(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 June 2008 (05.06.2008)

PCT

(10) International Publication Number
WO 2008/065506 A2

(51) International Patent Classification:
A61K 9/16 (2006.01) *A61K 9/51* (2006.01)
A61K 9/50 (2006.01) *A61K 31/135* (2006.01)

(21) International Application Number:
PCT/IB2007/003632

(22) International Filing Date:
16 November 2007 (16.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/867,662 29 November 2006 (29.11.2006) US

(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BEYERINCK, Ronald Arthur** [US/US]; Bend Research Inc. 64550 Research Road, Bend, OR 97701 (US). **BLOOM, Corey, Jay** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **CREW, Marshall, David** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **FRIESEN, Dwayne, Thomas** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **MORGEN, Michael, Mark** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **SMITHEY, Daniel, Tod** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US).

(74) Agent: **FULLER, Grover, F., Jr.**; c/o George, Nancy McGraw, Pfizer Inc. MS8260-1615, Eastern Point Road, Groton, CT 06340 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/065506 A2

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING NANOPARTICLES COMPRISING ENTERIC POLYMERS AND CASEIN

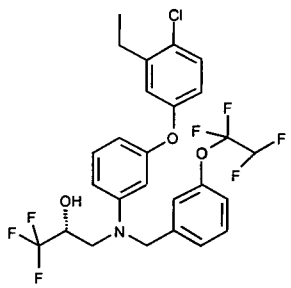
(57) Abstract: A pharmaceutical composition comprises nanoparticles comprising the poorly water soluble lipophilic compound (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2- tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol, and an enteric polymer.

NANOPARTICLES COMPRISING A LIPOPHILIC COMPOUND AND AN ENTERIC POLYMER

BACKGROUND OF THE INVENTION

The present invention relates to nanoparticles comprising a poorly water-soluble lipophilic compound and an enteric polymer.

The compound (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (hereinafter referred to as Compound A) has the chemical structure shown below, and is a cholesteryl ester transfer protein (CETP) inhibitor that may be used to treat dyslipidemia and other indications in human patients.



Compound A is disclosed in WO 00/018724, the disclosures of which are incorporated herein by reference.

Compound A is an extremely lipophilic compound, having a Clog P value of 9.8 and a solubility in phosphate buffered saline (PBS) of less than 0.1 µg/mL. Furthermore, Compound A has a very low melting point of 10°C, and a glass-transition temperature (T_g) of -16°C. These physical properties of Compound A make it advantageous to improve the bioavailability of Compound A when dosed orally to certain mammalian species.

BRIEF SUMMARY OF THE INVENTION

In a first aspect, a pharmaceutical composition comprises nanoparticles, the nanoparticles comprising Compound A; an enteric polymer; and an optional surface stabilizer; wherein the nanoparticles have an average size of less than 500 nm, wherein the nanoparticles comprise a core wherein Compound A and the enteric polymer collectively constitute at least 80 wt% of the core.

In one embodiment, the enteric polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethyl ethylcellulose, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, polyvinyl acetate phthalate, vinyl acetate-maleic anhydride copolymer, polyacrylates, methyl acrylate-methacrylic acid copolymers, ethyl acrylate-methacrylic acid copolymers, styrene-maleic acid copolymers, shellac, and mixtures thereof.

In another embodiment, the enteric polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, carboxymethylethyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl acrylate-methacrylic acid copolymers, ethyl acrylate-methacrylic acid copolymers, and mixtures thereof.

In still another embodiment, the enteric polymer is hydroxypropyl methyl cellulose acetate succinate.

In yet another embodiment, the nanoparticles comprise at least 20 wt% Compound A and at least 40 wt% of an enteric polymer, wherein the enteric polymer is hydroxypropyl methylcellulose acetate succinate.

In still another embodiment, the nanoparticles comprise from 20 wt% to 30 wt% Compound A and from 40 wt% to 55 wt% the enteric polymer, and wherein the enteric polymer is hydroxypropyl methylcellulose acetate succinate.

In another embodiment, the composition further comprises a matrix material, wherein a mass ratio of the nanoparticles to the matrix material ranges from 9:1 to 1:9.

In another embodiment, the matrix material is casein or a pharmaceutically acceptable form thereof.

