PROCESS FOR PRODUCTION OF ESSENTIALLY SOLVENT-FREE SMALL PARTICLES

CROSS-REFERENCE TO RELATED APPLICATIONS:

This application is a continuation-in-part of application serial no. 10/390,333 filed on March 17, 2003, which is a continuation-in-part of application serial no. 10/246,802 filed on September 17, 2002, which is a continuation-in-part of application serial no. 10/035,821 filed on October 19, 2001, which is a continuation-in-part of application serial no. 09/953,979 filed September 17, 2001 which is a continuation-in-part of application serial no. 09/874,637 filed on June 5, 2001, which claims priority from provisional application serial no. 60/258,160 filed December 22, 2000. All of the above-mentioned applications are incorporated herein by reference and made a part hereof.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT:

Not Applicable.

BACKGROUND OF THE INVENTION:

Technical Field

The present invention is concerned with the formation of small particles of an organic compound by mixing a solution of the organic compound dissolved in a water-miscible organic solvent with an aqueous medium to form a mix and simultaneously homogenizing the mix while continuously removing the organic solvent to form an aqueous suspension of small particles essentially free of the organic solvent. These processes are preferably used to prepare an aqueous suspension of small particles of a poorly water-soluble, pharmaceutically active compound suitable for *in vivo* delivery by an administrative route such as parenteral, oral, pulmonary, nasal, buccal, topical, ophthalmic, rectal, vaginal, transdermal or the like.

Background Art

There are an ever-increasing number of organic compounds being formulated for therapeutic or diagnostic effects that are poorly soluble or insoluble in aqueous solutions. Such drugs provide challenges to delivering them by the administrative

routes detailed above. Compounds that are insoluble in water can have significant benefits when formulated as a stable suspension of sub-micron particles. Accurate control of particle size is essential for safe and efficacious use of these formulations. Particles must be less than seven microns in diameter to safely pass through capillaries without causing emboli (Allen et al., 1987; Davis and Taube, 1978; Schroeder et al., 1978; Yokel et al., 1981). One solution to this problem is the production of small particles of the insoluble drug candidate and the creation of a microparticulate or nanoparticulate suspension. In this way, drugs that were previously unable to be formulated in an aqueous based system can be made suitable for intravenous administration. Suitability for intravenous administration includes small particle size (<7 μm), low toxicity (as from toxic formulation components or residual solvents), and bioavailability of the drug particles after administration.

Preparations of small particles of water insoluble drugs may also be suitable for oral, pulmonary, topical, ophthalmic, nasal, buccal, rectal, vaginal, transdermal administration, or other routes of administration. The small size of the particles improves the dissolution rate of the drug, and hence improving its bioavailability and potentially its toxicity profiles. When administered by these routes, it may be desirable to have particle size in the range of 5 to 100 μm, depending on the route of administration, formulation, solubility, and bioavailability of the drug. For example, for oral administration, it is desirable to have a particle size of less than about 7 μm. For pulmonary administration, the particles are preferably less than about 10 μm in size.

SUMMARY OF THE INVENTION:

The present invention provides methods for preparing an aqueous suspension of small particles of an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent that is aqueous. The methods include (i) dissolving the organic compound in the water-miscible first solvent to form a solution; (ii) mixing the solution with the second solvent to form a mix; and (iii) simultaneously homogenizing the mix and continuously removing the first solvent from the mix to form an aqueous suspension of small particles having an average effective particle size of less than about 100 μm. The aqueous suspension is essentially free of the first solvent. In an embodiment, the mixing of the first solution with the second solvent is

carried out simultaneously with homogenizing the mix while continuously removing the first solvent. The water-miscible first solvent can be a protic organic solvent or an aprotic organic solvent. In a preferred embodiment, the process further includes mixing one or more surface modifiers into the first water-miscible solvent or the second solvent, or both the first water-miscible solvent and the second solvent.

The methods can further include sterilizing the aqueous suspension by heat sterilization or gamma irradiaition. In an embodiment, heat sterilization is effected within the homogenizer in which the homogenizer serves as a heating and pressurization source for sterilization. Sterilization can also be accomplished by sterile filtering the solution and the second solvent before mixing and carrying out the subsequent steps under aseptic conditions.

The method can also further include removing the aqueous solvent to form a dry powder of the small particles.

These processes are preferably used to prepare an aqueous suspension of small particles of a poorly water-soluble, pharmaceutically active compound suitable for *in vivo* delivery by an administrative route such as parenteral, oral, pulmonary, nasal, buccal, topical, ophthalmic, rectal, vaginal, transdermal or the like.

These and other aspects and attributes of the present invention will be discussed with reference to the following drawings and accompanying specification.

BRIEF DESCRIPTION OF THE DRAWINGS:

FIG. 1 shows a diagrammatic representation of one method of the present invention;

FIG. 2 shows a diagrammatic representation of another method of the present invention;

FIG. 3 shows amorphous particles prior to homogenization;

FIG. 4 shows particles after annealing by homogenization;

FIG. 5 is an X-Ray diffractogram of microprecipitated itraconazole with polyethylene glycol-660 12-hydroxystearate before and after homogenization;

FIG. 6 shows Carbamazepine crystals before homogenization;

FIG. 7 shows Carbamazepine microparticulate after homogenization (Avestin C-50);

FIG. 8 is a diagram illustrating the Microprecipitation Process for Prednisolone;

FIG. 9 is a photomicrograph of prednisolone suspension before homogenization;

FIG. 10 is a photomicrograph of prednisolone suspension after homogenization;

FIG. 11 illustrates a comparison of size distributions of nanosuspensions (this invention) and a commercial fat emulsion;

FIG. 12 shows the X-ray powder diffraction patterns for raw material itraconazole (top) and SMP-2-PRE (bottom). The raw material pattern has been shifted upward for clarity;

FIG. 13a shows the DSC trace for raw material itraconazole;

FIG. 13b shows the DSC trace for SMP-2-PRE;

FIG. 14 illustrates the DSC trace for SMP-2-PRE showing the melt of the less stable polymorph upon heating to 160°C, a recrystallization event upon cooling, and the subsequent melting of the more stable polymorph upon reheating to 180°C;

FIG. 15 illustrates a comparison of SMP-2-PRE samples after homogenization. Solid line = sample seeded with raw material itraconazole. Dashed line = unseeded sample. The solid line has been shifted by 1 W/g for clarity;

FIG. 16 illustrates the effect of seeding during precipitation. Dashed line = unseeded sample, solid line = sample seeded with raw material itraconazole. The unseeded trace (dashed line) has been shifted upward by 1.5 W/g for clarity;

FIG. 17 illustrates the effect of seeding the drug concentrate through aging. Top x-ray diffraction pattern is for crystals prepared from fresh drug concentrate, and is consistent with the stable polymorph (see FIG. 12, top). Bottom pattern is for crystals prepared from aged (seeded) drug concentrate, and is consistent with the metastable polymorph (see FIG. 12, bottom). The top pattern has been shifted upward for clarity;

FIG. 18 is a schematic diagram illustrating the combined and continuous solvent removal process for producing an aqueous suspension of small particles which is essentially solvent-free;

FIG. 19 is a schematic diagram illustrating a continuous solvent removal process for producing an aqueous suspension of small particles which is essentially solvent-free using a cross-flow filtration;

FIG. 20 is a schematic diagram illustrating a continuous solvent removal process for producing an aqueous suspension of small particles of itraconazole which is essentially solvent-free;

FIG. 21 is a graph illustrating the removal NMP in scale up of the process described in Example 19 from the laboratory scale of 200 mL to the pilot scale of 10 L; and

FIG. 22 is a schematic diagram illustrating a combined, continuous process for producing aqueous suspension of small particles substantially free of solvent.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention is susceptible of embodiments in many different forms. Preferred embodiments of the invention are disclosed with the understanding that the present disclosure is to be considered as exemplifications of the principles of the invention and are not intended to limit the broad aspects of the invention to the embodiments illustrated.

The present invention provides compositions and methods for forming small particles of an organic compound. An organic compound for use in the process of this invention is any organic chemical entity whose solubility decreases from one solvent to another. This organic compound might be a pharmaceutically active compound, which can be selected from therapeutic agents, diagnostic agents, cosmetics, nutritional supplements, and pesticides.

The therapeutic agents can be selected from a variety of known pharmaceuticals such as, but are not limited to: analgesics, anesthetics, analeptics, adrenergic agents, adrenergic blocking agents, adrenolytics, adrenocorticoids, adrenomimetics, anticholinergic agents, anticholinesterases, anticonvulsants, alkylating agents, alkaloids, allosteric inhibitors, anabolic steroids, anorexiants, antacids, antidiarrheals, antidotes, antifolics, antipyretics, antirheumatic agents, psychotherapeutic agents, neural blocking agents, anti-inflammatory agents, antihelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antifungals, antihistamines, antihypertensive agents,

antimuscarinic agents, antimycobacterial agents, antimalarials, antiseptics, antineoplastic agents, antiprotozoal agents, immunosuppressants, immunostimulants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, hemostatics, hematological agents, hemoglobin modifiers, hormones, hypnotics, immuriological agents, antihyperlipidemic and other lipid regulating agents, muscarinics, muscle relaxants, parasympathomimetics, parathyroid calcitonin, prostaglandins, radio-pharmaceuticals, sedatives, sex hormones, anti-allergic agents, stimulants, sympathomimetics, thyroid agents, vasodilators, vaccines, vitamins, and xanthines. Antineoplastic, or anticancer agents, include but are not limited to paclitaxel and derivative compounds, and other antineoplastics selected from the group consisting of alkaloids, antimetabolites, enzyme inhibitors, alkylating agents and antibiotics. The therapeutic agent can also be a biologic, which includes but is not limited to proteins, polypeptides, carbohydrates, polynucleotides, and nucleic acids. The protein can be an antibody, which can be polyclonal or monoclonal.

Diagnostic agents include the x-ray imaging agents and contrast media. Examples of x-ray imaging agents include WIN-8883 (ethyl 3,5-diacetamido-2,4,6-triiodobenzoate) also known as the ethyl ester of diatrazoic acid (EEDA), WIN 67722, i.e., (6-ethoxy-6-oxohexyl-3,5-bis(acetamido)-2,4,6-triiodobenzoate; ethyl-2-(3,5-bis(acetamido)-2,4,6-triiodo-benzoyloxy) butyrate (WIN 16318); ethyl diatrizoxyacetate (WIN 12901); ethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy)propionate (WIN 16923); N-ethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy acetamide (WIN 65312); isopropyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy) acetamide (WIN 12855); diethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy malonate (WIN 67721); ethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy) phenylacetate (WIN 67585); propanedioic acid, [[3,5-bis(acetylamino)-2,4,5-triodobenzoyl]oxy]bis(1-methyl)ester (WIN 68165); and benzoic acid, 3,5-bis(acetylamino)-2,4,6-triodo-4-(ethyl-3-ethoxy-2-butenoate) ester (WIN 68209). Preferred contrast agents include those that are expected to disintegrate relatively rapidly under physiological conditions, thus minimizing any particle associated inflammatory response. Disintegration may result from enzymatic

hydrolysis, solubilization of carboxylic acids at physiological pH, or other mechanisms. Thus, poorly soluble iodinated carboxylic acids such as iodipamide, diatrizoic acid, and metrizoic acid, along with hydrolytically labile iodinated species such as WIN 67721, WIN 12901, WIN 68165, and WIN 68209 or others may be preferred.

Other contrast media include, but are not limited to, particulate preparations of magnetic resonance imaging aids such as gadolinium chelates, or other paramagnetic contrast agents. Examples of such compounds are gadopentetate dimeglumine (Magnevist®) and gadoteridol (Prohance®).

A description of these classes of therapeutic agents and diagnostic agents and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989 which is incorporated herein by reference and made a part hereof. The therapeutic agents and diagnostic agents are commercially available and/or can be prepared by techniques known in the art.

A cosmetic agent is any active ingredient capable of having a cosmetic activity. Examples of these active ingredients can be, *inter alia*, emollients, humectants, free radical-inhibiting agents, anti-inflammatories, vitamins, depigmenting agents, anti-acne agents, antiseborrhoeics, keratolytics, slimming agents, skin coloring agents and sunscreen agents, and in particular linoleic acid, retinol, retinoic acid, ascorbic acid alkyl esters, polyunsaturated fatty acids, nicotinic esters, tocopherol nicotinate, unsaponifiables of rice, soybean or shea, ceramides, hydroxy acids such as glycolic acid, selenium derivatives, antioxidants, beta-carotene, gamma-orizanol and stearyl glycerate. The cosmetics are commercially available and/or can be prepared by techniques known in the art.

