbiprofen, fluvastatin, fosphenytoin, frovatriptan, furazolidone, furosemide, gabapentin, gemfibrozil, genistein, glibenclamide, glipizide, glyburide, glimepiride, gossypol, griseofulvin, halofantrine, halopendol, hydralazine, iboga,

ibogaine, ibuprofen, idoxuridine, indomethacin, irbesartan, irinotecan, isoflavones, isosorbide dinitrate, isocarbostyril narciclasine, isotretinoin, itraconazole, ivermectin, keratin, ketoconazole, ketorolac, quinine, lamotrigine, lansoprazole, leflunomide, lisinopril, loperamide, loratadine, lovastatin, L-thryroxine, lutein, lycopene, medroxyprogesterone, mifepristone, mefloquine, megestrol acetate, methadone, methotrexate, methoxsalen, metronidazole, miconazole, midazolam, miglitol, minoxidil, mitoxantrone, montelukast, nabumetone, nalbuphine, naratriptan, nelfinavir, nelfinavir mesylate, nicarbazin, nifedipine, nilutanide, nimodipine, nisoldipine, nitazoxanide, nitrofuran, nitrofurantoin, nizatidine, nystatin, olanzapine, oltipraz, omeprazole, oprevelkin, oestradiol, oxaprozin, oxyclozamide, paclitaxel, pantoprazole, paracalcitol, paroxetine, pasoconazole, pentazocine, phenolphthalein, pioglitazone, piroxicam, pizofetin, platencin, platensimyin, polyenes, porfiromycin, pravastatin, prednisolone, probucol, progesterone, propofol, pseudoephedrine, pyridostigmine, quercitin, rabeprazole, raloxifene, relafen, repaglinide, rifabutine, rifapentine, rimexolone, risperidone, ritonavir, rizatriptan, rofecoxib, rosiglitazone, saquinavir, sequinavir, sertaconazole, sertraline, sevelamer, sevoflurane, sibutramine, sildenafil citrate, simvastatin, sirolimus, spironolactone, sporolide, sulfasalazine, sumatriptan, tacrine, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, telmisartan, teniposide, terbinafine, terazosin, tetrahydrocannabinol, thiocarbarsone, thiostrepton, tiagabine, ticlopidine, tinectin, tirofibran, tizanidine, tolnaftate, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, uncialamycin, valsartan, vannusal, venlafaxine, verteporfin, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, xanthine, zafirlukast, zileuton, zolmitriptan, zolpidem, zopiclone, and the like, and pharmaceutically acceptable salts, isomers and derivatives thereof, as well as mixtures thereof.

[0031] In some embodiment, exemplary substantially water-insoluble pharmacologically active agents include: acetretin, albendazole, albuterol, aminoglutethimide, amiodarone, amlodipine, amphetamine, amphotericin B, atorvastatin, atovaquone, azithromycin, baclofen, benzonatate, bicalutanide, busulfan, butenafine, calcifediol, calcipotriene, calcitriol, camptothecin, capsaicin, carbamezepine, carotenes, celecoxib, cerivastatin, chlorpheniramine, cholecaliferol, cimetidine, cinnarizine, ciprofloxacin, cisapride, cetirizine, clarithromycin, clemastine, clomiphene, codeine, coenzyme Q10, cyclosporin, danazol, dantrolene, dexchlorpheniramine, diclofenac, digoxin, dehydroepiandrosterone, dihydroergotamine, dihydrotachysterol, dirithromycin, donezepil, efavirenz, ergocalciferol,

ergotamine, esomeprazole, essential fatty acid sources, etodolac, etoposide, famotidine, fenofibrate, fentanyl, fexofenadine, finasteride, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, frovatriptan, furazolidone, gabapentin, gemfibrozil, glibenclamide, glipizide, glyburide, glimepiride, griseofulvin, halofantrine, ibuprofen, irinotecan, isotretinoin, itraconazole, ivermectin, ketoconazole, ketorolac, lamotrigine, lansoprazole, leflunomide, loperamide, loratadine, lovastatin, L-thryroxine, lutein, lycopene, mifepristone, mefloquine, megestrol acetate, methdone, methoxsalen, metronidazole, miconazole, midazolam, miglitol, mitoxantrone, medroxyprogesterone, montelukast, nabumetone, nalbuphine, naratriptan, nelfinavir, nilutanide, nitrofurantoin, nizatidine, omeprazole, oestradiol, oxaprozin, paclitaxel, paracalcitol, pentazocine, pioglitazone, pizofetin, pravastatin, probucol, progesterone, pseudoephedrine, pyridostigmine, rabeprazole, raloxifene, rofecoxib, repaglinide, rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rosiglitazone, saquinavir, sibutramine, sildenafil citrate, simvastatin, sirolimus, spironolactone, sumatriptan, tacrine, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, teniposide, terbinafine, tetrahydrocannabinol, tiagabine, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, verteporfin, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, zolmitriptan, zolpidem, zopiclone, and the like, and pharmaceutically acceptable salts, isomers and derivatives thereof, as well as mixtures thereof.

[0032] In other embodiments, exemplary substantially water-insoluble pharmacologically active agents include: acetretin, albuterol, aminoglutethimide, amiodarone, amlodipine, amprenavir, atorvastatin, atovaquone, baclofen, benzonatate, bicalutanide, busulfan, calcifediol, calcipotriene, calcitriol, camptothecin, capsaicin, carbamezepine, carotenes, celecoxib, chlorpheniramine, cholecaliferol, cimetidine, cinnarizine, cisapride, cetirizine, clemastine, coenzyme Q10, cyclosporin, danazol, dantrolene, dexchlorpheniramine, diclofenac, dehydroepiandrosterone, dihydroergotamine, dihydrotachysterol, efavirenz, ergocalciferol, ergotamine, essential fatty acid sources, etodolac, etoposide, famotidine, fenofibrate, fexofenadine, finasteride, fluconazole, flurbiprofen, fosphenytoin, frovatriptan, furazolidone, glibenclamide, glipizide, glyburide, glimepiride, ibuprofen, irinotecan, isotretinoin, itraconazole, ivermectin, ketoconazole, ketorolac, lamotrigine, lansoprazole, leflunomide, loperamide, loratadine, lovastatin, L-thryroxine, lutein, lycopene, medroxyprogesterone, mifepristone, megestrol acetate, methoxsalen, metronidazole, miconazole, miglitol, mitoxantrone, montelukast, nabumetone,

naratriptan, nelfinavir, nilutanide, nitrofurantoin, nizatidine, omeprazole, oestradiol, oxaprozin, paclitaxel, paracalcitol, pioglitazone, pizofetin, pranlukast, probucol, progesterone, pseudoephedrine, rabeprazole, raloxifene, rofecoxib, repaglinide, rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rosiglitazone, saquinavir, sildenafil citrate, simvastatin, sirolimus, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, teniposide, terbenafine, tetrahydrocannabinol, tiagabine, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, ziprasidone, zolmitriptan, and the like, and pharmaceutically acceptable salts, isomers and derivatives thereof, as well as mixtures thereof.

[0033] In certain embodiments, exemplary substantially water-insoluble pharmacologically active agents include: amlodipine, amprenavir, atorvastatin, atovaquone, carbamazepine, celecoxib, cisapride, coenzyme Q10, cyclosporin, famotidine, fenofibrate, fexofenadine, finasteride, ibuprofen, itraconazole, lansoprazole, loratadine, lovastatin, megestrol acetate, montelukast, nabumetone, nizatidine, omeprazole, oxaprozin, paclitaxel, paracalcitol, pioglitazone, pranlukast, progesterone, pseudoephedrine, rabeprazole, rapamycin, rofecoxib, repaglinide, rimexolone, ritanovir, rosiglitazone, saquinavir, sildenafil citrate, simvastatin, sirolimus, tacrolimus, tamsulosin, teniposide, terbenafine, tetrahydrocannabinol, tiagabine, tizanidine, tramadol, troglitazone, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, and the like, and pharmaceutically acceptable salts, isomers and derivatives thereof, as well as mixtures thereof.

[0034] As used herein, the term "substantially water-insoluble matrix forming materials" refers to substantially water insoluble solid materials that are capable of forming solid particles or granules that preferably are dry, non-sticky, free flowing, and/or non-hygroscopic, especially when such materials contain substantially water-insoluble pharmacologically active agents dispersed therein. Substantially water insoluble solid materials can have a solubility of, for example, less than 1.0 g/100g water, less than 0.1 g/100g water, less than 0.01 g/100g water, less than 0.001 g/100g, or less than 0.0001 g/100g water. When dispersed in a substantially water-insoluble matrix forming material, it is preferred that the pharmacologically active agents exist in a substantially amorphous form or are free of their original crystalline forms as determined by suitable methods, which can include, e.g., differential scanning calorimetry (DSC), differential thermal analyzer (DTA)

or X-ray powder diffraction (XRPD). As used herein, the term "substantially water-insoluble matrix forming materials" does not include any water-soluble liquid or semi-solid material, specifically, materials such as PEG, PVP, HPMC, HPC, cremophor, gelucire, vitamin E TPGS, water-soluble waxes, surfactants, or water soluble excipients, salts, or additives thereof.