In yet another embodiment, the nanoparticles comprise at least 20 wt% Compound A, at least 45 wt% the enteric polymer, and at least 20 wt% sodium caseinate, wherein the enteric polymer is hydroxypropyl methylcellulose acetate succinate.

Surprisingly, nanoparticles comprising Compound A and an enteric polymer result in a material that improves the bioavailability of Compound A when administered to an aqueous use environment.

The enteric polymer used in the nanoparticles helps stabilize the poorly water soluble drug. The enteric polymer is chosen so that a portion of the drug is soluble in the enteric polymer. This helps prevent or reduce the rate of crystallization of the non-crystalline drug in the nanoparticle.

The foregoing and other objectives, features, and advantages of the invention will be more readily understood upon consideration of the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The nanoparticles of the present invention comprise Compound A and an enteric polymer. The nature of the nanoparticles, suitable polymers, and methods for making nanoparticles are described in detail below.

Nanoparticles

The nanoparticles are small particles of Compound A and the polymer, with each particle containing Compound A and the enteric polymer. By "nanoparticles" is meant a plurality of small particles in which the average size of the particles in suspension is less than about 500 nm. By "average size" is meant the effective cumulant diameter as measured by dynamic light scattering, using for example, Brookhaven Instruments' 90Plus particle sizing instrument. By "size" is meant the diameter for spherical particles, or the maximum diameter for non-spherical particles. Preferably, the average size of the nanoparticles is less than 400 nm, more preferably less 300 nm, and most preferably less than 200 nm.

The width of the particle size distribution in suspension is given by the "polydispersity" of the particles, which is defined as the relative variance in the correlation decay rate distribution, as is known by one skilled in the art. See B.J. Fisken, "Revisiting the method of cumulants for the analysis of dynamic light-scattering data," *Applied Optics*, 40(24), 4087-4091 (2001) for a discussion of cumulant

diameter and polydispersity. Preferably, the polydispersity of the nanoparticles is less than 0.5. More preferably, the polydispersity of the nanoparticles is less than about 0.3. In one embodiment, the average size of the nanoparticles is less than 500 nm with a polydispersity of 0.5 or less. In another embodiment, the average size of the nanoparticles is less than 300 nm with a polydispersity of 0.5 or less.

In one embodiment, the nanoparticles comprise a core, the core comprising Compound A and the enteric polymer. As used herein, the term "core" refers to the central portion of the nanoparticle. In some embodiments, described herein below, materials may be adsorbed to the surface of the core. Materials adsorbed to the surface of the core are considered part of the nanoparticle, but are distinguishable from the core of the nanoparticle. Methods to distinguish materials present in the core versus materials adsorbed to the surface of the core include (1) thermal methods, such as differential scanning calorimetry (DSC); (2) spectroscopic methods, such as X-ray photoelectron spectroscopy (XPS), transmission electron microscopy (TEM) with energy dispersive X-ray (EDX) analysis, Fourier transform infra red (FTIR) analysis, and Raman spectroscopy; (3) chromatographic techniques, such as high performance liquid chromatography (HPLC), and gel-permeation chromatography (GPC); and (4) other techniques known in the art.

In one embodiment, Compound A and the enteric polymer constitute at least 80 wt% of the core, more preferably at least 90 wt% of the core. In another embodiment, the core consists essentially of Compound A and the enteric polymer.

The Compound A present in the core can exist in non-crystalline pure Compound A domains, as a thermodynamically stable solid solution of non-crystalline Compound A homogeneously distributed throughout the enteric polymer, as a supersaturated solid solution of non-crystalline Compound A homogeneously distributed throughout the enteric polymer, or any combination of these states or those states that lie between them. When the glass-transition temperature (Tg) of Compound A is different from the Tg of the pure polymer by at least about 20°C, the core may exhibit a Tg that is between the Tg of pure non-crystalline Compound A or pure polymer. Preferably, less than 20 wt% of Compound A is present in non-crystalline domains, with the remaining Compound A homogeneously distributed throughout the enteric polymer.

In yet another embodiment, the core comprises non-crystalline Compound A, the enteric polymer, and an optional surface stabilizer. The core may be (1) a homogeneous molecular mixture of Compound A, enteric polymer, and optional surface stabilizer, (2) domains of pure Compound A, domains of pure enteric polymer, and domains of pure surface stabilizer distributed throughout the core, or (3) any combination of these states or those states that lie between them. In one embodiment, Compound A, enteric polymer, and the optional surface stabilizer are homogeneously distributed throughout the core as a supersaturated solid solution. In another embodiment, the exterior surface of the core has a higher concentration of the optional surface stabilizer relative to the core as a whole.