Examples of nutritional supplements contemplated for use in the practice of the present invention include, but are not limited to, proteins, carbohydrates, water-soluble vitamins (e.g., vitamin C, B-complex vitamins, and the like), fat-soluble vitamins (e.g., vitamins A, D, E, K, and the like), and herbal extracts. The nutritional supplements are commercially available and/or can be prepared by techniques known in the art.

The term pesticide is understood to encompass herbicides, insecticides, acaricides, nematicides, ectoparasiticides and fungicides. Examples of compound

classes to which the pesticide in the present invention may belong include ureas, triazines, triazoles, carbamates, phosphoric acid esters, dinitroanilines, morpholines, acylalanines, pyrethroids, benzilic acid esters, diphenylethers and polycyclic halogenated hydrocarbons. Specific examples of pesticides in each of these classes are listed in Pesticide Manual, 9th Edition, British Crop Protection Council. The pesticides are commercially available and/or can be prepared by techniques known in the art.

Preferably the organic compound or the pharmaceutically active compound is poorly water-soluble. What is meant by "poorly water soluble" is a solubility of the compound in water of less than about 10 mg/mL, and preferably less than 1 mg/mL. These poorly water-soluble agents are most suitable for aqueous suspension preparations since there are limited alternatives of formulating these agents in an aqueous medium.

The present invention can also be practiced with water-soluble pharmaceutically active compounds, by entrapping these compounds in a solid carrier matrix (for example, polylactide- polyglycolide copolymer, albumin, starch), or by encapsulating these compounds in a surrounding vesicle that is impermeable to the pharmaceutical compound. This encapsulating vesicle can be a polymeric coating such as polyacrylate. Further, the small particles prepared from these water soluble pharmaceutical agents can be modified to improve chemical stability and control the pharmacokinetic properties of the agents by controlling the release of the agents from the particles. Examples of water-soluble pharmaceutical agents include, but are not limited to, simple organic compounds, proteins, peptides, nucleotides, oligonucleotides, and carbohydrates.

The particles of the present invention have an average effective particle size of generally less than about 100 μm as measured by dynamic light scattering methods, e.g., photocorrelation spectroscopy, laser diffraction, low-angle laser light scattering (LALLS), medium-angle laser light scattering (MALLS), light obscuration methods (Coulter method, for example), rheology, or microscopy (light or electron). However, the particles can be prepared in a wide range of sizes, such as from about 20 μm to about 10 nm, from about 10 μm to about 10 nm, from about 2 μm to about 10 nm, from about 1 μm to about 10 nm, from about 400 nm to about 50 nm, from about 200

nm to about 50 nm or any range or combination of ranges therein. The preferred average effective particle size depends on factors such as the intended route of administration, formulation, solubility, toxicity and bioavailability of the compound.

To be suitable for parenteral administration, the particles preferably have an average effective particle size of less than about 7 μm, and more preferably less than about 2 μm or any range or combination of ranges therein. Parenteral administration includes intravenous, intra-arterial, intrathecal, intraperitoneal, intraocular, intra-articular, intradural, intraventricular, intrapericardial, intramuscular, intradermal or subcutaneous injection.

Particles sizes for oral dosage forms can be in excess of 2 μm. The particles can range in size up to about 100 μm, provided that the particles have sufficient bioavailability and other characteristics of an oral dosage form. Oral dosage forms include tablets, capsules, caplets, soft and hard gel capsules, or other delivery vehicle for delivering a drug by oral administration.

The present invention is further suitable for providing particles of the organic compound in a form suitable for pulmonary administration. Particles sizes for pulmonary dosage forms can be in excess of 500 nm and typically less than about 10 μm. The particles in the suspension can be aerosolized and administered by a nebulizer for pulmonary administration. Alternatively, the particles can be administered as dry powder by a dry powder inhaler after removing the liquid phase from the suspension, or the dry powder can be resuspended in a non-aqueous propellant for administration by a metered dose inhaler. An example of a suitable propellant is a hydrofluorocarbon (HFC) such as HFC-134a (1,1,1,2-tetrafluoroethane) and HFC-227ea (1,1,1,2,3,3,3-heptafluoropropane). Unlike chlorofluorcarbons (CFC's), HFC's exhibit little or no ozone depletion potential.

Dosage forms for other routes of delivery, such as nasal, topical, ophthalmic, nasal, buccal, rectal, vaginal, transdermal and the like can also be formulated from the particles made from the present invention.

The processes for preparing the particles can be separated into four general categories. Each of the categories of processes share the steps of: (1) dissolving an organic compound in a water miscible first solvent to create a first solution, (2) mixing the first solution with a second solvent of water to precipitate the organic compound to

create a pre-suspension, and (3) adding energy to the presuspension in the form of high-shear mixing or heat, or a combination of both, to provide a stable form of the organic compound having the desired size ranges defined above. The mixing steps and the adding energy step can be carried out in consecutive steps or simultaneously.

The categories of processes are distinguished based upon the physical properties of the organic compound as determined through x-ray diffraction studies, differential scanning calorimetry (DSC) studies, or other suitable study conducted prior to the energy-addition step and after the energy-addition step. In the first process category, prior to the energy-addition step the organic compound in the presuspension takes an amorphous form, a semi-crystalline form or a supercooled liquid form and has an average effective particle size. After the energy-addition step the organic compound is in a crystalline form having an average effective particle size essentially the same or less than that of the presuspension.

In the second process category, prior to the energy-addition step the organic compound is in a crystalline form and has an average effective particle size. After the energy-addition step the organic compound is in a crystalline form having essentially the same average effective particle size as prior to the energy-addition step but the crystals after the energy-addition step are less likely to aggregate.

The lower tendency of the organic compound to aggregate is observed by laser dynamic light scattering and light microscopy.

In the third process category, prior to the energy-addition step the organic compound is in a crystalline form that is friable and has an average effective particle size. What is meant by the term "friable" is that the particles are fragile and are more easily broken down into smaller particles. After the energy-addition step the organic compound is in a crystalline form having an average effective particle size smaller than the crystals of the pre-suspension. By taking the steps necessary to place the organic compound in a crystalline form that is friable, the subsequent energy-addition step can be carried out more quickly and efficiently when compared to an organic compound in a less friable crystalline morphology.

In the fourth process category, the first solution and second solvent are simultaneously subjected to the energy-addition step. Thus, the physical properties of the organic compound before and after the energy addition step were not measured.

The energy-addition step can be carried out in any fashion wherein the presuspension or the first solution and second solvent are exposed to cavitation, shearing or impact forces. In one preferred form of the invention, the energy-addition step is an annealing step. Annealing is defined in this invention as the process of converting matter that is thermodynamically unstable into a more stable form by single or repeated application of energy (direct heat or mechanical stress), followed by thermal relaxation. This lowering of energy may be achieved by conversion of the solid form from a less ordered to a more ordered lattice structure. Alternatively, this stabilization may occur by a reordering of the surfactant molecules at the solid-liquid interface.

These four process categories will be discussed separately below. It should be understood, however, that the process conditions such as choice of surfactants or combination of surfactants, amount of surfactant used, temperature of reaction, rate of mixing of solutions, rate of precipitation and the like can be selected to allow for any drug to be processed under any one of the categories discussed next.

The first process category, as well as the second, third, and fourth process categories, can be further divided into two subcategories, Method A and B, shown diagrammatically in FIGS. 1 and 2.

The first solvent according to the present invention is a solvent or mixture of solvents in which the organic compound of interest is relatively soluble and which is miscible with the second solvent. Such solvents include, but are not limited to water-miscible protic compounds, in which a hydrogen atom in the molecule is bound to an electronegative atom such as oxygen, nitrogen, or other Group VA, VIA and VII A in the Periodic Table of elements. Examples of such solvents include, but are not limited to, alcohols, amines (primary or secondary), oximes, hydroxamic acids, carboxylic acids, sulfonic acids, phosphonic acids, phosphoric acids, amides and ureas.

Other examples of the first solvent also include aprotic organic solvents. Some of these aprotic solvents can form hydrogen bonds with water, but can only act as proton acceptors because they lack effective proton donating groups. One class of aprotic solvents is a dipolar aprotic solvent, as defined by the International Union of Pure and Applied Chemistry (IUPAC Compendium of Chemical Terminology, 2nd Ed., 1997):

A solvent with a comparatively high relative permittivity (or dielectric constant), greater than ca. 15, and a sizable permanent dipole moment, that cannot donate suitably labile hydrogen atoms to form strong hydrogen bonds, e.g. dimethyl sulfoxide.

Dipolar aprotic solvents can be selected from the group consisting of: amides (fully substituted, with nitrogen lacking attached hydrogen atoms), ureas (fully substituted, with no hydrogen atoms attached to nitrogen), ethers, cyclic ethers, nitriles, ketones, sulfones, sulfoxides, fully substituted phosphates, phosphonate esters, phosphoramides, nitro compounds, and the like. Dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidinone (NMP), 2-pyrrolidinone, 1,3-dimethylimidazolidinone (DMI), dimethylacetamide (DMA), dimethylformamide (DMF), dioxane, acetone, tetrahydrofuran (THF), tetramethylenesulfone (sulfolane), acetonitrile, and hexamethylphosphoramide (HMPA), nitromethane, among others, are members of this class.

Solvents may also be chosen that are generally water-immiscible, but have sufficient water solubility at low volumes (less than 10%) to act as a water-miscible first solvent at these reduced volumes. Examples include aromatic hydrocarbons, alkenes, alkanes, and halogenated aromatics, halogenated alkenes and halogenated alkanes. Aromatics include, but are not limited to, benzene (substituted or unsubstituted), and monocyclic or polycyclic arenes. Examples of substituted benzenes include, but are not limited to, xylenes (ortho, meta, or para), and toluene. Examples of alkanes include but are not limited to hexane, neopentane, heptane, isooctane, and cyclohexane. Examples of halogenated aromatics include, but are not restricted to, chlorobenzene, bromobenzene, and chlorotoluene. Examples of halogenated alkanes and alkenes include, but are not restricted to, trichloroethane, methylene chloride, ethylenedichloride (EDC), and the like.

Examples of the all of the above solvent classes include but are not limited to: N-methyl-2-pyrrolidinone (also called N-methyl-2-pyrrolidone), 2-pyrrolidinone (also called 2-pyrrolidone), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylsulfoxide, dimethylacetamide, acetic acid, lactic acid, methanol, ethanol, isopropanol, 3-pentanol, n-propanol, benzyl alcohol, glycerol, butylene glycol (butanediol), ethylene glycol,

propylene glycol, mono- and diacylated monoglycerides (such as glyceryl caprylate), dimethyl isosorbide, acetone, dimethylsulfone, dimethylformamide, 1,4-dioxane, tetramethylenesulfone (sulfolane), acetonitrile, nitromethane, tetramethylurea, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF), dioxane, diethylether, tert-butylmethyl ether (TBME), aromatic hydrocarbons, alkenes, alkanes, halogenated aromatics, halogenated alkenes, halogenated alkanes, xylene, toluene, benzene, substituted benzene, ethyl acetate, methyl acetate, butyl acetate, chlorobenzene, bromobenzene, chlorotoluene, trichloroethane, methylene chloride, ethylenedichloride (EDC), hexane, neopentane, heptane, isooctane, cyclohexane, polyethylene glycol (PEG, for example, PEG-4, PEG-8, PEG-9, PEG-12, PEG-14, PEG-16, PEG-120, PEG-75, PEG-150), polyethylene glycol esters (examples such as PEG-4 dilaurate, PEG-20 dilaurate, PEG-6 isostearate, PEG-8 palmitostearate, PEG-150 palmitostearate), polyethylene glycol sorbitans (such as PEG-20 sorbitan isostearate), polyethylene glycol monoalkyl ethers (examples such as PEG-3 dimethyl ether, PEG-4 dimethyl ether), polypropylene glycol (PPG), polypropylene alginate, PPG-10 butanediol, PPG-10 methyl glucose ether, PPG-20 methyl glucose ether, PPG-15 stearyl ether, propylene glycol dicaprylate/dicaprate, propylene glycol laurate, and glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether). A preferred first solvent is N-methyl-2-pyrrolidinone. Another preferred first solvent is lactic acid.