[0035] In some embodiments, the substantially water-insoluble matrix forming materials comprise water-insoluble nutrient(s). As used herein, the term "nutrient(s)" refers to ingredients that are derived from a natural source found in human diet and digestible by the human digestive system to provide nutritional benefit, i.e. enzymatically digestable by the gastrointestinal enzymes or soluble in bile ("enzyme digestible" or "bile soluble"). The nutrients contemplated for use herein are traditionally used as food additives, nutritional supplements or as a pharmaceutical ingredient for purposes other than a pharmacologically active agent or a matrix forming material. Unexpectedly, these insoluble nutrients enhance dissolution and increase oral absorption of the substantially water-insoluble pharmacologically active agents.

[0036] Without being bound by any theory or mechanism, it is proposed that the water-insoluble nutrients provide improved dissolution and oral absorption for substantially water-insoluble pharmacologically active agents by one or more of the following mechanisms:

[0037] Initially, a substantially water-insoluble pharmacologically active agent is dispersed in a substantially water-insoluble matrix forming material (e.g. enzyme digestible or bile soluble nutrients) according to the process described herein, wherein the substantially water-insoluble pharmacologically active agent exists in an amorphous, partially crystalline, or crystalline form that is more energetically favorable for dissolution, once the surrounding matrix is removed.

[0038] When exposed to an aqueous milieu (e.g., gastrointestinal fluid), the water-insoluble matrix, due to its insoluble nature, continues to hold the pharmacologically active agent in the matrix. This prevents the pharmacologically active agent from being immediately released ("dumped") into the aqueous milieu. An immediate release is not desirable because it can lead to a rapid increase in concentration that exceeds the solubility in the aqueous milieu, which in turn can lead to rapid precipitation of the pharmacologically active agent before it reaches its potential absorption site, e.g., in the intestines. Such

premature drug release is common with other approaches where an insoluble drug in a very water-soluble matrix is released immediately upon exposure to an aqueous milieu.

[0039] In some instances, the water-insoluble matrix as described herein is designed to release the drug only when an additional locally released external factor is present. The locally released external factor can be for example, a gastrointestinal enzyme that digests the water-insoluble digestible matrix, or a bile salt or a surfactant that dissolves the water-insoluble matrix. In some embodiments, the matrix includes a nutrient chosen to be digested or dissolved by a desired external factor. This localized enzyme- or bile-induced release allows the matrix particles to first reach the absorption sites prior to releasing the trapped pharmacologically active agents, which would occur at a rate similar to the natural digestion/absorption rate of the nutrients.

[0040] In a specific embodiment, the substantially water-insoluble matrix-forming materials are solid, insoluble and enzymatically digestable nutrients comprising proteins, peptides, amino acids, carbohydrates, lipids, phospholipds, vitamins, coenzymes or combinations thereof.

[0041] In another embodiment, the matrix forming materials are solid, substantially water-insoluble and enzymatically digestable or bile-soluble materials comprising synthetic polymers and naturally occuring celluloses, excluding the enteric-coating polymers, , e.g., polymethacrylate or phthalate An enteric-coating polymer is water soluble at a neutral pH.

[0042] In a yet another specific embodiment, the substantially water-insoluble matrix-forming materials are solid, substantially water-insoluble and digestable plant proteins, milk proteins and animal proteins.

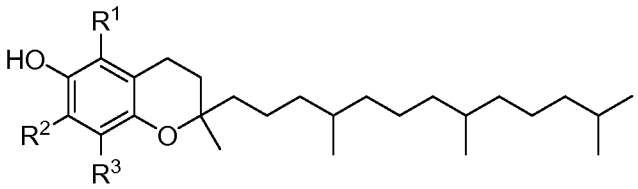
[0043] In certain embodiments, the substantially water-insoluble matrix-forming materials are zein, casein, whey, collagen, gelatin, insoluble amino acid, protein hydrolysates, or combinations thereof.

[0044] In certain embodiments provide herein compositions comprising (1) a substantially water-insoluble pharmacologically active agent and (2) zein, alpha-tocopherol derivative, lecithin of high melting point, or a combination thereof, wherein the composition improves the bioavailability of said substantially water-insoluble

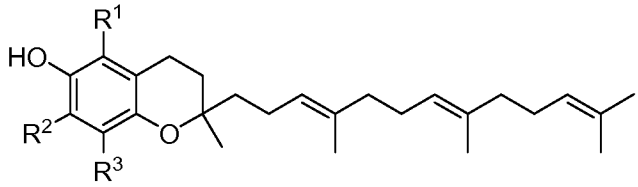
pharmacologically active agent, and wherein said composition is in the form of a free-flowing, compressible and non-hygroscopic powder.

[0045] In another embodiment, the substantially water-insoluble matrix- forming material includes a vitamin E derivative, such as, for example, a vitamin E semi-ester derivative where "vitamin E" refers to tocopherols, tocotrienols, and mixtures thereof. Tocopherols are a class of chemical compounds of various methylated phenols of which many have vitamin E activity. Tocotrienols are a related class of compounds, differing by unsaturation in the isoprenoid tail. Tocopherols and tocotrienols include alpha, beta, gamma and delta analogs (Scheme 1).

[0046] **Scheme 1.** Chemical structure of tocopherols and tocotrienols



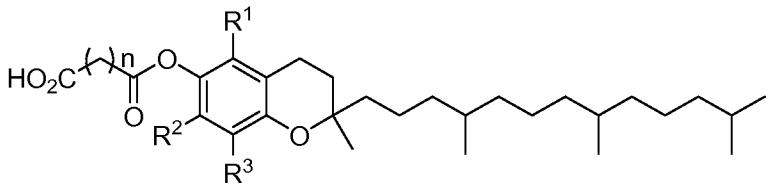
tocopherol



tocotrienol

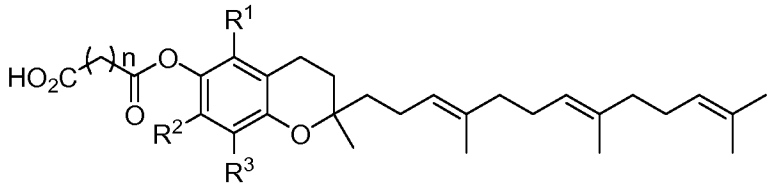
Designation	R_1	R_2	R_3
Alpha	CH_3	CH_3	CH_3
Beta	CH_3	H	CH_3
Gamma	H	CH_3	CH_3
Delta	H	H	CH_3

[0047] A tocopherol semi-ester derivative is given by the general formula I,



(I); or

a tocotrienol semi-ester derivative of the general formula II,



(II),

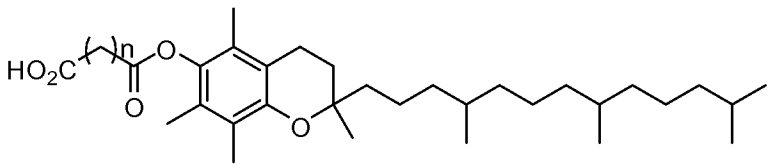
wherein R^1, R^2, and R^3 are each, independently, -H or $-CH_3$, and n is an integer in the range of 0 to 7.

[0048] As used herein, the term "vitamin E semi-ester" includes vitamin E derivatives that are hemi-esters of short-chain dicarboxylic acids with alpha tocopherol (or other tocopherols or tocotrienols), wherein the dicarboxylic acids have the general type formula:

$$HOOC\text{-}(CH_2)_n\text{-}COOH$$

Short-chain dicarboxylic acids comprise oxalic acid (n=0), malonic acid (n=1), succinic acid (n=2), glutaric acid (n=3), adipic acid (n=4), pimelic acid (n=5), suberic acid (n=6) and azelaic acid (n=7) acids (Scheme 2).

Scheme 2: alpha-tocopherol semi-ester derivatives:



Designation	n	Dicarboxylic acid
Alpha-tocopheryl oxalate	0	Oxalic acid
Alpha-tocopheryl malonate	1	Malonic acid
Alpha-tocopheryl succinate	2	Succinic acid
Alpha-tocopheryl glutarate	3	Glutaric acid
Alpha-tocopheryl adipate	4	Adipic acid
Alpha-tocopheryl pimelate	5	Pimelic acid
Alpha-tocopheryl suberate	6	Suberic acid
Alpha-tocopheryl azelate	7	Azelaic acid

[0049] The chemical name of racemic alpha tocopherol is (±)-2, 5, 7, 8-tetramethyl-2-(4', 8', 12'-trimethyltridecyl)-6-chromanol (CAS Registry Number, 10191-41-0). It contains

three chiral centers giving rise to eight isomers. The naturally occurring d- isomeric form represents the (2*R*, 4'*R*, 8'*R*)-alpha-tocopherol or *RRR*-alpha-tocopherol.