In still another embodiment, the core comprises the non-crystalline Compound A and the enteric polymer, with the optional surface stabilizer adsorbed to the surface of the core.

In yet another embodiment, the core comprises non-crystalline Compound A, the enteric polymer, and a portion of the optional surface stabilizer. The remaining portion of the optional surface stabilizer is adsorbed to the surface of the core. In this embodiment, a portion of the optional surface

stabilizer is integral to the core, while the remaining portion of optional surface stabilizer is adsorbed to the surface of the core.

Compound A is present in the nanoparticles in non-crystalline form. The term "crystalline," as used herein, means a particular solid form of a compound that exhibits long-range order in three dimensions. "Non-crystalline" refers to material that does not have long-range three-dimensional order, and is intended to include not only material which has essentially no order, but also material which may have some small degree of order, but the order is in less than three dimensions and/or is only over short distances. Another term for a non-crystalline form of a material is the "amorphous" form of the material. Preferably at least 95 wt% of Compound A in the nanoparticle is non-crystalline; in other words, the amount of Compound A in crystalline form is below detection limits and does not exceed about 5 wt%. Amounts of crystalline Compound A may be measured by Powder X Ray Diffraction (PXRD), by Differential Scanning Calorimetry (DSC), by solid-state nuclear magnetic resonance (NMR), or by any other known quantitative measurement.

In another embodiment, at least 95 wt% of Compound A in the nanoparticle is amorphous, meaning that the compound exhibits no crystalline peaks when evaluated by PXRD.

Compound A and the enteric polymer are collectively present in the core in an amount ranging from about 80 wt% to 100 wt%. Preferably, Compound A and polymer collectively constitute at least 90 wt%, more preferably at least 95 wt% of the core. In one embodiment, the nanoparticles consist essentially of Compound A, the enteric polymer, and an optional surface stabilizer. By "consist essentially of" is meant that the nanoparticle contains less than 1 wt% of any other excipients and that any such excipients have no affect on the performance or properties of the nanoparticle.

The amount of Compound A in the nanoparticle may range from 0.1 wt% to 90 wt%. Preferably the amount of Compound A in the nanoparticle ranges from about 1 wt% to about 85 wt%, more preferably from about 5 wt% to about 80 wt%, even more preferably from about 10 wt% to about 75 wt%, and most preferably from about 20 wt% to about 75 wt%. In one embodiment, the amount of Compound A in the nanoparticle is at least 20 wt%. In another embodiment, the amount of Compound A in the nanoparticle ranges from 20 wt% to 30 wt%.

The amount of enteric polymer may range from 10 wt% to 99.9 wt%. The physical stability of Compound A in the nanoparticle tends to improve with increasing amounts of the enteric polymer. Accordingly, it is preferred that the amount of enteric polymer in the nanoparticle is at least 15 wt%, more preferably at least 20 wt%, more preferably at least 25 wt%, more preferably at least 30 wt%, more preferably at least 35 wt%, and most preferably at least 40 wt%. However, too much enteric polymer will lead to low Compound A loading in the nanoparticle. Thus, it is preferred that the amount of enteric polymer in the nanoparticle is 75% or less, and most preferably 70 wt% or less.

The amount of optional surface stabilizer may range from 0 wt% to 40 wt%. When a surface stabilizer is present in the nanoparticle, it preferably constitutes at least 0.1 wt% of the total mass of the nanoparticle. Often, even greater amounts of surface stabilizer are desired. Thus, the surface stabilizer may constitute at least 1 wt%, 5 wt%, or even 10 wt% or more of the total mass of the nanoparticle. The surface stabilizer acts to reduce or prevent aggregation or flocculation of the nanoparticles in an aqueous suspension, resulting in nanoparticles with improved stability. Generally, lower concentrations of surface stabilizer are preferred. Thus, preferably the surface stabilizer constitutes

about 35 wt% or less, more preferably about 30 wt% or less, and most preferably about 25 wt% or less the total mass of the nanoparticles.