The second solvent is an aqueous solvent. This aqueous solvent may be water by itself. This solvent may also contain buffers, salts, surfactant(s), water-soluble polymers, and combinations of these excipients.

Method A

In Method A (see FIG. 1), the organic compound ("drug") is first dissolved in the first solvent to create a first solution. The organic compound can be added from about 0.1% (w/v) to about 50% (w/v) depending on the solubility of the organic compound in the first solvent. Heating of the concentrate from about 30°C to about 100°C may be necessary to ensure total dissolution of the compound in the first solvent.

A second aqueous solvent is provided with one or more optional surface modifiers such as an anionic surfactant, a cationic surfactant, a nonionic surfactant or a biologically surface active molecule added thereto. Suitable anionic surfactants

include but are not limited to alkyl sulfonates, alkyl phosphates, alkyl phosphonates, potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl choline, phosphatidyl glycerol, phosphatidyl inosine, phosphatidylserine, phosphatidic acid and their salts, glyceryl esters, sodium carboxymethylcellulose, cholic acid and other bile acids (e.g., cholic acid, deoxycholic acid, glycocholic acid, taurocholic acid, glycodeoxycholic acid) and salts thereof (e.g., sodium deoxycholate, etc.). Suitable cationic surfactants include but are not limited to quaternary ammonium compounds, such as benzalkonium chloride, cetyltrimethylammonium bromide, chitosans, lauryldimethylbenzylammonium chloride, acyl carnitine hydrochlorides, or alkyl pyridinium halides. As anionic surfactants, phospholipids may be used. Suitable phospholipids include, for example phosphatidylcholine, phosphatidylethanolamine, diacyl-glycero-phosphoethanolamine (such as dimyristoyl-glycero-phosphoethanolamine (DMPE), dipalmitoyl-glycero-phosphoethanolamine (DPPE), distearoyl-glycero-phosphoethanolamine (DSPE), and dioleolyl-glycero-phosphoethanolamine (DOPE)), phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg or soybean phospholipid or a combination thereof. The phospholipid may be salted or desalted, hydrogenated or partially hydrogenated or natural semisynthetic or synthetic. The phospholipid may also be conjugated with a water-soluble or hydrophilic polymer. A preferred polymer is polyethylene glycol (PEG), which is also known as the monomethoxy polyethyleneglycol (mPEG). The molecule weights of the PEG can vary, for example, from 200 to 50,000. Some commonly used PEG's that are commercially available include PEG 350, PEG 550, PEG 750, PEG 1000, PEG 2000, PEG 3000, and PEG 5000. The phospholipid or the PEG-phospholipid conjugate may also incorporate a functional group which can covalently attach to a ligand including but not limited to proteins, peptides, carbohydrates, glycoproteins, antibodies, or pharmaceutically active agents. These functional groups may conjugate with the ligands through, for example, amide bond formation, disulfide or thioether formation, or biotin/streptavidin binding. Examples of the ligand-binding functional groups include but are not limited to hexanoylamine, dodecanylamine, 1,12-dodecanedicarboxylate, thioethanol, 4-(p-maleimidophenyl)butyramide (MPB), 4-(p-

maleimidomethyl)cyclohexane-carboxamide (MCC), 3-(2-pyridyldithio)propionate (PDP), succinate, glutarate, dodecanoate, and biotin.

Suitable nonionic surfactants include: polyoxyethylene fatty alcohol ethers (Macrogol and Brij), polyoxyethylene sorbitan fatty acid esters (Polysorbates), polyoxyethylene fatty acid esters (Myrj), sorbitan esters (Span), glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether alcohols, polyoxyethylene-polyoxypropylene copolymers (poloxamers), poloxamines, methylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, noncrystalline cellulose, polysaccharides including starch and starch derivatives such as hydroxyethylstarch (HES), polyvinyl alcohol, and polyvinylpyrrolidone. In a preferred form of the invention, the nonionic surfactant is a polyoxyethylene and polyoxypropylene copolymer and preferably a block copolymer of propylene glycol and ethylene glycol. Such polymers are sold under the tradename POLOXAMER also sometimes referred to as PLURONIC®, and sold by several suppliers including Spectrum Chemical and Ruger. Among polyoxyethylene fatty acid esters is included those having short alkyl chains. One example of such a surfactant is SOLUTOL® HS 15, polyethylene-660-hydroxystearate, manufactured by BASF Aktiengesellschaft.

Surface-active biological molecules include such molecules as albumin, casein, hirudin or other appropriate proteins. Polysaccharide biologics are also included, and consist of but not limited to, starches, heparin and chitosans.

It may also be desirable to add a pH adjusting agent to the second solvent such as sodium hydroxide, hydrochloric acid, tris buffer or citrate, acetate, lactate, meglumine, or the like. The second solvent should have a pH within the range of from about 3 to about 11.

For oral dosage forms one or more of the following excipients may be utilized: gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens™, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide,

phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

In a preferred form of the invention, the method for preparing small particles of an organic compound includes the steps of adding the first solution to the second solvent. The addition rate is dependent on the batch size, and precipitation kinetics for the organic compound. Typically, for a small-scale laboratory process (preparation of 1 liter), the addition rate is from about 0.05 cc per minute to about 10 cc per minute. During the addition, the solutions should be under constant agitation. It has been observed using light microscopy that amorphous particles, semi-crystalline solids, or a supercooled liquid are formed to create a pre-suspension. The method further includes the step of subjecting the pre-suspension to an energy-addition step to convert the amorphous particles, supercooled liquid or semicrystalline solid to a more stable, crystalline solid state. The resulting particles will have an average effective particles size as measured by dynamic light scattering methods (e.g., photocorrelation spectroscopy, laser diffraction, low-angle laser light scattering (LALLS), medium-angle laser light scattering (MALLS), light obscuration methods (Coulter method, for example), rheology, or microscopy (light or electron) within the ranges set forth above). In process category four, the first solution and the second solvent are combined while simultaneously conducting the energy-addition step.

The energy-addition step involves adding energy through sonication, homogenization, countercurrent flow homogenization, microfluidization, or other methods of providing impact, shear or cavitation forces. The sample may be cooled or heated during this stage. In one preferred form of the invention, the energy-addition step is effected by a piston gap homogenizer such as the one sold by Avestin Inc.

under the product designation EmulsiFlex-C160. In another preferred form of the invention, the energy-addition step may be accomplished by ultrasonication using an ultrasonic processor such as the Vibra-Cell Ultrasonic Processor (600W), manufactured by Sonics and Materials, Inc. In yet another preferred form of the invention, the energy-addition step may be accomplished by use of an emulsification apparatus as described in U.S. Patent No. 5,720,551 which is incorporated herein by reference and made a part hereof.

Depending upon the rate of energy addition, it may be desirable to adjust the temperature of the processed sample to within the range of from approximately –30°C to 30°C. Alternatively, in order to effect a desired phase change in the processed solid, it may also be necessary to heat the pre-suspension to a temperature within the range of from about 30°C to about 100°C during the energy-addition step.

Method B

Method B differs from Method A in the following respects. The first difference is a surfactant or combination of surfactants is added to the first solution. The surfactants may be selected from the groups of anionic, nonionic, cationic surfactants, and surface-active biological modifiers set forth above.

Comparative Example of Method A and Method B and USPN 5,780,062

United States Patent No. 5,780,062 discloses a process for preparing small particles of an organic compound by first dissolving the compound in a suitable water-miscible first solvent. A second solution is prepared by dissolving a polymer and an amphiphile in aqueous solvent. The first solution is then added to the second solution to form a precipitate that consists of the organic compound and a polymer-amphiphile complex. The '062 Patent does not disclose utilizing the energy-addition step of this invention in Methods A and B. Lack of stability is typically evidenced by rapid aggregation and particle growth. In some instances, amorphous particles recrystallize as large crystals. Adding energy to the pre-suspension in the manner disclosed above typically affords particles that show decreased rates of particle aggregation and growth, as well as the absence of recrystallization upon product storage.

Methods A and B are further distinguished from the process of the '062 patent by the absence of a step of forming a polymer-amphiphile complex prior to

precipitation. In Method A, such a complex cannot be formed as no polymer is added to the diluent (aqueous) phase. In Method B, the surfactant, which may also act as an amphiphile, or polymer, is dissolved with the organic compound in the first solvent. This precludes the formation of any amphiphile-polymer complexes prior to precipitation. In the '062 Patent, successful precipitation of small particles relies upon the formation of an amphiphile-polymer complex prior to precipitation. The '062 Patent discloses the amphiphile-polymer complex forms aggregates in the aqueous second solution. The '062 Patent explains the hydrophobic organic compound interacts with the amphiphile-polymer complex, thereby reducing solubility of these aggregates and causing precipitation. In the present invention, it has been demonstrated that the inclusion of the surfactant or polymer in the first solvent (Method B) leads, upon subsequent addition to second solvent, to formation of a more uniform, finer particulate than is afforded by the process outlined by the '062 Patent.

To this end, two formulations were prepared and analyzed. Each of the formulations has two solutions, a concentrate and an aqueous diluent, which are mixed together and then sonicated. The concentrate in each formulation has an organic compound (itraconazole), a water miscible solvent (N-methyl-2-pyrrolidinone or NMP) and possibly a polymer (poloxamer 188). The aqueous diluent has water, a tris buffer and possibly a polymer (poloxamer 188) and/or a surfactant (sodium deoxycholate). The average particle diameter of the organic particle is measured prior to sonication and after sonication.

The first formulation A has as the concentrate itraconazole and NMP. The aqueous diluent includes water, poloxamer 188, tris buffer and sodium deoxycholate. Thus the aqueous diluent includes a polymer (poloxamer 188), and an amphiphile (sodium deoxycholate), which may form a polymer/amphiphile complex, and, therefore, is in accordance with the disclosure of the '062 Patent. (However, again the '062 Patent does not disclose an energy addition step.)

The second formulation B has as the concentrate itraconazole, NMP and poloxamer 188. The aqueous diluent includes water, tris buffer and sodium deoxycholate. This formulation is made in accordance with the present invention. Since the aqueous diluent does not contain a combination of a polymer (poloxamer)

and an amphiphile (sodium deoxycholate), a polymer/amphiphile complex cannot form prior to the mixing step.

Table 1 shows the average particle diameters measured by laser diffraction on three replicate suspension preparations. An initial size determination was made, after which the sample was sonicated for 1 minute. The size determination was then repeated. The large size reduction upon sonication of Method A was indicative of particle aggregation.

Table 1:

Method	Concentrate	Aqueous Diluent	Average particle diameter (microns)	After sonication (1 minute)
A	itraconazole (18%),N-methyl-2-pyrrolidinone (6 mL)	poloxamer 188 (2.3%),sodium deoxycholate (0.3%)tris buffer (5 mM, pH 8)water (qs to 94 mL)	18.7 10.7 12.1	2.36 2.46 1.93
B	itraconazole (18%)poloxamer 188 (37%)N-methyl-2-pyrrolidinone (6 mL)	sodium deoxycholate (0.3%)tris buffer (5 mM, pH 8)water (qs to 94 mL)	0.194 0.178 0.181	0.198 0.179 0.177

A drug suspension resulting from application of the processes described in this invention may be administered directly as an injectable solution, provided Water for Injection is used in formulation and an appropriate means for solution sterilization is applied. Sterilization may be accomplished by methods well known in the art such as steam or heat sterilization, gamma irradiation and the like. Other sterilization methods, especially for particles in which greater than 99% of the particles are less than 200 nm, would also include pre-filtration first through a 3.0 micron filter followed by filtration through a 0.45-micron particle filter, followed by steam or heat sterilization or sterile filtration through two redundant 0.2-micron membrane filters. Yet another means of sterilization is sterile filtration of the concentrate prepared from the first solvent containing drug and optional surfactant or surfactants and sterile filtration of the aqueous diluent. These are then combined in a sterile mixing container, preferably in an isolated, sterile environment. Mixing, homogenization, and further processing of the suspension are then carried out under aseptic conditions.

Yet another procedure for sterilization would consist of heat sterilization or autoclaving within the homogenizer itself, before, during, or subsequent to the

homogenization step. Processing after this heat treatment would be carried out under aseptic conditions.