[0050] As used herein, the alpha-tocopheryl succinate preferably is d-alpha-tocopheryl acid succinate (CAS number 4345-03-3). The alpha-tocopheryl succinate may optionally comprise isomers such as dl-alpha-tocopheryl acid succinate. It may further comprise beta tocopheryl acid succinate, delta tocopheryl acid succinate, gamma tocopheryl acid succinate, alpha-tocotrienyl succinate, beta-tocotrienyl succinate, gamma-tocotrienyl succinate, delta-tocotrienyl succinate, or isomers thereof. The terms vitamin E succinate (VES) or alpha-tocopheryl succinate (ATS) refer to d-alpha-tocopheryl acid succinate and are used interchangeably.

[0051] As used herein, the "salts" of alpha-tocopherol semi-ester derivatives comprise ionic salts of pharmaceutically acceptable inorganic counter ions such as sodium, potassium, lithium, calcium, magnesium, aluminum, or the like as well as organic counter ions such as amines, lysine, arginine, or the like.

[0052] In certain embodiments, the vitamin E semiester used as the substantially water-insoluble matrix forming material comprises alpha-tocopheryl succinate, its salts or solvate.

[0053] All of the above tocopherol derivatives including alpha-tocopheryl succinate with vitamin activity may correctly be referred to as "vitamin E." The most common form of "vitamin E" used as an antioxidant and as a dietary supplement for vitamin E deficiency are tocopherol and tocopheryl acetate. Vitamin E TPGS (tocopherol polyetheleneglycol succinate) is used primarily as a surfactant in oral and parenteral drug formulations as a solubilizer or emulsifier.

[0054] Alpha-tocopherol semi-ester derivatives are structurally and functionally different from the other three common types of vitamin E derivatives, i.e., tocopherol, tocopherol monoester (e.g., acetate), and tocopherol polyetheleneglycol succinate (also referred to as tocopherol PEG ester or vitamin E TPGS). The semi-esters contain an open (non-esterified) carboxylic acid group and are ionizable, whereas all the other forms of vitamin E are non-ionizable. Thus, when included as a component in a formulation, the semi-esters behave differently from the monoesters or the parent tocopherol. While a monoester or the parent tocopherol is lipophilic and oil soluble, the semi-esters are not soluble in either water or oil,

and so are poor solvents for either hydrophilic or hydrophobic pharmacologically active agents. By appearance, alpha-tocopheryl succinate is a crystalline, water-insoluble solid with a melting point of 75 °C, whereas tocopherol and tocopherol acetate are oily liquids, and vitamin E TPGS is water-soluble semi-solid with a melting point of about 50 °C. For clarification, tocopherol, tocopherol monoester (e.g., acetate) and vitamin E TPGS are not embraced by the term "substantially water-insoluble matrix forming materials."

[0055] In some embodiments, one substantially water-insoluble matrix forming material for compositions is zein.

[0056] Zein is a class of prolamine protein found in maize and is one of the most well understood plant proteins, having a variety of food and industrial uses. Pure zein is clear, odorless, tasteless, hard, edible and water-insoluble, and is commonly used in processed foods. Zein does not melt but will decompose upon heating to about 200 °C.

[0057] In the nutritional or pharmaceutical fields, zein is almost exclusively used as a coating for candy, nuts, fruit, pills, and other encapsulated foods and pharmacologically active agents. In the United States it may be labeled as "confectioner's glaze" and used as a coating on bakery products or as "vegetable protein." It is classified as GRAS (Generally Recognized as Safe) by the U.S. Food and Drug Administration. Historically zein has been used in the manufacture of a wide variety of commercial products including coatings for paper cups, soda bottle cap linings, clothing fabrics, buttons, adhesives, coatings and binders. In pharmaceutical industry, zein, owning to its water-insoluble nature, has been used primarily as tablet coatings to slow down the dissolution of water soluble drugs (see, e.g., U.S. Patent Nos. 7,214,387; 6,913,768; and 6,905,707, each of which is incorporated by reference in its entirety). Surprisingly, zein can be used as a substantially water-insoluble matrix forming material to provide fast dissolution for a substantially water-insoluble pharmacologically active agent.

[0058] In certain embodiments, the substantially water-insoluble matrix forming material is purified zein suitable for use in a pharmaceutical product. In certain embodiments, the substantially water-insoluble matrix forming material comprises a combination of zein and alpha-tocopheryl succinate. In some embodiments, the combination is at a weight ratio in the range of 1:99 to 99:1, 1:20 to 20:1, 1:9 to 9:1 or 1:2 to 2:1.

[0059] In certain embodiments, the substantially water-insoluble matrix forming material is casein. In certain embodiments, the substantially water-insoluble matrix forming material comprises micellar casein, casein acid or salt of casein, such as sodium caseinate, potassium caseinate, ammonium caseinate, or a combination thereof.

[0060] Casein is the predominant phosphoprotein (αS1, αS2, β, κ) that accounts for nearly 80% of proteins in milk and cheese. Casein consists of a fairly high number of proline peptides, which do not interact. There are also no disulfide bridges. As a result, it has relatively little secondary structure or tertiary structure. Casein includes micellar casein, casein acid and casein salts, which are insoluble in water.

[0061] Casein is used in the manufacture of adhesives, binders, protective coatings, plastics, fabrics, food additives and many other products. Casein is not commonly used in drug products and is not listed either in the Handbook of Pharmaceutical Excipients (2^{nd} ed, Ainley Wade and Paul Weller, APA press, 1994) or by the United States Pharmacopoeia (USP) as an excipient. Previously casein was used exclusively as a sustained release agent to slow down the dissolution of certain drugs and as a surface active agent to stabilize certain particle or emulsion compositions (see, e.g., U.S. Patent Nos. 6,969,529, and 7,244,451, each of which is incorporated by reference in its entirety). Surprisingly, casein can be used as a substantially water-insoluble matrix forming material to provide fast dissolution for a substantially water-insoluble pharmacologically active agent.

[0062] A water-insoluble casein can be used to form a matrix with a substantially water-insoluble pharmacologically active agent in a composition that exhibits faster dissolution in aqueous medium, relative to a composition of the water-insoluble pharmacologically active agent in the absence of casein.

[0063] The substantially water-insoluble matrix forming materials include substantially water-insoluble proteins, proteinoids, protein hydrolysates, peptides and amino acids.

[0064] The substantially water-insoluble matrix forming materials include phospholipids or lecithins of very high lipophilicity.

[0065] According to the USP, lecithin is a non-proprietary name describing a complex mixture of acetone-insoluble phospholipids, which consists chiefly of phosphotidylcholine, phosphotidylethanolamine, phosphotidylserine and phosphotidylinositol, combined with

various amounts of other minor substances such as triglycerides, fatty acids, and carbohydrates. The naturally occurring lecithins consist of soy lecithin and egg lecithin.

[0066] Lecithins with high melting point and high lipophilicity are used to form a matrix with a substantially water-insoluble pharmacological active agent. Such lecithins may contain a low amount, i.e., < 50%, of phosphotidylcholine (e.g., LIPOID® S45 or LIPOID® S20), primarily saturated fatty acids, e.g., stearic acid, palmitic acid, etc., or a product of controlled hydrogenation of lecithin (e.g., Phospholipon® 90H). Specifically, the lecithins commonly used in other formulations as a solublizer, liposome forming agent, emulsifier, penetration enhancer, particle stabilizer, etc., are not contemplated for use in this matrix because they typically require certain hydrophilicity levels, i.e., potential to dissolve or disperse in water, for those applications, which can be undesirable for the matrix.

[0067] As used herein, the term "lecithin with high melting point" refers to lecithin with a melting point exceeding about 120 °C. In certain embodiments, the lecithin with high melting point may also have high hydrophobicity. The lecithins with high melting point do not include egg or soy lecithins (m.p. about 50-60 °C) that are commonly used in other type of drug formulations as emulsifying, and liposome forming agents. Examples of these egg or soy lecithins include the commercial products under trade names of LIPOID®E80, LIPOID®S75, LIPOID®S80, LIPOID®S90, Phospholipon® 80G, Phospholipon® 90G. Similarly, an oil or triglyceride (such as in an emulsion formulation) or a secondary vesicle stabilizer such as cholesterol or phospholipids as in liposomal formulations are not considered to be high melting point lecithins.