Preferred embodiments of nanoparticles have the following amounts of Compound A, enteric polymer, and optional surface stabilizer:

5 to 80 wt%, preferably 10 to 75 wt%, and most preferably 20 to 75 wt% Compound A;

20 to 95 wt%, enteric polymer; and

0 to 40 wt% optional surface stabilizer.

In one embodiment, the nanoparticles comprise at least 20 wt% Compound A and at least 40 wt% of an enteric polymer.

In another embodiment, the nanoparticles comprise 20 to 30 wt% Compound A and 40 to 55 wt% of an enteric polymer.

Enteric Polymers

The term "polymer" is used conventionally, meaning a compound that is made of monomers connected together to form a larger molecule. A polymer generally consists of at least about 20 monomers connected together. Thus, the molecular weight of the polymer generally will be about 2000 daltons or more. The polymer should be inert, in the sense that it does not chemically react with Compound A in an adverse manner, and should be pharmaceutically acceptable.

The polymer is an "enteric polymer," meaning that the polymer is poorly soluble in water at a pH of about 4.5 or less, but is soluble in water at a pH of greater than about 5. Except as indicated otherwise below, the term "poorly soluble" as used in connection with enteric polymers herein refers to a solubility of less than about 0.1 mg/ml or less when administered at a concentration of 0.2 mg/mL to water having a pH of about 4.5 or less. Enteric polymers have at least one ionizable substituent that is capable of being ionized at a pH of greater than about 5. Enteric polymers are typically polyacids having a pKa of about 3 to 6. Exemplary ionizable substituents include carboxylic acids, thiocarboxylic acids, and sulfonates. Preferred ionizable substituents include ether-lined alkyl sulfonates such as ethyl sulfonates, ether-linked alkyl carboxy groups, such as carboxy methyl and carboxy ethyl, and ester-linked substituents comprising a carboxylic acid group such as succinate, phthalate, trimellitate, and maleate. The number of ionizable groups covalently attached to the polymer is preferably at least about 0.05 milliequivalents per gram of polymer. Preferably, the number is at least about 0.1 milliequivalents per gram of polymer.

At a pH of greater than about 5, the enteric polymer is aqueous soluble. By "aqueous soluble" is meant that when the polymer is administered alone at a solids concentration of 0.2 mg/mL to a phosphate buffered saline (PBS) solution consisting of an aqueous solution of 20 mM sodium phosphate (Na_2HPO_4), 47 mM potassium phosphate (KH_2PO_4), 87 mM NaCl, and 0.2 mM KCl, adjusted to pH 6.5 with NaOH, the polymer has a solubility of greater than 0.1 mg/mL. Preferably, the polymer has a solubility of at least 0.13 mg/mL, more preferably at least 0.15 mg/mL, and most preferably at least 0.17 mg/mL.

It is also preferred that the enteric polymer be soluble in an organic solvent. Preferably the enteric polymer has a solubility in an organic solvent of at least about 0.1 mg/mL, and preferably at least 1 mg/mL. Preferably the enteric polymer is not crosslinked.

In order to promote physical stability of Compound A in the nanoparticle in the dry state during storage, it is preferred that the enteric polymer have a relatively high glass transition temperature (T_g). By physical stability of Compound A is meant the tendency of a solid solution of Compound A and the enteric polymer to phase separate into domains of pure Compound A. Physical stability of Compound A is a function of the T_g of the Compound A/enteric polymer phase of the nanoparticle, which in turn is a function of the T_g of the polymer. Stability of Compound A in the nanoparticle increases as the T_g of the polymer increases. In one embodiment, the T_g of the enteric polymer at a relative humidity (RH) of 5% or less may be at least 100°C, at least 110°C, at least 120°C, or even at least 130°C.

Suitable enteric polymers include substituted polysaccharides, and non-polysaccharides. By substituted polysaccharides is meant that the enteric polymer has a polysaccharide backbone that has been modified by reaction of at least a portion of the hydroxyl groups on the saccharide repeating units with a compound to form an ester or an ether substituent. Exemplary polysaccharide backbone polymers include cellulose, starch, dextran, dextrin, amylose, amylose pectin, and pullulan.

In one embodiment, the substituted polysaccharide enteric polymer is a cellulosic polymer. By "cellulosic" is meant a cellulose polymer that has been modified by reaction of at least a portion of the hydroxyl groups on the saccharide repeating units with a compound to form an ester or an ether substituent.