Optionally, a solvent-free suspension may be produced by solvent removal after precipitation. This can be accomplished by centrifugation, dialysis, diafiltration, force-field fractionation, high-pressure filtration, reverse osmosis, or other separation techniques well known in the art. Complete removal of N-methyl-2-pyrrolidinone was typically carried out by one to three successive centrifugation runs; after each centrifugation (18,000 rpm for 30 minutes) the supernatant was decanted and discarded. A fresh volume of the suspension vehicle without the organic solvent was added to the remaining solids and the mixture was dispersed by homogenization. It will be recognized by those skilled in the art that other high-shear mixing techniques could be applied in this reconstitution step. Alternatively, the solvent-free particles can be formulated into various dosage forms as desired for a variety of administrative routes, such as oral, pulmonary, nasal, topical, intramuscular, and the like.

Furthermore, any undesired excipients such as surfactants may be replaced by a more desirable excipient by use of the separation methods described in the above paragraph. The solvent and first excipient may be discarded with the supernatant after centrifugation or filtration. A fresh volume of the suspension vehicle without the solvent and without the first excipient may then be added. Alternatively, a new surfactant may be added. For example, a suspension consisting of drug, N-methyl-2-pyrrolidinone (solvent), poloxamer 188 (first excipient), sodium deoxycholate, glycerol and water may be replaced with phospholipids (new surfactant), glycerol and water after centrifugation and removal of the supernatant.

I. First Process Category

The methods of the first process category generally include the step of dissolving the organic compound in a water miscible first solvent followed by the step of mixing this solution with an aqueous solvent to form a presuspension wherein the organic compound is in an amorphous form, a semicrystalline form or in a supercooled liquid form as determined by x-ray diffraction studies, DSC, light microscopy or other analytical techniques and has an average effective particle size within one of the effective particle size ranges set forth above. The mixing step is followed by an energy-addition step.

II. Second Process Category

The methods of the second processes category include essentially the same steps as in the steps of the first processes category but differ in the following respect. An x-ray diffraction, DSC or other suitable analytical techniques of the presuspension shows the organic compound in a crystalline form and having an average effective particle size. The organic compound after the energy-addition step has essentially the same average effective particle size as prior to the energy-addition step but has less of a tendency to aggregate into larger particles when compared to that of the particles of the presuspension. Without being bound to a theory, it is believed the differences in the particle stability may be due to a reordering of the surfactant molecules at the solid-liquid interface.

III. Third Process Category

The methods of the third category modify the first two steps of those of the first and second processes categories to ensure the organic compound in the presuspension is in a friable form having an average effective particle size (e.g., such as slender needles and thin plates). Friable particles can be formed by selecting suitable solvents, surfactants or combination of surfactants, the temperature of the individual solutions, the rate of mixing and rate of precipitation and the like. Friability may also be enhanced by the introduction of lattice defects (e.g., cleavage planes) during the steps of mixing the first solution with the aqueous solvent. This would arise by rapid crystallization such as that afforded in the precipitation step. In the energy-addition step these friable crystals are converted to crystals that are kinetically stabilized and having an average effective particle size smaller than those of the presuspension. Kinetically stabilized means particles have a reduced tendency to aggregate when compared to particles that are not kinetically stabilized. In such instance the energy-addition step results in a breaking up of the friable particles. By ensuring the particles of the presuspension are in a friable state, the organic compound can more easily and more quickly be prepared into a particle within the desired size ranges when compared to processing an organic compound where the steps have not been taken to render it in a friable form.

IV. Fourth Process Category

The methods of the fourth process category include the steps of the first process category except that the mixing step is carried out simultaneously with the energy-addition step.

Polymorph Control

The present invention further provides additional steps for controlling the crystal structure of an organic compound to ultimately produce a suspension of the compound in the desired size range and a desired crystal structure. What is meant by the term "crystal structure" is the arrangement of the atoms within the unit cell of the crystal. Compounds that can be crystallized into different crystal structures are said to be polymorphic. Identification of polymorphs is important step in drug formulation since different polymorphs of the same drug can show differences in solubility, therapeutic activity, bioavailability, and suspension stability. Accordingly, it is important to control the polymorphic form of the compound for ensuring product purity and batch-to-batch reproducibility.

The steps to control the polymorphic form of the compound includes seeding the first solution, the second solvent or the pre-suspension to ensure the formation of the desired polymorph. Seeding includes using a seed compound or adding energy. In a preferred form of the invention the seed compound is a pharmaceutically-active compound in the desired polymorphic form. Alternatively, the seed compound can also be an inert impurity, a compound unrelated in structure to the desired polymorph but with features that may lead to templating of a crystal nucleus, or an organic compound with a structure similar to that of the desired polymorph.

The seed compound can be precipitated from the first solution. This method includes the steps of adding the organic compound in sufficient quantity to exceed the solubility of the organic compound in the first solvent to create a supersaturated solution. The supersaturated solution is treated to precipitate the organic compound in the desired polymorphic form. Treating the supersaturated solution includes aging the solution for a time period until the formation of a crystal or crystals is observed to create a seeding mixture. It is also possible to add energy to the supersaturated solution to cause the organic compound to precipitate out of the solution in the desired polymorph. The energy can be added in a variety of ways including the energy addition steps described above. Further energy can be added by heating, or by

exposing the pre-suspension to electromagnetic energy, particle beam or electron beam sources. The electromagnetic energy includes light energy (ultraviolet, visible, or infrared) or coherent radiation such as that provided by a laser, microwave energy such as that provided by a maser (microwave amplification by stimulated emission of radiation), dynamic electromagnetic energy, or other radiation sources. It is further contemplated utilizing ultrasound, a static electric field, or a static magnetic field, or combinations of these, as the energy-addition source.

In a preferred form of the invention, the method for producing seed crystals from an aged supersaturated solution includes the steps of: (i) adding a quantity of an organic compound to the first organic solvent to create a supersaturated solution, (ii) aging the supersaturated solution to form detectable crystals to create a seeding mixture; and (iii) mixing the seeding mixture with the second solvent to precipitate the organic compound to create a pre-suspension. The presuspension can then be further processed as described in detail above to provide an aqueous suspension of the organic compound in the desired polymorph and in the desired size range.

Seeding can also be accomplished by adding energy to the first solution, the second solvent or the pre-suspension provided that the exposed liquid or liquids contain the organic compound or a seed material. The energy can be added in the same fashion as described above for the supersaturated solution.

Accordingly, the present invention provides a composition of matter of an organic compound in a desired polymorphic form essentially free of the unspecified polymorph or polymorphs. In a preferred form of the present invention, the organic compound is a pharmaceutically active substance. One such example is set forth in Example 16 below where seeding during microprecipitation provides a polymorph of itraconazole essentially free of the polymorph of the raw material. It is contemplated the methods of this invention can be used to selectively produce a desired polymorph for numerous pharmaceutically active compounds.

Combined and Continuous Process for Producing Aqueous Suspension of Small Particles

The small particles of the present invention can also be prepared as an essentially solvent-free aqueous suspension by a combined and continuous process in which microprecipitation is combined with homogenization and simultaneous

continuous removal of the water-miscible first solvent, which is generally an organic solvent (referred to as "solvent" hereafter in this section and related Examples 19-25 unless otherwise specified). Presence of solvents is undesirable in suspensions, especially for therapeutic use. Solvents are known to enhance Oswald ripening of the particles in the suspension, leading to increased particle size and poor stability induced by particle aggregation. This phenomenon typically begins immediately after nucleation, and is further catalyzed by higher temperatures which are common during the energy adding step, such as high pressure homogenization, sonication and other particle size reduction processes. Hence, a process that involves continuous solvent removal during particle reduction may be beneficial in obtaining particles that are small and stable. Furthermore, such a continuous process will reduce processing time, provide consistency and process control and eliminate the need for additional particle size reduction steps after solvent removal. Such a process is also easy to scale up.

In this combined and continuous process, the solvent is removed simultaneously and continuously while the particles are being formed from the combined microprecipitation and homogenization steps. This process differs from the previously described methods or other microprecipitation methods in that this process does not require an additional and separate step of removing the solvent after the completion of the particle formation step. Common solvent removal processes such as centrifugation often induce particle aggregation which may require an additional particle size reduction step to break the aggregates after the solvent removal step. The combined and continuous process produces an aqueous suspension of the small particles which is essentially free of any residual organic solvent. What is meant by "essentially free of any residual organic solvent" is that the aqueous suspension contains less than about 100 ppm of the solvent, more preferably less than about 50 ppm of the solvent, and most preferably less than about 10 ppm of the solvent.

The process, illustrated schematically in FIG. 18, generally includes (i) dissolving the organic compound in a water-miscible first solvent to form a drug solution (also known as drug concentrate); (ii) mixing the solution with a second solvent which is aqueous (the anti-solvent), to form a mix which initiates the microprecipitation process; and (iii) simultaneously homogenizing the mix and continuously removing the first solvent from the mix. Step (iii) is repeated until small

particles are formed in the aqueous suspension having an average effective particle size of less than about 100 μm. The microprecipitation step can be carried out simultaneously with the homogenization/solvent remover step. The aqueous suspension obtained is essentially free of the first solvent.

The water-miscible first solvent is generally an organic solvent, which can be a protic organic solvent or an aprotic organic solvent as described previously in the present application. A preferred solvent is N-methyl-2-pyrrolidinone (NMP). Another preferred solvent is lactic acid. In a preferred embodiment, the process further includes mixing one or more surface modifiers into the first water-miscible solvent or the aqueous second solvent, or both the first water-miscible solvent and the aqueous second solvent.

The simultaneous homogenization and continuous solvent removal can be initiated immediately upon the onset of microprecipitation when the drug solution and the second aqueous solvent are mixed. Alternatively, homogenization and continuous solvent removal can be carried out simultaneously while the drug solution and the second solvent are being mixed. In both cases, the solvent removal is conducted on a continuous basis until the end of the process when the aqueous suspension is substantially free of the first solvent.

The size of the particle in the present invention is generally less than about 100 μm as measured by dynamic light scattering methods, e.g., photocorrelation spectroscopy, laser diffraction, low-angle laser light scattering (LALLS), medium-angle laser light scattering (MALLS), light obscuration methods (Coulter method, for example), rheology, or microscopy (light or electron). However, the particles can be prepared in a wide range of sizes, such as from about 20 μm to about 10 nm, from about 10 μm to about 10 nm, from about 2 μm to about 10 nm, from about 1 μm to about 10 nm, from about 400 nm to about 50 nm, from about 200 nm to about 50 nm or any range or combination of ranges therein. The particle size can be controlled by controlling various factors such as, but are not limited to, the speed of homogenization, the temperature of homogenization, the time of homogenization and the rate of solvent removal.

Any commercially available homogenizer can be used in the present invention. An example of a suitable homogenizer is a piston gap homogenizer such as the one

sold by Avestin Inc. under the product designation EmulsiFlex-C160. More than one homogenizer can be arranged in series.

While several solvent removal techniques can be utilized for continuous solvent removal in the present disclosure, the preferred technique is cross-flow ultrafiltration. FIG. 19 is a schematic diagram illustrating a continuous solvent removal process for producing an aqueous suspension of small particles which is essentially solvent-free using a cross-flow ultrafiltration. As illustrated in FIG. 19, after the mixing of the drug solution in the water-miscible organic solvent (the drug concentrate) and the aqueous second solvent (the anti-solvent) to form a mix, the mix is immediately introduced to a homogenizer and homogenized. Simultaneously, the mix is circulated by a recirculating pump within a closed loop system from the homogenizer, through an ultrafiltration unit, and back to the homogenizer. This recirculation repeats for as many number of cycles as needed until the aqueous suspension is substantially free of the water-miscible first solvent. The suspension is then collected from the homogenizer.

The membrane used in the ultrafiltration is preferably sterilizable and amenable to cleaning processes. Suitable membranes include but are not limited to polymeric membranes (including but not limited to polysulfone and cellulose membranes) and ceramic membranes. Ceramic membranes are particularly desirable for solvents, such as NMP, that are not compatible with the polymeric membranes. Preferably, the cross-flow filtration membranes have molecular weight cut-offs of from about 300,000 nm to about 10 nm. The molecular weight cut-off of the membrane generally depends on the size of the particles prepared. In an embodiment, the cross-flow ultrafiltration also includes a "backpulse" operation, wherein the permeate flow in the cross-flow membrane is reversed for a very short period of time (a pulse), to dislodge particles that are caking on the membrane surface.