[0068] In certain embodiments, some powdered lecithin products containing a significant amount of non-lecithin components are not be considered to be lecithins with high melting point. An example of such a powdered lecithin product is the SOLUTHIN® MD made by the LIPOID Company. Such powdered lecithin product typically contains a low amount of lecithin (about 20%) and a high amount of water-soluble material (e.g. 80% maltodextrin as in SOLUTHIN® MD).

[0069] In another embodiment, the substantially water-insoluble matrix forming material comprises in the range of 10% to 95% by weight of the matrix composition; preferably to be within the range of 25% to 90%, and more preferably to be at about 50% to 80% by weight.

[0070] In a preferred embodiment, the substantially water-insoluble matrix forming material comprises a combination of a high melting point lecithin and alpha-tocopheryl succinate, or a combination of a high melting point lecithin and zein. The combination may be at a weight ratio in the range of 1:99 to 99:1, 1:20 to 20:1, 1:9 to 9:1 or 1:2 to 2:1.

[0071] In another embodiment, the substantially water-insoluble matrix forming material comprises alpha-tocopheryl succinate, zein or a high melting point lecithin in combination with povidone at a weight concentration of no more than 25%.

[0072] In yet another embodiment, the compositions provide improved bioavailability of the substantially water-insoluble pharmacologically active agent relative to said pharmacologically active agent in the absence of said matrix forming material.

[0073] In yet another embodiment, the compositions exhibit faster dissolution in aqueous medium, relative to the water-insoluble pharmacologically active agent in the absence of said matrix forming material.

[0074] In certain embodiments, a composition includes (1) a substantially water-insoluble pharmacologically active agent and (2) zein, alpha-tocopheryl succinate, casein, or combinations thereof, wherein the compositions improve the bioavailability of said substantially water-insoluble pharmacologically active agent, and wherein said compositions are in the form of free-flowing, compressible and non-hydroscopic powder.

[0075] In another embodiment, a composition includes (1) a substantially water-insoluble pharmacologically active agent and (2) zein, alpha-tocopheryl succinate, casein or combinations thereof, wherein the pharmacologically active agent exhibits faster dissolution as compared to the unmodified pharmacologically active agent and the total matrix-forming ingredient is in a range of 20% to 99% by weight of the solid composition.

[0076] As used herein, the term "powdered, free-flowing solid" or "dry free-flowing solid particles" refers to solid mass of small particles capable to passing through a standard 10 mesh sieve (2 mm) having a free-flowing property as defined by an angle of repose of less than 60 degrees. When bulk solid materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the "angle of repose" and is related to the density, surface area, and coefficient of friction of the material. Material with a low angle of repose forms flatter piles

than material with a high angle of repose. In other words, the angle of repose is the angle a pile forms with the ground.

[0077] As used herein, the term "amorphous" refers to a state in which the material devoid long range order of the positions of the atoms and, depending upon temperature, may exhibit the physical properties of a solid or a liquid (e.g. free flowing). Typically such materials do not give distinctive X-ray diffraction patterns, and lack a distinct melting event when examined by differential scanning calorimetry (DSC). It can be difficult to make a distinction between truly amorphous solids and crystalline solids if the size of the crystals is very small. Even amorphous materials have some short-range order at the atomic length scale due the nature of chemical bonding. Thus, the pharmacologically active agents in the matrix may be about 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.9%, or 99.99% or more amorphous by weight.

[0078] As used herein, the term "dissolution" refers to a process of dissolving a solid substance into a solvent to yield a solution. In pharmaceutical practices, dissolution usually refers to the rate, kinetics and extent to which the pharmacologically active agent dissolves from its dosage form into a selected dissolution medium in a test vessel (in vitro dissolution) or into a biological milieu such as gastric fluid in the body (in vivo dissolution). Dissolution refers to the in vitro dissolution rate of the pharmacologically active agent in a typical in vitro dissolution medium, such as water, water with some surfactant, simulated gastric fluid, USP or simulated intestinal fluid, USP, tested by a standard USP dissolution apparatus (Type 1 or Type 2). It is generally agreed that a fast and complete in vitro dissolution is indicative of better absorption of the pharmacologically active agent in vivo.

[0079] The compositions can optionally be combined with one or more additives, sometimes referred to as excipients. The excipients that can be combined to improve or control the tableting or encapsulation or dissolution property of powdered, free-flowing amorphous pharmaceutical compositions may include, but are not limited to (1) binders, (2) bulking agents, (3) wetting agents, (4) disintegrants, (5) sustained release matrix forming agents, (6) lubricants or glidants, (7) antioxidants, (8) buffer, (9) colorants or flavorants, (10) coating agents. Alternatively, the additives can be contained in the pharmaceutical composition. The functions and selection of these additives are well known in the art, and

are further described in such references as Pharmaceutical Dosage Forms: Tablets, Vol.1-3, by Herbert Lieberman et al., which is incorporated by reference in its entirety.

[0080] In another embodiment, there are provided methods for delivery of a substantially water-insoluble pharmacologically active agent to a subject in need thereof, said methods comprising administering to said subject an effective amount of a composition.

[0081] In yet another embodiment, there are provided fast dissolving particles comprising substantially water-insoluble pharmacologically active agents dispersed in a substantially water-insoluble matrix comprising enzyme digestible or bile soluble nutrients wherein said fast dissolving particle is in the form of a free-flowing, compressible and non-hydroscopic powder.

[0082] There are also provided processes for preparing a solid matrix comprising a substantially water-insoluble pharmacologically active agent or salt or solvate thereof, dispersed in a substantially water-insoluble matrix-forming material comprising enzyme digestible or bile soluble nutrients. The process includes: (a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and the substantially water-insoluble matrix-forming material therefor in one or more solvents; and (b) removing solvent(s) under suitable conditions. In certain embodiments, step (b) is carried out by suitable means, such as vacuum drying, air drying or spray drying. In other embodiments, step (b) is carried out to form particles of size in the range of about 1 μm to about 1 mm in diameter. In another embodiment, the processes further comprise pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder. In certain embodiments, the processes further comprising pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder wherein step (b) is carried out to form particles of size in less than 500 micron in diameter.

[0083] In some embodiments, there are provided processed for preparing a solid matrix in the form of a free-flowing, compressible and non-hygroscopic powder comprising a substantially water-insoluble pharmacologically active agent or salt or solvate thereof, dispersed in a substantially water-insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients therefor, said process comprising: (a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and

the substantially water-insoluble matrix forming material therefor in one or more solvents; and (b) removing solvent(s) under suitable conditions. In certain embodiments, step (b) is carried out by suitable means, such as vacuum drying, air drying or spray drying. In other embodiments, step (b) is carried out to form particles of size in the range of about 1 μm to about 1 mm in diameter. In another embodiment, the processes further comprise pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder. In certain embodiments, the processes further comprising pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder wherein step (b) is carried out to form particles of size in less than 500 micron in diameter.

[0084] In certain embodiments, there are provided processes for preparing a solid composition for in vivo delivery of a substantially water-insoluble pharmacologically active agent to a subject in need thereof, said processed comprising: (a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and a substantially water-insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients in at least one or more solvents; and (b) removing said solvent(s) under suitable conditions. In certain embodiments, step (b) is carried out by suitable means, such as vacuum drying, air drying or spray drying. In other embodiments, step (b) is carried out to form particles of size in the range of about 1 μm to about 1 mm in diameter. In another embodiment, the processes further comprise pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder. In certain embodiments, the processes further comprising pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder wherein step (b) is carried out to form particles of size in less than 500 micron in diameter.

[0085] In certain embodiments provide herein processes for preparing a solid composition for improving the bioavailability of a substantially water-insoluble pharmacologically active agent, said process comprising (a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and a substantially water-insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients in at least one or more solvents; and (b) removing said solvent(s) under suitable conditions. In certain embodiments, step (b) is carried out by suitable means, such as vacuum drying, air drying or spray drying. In other embodiments, step (b) is carried out to

form particles of size in the range of about 1 μm to about 1 mm in diameter. In another embodiment, the processes further comprise pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder. In certain embodiments, the processes further comprising pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder wherein step (b) is carried out to form particles of size in less than 500 micron in diameter.