Exemplary enteric cellulosic polymers include: hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethyl ethylcellulose, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, and mixtures thereof.

In another embodiment, the enteric polymer is a non-polysaccharide polymer. Exemplary non-polysaccharide enteric polymers include vinyl polymers, such as polyvinyl acetate phthalate, vinyl acetate-maleic anhydride copolymer; polyacrylates, polymethacrylates, and copolymers thereof, such as methyl acrylate-methacrylic acid copolymer, ethyl acrylate-methacrylic acid copolymers; styrene-maleic acid copolymers; shellac, and mixtures thereof.

In one embodiment, the enteric polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethylethyl cellulose, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, polyvinyl acetate phthalate, vinyl acetate-maleic anhydride copolymer, polyacrylates, methyl acrylate-methacrylic acid copolymers, ethyl acrylate-methacrylic acid copolymers, styrene-maleic acid copolymers, shellac, and mixtures thereof.

In another embodiment, the enteric polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, carboxymethylethyl cellulose, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl acrylate-methacrylic acid copolymers, ethyl acrylate-methacrylic acid copolymers, and mixtures thereof.

In one embodiment, the enteric polymer is hydroxypropyl methyl cellulose acetate succinate.

In another embodiment, the enteric polymer is carboxymethyl ethylcellulose.

Optional Surface Stabilizers

The nanoparticles of the present invention may optionally comprise a surface stabilizer in addition to Compound A and the enteric polymer. The purpose of the surface stabilizer is to reduce or prevent aggregation or flocculation of the nanoparticles in an aqueous suspension, resulting in nanoparticles with improved stability. In one embodiment, the surface stabilizer is used to stabilize the nanoparticles during the formation process. The stabilizer should be inert, in the sense that it does not chemically react with Compound A in an adverse manner, and should be pharmaceutically acceptable.

In one embodiment, the surface stabilizer is an amphiphilic compound, meaning that it has both hydrophobic and hydrophilic regions. In another embodiment, the surface stabilizer is a surfactant, including anionic, cationic, zwitterionic, and non-ionic surfactants. Mixtures of surface stabilizers may also be used.

Exemplary surface stabilizers include casein, caseinates, polyvinyl pyrrolidone (PVP), polyoxyethylene alkyl ethers, polyoxyethylene stearates, polyoxyethylene castor oil derivatives, poly(ethylene oxide-propylene oxide) (also known as poloxamers), tragacanth, gelatin, polyethylene glycol, bile salts (such as salts of dihydroxy cholic acids, including sodium and potassium salts of cholic acid, glycocholic acid, and taurocholic acid), phospholipids (such as phosphatidyl cholines, including 1,2-diacylphosphatidylcholine also referred to as PPC or lecithin), sodium dodecylsulfate (also known as sodium lauryl sulfate), benzalkonium chloride, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (polysorbates), polyoxyethylene stearates, triethanolamine, sodium docusate, sodium stearyl fumarate, sodium cyclamate, and mixtures and pharmaceutically acceptable forms thereof.

Process for Making Nanoparticles

The nanoparticles may be formed by any process that results in formation of nanoparticles of Compound A and an enteric polymer.

One process for forming nanoparticles is an emulsification process. In this process, Compound A and polymer are dissolved in a solvent that is immiscible with an aqueous solution in which Compound A and the polymer are poorly soluble, forming an organic solution. Solvents suitable for forming the solution of dissolved Compound A and polymer can be any compound or mixture of compounds in which Compound A and the polymer are mutually soluble and which is immiscible in the aqueous solution. As used herein, the term "immiscible" means that the organic solvent has a solubility in the aqueous solution of less than about 10 wt%, preferably less than about 5 wt%, and most preferably less than about 3 wt%. Preferably, the solvent is also volatile with a boiling point of 150°C or less. In addition, the solvent should have relatively low toxicity. Exemplary solvents include methylene chloride, trichloroethylene, tetrachloroethane, trichloroethane, dichloroethane, dibromoethane, ethyl acetate, phenol, chloroform, toluene, xylene, ethyl-benzene, methyl-ethyl ketone, methyl-isobutyl ketone, and mixtures thereof. Preferred solvents are methylene chloride, ethyl acetate, benzyl alcohol, and mixtures thereof. The aqueous solution is preferably water.