Ultrafiltration can be conducted in two steps in order to reduce processing time. The first step is a concentration step to reduce the overall batch volume in which a concentrate is prepared from the mix. The second step is a diafiltration step to remove the solvent as well as any soluble impurities.

The method can further include sterilizing the aqueous suspension by, for example, heat sterilization or gamma irradiation. In an embodiment, heat sterilization

is effected within the homogenizer in which the homogenizer serves as a heating and pressurization source for sterilization. Sterilization can also be accomplished by sterile filtering the drug solution and the aqueous solvent before mixing and carrying out the subsequent steps under aseptic conditions.

The method can also further include removing the aqueous medium in the aqueous suspension to form a dry powder of the small particles. Dry powder is most suitable for administering the small particles by inhalation or the pulmonary route. Alternatively, the dry powder can be resuspended in a suitable medium for other routes of administration such as parenteral administration. An example of a suitable medium for parenteral administration is an aqueous medium, such as but is not limited to, saline or a buffer with a physiological pH.

Examples

A. Examples of Process Category 1

Example 1: Preparation of itraconazole suspension by use of Process Category 1, Method A with homogenization.

To a 3-L flask add 1680 mL of Water for Injection. Heat liquid to 60-65°C, and then slowly add 44 grams of Pluronic F-68 (poloxamer 188), and 12 grams of sodium deoxycholate, stirring after each addition to dissolve the solids. After addition of solids is complete, stir for another 15 minutes at 60-65°C to ensure complete dissolution. Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. Add 200 mL of the tris buffer to the poloxamer/deoxycholate solution. Stir thoroughly to mix solutions.

In a 150-mL beaker add 20 grams of itraconazole and 120 mL of N-methyl-2-pyrrolidinone. Heat mixture to 50-60°C, and stir to dissolve solids. After total dissolution is visually apparent, stir another 15 minutes to ensure complete dissolution. Cool itraconazole-NMP solution to room temperature.

Charge a syringe pump (two 60-mL glass syringes) with the 120-mL of itraconazole solution prepared previously. Meanwhile pour all of the surfactant solution into a homogenizer hopper that has been cooled to 0-5°C (this may either by accomplished by use of a jacketed hopper through which refrigerant is circulated, or

by surrounding the hopper with ice). Position a mechanical stirrer into the surfactant solution so that the blades are fully immersed. Using the syringe pump, slowly (1-3 mL/min) add all of the itraconazole solution to the stirred, cooled surfactant solution. A stirring rate of at least 700 rpm is recommended. An aliquot of the resulting suspension (Suspension A) is analyzed by light microscopy (Hoffman Modulation Contrast) and by laser diffraction (Horiba). Suspension A is observed by light microscopy to consist of roughly spherical amorphous particles (under 1 micron), either bound to each other in aggregates or freely moving by Brownian motion. See FIG. 3. Dynamic light scattering measurements typically afford a bimodal distribution pattern signifying the presence of aggregates (10-100 microns in size) and the presence of single amorphous particles ranging 200-700 nm in median particle diameter.

The suspension is immediately homogenized (at 10,000 to 30,000 psi) for 10-30 minutes. At the end of homogenization, the temperature of the suspension in the hopper does not exceed 75°C. The homogenized suspension is collected in 500-mL bottles, which are cooled immediately in the refrigerator (2-8°C). This suspension (Suspension B) is analyzed by light microscopy and is found to consist of small elongated plates with a length of 0.5 to 2 microns and a width in the 0.2-1 micron range. See FIG. 4. Dynamic light scattering measurements typically indicate a median diameter of 200-700 nm.

Stability of Suspension A ("Pre-suspension") (Example 1)

During microscopic examination of the aliquot of Suspension A, crystallization of the amorphous solid was directly observed. Suspension A was stored at 2-8°C for 12 hours and examined by light microscopy. Gross visual inspection of the sample revealed severe flocculation, with some of the contents settling to the bottom of the container. Microscopic examination indicated the presence of large, elongated, plate-like crystals over 10 microns in length.

Stability of Suspension B

As opposed to the instability of Suspension A, Suspension B was stable at 2-8°C for the duration of the preliminary stability study (1 month). Microscopy on the aged sample clearly demonstrated that no significant change in the morphology or size of the particles had occurred. This was confirmed by light scattering measurement.

Example 2: Preparation of itraconazole suspension by use of Process Category 1, Method A with ultrasonication.

To a 500-mL stainless steel vessel add 252 mL of Water for Injection. Heat liquid to 60-65°C, and then slowly add 6.6 grams of Pluronic F-68 (poloxamer 188), and 0.9 grams of sodium deoxycholate, stirring after each addition to dissolve the solids. After addition of solids is complete, stir for another 15 minutes at 60-65°C to ensure complete dissolution. Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. Add 30 mL of the tris buffer to the poloxamer/deoxycholate solution. Stir thoroughly to mix solutions.

In a 30-mL container add 3 grams of itraconazole and 18 mL of N-methyl-2-pyrrolidinone. Heat mixture to 50-60°C, and stir to dissolve solids. After total dissolution is visually apparent, stir another 15 minutes to ensure complete dissolution. Cool itraconazole-NMP solution to room temperature.

Charge a syringe pump with 18-mL of itraconazole solution prepared in a previous step. Position a mechanical stirrer into the surfactant solution so that the blades are fully immersed. Cool the container to 0-5°C by immersion in an ice bath. Using the syringe pump, slowly (1-3 mL/min) add all of the itraconazole solution to the stirred, cooled surfactant solution. A stirring rate of at least 700 rpm is recommended. Immerse an ultrasonicator horn in the resulting suspension so that the probe is approximately 1 cm above the bottom of the stainless steel vessel. Sonicate (10,000 to 25,000 Hz, at least 400W) for 15 to 20 minute in 5-minute intervals. After the first 5-minute sonication, remove the ice bath and proceed with further sonication. At the end of ultrasonication, the temperature of the suspension in the vessel does not exceed 75°C.

The suspension is collected in a 500-mL Type I glass bottle, which is cooled immediately in the refrigerator (2-8°C). Characteristics of particle morphology of the suspension before and after sonication were very similar to that seen in Method A before and after homogenization (see Example 1).

Example 3: Preparation of itraconazole suspension by use of Process Category 1, Method B with homogenization.

Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. To a 3-L flask add 1680 mL of Water for Injection. Add 200 mL of the tris buffer to the 1680 mL of water. Stir thoroughly to mix solutions.

In a 150-mL beaker add 44 grams of Pluronic F-68 (poloxamer 188) and 12 grams of sodium deoxycholate to 120 mL of N-methyl-2-pyrrolidinone. Heat the mixture to 50-60°C, and stir to dissolve solids. After total dissolution is visually apparent, stir another 15 minutes to ensure complete dissolution. To this solution, add 20 grams of itraconazole, and stir until totally dissolved. Cool the itraconazole-surfactant-NMP solution to room temperature.

Charge a syringe pump (two 60-mL glass syringes) with the 120-mL of the concentrated itraconazole solution prepared previously. Meanwhile pour the diluted tris buffer solution prepared above into a homogenizer hopper that has been cooled to 0-5°C (this may either by accomplished by use of a jacketed hopper through which refrigerant is circulated, or by surrounding the hopper with ice). Position a mechanical stirrer into the buffer solution so that the blades are fully immersed. Using the syringe pump, slowly (1-3 mL/min) add all of the itraconazole-surfactant concentrate to the stirred, cooled buffer solution. A stirring rate of at least 700 rpm is recommended. The resulting cooled suspension is immediately homogenized (at 10,000 to 30,000 psi) for 10-30 minutes. At the end of homogenization, the temperature of the suspension in the hopper does not exceed 75°C.

The homogenized suspension is collected in 500-mL bottles, which are cooled immediately in the refrigerator (2-8°C). Characteristics of particle morphology of the suspension before and after homogenization were very similar to that seen in Example 1, except that in process category 1 B, the pre-homogenized material tended to form fewer and smaller aggregates which resulted in a much smaller overall particle size as measured by laser diffraction. After homogenization, dynamic light scattering results were typically identical to those presented in Example 1.

Example 4: Preparation of itraconazole suspension by use of Process Category 1, Method B with ultrasonication.

To a 500-mL flask add 252 mL of Water for Injection. Prepare a 50 mM tris (tromethamine) buffer by dissolving 6.06 grams of tris in 800 mL of Water for Injection. Titrate this solution to pH 8.0 with 0.1 M hydrochloric acid. Dilute the resulting solution to 1 liter with additional Water for Injection. Add 30 mL of the tris buffer to the water. Stir thoroughly to mix solutions.

In a 30-mL beaker add 6.6 grams of Pluronic F-68 (poloxamer 188) and 0.9 grams of sodium deoxycholate to 18 mL of N-methyl-2-pyrrolidinone. Heat the mixture to 50-60°C, and stir to dissolve solids. After total dissolution is visually apparent, stir another 15 minutes to ensure complete dissolution. To this solution, add 3.0 grams of itraconazole, and stir until totally dissolved. Cool the itraconazole-surfactant-NMP solution to room temperature.

Charge a syringe pump (one 30-mL glass syringe with the 18-mL of the concentrated itraconazole solution prepared previously. Position a mechanical stirrer into the buffer solution so that the blades are fully immersed. Cool the container to 0-5°C by immersion in an ice bath. Using the syringe pump, slowly (1-3 mL/min) add all of the itraconazole-surfactant concentrate to the stirred, cooled buffer solution. A stirring rate of at least 700 rpm is recommended. The resulting cooled suspension is immediately sonicated (10,000 to 25,000 Hz, at least 400 W) for 15-20 minutes, in 5-minute intervals. After the first 5-minute sonication, remove the ice bath and proceed with further sonication. At the end of ultrasonication, the temperature of the suspension in the hopper does not exceed 75°C.

The resultant suspension is collected in a 500-mL bottle, which is cooled immediately in the refrigerator (2-8°C). Characteristics of particle morphology of the suspension before and after sonication were very similar to that seen in Example 1, except that in Process Category 1, Method B, the pre-sonicated material tended to form fewer and smaller aggregates which resulted in a much smaller overall particle size as measured by laser diffraction. After ultrasonication, dynamic light scattering results were typically identical to those presented in Example 1

B. Examples of Process Category 2

Example 5: Preparation of itraconazole suspension (1%) with 0.75% Solutol® HR (PEG-660 12-hydroxystearate) Process Category 2, Method B.

Solutol (2.25 g) and itraconazole (3.0 g) were weighed into a beaker and 36 mL of filtered N-methyl-2-pyrrolidinone (NMP) was added. This mixture was stirred under low heat (up to 40°C) for approximately 15 minutes until the solution ingredients were dissolved. The solution was cooled to room temperature and was filtered through a 0.2-micron filter under vacuum. Two 60-mL syringes were filled with the filtered drug concentrate and were placed in a syringe pump. The pump was set to deliver approximately 1 mL/min of concentrate to a rapidly stirred (400 rpm) aqueous buffer solution. The buffer solution consisted of 22 g/L of glycerol in 5 mM tris buffer. Throughout concentrate addition, the buffer solution was kept in an ice bath at 2-3°C. At the end of the precipitation, after complete addition of concentrate to the buffer solution, about 100 mL of the suspension was centrifuged for 1 hour, the supernatant was discarded. The precipitate was resuspended in a 20% NMP solution in water, and again centrifuged for 1 hour. The material was dried overnight in a vacuum oven at 25°C. The dried material was transferred to a vial and analyzed by X-ray diffractometry using chromium radiation (see FIG. 5).

Another 100 mL-aliquot of the microprecipitated suspension was sonicated for 30 minutes at 20,000 Hz, 80% full amplitude (full amplitude = 600 W). The sonicated sample was homogenized in 3 equal aliquots each for 45 minutes (Avestin C5, 2-5°C, 15,000-20,000 psi). The combined fractions were centrifuged for about 3 hours, the supernatant removed, and the precipitate resuspended in 20% NMP. The resuspended mixture was centrifuged again (15,000 rpm at 5°C). The supernatant was decanted off and the precipitate was vacuum dried overnight at 25°C. The precipitate was submitted for analysis by X-ray diffractometry (see FIG. 5). As seen in FIG. 5, the X-ray diffraction patterns of processed samples, before and after homogenization, are essentially identical, yet show a significantly different pattern as compared with the starting raw material. The unhomogenized suspension is unstable and agglomerates upon storage at room temperature. The stabilization that occurs as a result of homogenization is believed to arise from rearrangement of surfactant on the surface of the particle. This rearrangement should result in a lower propensity for particle aggregation.