[0086] In general, the compositions are prepared by (1) co-dissolution, (2) drying, and (3) comminution. The co-dissolution is the dissolution of the substantially water-insoluble pharmacologically active agent and the substantially water-insoluble matrix forming material, e.g., zein, casein, vitamin E succinate, and optional lecithin, in a volatile solvent or mixture of volatile solvents to form a solution. A volatile solvent refers to a solvent that can be removed by a common drying method. The volatile solvent may include water and pharmaceutical solvents such as those defined by the FDA as Class 3 and Class 2 solvents (FDA's Guidance for Industry, Q3C, which is incorporated by reference in its entirety). Examples of Class 3 solvents, which are the most preferred, are as follows:

[0087] Table 2. - Class 3 Solvents Which Should Be Limited by GMP or Other Quality-Based Requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

[0088] The solution of the pharmacologically active agent and the matrix forming material in a volatile solvent is subsequently reduced to remove the solvent and to produce a dry solid mass. The drying method may include vacuum drying, rotary drying, drum drying, spray drying, freeze-drying, lyophilization, drug layering, spray granulation, or other drying method. Drug layering involves spraying the solution onto inert cores (e.g., sugar spheres or microcrystalline cellulose spheres) and directly filling into capsules or compression into tablets, avoiding a milling step. Spray granulation involves spraying the solution onto a powder of inert pharmaceutical excipients to form a granulation, which is then filled into capsules or compressed into tablets, avoiding a milling step. The residual level of the solvent in the dry mass is preferably less than 10%, more preferably less than 5% and most preferably less than 1%.

[0089] The dried solid mass can be further reduced in size by a comminution method to produce a powdered, free-flowing amorphous pharmaceutical composition. Comminution refers to process to reduce particle size of solids. Machines used for comminution may include jaw crusher, cone and gyratory crushers, roller crusher, impact crusher, tube mills, ball mills, autogenous mills, vertical roller mills, and roller presses. Common comminutors found in the field include ball mill, Fitzmill, and Quadro Comil, etc. The comminution may include a sieving step at the end to control the particle size of the powdered, free-flowing amorphous pharmaceutical compositions.

[0090] Some compositions are suitable for manufacture by melt granulation or hot melt extrusion. Melt granulation involves melting the carrier and dissolving the active pharmaceutical ingredient in the resulting melt. The melt can be granulated with a diluent such as microcrystalline cellulose, then blended with other excipients and filled into capsules or compressed into tablets. Similarly, hot melt extrusion involves melting the carrier and dissolving the active pharmaceutical ingredient in the resulting melt, followed by blending and extrusion.

[0091] The final dosage forms comprising the powdered, free-flowing compositions can be provided in the form of a capsule, a tablet, an implant, a troche, a lozenge, a temporary or permanent suspension, an ovule, a suppository, a wafer, a chewable tablet, a quick or fast dissolving tablet, an effervescent tablet, a buccal or sublingual solid, a granule, a film, a sprinkle, a pellet, a bead, a pill, a powder, a triturate, a platelet, a strip or a sachet. Compositions can also be administered as a "dry powder," where the finished dosage form is placed directly on the tongue and swallowed or followed with a drink or beverage. These forms are well known in the art and are packaged appropriately. The compositions can be formulated for oral, nasal, buccal, ocular, urethral, transmucosal, vaginal, topical or rectal delivery, although oral delivery is presently preferred.

[0092] The final dosage forms can be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings, compress coatings, fast disintegrating coatings, or enzyme degradable coatings. Multiple coatings can be applied for desired performance. Further, the final dosage forms can be designed for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release. For release/absorption control, the release profile can be

effected by a polymeric matrix composition, a coated matrix composition, a multiparticulate composition, a coated multiparticulate composition, an ion-exchange resin-based composition, an osmosis-based composition, or a biodegradable polymeric composition.

EXAMPLE 1. Preparation of a Fast Dissolving Matrix Containing Itraconazole with Alpha-tocopheryl succinate by Vacuum Drying

[0093] In a 100 mL round bottom flask, 500 mg itraconazole and 4500 mg alpha-tocopheryl succinate (ATS) was mixed in 30 mL of acetone and heated to about 50 °C in a water bath to obtain a clear solution. The flask was attached to a rotary evaporator (Buchi RotaVapor R-205), rotated in a water bath (50 °C) under vacuum for about 30 minutes to remove the acetone. After the majority of acetone was evaporated, the flask was immediately placed in a –30 °C freezer overnight to obtain a clear yellow glassy soft mass. The mass was then transferred onto a glass tray and stirred by a spatula to solidify to form a solid matrix. The solid matrix was ground in a mortar with a pestle and sifted through a 60-mesh screen to yield the preparation.

EXAMPLE 2. Preparation of a Fast Dissolving Matrix Containing Itraconazole with Alpha-tocopheryl succinate and Zein by Spray Drying

[0094] In a glass bottle, 500 mg itraconazole, 4500 mg alpha-tocopheryl succinate and 2500 mg zein were dissolved in 50 mL of acetone and water mixture (3:1 by volume) at about 50 °C. The resulting solution was spray-dried using a Yamato, Pulvis GB22 spray-dryer under conditions: flow rate at about 6 mL/min, inlet temperature at about 120 °C, outlet temperature at about 73 °C, drying air flow at about 0.35 m^3/min and atomizing air at 1.0 kgf/cm^2 to obtain homogeneous powder. The powder was transferred to a dish and placed under oven at about 50 °C overnight to remove residual solvent. The dry powder was finally sifted through a 70-mesh screen to yield the preparation.

EXAMPLE 3. Preparation of a Matrix Containing Itraconazole with Zein by Spray Drying

[0095] In a glass bottle, 500 mg itraconazole and 2000 mg zein were dissolved in 50 mL of acetone and water mixture (3:1 by volume) at about 50 °C. The resulting solution was spray-dried to obtain the preparation using the method described in Example 2.

EXAMPLE 4. Preparation of a Fast Dissolving Matrix Containing Cyclosporin A with Micellar Casein by Freeze drying

[0096] In a 100 mL glass bottle, 200 mg cyclosporin A and 1800 mg micellar casein (which is water insoluble) was mixed in 18 g of dimethyl sulfoxide and heated to about 50 °C in a water bath to obtain a clear solution. The resulting solution was quickly cooled in a -30 °C freezer for 2 hour and then freeze-dried using a VIRTIS, Model Advantage lyophilizer to obtain powder. The powder was transferred to a dish and placed in an oven at about 60 °C overnight to remove residual solvent. The dry powder was finally sifted through a 70-mesh screen to yield the preparation.

EXAMPLE 5. Preparation of a Fast Dissolving Matrix Containing Cyclosporin A with Sodium Casein by Freeze-dry

[0097] A dry powder fast dissolving solid matrix containing cyclosporin A with sodium casein (which is water insoluble) was prepared using the method described in Example 4.

EXAMPLE 6. Preparation of a Fast Dissolving Matrix Containing Cyclosporin A with Acid Casein by Freeze drying

[0098] A dry powder fast dissolving solid matrix containing cyclosporin A with acid casein (which is water insoluble) was prepared using the method described in Example 4.

EXAMPLE 7. Differential Scanning Calorimeter (DSC)

[0099] Samples (about twenty milligrams) prepared according to Examples 1, 2 and 3 were measured by a differential scanning calorimeter (DSC, by Seiko Instruments, Model SSC/5200) at a temperature ramping rate of 10 °C/minute. The temperature at the tip of an endothermic peak (pointing down) is regarded as the melting point. FIG. 1A shows that itraconazole without formulation is a crystalline material with a melting point at about 168 °C and that alpha-tocopheryl succinate is also a crystalline material with a melting point at about 81 °C (FIG. 1B). DSC generated from the samples of Example 1 (FIG. 1C) and 2 (FIG. 1D) do not show distinct endothermic peaks indicating these solid matrixes are substantially free of the original crystalline form of itraconazole. FIG 1A shows that the itraconazole without formulation is a crystalline material with a melting point at about 168 °C. Alpha-tocopheryl succinate is also a crystalline material with a melting point at about

83 °C (FIG 1B). Zein is an amorphous material without a melting point (FIG 1C). DSC thermograms generated from the preparations according to Example 1 (FIG 1D), Example 2 (FIG 1E) and Example 3 (FIG 1F) do not show the distinct melting peak of crystalline itraconazale, indicating these solid matrixes are substantially free of the original crystalline form of itraconazole.

EXAMPLE 8. In Vitro Dissolution

[00100] Preparations obtained in Example 1 and 2 were filled into empty gelatin capsules to obtain 5.5 mg itraconazole in each capsule for in vitro dissolution test. The test was performed on a standard USP dissolution apparatus (Van Kel Model VK7000) using the following conditions:

Method	USP <711>, Paddle
Medium	0.2% SDS, 500 mL
Speed	100 RPM
Temp.	37 °C
Sampling method	At each sampling time point, remove 2 mL medium sample, filter through a 0.45 μm filter, discard the first 1 mL filtrate and collect the rest filtrate for HPLC analysis for itraconazole concentration.

[00101] In vitro dissolution of the matrix samples from Example 1 and 2 and itraconazole without formulation are shown in FIG 2, which indicates that matrix preparations according to Example 1 and 2 markedly improved the dissolution of itraconazole as compared to the unformulated itraconazole.