Once the organic solution is formed, it is then mixed with the aqueous solution and homogenized to form an emulsion of fine droplets of the water immiscible solvent distributed throughout the aqueous phase. The volume ratio of organic solvent to aqueous solution used in the process will

generally range from 1:100 (organic solvent:aqueous solution) to 2:3 (organic solvent:aqueous solution). Preferably, the organic solvent:aqueous solution volume ratio ranges from 1:9 to 1:2 (organic solvent:aqueous solution). The emulsion is generally formed by a two-step homogenization procedure. The solution of Compound A, polymer and solvent are first mixed with the aqueous solution using a rotor/stator or similar mixer to create a "pre-emulsion". This mixture is then further processed with a high-pressure homogenizer that subjects the droplets to very high shear, creating a uniform emulsion of very small droplets. A portion of the solvent is then removed forming a suspension of the nanoparticles in the non-solvent. Exemplary processes for removing the solvent include evaporation, extraction, diafiltration, pervaporation, vapor permeation, distillation, and filtration. Preferably, the organic solvent is removed to a level that is acceptable according to The International Committee on Harmonization (ICH) guidelines. Preferably, the concentration of organic solvent in the nanoparticle suspension is less than the solubility of the organic solvent in the aqueous solution. Even lower concentrations of organic solvent are preferred. Thus, the concentration of organic solvent in the nanoparticle suspension may be less than about 5 wt%, less than about 3 wt%, less than 1 wt%, and even less than 0.1 wt%.

Thus, in one embodiment, a process for forming nanoparticles comprises: (a) dissolving Compound A and an enteric polymer in an organic solvent to form an organic solution; (b) forming an aqueous solution in which Compound A is poorly soluble and which is immiscible with the organic solvent; (c) forming an emulsion comprising the organic solution and the aqueous solution; (d) removing the organic solvent to form a suspension of solid nanoparticles having an average size of less than 500 nm, wherein Compound A and the enteric polymer collectively constitute at least 80 wt% of the nanoparticles.

An alternative process to form the nanoparticles is a precipitation process. In this process, Compound A and polymer are first dissolved in an organic solvent that is miscible with an aqueous solution in which Compound A and the polymer are poorly soluble to form an organic solution. The organic solution is mixed with the aqueous solution causing the nanoparticles to precipitate. Solvents suitable for forming the solution of dissolved Compound A and polymer can be any compound or mixture of compounds in which Compound A and the polymer are mutually soluble and which is miscible in the aqueous solution. Preferably, the solvent is also volatile with a boiling point of 150°C or less. In addition, the solvent should have relatively low toxicity. Exemplary solvents include acetone, methanol, ethanol, tetrahydrofuran (THF), and dimethylsulfoxide (DMSO). Mixtures of solvents, such as 50% methanol and 50% acetone, can also be used, so long as the polymer and Compound A are sufficiently soluble to dissolve Compound A and polymer. Preferred solvents are methanol, acetone, and mixtures thereof.

The aqueous solution may be any compound or mixture of compounds in which Compound A and polymer are sufficiently insoluble so as to precipitate to form nanoparticles. The aqueous solution is preferably water.

The solvent solution and aqueous solution are combined under conditions that cause solids to precipitate as nanoparticles. The mixing can be by addition of a bolus or stream of organic solvent to a container of stirred aqueous solution. Alternately a stream or jet of organic solvent can be mixed with a moving stream of aqueous solution. In either case, the precipitation results in the formation of a suspension of nanoparticles in the aqueous solution.

For the precipitation process, the amount of Compound A and polymer in the solvent solution depends on the solubility of each in the solvent and the desired ratios of Compound A to polymer

in the resulting nanoparticles. The solution may comprise from about 0.1 wt% to about 20 wt% dissolved solids. A dissolved solids content of from about 0.5 wt% to 10 wt% is preferred.

The organic solvent:aqueous solution volume ratio should be selected such that there is sufficient aqueous soloution in the nanoparticle suspension that the nanoparticles solidify and do not rapidly agglomerate. However, too much aqueous solution will result in a very dilute suspension of nanoparticles, which may require further processing for ultimate use. Generally, the organic solvent:aqueous solution volume ratio should be at least 1:100, but generally should be less than 1:2 (organic solvent:aqueous solution). Preferably, the solvent:non-solvent volume ratio ranges from about 1:20 to about 1:3.