C. Examples of Process Category

Example 6: Preparation of carbamazepine suspension by use of Process Category 3, Method A with homogenization.

2.08 g of carbamazepine was dissolved into 10 mL of NMP. 1.0 mL of this concentrate was subsequently dripped at 0.1 mL/min into 20 mL of a stirred solution of 1.2% lecithin and 2.25% glycerin. The temperature of the lecithin system was held at 2-5°C during the entire addition. The predispersion was next homogenized cold (5-15°C) for 35 minutes at 15,000 psi. The pressure was increased to 23,000 psi and the homogenization was continued for another 20 minutes. The particles produced by the process had a mean diameter of 0.881 μm with 99% of the particles being less than 2.44 μm.

Example 7: Preparation of 1% carbamazepine suspension with 0.125% Solutol® by use of Process Category 3, Method B with homogenization.

A drug concentrate of 20% carbamazepine and 5% glycodeoxycholic acid (Sigma Chemical Co.) in N-methyl-2-pyrrolidinone was prepared. The microprecipitation step involved adding the drug concentrate to the receiving solution (distilled water) at a rate of 0.1 mL/min. The receiving solution was stirred and maintained at approximately 5°C during precipitation. After precipitation, the final ingredient concentrations were 1% carbamazepine and 0.125% Solutol®. The drug crystals were examined under a light microscope using positive phase contrast (400X). The precipitate consisted of fine needles approximately 2 microns in diameter and ranging from 50 – 150 microns in length.

Homogenization (Avestin C-50 piston-gap homogenizer) at approximately 20,000 psi for approximately 15 minutes results in small particles, less than 1 micron in size and largely unaggregated. Laser diffraction analysis (Horiba) of the homogenized material showed that the particles had a mean size of 0.4 micron with 99% of the particles less than 0.8 micron. Low energy sonication, suitable for breaking agglomerated particles, but not with sufficient energy to cause a comminution of individual particles, of the sample before Horiba analysis had no effect on the results (numbers were the same with and without sonication). This result was consistent with the absence of particle agglomeration.

Samples prepared by the above process were centrifuged and the supernatant solutions replaced with a replacement solution consisting of 0.125% Solutol®. After centrifugation and supernatant replacement, the suspension ingredient concentrations were 1% carbamazepine and 0.125% Solutol®. The samples were re-homogenized by piston-gap homogenizer and stored at 5°C. After 4 weeks storage, the suspension had a mean particle size of 0.751 with 99% less than 1.729. Numbers reported are from Horiba analysis on unsonicated samples.

Example 8: Preparation of 1% carbamazepine suspension with 0.06% sodium glycodeoxycholate and 0.06% poloxamer 188 by use of Process Category 3, Method B with homogenization.

A drug concentrate comprising 20% carbamazepine and 5% glycodeoxycholate in N-methyl-2-pyrrolidinone was prepared. The microprecipitation step involved adding the drug concentrate to the receiving solution (distilled water) at a rate of 0.1 mL/min. Thus the following examples demonstrate that adding a surfactant or other excipient to the aqueous precipitating solution in Methods A and B above is optional. The receiving solution was stirred and maintained at approximately 5°C during precipitation. After precipitation, the final ingredient concentrations were 1% carbamazepine and 0.125% Solutol®. The drug crystals were examined under a light microscope using positive phase contrast (400X). The precipitate consisted of fine needles approximately 2 microns in diameter and ranging from 50 – 150 microns in length. Comparison of the precipitate with the raw material before precipitation reveals that the precipitation step in the presence of surface modifier (glycodeoxycholic acid) results in very slender crystals that are much thinner than the starting raw material (see FIG. 6).

Homogenization (Avestin C-50 piston-gap homogenizer) at approximately 20,000 psi for approximately 15 minutes results in small particles, less than 1 micron in size and largely unaggregated. See FIG. 7. Laser diffraction analysis (Horiba) of the homogenized material showed that the particles had a mean size of 0.4 micron with 99% of the particles less than 0.8 micron. Sonication of the sample before Horiba analysis had no effect on the results (numbers were the same with and without sonication). This result was consistent with the absence of particle agglomeration.

Samples prepared by the above process were centrifuged and the supernatant solutions replaced with a replacement solution consisting of 0.06% glycodeoxycholic acid (Sigma Chemical Co.) and 0.06% Poloxamer 188. The samples were re-homogenized by piston-gap homogenizer and stored at 5°C. After 2 weeks storage, the suspension had a mean particle size of 0.531 micron with 99% less than 1.14 micron. Numbers reported are from Horiba analysis on unsonicated samples.

Mathematical Analysis (Example 8) of force required to break precipitated particles as compared to force required to break particles of the starting raw material (carbamazepine):

The width of the largest crystals seen in the carbamazepine raw material (FIG. 6, picture on left) are roughly 10-fold greater than the width of crystals in the microprecipitated material (FIG. 6, picture on right). On the assumption that the ratio of crystal thickness (1:10) is proportional to the ratio of crystal width (1:10), then the moment of force required to cleave the larger crystal in the raw material should be approximately 1,000-times greater than the force needed to break the microprecipitated material, since:

$$e_L = 6PL/(Ewx^2) \qquad \text{Eq. 1}$$

where,

e_L = longitudinal strain required to break the crystal ("yield value")

P = load on beam

L = distance from load to fulcrum

E = elasticity modulus

w = width of crystal

x = thickness of crystal

Let us assume that L and E are the same for the raw material and the precipitated material. Additionally, let us assume that $w/w_0 = x/x_0 = 10$. Then,

$(e_L)_0 = 6P_0L/(Ew_0x_0^2)$, where the '0' subscripts refer to raw material

$e_L = 6PL/(Ewx^2)$, for the microprecipitate

Equating $(e_L)_0$ and e_L,

$$6PL/(Ewx^2) = 6P_0L/(Ew_0x_0^2)$$

After simplification,

$$P = P_0 (w/w_0) (x/x_0)^2 = P_0 (0.1) (0.1)^2 = 0.001 P_0$$

Thus, the yield force, P, required to break the microprecipitated solid is one-thousandth the required force necessary to break the starting crystalline solid. If, because of rapid precipitation, lattice defects or amorphic properties are introduced, then the modulus (E) should decrease, making the microprecipitate even easier to cleave.

Example 9: Preparation of 1.6% (w/v) prednisolone suspension with 0.05% sodium deoxycholate and 3% N-methyl-2-pyrrolidinone Process Category 3, Method B

A schematic of the overall manufacturing process is presented in FIG. 8. A concentrated solution of prednisolone and sodium deoxycholate was prepared. Prednisolone (32g) and sodium deoxycholate (1g) were added to a sufficient volume of 1-methyl 2-pyrrolidinone (NMP) to produce a final volume of 60 mL. The resulting prednisolone concentration was approximately 533.3 mg/mL and the sodium deoxycholate concentration was approximately 16.67 mg/mL. 60mL of NMP concentrate was added to 2 L of water cooled to 5°C at an addition rate of 2.5 mL/min while stirring at approximately 400 rpm. The resulting suspension contained slender needle-shaped crystals less than 2 μm in width (FIG. 9). The concentration contained in the precipitated suspension was 1.6% (w/v) prednisolone, 0.05% sodium deoxycholate, and 3% NMP.

The precipitated suspension was pH adjusted to 7.5-8.5 using sodium hydroxide and hydrochloric acid then homogenized (Avestin C-50 piston-gap homogenizer) for 10 passes at 10,000 psi. The NMP was removed by performing 2 successive centrifugation steps replacing the supernatant each time with a fresh surfactant solution, which contained the desired concentrations of surfactants needed to stabilize the suspension (see Table 2). The suspension was homogenized for another 10 passes at 10,000 psi. The final suspension contained particles with a mean particle size of less than 1 μm, and 99% of particles less than 2 μm. FIG. 10 is a photomicrograph of the final prednisolone suspension after homogenization.

A variety of different surfactants at varying concentrations were used in the centrifugation/surfactant replacement step (see Table 2). Table 2 lists combinations of

surfactants that were stable with respect to particle size (mean < 1 μm, 99%< 2 μm), pH (6-8), drug concentration (less than 2% loss) and re-suspendability (resuspended in 60 seconds or less).

Notably this process allows for adding the active compound to an aqueous diluent without the presence of a surfactant or other additive. This is a modification of process Method B in FIG. 2.

Table 2: List of stable prednisolone suspensions prepared by microprecipitation process of FIG. 8 (Example 9)

			2 Weeks		2 Months						
	Initial		40°C		5°C		25°C		40°C		
Formulation	Mean	>99%	Mean	>99%	Mean	>99%	Mean	>99%	Mean	>99%	% Loss*
1.6% prednisolone, 0.6% phospholipids, 0.5% sodium deoxycholate, 5 mM TRIS, 2.2% glycerol **	0.79	1.65	0.84	1.79	0.83	1.86	0.82	1.78	0.82	1.93	<2%
1.6% prednisolone, 0.6% Solutol®, 0.5% sodium deoxycholate, 2.2% glycerol	0.77	1.52	0.79	1.67	0.805	1.763	0.796	1.693	0.81	1.633	<2%
1.6% prednisolone, 0.1% poloxamer 188, 0.5% sodium deoxycholate, 2.2% glycerol	0.64	1.16	0.82	1.78	0.696	1.385	0.758	1.698	0.719	1.473	<2%
1.6% prednisolone, 5% phospholipids, 5 mM TRIS, 2.2% glycerol	0.824	1.77	0.87	1.93	0.88	1.95	0.869	1.778	0.909	1.993	<2%

* Difference in itraconazole concentration between samples stored for 2 months at 5 and 25°C.

** Stable through at least 6 months.

Particle sizes (by laser light scattering), in microns:

5°C: 0.80 (mean), 1.7 (99%)

25°C: 0.90 (mean); 2.51 (99%)

40°C: 0.99 (mean); 2.03 (99%)

Difference in itraconazole concentration between samples stored at 5 and 25°C: <2%

Example 10: Preparation of prednisolone suspension by use of Process Category 3, Method A with homogenization.

32 g of prednisolone was dissolved into 40 mL of NMP. Gentle heating at 40-50°C was required to effect dissolution. The drug NMP concentrate was subsequently

dripped at 2.5 mL/min into 2 liters of a stirred solution that consisted of 0.1.2% lecithin and 2.2% glycerin. No other surface modifiers were added. The surfactant system was buffered at pH = 8.0 with 5 mM tris buffer and the temperature was held at 0° to 5°C during the entire precipitation process. The post-precipitated dispersion was next homogenized cold (5-15 °C) for 20 passes at 10,000 psi. Following homogenization, the NMP was removed by centrifuging the suspension, removing the supernatant, and replacing the supernatant with fresh surfactant solution. This post-centrifuged suspension was then rehomogenized cold (5-15 °C) for another 20 passes at 10,000 psi. The particles produced by this process had a mean diameter of 0.927 μm with 99% of the particles being less than 2.36 μm.

Example 11: Preparation of nabumetone suspension by use of Process Category 3, Method B with homogenization.

Surfactant (2.2 g of poloxamer 188) was dissolved in 6 mL of N-methyl-2-pyrrolidinone. This solution was stirred at 45°C for 15 minutes, after which 1.0 g of nabumetone was added. The drug dissolved rapidly. Diluent was prepared which consisted of 5 mM tris buffer with 2.2% glycerol, and adjusted to pH 8. A 100-mL portion of diluent was cooled in an ice bath. The drug concentrate was slowly added (approximately 0.8 mL/min) to the diluent with vigorous stirring. This crude suspension was homogenized at 15,000 psi for 30 minutes and then at 20,000 psi for 30 minutes (temperature = 5°C). The final nanosuspension was found to be 930 nm in effective mean diameter (analyzed by laser diffraction). 99% of the particles were less than approximately 2.6 microns.

Example 12: Preparation of nabumetone suspension by use of Process Category 3, Method B with homogenization and the use of Solutol® HS 15 as the surfactant. Replacement of supernatant liquid with a phospholipid medium.