EXAMPLE 9. Flow Property, Compressibility and Hygroscopicity

[00102] Preparation from in Example 1 was measured for flow property by the method of angle of repose and exhibited angle of repose of 39 degrees, suggesting the preparation according the Example 1 is free-flowing.

[00103] The preparation from Example 2 was mixed with 35% microcrystalline cellulose (Avicel PH101), 4% croscarmellose sodium (Ac-Di-Sol) and 1% magnesium stearate and

the blend was compressed using a tablet press (Piccola, Model RIVA) to obtain 1g tablets with hardness of 9.6 kg. The preparation according the Example 2 is readily compressible.

[00104] The hygroscopicity of the preparation according the Example 2 was measured using a dynamic vapor sorption method. The result (FIG 3) indicates that at the relative humidity of 70% RH, the solid matrix absorbed only 3.5% water. The preparation according the Example 2 is thus regarded non-hygroscopic.

EXAMPLE 10. Solubility

[00105] About 5.5 mg itraconazole or an amount of the preparations obtained according to Example 3 containing 5.5 mg itraconazole was placed in 500 mL aqueous solution of 0.2% SDS. The mixture was stirred at 37 °C for 24 hours. About 5 mL of the solution was taken and filtered through a 0.45 μm filter. The filtrate was analyzed by HPLC for concentration of itraconazole. The solubility of itraconazole and the preparation according to Example 3 were, respectively, 6.44 ± 0.08 μg/mL and 9.94 ± 0.25 μg/mL, indicating that solid matrix prepared according to Example 3 using insoluble zein as the matrix-forming material has increased the apparent solubility of itraconazole as compared to the unformulated itraconazole.

EXAMPLE 11. Preparation of other Fast Dissolving Solid Matrix Preparations

[00106] Other fast dissolving solid matrix preparations for intraconazole or other insoluble drugs are prepared in the following compositions using the methods described in Example 1, 2 or 4.

Insoluble Drug	Insoluble matrix forming material		Preparation method according to
	#1	#2	
Itraconazole	alpha-tocopheryl succinate (ATS)		Example 2
	Zein		Example 1
	ATS	Zein	Example 1
	Zein	Phospholipon 90H	Example 1 or 2
	Valine		Example 1, 2 or 4
	Leucine		Example 1, 2 or 4
	Isoleucine		Example 1, 2 or 4
	Phenylalanine		Example 1, 2 or 4
	Tryptophan		Example 1, 2 or 4
	Tyrosine		Example 1, 2 or 4
	Whey		Example 1, 2 or 4
	Collagen		Example 1, 2 or 4
	Gelatin		Example 1, 2 or 4
	Ethyl cellulose		Example 1, 2 or 4
	Carboxymethyl cellulose		Example 1, 2 or 4
Cyclosporin A	ATS		Example 1, 2 or 4
	ATS	Phospholipon 90H	Example 1, 2 or 4
	Zein	Phospholipon 90H	Example 1, 2 or 4
Progesterone	ATS		Example 1 or 2
	ATS	Phospholipon 90H	Example 1 or 2
	ATS	Zein	Example 1 or 2

EXAMPLE 12. Oral Bioavailability

[00107] A powder matrix preparation comprising itraconazole or progesterone prepared according to Example 1, 2 or 4 is orally administered to rodents; the plasma concentration of the drug is obtained by a chromatography method and is plotted against time. The area under curve is used to quantitate oral bioavailability. The areas obtained from Example 1, 2, or 4 are greater compared to the area obtained from itraconazole or progesterone without formulation. These results indicate a greater oral bioavailability than the unformulated drug.

EXAMPLE 13. Preparation of a Fast Dissolving Matrix Comprising an Anticancer Drug (Compound AC) with an Insoluble and High Melting Lecithin (Phospholipon® 90H) by Spray Drying

[00108] In a 2000 mL glass bottle, eight (8) g water insoluble Compound AC and 32 g Phospholipon® 90H were mixed with 1500 mL tertbutyl alcohol. The mixture was heated at

60 °C until all solids were dissolved to form a clear solution. The solution was spray dried using a Yamoto Spray Dryer Model Pulvis GB22 with the following conditions: (1) flow rate: 3-4 mL/min; (2) drying airflow rate: 0.3-0.4 m^3/min; (3) inlet air temperature: 105°C. The dry powder was collected and placed in a vacuum oven at 40°C until the residual solvent is less than 2% by thermogravimetric analysis. The powder was passed through a 100-mesh sieve (150 μm) and was then stored in a sealed container.

[00109] The obtained powder matrix had particle size range of D (v, 0.1) = 5-20 μm, D (v, 0.5) = 15-50 μm, D (v, 0.9) = 40-100 μm, as measured by light diffraction (Mastersize, by Malvern).

[00110] The obtained powder matrix was filled into 00 size gelatin capsules to obtain 20 mg Compound AC in each capsule for *in vitro* dissolution test. The test was performed on a standard USP dissolution apparatus (Van KeL Model VK 7000) using the following conditions.

Method	USP <711>, Paddle
Dissolution Medium	1.0% (w/v) SDS in DI-water, 900 mL
Temperature	37.0°C (± 0.5)°C
Speed	100 RPM

[00111] In vitro dissolution of the capsule samples and unformulated Compound AC were compared, which demonstrates that matrix preparations according to Example 13 markedly improved the dissolution for the anticancer drug Compound AC (about 30% dissolved at 60 min) as compared to the unformulated Compound AC (about 2.5% dissolved at 60 min).

[00112] Pharmacokinetic tests in mice indicated that powder matrix containing Compound AC prepared according to Example 13 provided a greatly improved oral bioavailability than that of Compound AC without such matrix formulation.

Pharmacokinetic parameters of Compound AC dosed in mice at 10 mg/kg.

Formulation	T1/2 (h)	Tmax (h)	Cmax (μM)	AUC24 (h*μM)
Compound AC in the Example 13 Matrix Formulation	3.2	0.3	4.5	23.4
Compound AC, without the Example 13 Matrix Formulation	4.5	0.1	3.7	4.3

EXAMPLE 14. Preparation of a Fast Dissolving Matrix Comprising an Insoluble Drug for Treatment of Naturopathic Pain (Compound NP) with Alpha Tocopheryl Succinate by Vacuum Drying

[00113] To a 2000 mL round bottom flask, 8.5 g water-insoluble Compound NP and 76.5 g alpha-tocopheryl succinate (ATS) were added. 500 mL acetone was then added to dissolve the solids to obtain a clear solution. The flask was attached to a rotary evaporator (Buchi RotaVapor R-205) and rotated in a water bath (50 °C) under vacuum for about 1 hour to remove the acetone. After the majority of acetone was evaporated, the flask was immediately placed in a –20 °C freezer overnight to obtain a clear yellow glassy soft mass. The mass was then transferred onto a glass tray and stirred by a spatula to solidify to form a hard solid mass. The solid mass was ground in a mortar with a pestle and sifted through a 60-mesh screen to yield a powder matrix preparation.

[00114] The resulting powder matrix had a particle size range of D (v, 0.1) = 20-40 μm, D (v, 0.5) = 100-200 μm, D (v, 0.9) = 200-500 μm, as measured by light diffraction (Mastersize, by Malvern). The powder was reduced in particle size by a Jet-Mill to obtain a micronized powder matrix with particle size range of D (v, 0.1) = 5-20 μm, D (v, 0.5) = 20-40 μm, D (v, 0.9) = 40-100 μm

[00115] The solubility of the powder matrix samples of Example 14 and the unformulated Compound NP in DI-water were measured to be 210 μg/mL and 80 μg/mL, respectively.

EXAMPLE 15 Preparation of a Fast Dissolving Matrix Containing the Insoluble Calcium Channel Blocker Anti-hypertension Drug Amlodipine with Insoluble Ethyl Cellulose by Spray Drying

[00116] A dry powder of fast dissolving solid matrix comprising amlodipine and ethyl cellulose (a water insoluble cellulose) is prepared by spray drying using the method described in Example 13.

EXAMPLE 16 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Antiandrogen Drug Finasteride with Water Insoluble Carboxymethyl Cellulose by Spray Drying

[00117] A dry powder of fast dissolving solid matrix comprising finasteride and water insoluble carboxymethyl cellulose (the free acid) prepared by spray drying the solution is prepared using the method described in Example 13.

EXAMPLE 17 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Protease Inhibitor Drug Amprenavir with a Water Insoluble Collagen by Freeze Drying

[00118] A dry powder of fast dissolving solid matrix comprising amprenavire and a water insoluble collagen (such as a collagen prepared by removal of proteoglycans from human cartilage by sequential treatments with H_2O_2 followed by trypsin digestion) is prepared by freeze drying using the method described in Example 4.