Nabumetone (0.987 grams) was dissolved in 8 mL of N-methyl-2-pyrrolidinone. To this solution was added 2.2 grams of Solutol® HS 15. This mixture was stirred until complete dissolution of the surfactant in the drug concentrate. Diluent was prepared, which consisted of 5 mM tris buffer with 2.2% glycerol, and which was adjusted to pH 8. The diluent was cooled in an ice bath, and the drug concentrate was slowly added (approximately 0.5 mL/min) to the diluent with

vigorous stirring. This crude suspension was homogenized for 20 minutes at 15,000 psi, and for 30 minutes at 20,000 psi.

The suspension was centrifuged at 15,000 rpm for 15 minutes and the supernatant was removed and discarded. The remaining solid pellet was resuspended in a diluent consisting of 1.2% phospholipids. This medium was equal in volume to the amount of supernatant removed in the previous step. The resulting suspension was then homogenized at approximately 21,000 psi for 30 minutes. The final suspension was analyzed by laser diffraction and was found to contain particles with a mean diameter of 542 nm, and a 99% cumulative particle distribution sized less than 1 micron.

Example 13: Preparation of 1% itraconazole suspension with poloxamer with particles of a mean diameter of approximately 220 nm

Itraconazole concentrate was prepared by dissolving 10.02 grams of itraconazole in 60 mL of N-methyl-2-pyrrolidinone. Heating to 70°C was required to dissolve the drug. The solution was then cooled to room temperature. A portion of 50 mM tris(hydroxymethyl)aminomethane buffer (tris buffer) was prepared and was pH adjusted to 8.0 with 5M hydrochloric acid. An aqueous surfactant solution was prepared by combining 22 g/L poloxamer 407, 3.0 g/L egg phosphatides, 22g/L glycerol, and 3.0 g/L sodium cholate dihydrate. 900 mL of the surfactant solution was mixed with 100 mL of the tris buffer to provide 1000 mL of aqueous diluent.

The aqueous diluent was added to the hopper of the homogenizer (APV Gaulin Model 15MR-8TA), which was cooled by using an ice jacket. The solution was rapidly stirred (4700 rpm) and the temperature was monitored. The itraconazole concentrate was slowly added, by use of a syringe pump, at a rate of approximately 2 mL/min. Addition was complete after approximately 30 minute. The resulting suspension was stirred for another 30 minutes while the hopper was still being cooled in an ice jacket, and an aliquot was removed for analysis by light microscopy any dynamic light scatting. The remaining suspension was subsequently homogenized for 15 minutes at 10,000 psi. By the end of the homogenization the temperature had risen to 74°C. The homogenized suspension was collected in a 1-L Type I glass bottle and sealed with a rubber closure. The bottle containing suspension was stored in a refrigerator at 5°C.

A sample of the suspension before homogenization showed the sample to consist of both free particles, clumps of particles, and multilamellar lipid bodies. The free particles could not be clearly visualized due to Brownian motion; however, many of the aggregates appeared to consist of amorphous, non-crystalline material.

The homogenized sample contained free submicron particles having excellent size homogeneity without visible lipid vesicles. Dynamic light scattering showed a monodisperse logarithmic size distribution with a median diameter of approximately 220 nm. The upper 99% cumulative size cutoff was approximately 500 nm. FIG. 11 shows a comparison of the size distribution of the prepared nanosuspension with that of a typical parenteral fat emulsion product (10% Intralipid®, Pharmacia).

Example 14: Preparation of 1% itraconazole nanosuspension with hydroxyethylstarch

Preparation of Solution A: Hydroxyethylstarch (1 g, Ajinomoto) was dissolved in 3 mL of N-methyl-2-pyrrolidinone (NMP). This solution was heated in a water bath to 70-80°C for 1 hour. In another container was added 1 g of itraconazole (Wyckoff). Three mL of NMP were added and the mixture heated to 70-80°C to effect dissolution (approximately 30 minutes). Phospholipid (Lipoid S-100) was added to this hot solution. Heating was continued at 70-90°C for 30 minutes until all of the phospholipid was dissolved. The hydroxyethylstarch solution was combined with the itraconazole/ phospholipid solution. This mixture was heated for another 30 minutes at 80-95°C to dissolve the mixture.

Addition of Solution A to Tris Buffer: Ninety-four (94) mL of 50 mM tris(hydroxymethyl)aminomethane buffer was cooled in an ice bath. As the tris solution was being rapidly stirred, the hot Solution A (see above) was slowly added dropwise (less than 2 cc/minute).

After complete addition, the resulting suspension was sonicated (Cole-Parmer Ultrasonic Processor - 20,000 Hz, 80% amplitude setting) while still being cooled in the ice bath. A one-inch solid probe was utilized. Sonication was continued for 5 minutes. The ice bath was removed, the probe was removed and retuned, and the probe was again immersed in the suspension. The suspension was sonicated again for another 5 minutes without the ice bath. The sonicator probe was once again removed and retuned, and after immersion of the probe the sample was sonicated for another 5 minutes. At this point, the temperature of the suspension had risen to 82°C. The

suspension was quickly cooled again in an ice bath and when it was found to be below room temperature it was poured into a Type I glass bottle and sealed. Microscopic visualization of the particles indicated individual particle sizes on the order of one micron or less.

After one year of storage at room temperature, the suspension was reevaluated for particle size and found to have a mean diameter of approximately 300 nm.

Example 15: Prophetic example of Method A using HES

The present invention contemplates preparing a 1% itraconazole nanosuspension with hydroxyethylstarch utilizing Method A by following the steps of Example 14 with the exception the HES would be added to the tris buffer solution instead of to the NMP solution. The aqueous solution may have to be heated to dissolve the HES.

Example 16: Seeding during Homogenization to Convert a Mixture of Polymorphs to the More Stable Polymorph

Sample preparation. An itraconazole nanosuspension was prepared by a microprecipitation-homogenization method as follows. Itraconazole (3g) and Solutol HR (2.25g) were dissolved in 36mL of N-methyl-2-pyrrolidinone (NMP) with low heat and stirring to form a drug concentrate solution. The solution was cooled to room temperature and filtered through a 0.2 μm nylon filter under vacuum to remove undissolved drug or particulate matter. The solution was viewed under polarized light to ensure that no crystalline material was present after filtering. The drug concentrate solution was then added at 1.0 mL/minute to approximately 264 mL of an aqueous buffer solution (22 g/L glycerol in 5 mM tris buffer). The aqueous solution was kept at 2-3°C and was continuously stirred at approximately 400 rpm during the drug concentrate addition. Approximately 100 mL of the resulting suspension was centrifuged and the solids resuspended in a pre-filtered solution of 20% NMP in water. This suspension was re-centrifuged and the solids were transferred to a vacuum oven for overnight drying at 25°C. The resulting solid sample was labeled SMP 2 PRE.

Sample characterization. The sample SMP 2 PRE and a sample of the raw material itraconazole were analyzed using powder x-ray diffractometry. The measurements were performed using a Rigaku MiniFlex+ instrument with copper

radiation, a step size of 0.02° 22 and scan speed of 0.25° 22/minute. The resulting powder diffraction patterns are shown in FIG. 12. The patterns show that SMP-2-PRE is significantly different from the raw material, suggesting the presence of a different polymorph or a pseudopolymorph.

Differential scanning calorimetry (DSC) traces for the samples are shown in FIGS. 13a and b. Both samples were heated at 2°/min to 180°C in hermetically sealed aluminum pans.

The trace for the raw material itraconazole (FIG. 13a) shows a sharp endotherm at approximately 165°C.

The trace for SMP 2 PRE (FIG. 13b) exhibits two endotherms at approximately 159°C and 153°C. This result, in combination with the powder x-ray diffraction patterns, suggests that SMP 2 PRE consists of a mixture of polymorphs, and that the predominant form is a polymorph that is less stable than polymorph present in the raw material.

Further evidence for this conclusion is provided by the DSC trace in FIG. 14, which shows that upon heating SMP 2 PRE through the first transition, then cooling and reheating, the less stable polymorph melts and recrystallizes to form the more stable polymorph.

Seeding. A suspension was prepared by combining 0.2g of the solid SMP 2 PRE and 0.2g of raw material itraconazole with distilled water to a final volume of 20 mL (seeded sample). The suspension was stirred until all the solids were wetted. A second suspension was prepared in the same manner but without adding the raw material itraconazole (unseeded sample). Both suspensions were homogenized at approximately 18,000 psi for 30 minutes. Final temperature of the suspensions after homogenization was approximately 30°C. The suspensions were then centrifuged and the solids dried for approximately 16 hours at 30°C.

FIG. 15 shows the DSC traces of the seeded and unseeded samples. The heating rate for both samples was 2°/min to 180°C in hermetically sealed aluminum pans. The trace for the unseeded sample shows two endotherms, indicating that a mixture of polymorphs is still present after homogenization. The trace for the seeded sample shows that seeding and homogenization causes the conversion of the solids to

the stable polymorph. Therefore, seeding appears to influence the kinetics of the transition from the less stable to the more stable polymorphic form.

Example 17: Seeding during Precipitation to Preferentially Form a Stable Polymorph

Sample preparation. An itraconazole-NMP drug concentrate was prepared by dissolving 1.67g of itraconazole in 10mL of NMP with stirring and gentle heating. The solution was filtered twice using 0.2 μm syringe filters. Itraconazole nanosuspensions were then prepared by adding 1.2 mL of the drug concentrate to 20 mL of an aqueous receiving solution at approx. 3°C and stirring at approx. 500 rpm. A seeded nanosuspension was prepared by using a mixture of approx. 0.02g of raw material itraconazole in distilled water as the receiving solution. An unseeded nanosuspension was prepared by using distilled water only as the receiving solution. Both suspensions were centrifuged, the supernatants decanted, and the solids dried in a vacuum oven at 30°C for approximately 16 hours.

Sample characterization. FIG. 16 shows a comparison of the DSC traces for the solids from the seeded and unseeded suspensions. The samples were heated at 2^0/min to 180°C in hermetically sealed aluminum pans. The dashed line represents the unseeded sample, which shows two endotherms, indicating the presence of a polymorphic mixture.

The solid line represents the seeded sample, which shows only one endotherm near the expected melting temperature of the raw material, indicating that the seed material induced the exclusive formation of the more stable polymorph.

Example 18: Polymorph control by seeding the drug concentrate

Sample preparation. The solubility of itraconazole in NMP at room temperature (approximately 22°C) was experimentally determined to be 0.16 g/mL. A 0.20 g/mL drug concentrate solution was prepared by dissolving 2.0 g of itraconazole and 0.2 g Poloxamer 188 in 10 mL NMP with heat and stirring. This solution was then allowed to cool to room temperature to yield a supersaturated solution. A microprecipitation experiment was immediately performed in which 1.5 mL of the drug concentrate was added to 30 mL of an aqueous solution containing 0.1% deoxycholate, 2.2% glycerol. The aqueous solution was maintained at ~2°C and a stir rate of 350 rpm during the addition step. The resulting presuspension was

homogenized at ~13,000 psi for approx. 10 minutes at 50°C. The suspension was then centrifuged, the supernatant decanted, and the solid crystals dried in a vacuum oven at 30°C for 135 hours.

The supersaturated drug concentrate was subsequently aged by storing at room temperature in order to induce crystallization. After 12 days, the drug concentrate was hazy, indicating that crystal formation had occurred. An itraconazole suspension was prepared from the drug concentrate, in the same manner as in the first experiment, by adding 1.5 mL to 30 mL of an aqueous solution containing 0.1% deoxycholate, 2.2% glycerol. The aqueous solution was maintained at ~5°C and a stir rate of 350 rpm during the addition step. The resulting presuspension was homogenized at ~13,000 psi for approx. 10 minutes at 50°C. The suspension was then centrifuged, the supernatant decanted, and the solid crystals dried in a vacuum oven at 30°C for 135 hours.

Sample characterization. X-ray powder diffraction analysis was used to determine the morphology of the dried crystals. The resulting patterns are shown in FIG. 17. The crystals from the first experiment (using fresh drug concentrate) were determined to consist of the more stable polymorph. In contrast, the crystals from the second experiment (aged drug concentrate) were predominantly composed of the less stable polymorph, with a small amount of the more stable polymorph also present. Therefore, it is believed that aging induced the formation of crystals of the less stable polymorph in the drug concentrate, which then acted as seed material during the microprecipitation and homogenization steps such that the less stable polymorph was preferentially formed.

Example 19: Continuous Solvent Removal Process by Cross-Flow Ultrafiltration

FIG. 20 is a schematic diagram illustrating a continuous solvent removal process by cross-flow filtration for producing an aqueous suspension of small particles of itraconazole which is essentially solvent-free. A solution of 20 g of itraconazole in 120 mL of NMP was mixed with a surfactant solution containing 24 g of phospholipids and 44 g of glycerin in 2 L of WFI to form a mix to initiate the microprecipitation process. The mix was then introduced to the homogenizer in which the mix was homogenized. After homogenization, the mix was transferred to a feed tank. An additional 4.5 L of WFI was also added to the feed tank to wash the mix.

The washed mix then underwent an ultrafiltration process three times in which the retentate, consisting of the aqueous suspension of the particles, was recirculated into the feed tank while the permeate was removed and analyzed for the NMP The process also included an additional step of washing the solvent-free aqueous suspension with 1 L of a replacement surfactant solution containing 12 g of phospholipids, 22 g of glycerin, and 1.42 g of sodium phosphate. The small particles in the replacement surfactant solution was further homogenized.

Example 20: Continuous Solvent Removal Process by Cross-Flow Ultrafiltration Including A Concentration Step

The process described in Example 19 included an additional step of concentrating the washed batch, which is from 10 L to 2L in this example, before undergoing diafiltration for 10 wash cycles. This method is particularly amenable to organic compounds that have limited aqueous solubility.

Example 21: NMP Removal in Scale Up of the Process

The continuous solvent removal process as described in Example 19 can be scaled up from a 200 mL batch to a 10 L batch, and the levels of NMP after solvent removal for each batch are shown in FIG. 21.

Example 22: NMP Removal at Different Scales, for Two Different Drugs and Different Surfactants

The process described in Example 19 was also applied at different scales, for itraconazole and budesonide with two different surfactants. The residual NMP levels in the aqueous suspension are summarized in Table 3.

Table 3: NMP removal achieved at different scales, for two different drugs, two different surfactansts

Batch #	Drug	Surfactants	Scale	Residual NMP Level
23161-103	Budesonide	Phospholipid	200 mL	2.9 ppm
2-02-010-5	Itraconazole	Poloxamer 188, Deoxycholate	10 L	6.4 ppm
2-02-010-6	Itraconazole	Poloxamer 188, Deoxycholate	10 L	3.4 ppm
23161-112	Itraconazole	Poloxamer 188, Deoxycholate	300 mL	4.3 ppm

Example 23: Mass Balance for NMP and Drug Potency in Various Batches with Various Scales

Mass balance was calculated for various batches of samples from the continuous solvent removal process as described in Example 19 at different scales. In four pilot scale 10 L batches, 83% NMP was accounted for. In two 200 mL laboratory scale batches, 79% NMP was accounted for. The unaccounted NMP was potentially adsorbed to the ultrafiltration membrane, tubing, and/or the particles.

Greater than 95% drug potency was maintained for the 10 L batches while 70% drug potency was retained for the 200 mL batches. Loss of drug potency was probably due to transfer operations.

Example 24: Combined, and Continuous Process for Producing Small Particles

In the combined, and continuous process, the drug concentrate containing a drug dissolved in the water-miscible solvent and the aqueous second solvent (the anti-solvent) are mixed in-line in the homogenization vessel. Homogenization and cross-flow ultrafiltration are carried out simultaneously with the mix circulating in a close loop from the homogenizer to the ultrafiltration unit and then back to the homogenizer. The circulation repeats for as many cycles as needed in order to remove the organic solvent to the desired level. The process is schematically illustrated in FIG. 22.

Example 25: Combined and Continuous Process for Producing Small Particles of Itraconazole Precipitated in An Aqueous Medium of Poloxamer 188

A solution of itraconazole in NMP was precipitated in an aqueous surfactant solution containing 0.1% poloxamer 188, 0.1% deoxycholate and 2.2% glycerine. High pressure homogenization and solvent removal were initiated upon the onset of microprecipitation and continued till the end of microprecipitation. The final mean particle size was 340 nm, and no aggregation was observed under microscope. The residual NMP level was less than 10 ppm. The entire process was conducted in two hours, which represents a 50% reduction in processing time as compared to a similar batch made using microprecipitation, followed by homogenization, followed by centrifugation, followed by homogenization.

While specific embodiments have been illustrated and described, numerous modifications come to mind without departing from the spirit of the invention and the scope of protection is only limited by the scope of the accompanying claims.

CLAIMS

What is claimed is:

1. A method for preparing small particles of an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent that is aqueous, the method comprising:

(i) dissolving the organic compound in the water-miscible first solvent to form a solution;

(ii) mixing the solution with the second solvent to form a mix; and

(iii) simultaneously homogenizing the mix and continuously removing the first solvent from the mix to form an aqueous suspension of small particles having an average effective particle size of less than about 100 μm wherein the aqueous suspension is essentially free of the first solvent.

2. The method of claim 1, wherein the water-miscible first solvent is a protic organic solvent.

3. The method of claim 2, wherein the protic organic solvent is selected from the group consisting of alcohols, amines, oximes, hydroxamic acids, carboxylic acids, sulfonic acids, phosphonic acids, phosphoric acids, amides and ureas.

4. The method of claim 1, wherein the water-miscible first solvent is an aprotic organic solvent.

5. The method of claim 4, wherein the aprotic organic solvent is a dipolar aprotic solvent.

6. The method of claim 5, wherein the dipolar aprotic solvent is selected from the group consisting of: fully substituted amides, fully substituted ureas, ethers, cyclic ethers, nitriles, ketones, sulfones, sulfoxides, fully substituted phosphates, phosphonate esters, phosphoramides, and nitro compounds.

7. The method of claim 1, wherein the water-miscible first solvent is selected from the group consisting of: N-methyl-2-pyrrolidinone (N-methyl-2-pyrrolidone), 2-pyrrolidinone (2-pyrrolidone), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylsulfoxide, dimethylacetamide, acetic acid, lactic acid, methanol, ethanol,

isopropanol, 3-pentanol, n-propanol, benzyl alcohol, glycerol, butylenes glycol (butanediol), ethylene glycol, propylene glycol, mono- and diacylated monoglycerides, glyceryl caprylate, dimethyl isosorbide, acetone, dimethylsulfone, dimethylformamide, 1,4-dioxane, tetramethylenesulfone (sulfolane), acetonitrile, nitromethane, tetramethylurea, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF), dioxane, diethylether, tert-butylmethyl ether (TBME), aromatic hydrocarbons, alkenes, alkanes, halogenated aromatics, halogenated alkenes, halogenated alkanes, xylene, toluene, benzene, substituted benzene, ethyl acetate, methyl acetate, butyl acetate, chlorobenzene, bromobenzene, chlorotoluene, trichloroethane, methylene chloride, ethylenedichloride (EDC), hexane, neopentane, heptane, isooctane, cyclohexane, polyethylene glycol (PEG), PEG-4, PEG-8, PEG-9, PEG-12, PEG-14, PEG-16, PEG-120, PEG-75, PEG-150, polyethylene glycol esters, PEG-4 dilaurate, PEG-20 dilaurate, PEG-6 isostearate, PEG-8 palmitostearate, PEG-150 palmitostearate, polyethylene glycol sorbitans, PEG-20 sorbitan isostearate, polyethylene glycol monoalkyl ethers, PEG-3 dimethyl ether, PEG-4 dimethyl ether, polypropylene glycol (PPG), polypropylene alginate, PPG-10 butanediol, PPG-10 methyl glucose ether, PPG-20 methyl glucose ether, PPG-15 stearyl ether, propylene glycol dicaprylate/dicaprate, propylene glycol laurate, and glycofurol (tetrahydrofurfuryl alcohol polyethylene glycol ether).

8. The composition of claim 1, wherein the water-miscible first solvent is N-methyl-2-pyrrolidinone.

9. The composition of claim 1, wherein the water-miscible first solvent is lactic acid.

10. The method of claim 1 further comprising mixing into the water-miscible first solvent or the second solvent or both the water-miscible first solvent and the second solvent one or more surface modifiers selected from the group consisting of: anionic surfactants, cationic surfactants, nonionic surfactants and surface active biological modifiers.

11. The method of claim 1, wherein the removal of the first solvent is by filtration.

12. The method of claim 11, wherein the filtration is cross-flow ultrafiltration.

13. The method of claim 12, wherein the ultrafiltration comprises concentrating the mix to form a concentrate and diafiltering the concentrate to remove the first solvent.

14. The method of claim 11, wherein a polymeric membrane filter is used for the ultrafiltration.

15. The method of claim 11, wherein a ceramic membrane filter is used for the ultrafiltration.

16. The method of claim 1, wherein the first solvent is present in the aqueous suspension at less than about 100 ppm

17. The method of claim 1, wherein the first solvent is present in the aqueous suspension at less than about 50 ppm.

18. The method of claim 1, wherein the first solvent is present in the aqueous suspension at less than about 10 ppm.

19. The method of claim 1, wherein the organic compound is poorly water soluble.

20. The method of claim 19, wherein the organic compound has a solubility in water of less than about 10 mg/mL.

21. The method of claim 1, wherein the organic compound is a pharmaceutically active compound.

22. The method of claim 21, wherein the pharmaceutically active compound is itraconazole.

23. The method of claim 21, wherein the pharmaceutically active compound is budesonide.

24. The composition of claim 21, wherein the pharmaceutically active agent is carbamazepine.

25. The composition of claim 21, wherein the pharmaceutically active agent is prednisolone.

26. The composition of claim 21, wherein the pharmaceutically active agent is nabumetone.

27. The method of claim 1, wherein the small particles have an average effective particle size of from about 20 μm to about 10 nm.

28. The method of claim 1, wherein the small particles have an average effective particle size of from about 10 μm to about 10 nm.

29. The method of claim 1, wherein the small particles have an average effective particle size of from about 2 μm to about 10 nm.

30. The method of claim 1, wherein the small particles have an average effective particle size of from about 1 μm to about 10 nm.

31. The method of claim 1, wherein the small particles have an average effective particle size of from about 400 nm to about 50 nm.

32. The method of claim 1, wherein the small particles have an average effective particle size of from about 200 nm to about 50 nm.

33. The method of claim 1 further comprising sterilizing the aqueous suspension.

34. The method of claim 33, wherein sterilizing the aqueous suspension comprises sterile filtering the solution and the second solvent before mixing and carrying out the subsequent steps under aseptic conditions.

35. The composition of claim 33, wherein sterilizing comprises heat sterilization.

36. The method of claim 35, wherein the heat sterilization is effected within the homogenizer in which the homogenizer serves as a heating and pressurization source for sterilization.

37. The method of claim 33, wherein sterilizing comprises the gamma irradiation.

38. The method of claim 1 further comprising removing the aqueous phase of the aqueous suspension to form a dry powder of the small particles.

39. The method of claim 38, wherein removing the aqueous phase is selected from the group consisting of: evaporation, rotary evaporation, lyophilization, freeze-drying, diafiltration, centrifugation, force-field fractionation, high-pressure filtration, and reverse osmosis.

40. The method of claim 38 further comprising the step of adding a diluent to the small particles.

41. The method of claim 40, wherein the diluent is suitable for parenteral administration of the particles.

42. A composition of small particles prepared by the method of claim 1.

43. The composition of claim 42 is administered to a subject in need of the composition by a route selected from the group consisting of: parenteral, oral, pulmonary, topical, ophthalmic, nasal, buccal, rectal, vaginal, and transdermal.

44. The method of claim 1 wherein the solution and the second solvent are mixed while simultaneously homogenizing the mix and continuously removing the first solvent from the mix.

45. A method for preparing small particles of an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent that is aqueous, the method comprising:

(i) dissolving the organic compound in the water-miscible first solvent to form a solution;

(ii) mixing the solution with the second solvent to form a mix; and

(iii) simultaneously homogenizing the mix and continuously removing the first solvent from the mix by cross-flow ultrafiltration to form an aqueous suspension of small particles having an average effective particle size of less than about 100 μm wherein the aqueous suspension is essentially free of the first solvent.

46. A method for preparing small particles of an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent that is aqueous, the method comprising:

(i) dissolving the organic compound in the water-miscible first solvent to form a solution; and

(ii) simultaneously mixing the solution with the second solvent to form a mix while homogenizing the mix and continuously removing the first solvent from the mix to form an aqueous suspension of small particles having an average effective particle size of less than about 100 μm wherein the aqueous suspension is essentially free of the first solvent.