EXAMPLE 18 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Muscle Relaxant Drug Tizanidine with Insoluble Gelatin by Freeze Drying

[00119] A dry powder of fast dissolving solid matrix comprising tizanidine and insoluble gelatin, such as the gelatin produced by using hexamine and high temperature, is prepared by freeze drying the solution using the method described in Example 4.

EXAMPLE 19 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Cholesterol Regulating Drug Fenofibrate with Insoluble Amino Acid Tyrosine by Freeze Drying

[00120] A dry powder of fast dissolving solid matrix comprising fenofibrate and tyrosine is prepared by freeze drying the solution using the method described in Example 4.

EXAMPLE 20 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Anti-inflammatory Drug Celecoxib with Water-insoluble Isoleucine by Freeze Drying

[00121] A dry powder fast dissolving solid matrix comprising celecoxib and water-insoluble isoleucine, is prepared by freeze drying the solution using the method described in Example 4.

EXAMPLE 21 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Proton-pump Inhibitor Drug Lansoprazole with Denatured Insoluble Whey by Freeze Drying

[00122] A dry powder of fast dissolving solid matrix comprising lansoprazole and denatured insoluble whey is then prepared by freeze drying the solution using the method described in Example 4.

EXAMPLE 22 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Anticancer Drug Paclitaxel with an Insoluble Lecithin Phospholipon® 90 H and Ethyl Cellulose by Spray Drying

[00123] A dry powder of fast dissolving solid matrix comprising paclitaxel, Phospholipon® 90 H and ethyl cellulose then prepared by spray drying the solution using the method described in Example 13.

EXAMPLE 23 Preparation of a Fast Dissolving Matrix Comprising the Insoluble Immunosuppressant Drug Rapamycin with Alpha-tocopheryl Succinate (ATS) by Vacuum Drying

[00124] A dry powder of fast dissolving solid matrix comprising rapamycin and ATS is prepared by spray drying the solution using the method described in Example 1.

EXAMPLE 24 Preparation of a Fast Dissolving Matrix Comprising the an Insoluble Erectile Dysfunction Therapy Drug Sildenafil Citrate with Insoluble Zein and Phospholipon® 90 H by Spray Drying

[00125] A dry powder of fast dissolving solid matrix comprising sildenafil citrate, zein and Phospholipon® 90 is prepared by spray drying the solution using the method described in Example 2.

[00126] The contents of the articles, patents, and patent applications, and all other documents and electronically available information mentioned or cited herein, are hereby incorporated by reference for purposes cited. Applicants reserve the right to physically incorporate into this application any and all materials and information from any such articles, patents, patent applications, or other documents.

[00127] Other embodiments are set forth within the following claims.

WHAT IS CLAIMED IS:

1. A solid composition for improving the bioavailability of a substantially water-insoluble pharmacologically active agent comprising: (1) a substantially water-insoluble pharmacologically active agent, and (2) a substantially water–insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients wherein the substantially water-insoluble pharmacologically active agent is dispersed in a solid matrix and wherein said pharmacologically active agent in said matrix is substantially free of the original crystalline form.

2. The composition of claim 1, wherein said composition has particle size less than about 500 micron in diameter.

3. The composition of claim 1, wherein said composition has particle size less than about 200 micron in diameter.

4. A solid composition comprising: (1) a substantially water-insoluble pharmacologically active agent, and (2) a substantially water–insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients wherein the substantially water-insoluble pharmacologically active agent is dispersed in a solid matrix and wherein said pharmacologically active agent in said matrix is substantially free of the original crystalline form and wherein the composition has particle size less than about 500 micron in diameter.

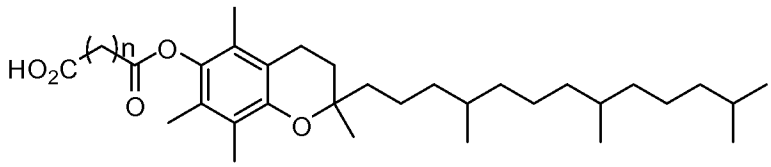
5. A composition according to any of the preceding claims, wherein said composition is in the form of a powder, granule or pellet.

6. A composition according to any of the preceding claims, wherein said composition is filled into capsules or compressed into tablets, optionally containing other capsule or tablet excipients.

7. A composition according to any of the preceding claims, wherein said composition is formulated for oral, topical, inhalation or transmucosal drug delivery.

8. The composition of any of the preceding claims, wherein said nutrients comprise substantially water-insoluble zein, casein, whey, collagen, gelatin, lecithin of high melting point, alpha-tocopherol semi-ester derivatives, amino acids, cellulose, or combinations thereof.

9. The composition of claim 8, wherein the alpha-tocopherol derivative comprises a compound of formula I, its salts or solvates,



(I)

wherein n = 0 – 7.

10. The composition of claim 9, wherein the alpha-tocopherol derivative comprises alpha-tocopheryl succinate, its salts or solvates.

11. The composition according to any of the preceding claims, wherein said matrix forming material is a combination of zein and alpha-tocopheryl succinate, its salts or solvates at a weight ratio in the range of 1:99 to 99:1.

12. The composition according to any of the preceding claims, wherein said matrix forming material comprises in the range of 20% to 99% by weight of the composition.

13. The composition according to any of the preceding claims, wherein the composition exhibits faster dissolution in an aqueous medium, relative to the water-insoluble pharmacologically active agent in the absence of said matrix forming material.

14. A composition comprising (1) a substantially water-insoluble pharmacologically active agent and (2) zein, alpha-tocopherol derivative, lecithin of high melting point, or a combination thereof, wherein the composition improves the bioavailability of said substantially water-insoluble pharmacologically active agent, and wherein said composition is in the form of a free-flowing, compressible and non-hygroscopic powder.

15. A method for delivery of a substantially water-insoluble pharmacologically active agent to a subject in need thereof, said method comprising administering to said subject an effective amount of a composition according to any of the preceding claims.

16. A fast dissolving particle comprising a substantially water-insoluble pharmacologically active agent dispersed in a substantially water-insoluble matrix comprising enzyme digestible or bile soluble nutrients, wherein said fast dissolving particle is in the form of a free-flowing, compressible and non-hygroscopic powder.

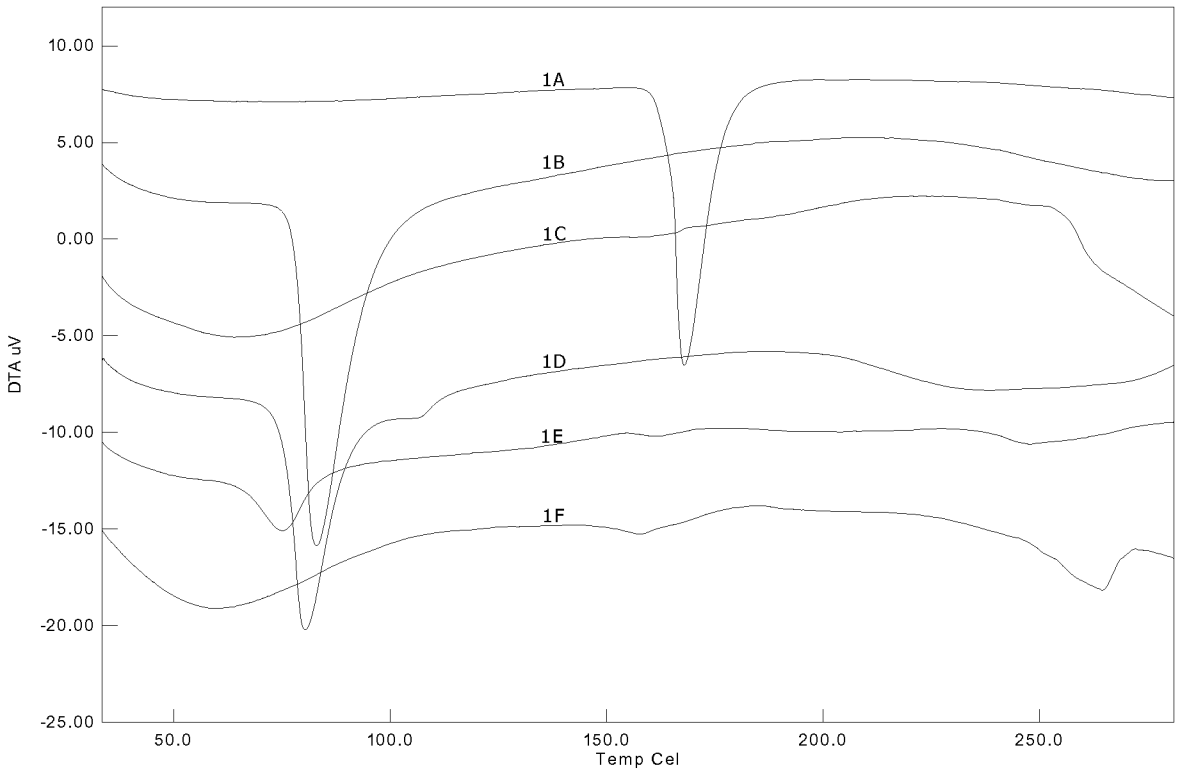
17. A process for preparing a solid matrix in the form of a free-flowing, compressible and non-hygroscopic powder comprising a substantially water-insoluble pharmacologically active agent or salt or solvate thereof, dispersed in a substantially water-insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients therefor, said process comprising:
(a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and the substantially water-insoluble matrix forming material therefor in one or more solvents; and
(b) removing solvent(s) under suitable conditions.

18. A process for preparing a solid composition for improving the bioavailability of a substantially water-insoluble pharmacologically active agent, said process comprising
(a) dissolving the substantially water-insoluble pharmacologically active agent or salt or solvate thereof and a substantially water-insoluble matrix forming material comprising enzyme digestible or bile soluble nutrients in at least one or more solvents; and
(b) removing said solvent(s) under suitable conditions.

19. The process of claim 18, wherein step (b) is carried out by vacuum drying, freeze-drying, air drying or spray drying.

20. The process according to claims 17-19, further comprising pulverizing, ball-milling, comminuting or jet milling to form a free-flowing, compressible and non-hydroscopic powder wherein step (b) is carried out to form particles of size in less than 500 micron in diameter.

FIGURE 1A-1F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-5.00
-10.00
-15.00
-20.00
-25.00
DTA uV
1A
1B
1C
1D
1E
1F
50.0
100.0
150.0
200.0
250.0
Temp Cel

FIGURE 2

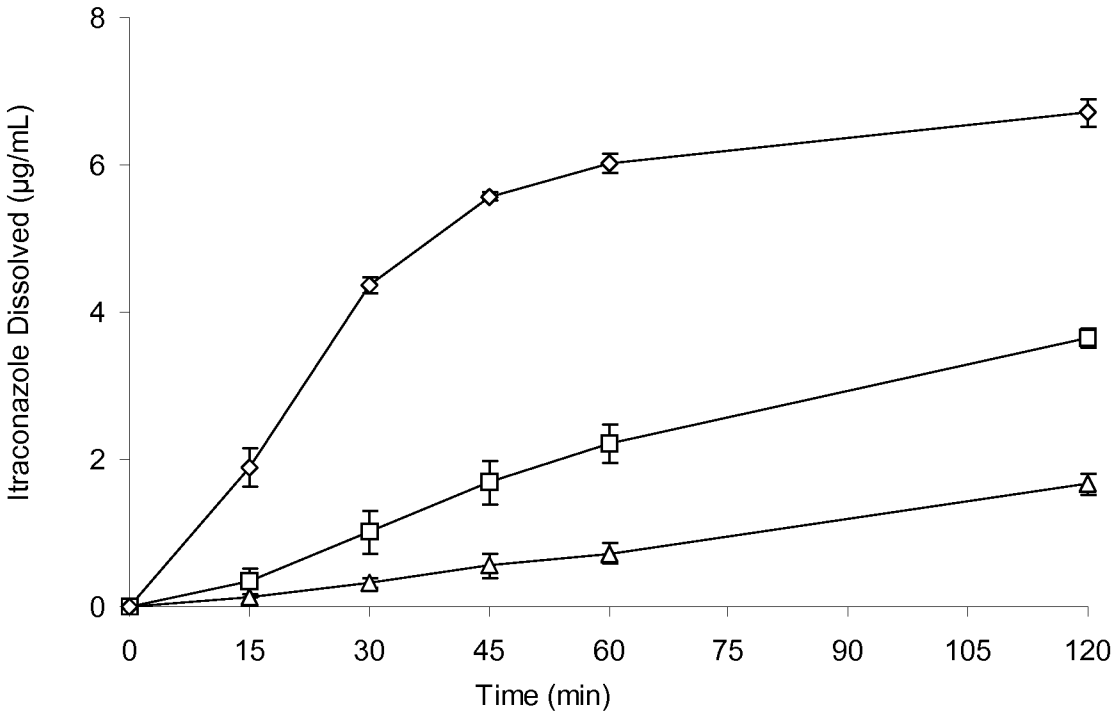
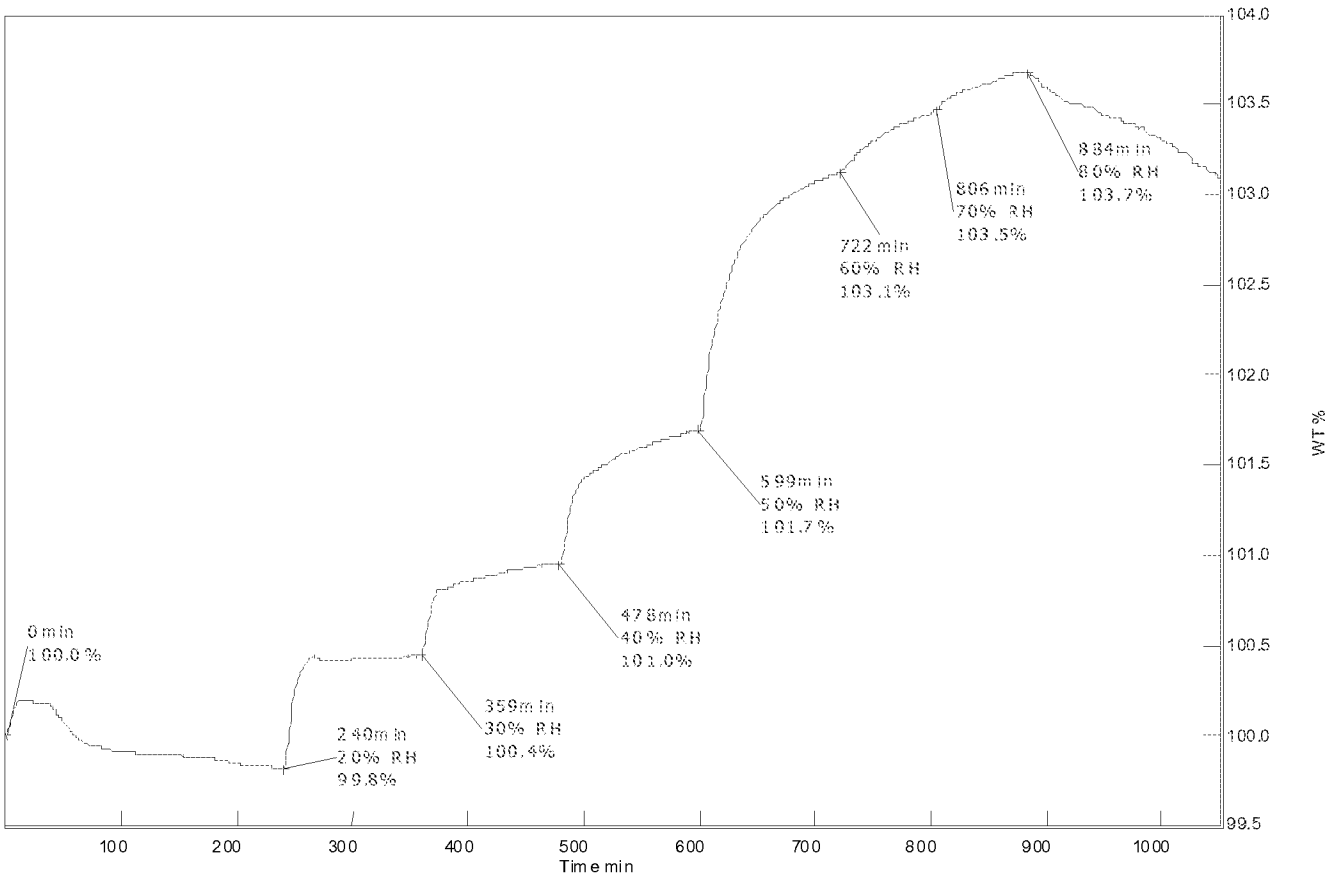

Itraconazole Dissolved (µg/mL)
8
6
4
2
0
0
15
30
45
60
75
90
105
120
Time (min)

FIGURE 3


0 min
100.0 %
240 min
20% RH
99.8%
359 min
30% RH
100.4%
478 min
40% RH
101.0%
599 min
50% RH
101.7%
722 min
60% RH
103.1%
806 min
70% RH
103.5%
884 min
80% RH
103.7%
104.0
103.5
103.0
102.5
102.0
101.5
101.0
100.5
100.0
99.5
WT %
100
200
300
400
500
600
700
800
900
1000
Time min