Once the nanoparticle suspension is made, a portion of the organic solvent may be removed from the suspension using methods known in the art. Exemplary processes for removing the organic solvent include evaporation, extraction, diafiltration, pervaporation, vapor permeation, distillation, and filtration. Preferably, the solvent is removed to a level that is acceptable according to ICH guidelines. Thus, the concentration of solvent in the nanoparticle suspension may be less than about 10 wt%, less than about 5 wt%, less than about 3 wt%, less than 1 wt%, and even less than 0.1 wt%.

When the optional surface stabilizer is included in the nanoparticle composition, it may be added to either the organic solution or the aqueous solution for either of the processes described above.

Thus, in another embodiment, a process for forming nanoparticles, comprises: (a) forming an organic solution comprising the compound (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol and an enteric polymer dissolved in a solvent; (b) forming an aqueous solution; (c) mixing the organic solution with the aqueous solution to form a first mixture; (d) removing the solvent from the first mixture to form a suspension comprising the nanoparticles and the aqueous solution, wherein (i) the nanoparticles have an average size of less than 500 nm, and (ii) the nanoparticles comprising a core, wherein the compound and the enteric polymer, collectively constitute at least 80 wt% of the core.

Both the emulsion process and the precipitation process result in the formation of a suspension of the nanoparticles in the aqueous solution. In some instances it is desirable to concentrate the nanoparticles or to isolate the nanoparticles in solid form by removing some or all of the liquids from the suspension. Exemplary processes for removing at least a portion of the liquids include spray drying, spray coating, spray layering, lyophylization, evaporation, vacuum evaporation, filtration, ultrafiltration, reverse osmosis, and other processes known in the art. Preferably, the liquid is removed by a process selected from spray drying, evaporation, and lyophylization. In one embodiment, the liquid is removed by spray drying. In another embodiment, the liquid is removed by evaporation. In still another embodiment, the liquid is removed by lyophylization. In yet another embodiment, the liquid is removed by a combination of processes selected from the group consisting of spray drying, spray coating, spray layering, lyophylization, evaporation, vacuum evaporation, filtration, ultrafiltration, and reverse osmosis. For example, the liquid may be removed by ultrafiltration, followed by spray drying, followed by evaporation in a tray dryer.

When isolating the nanoparticles in solid form, it is often desirable to include a matrix material in the suspension of nanoparticles prior to removal of the liquid. The matrix material functions to help slow or prevent agglomeration of the nanoparticles as the liquid is being removed, as well as to help

re-suspend the nanoparticles when the solid composition is added to the aqueous solution. The matrix material is preferably pharmaceutically acceptable and water soluble. Examples of matrix materials include polyvinyl pyrrolidone (PVP), trehalose, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), casein, caseinate, albumin, gelatin, acacia, lactose, mannitol, other matrix materials know in the art, and pharmaceutically acceptable forms and mixtures thereof.

The amount of matrix material present with the nanoparticles will depend on the matrix material used and the nanoparticle composition. Generally, the mass ratio of nanoparticles to matrix material ranges from 9:1 to 1:9 (that is, 10 wt% matrix material to 90 wt% matrix material relative to the total mass of nanoparticles and matrix material in the composition). Preferably the mass ratio of nanoparticle to matrix material is at least 4:1, and more preferably at least 3:1. However, too much matrix material leads to low amounts of Compound A in the composition. Thus, the mass ratio of nanoparticles to matrix material is preferably less than 1:4, and most preferably less than 1:3.

In one embodiment of the invention, a solid composition comprises (a) a plurality of nanoparticles comprising Compound A and an enteric polymer, and (b) a matrix. As used herein, the term "solid composition" means that the composition is in a solid form and substantially free of liquids. The nanoparticles are entrapped or encapsulated in the matrix material.

In another embodiment, a composition comprises nanoparticles and a matrix material, wherein a mass ratio of the nanoparticles to the matrix material ranges from 9:1 to 1:9.

In still another embodiment, the matrix material is casein or a pharmaceutically acceptable form thereof.

In yet another embodiment, the composition of the invention comprises nanoparticles, wherein the nanoparticles comprise at least 20 wt% Compound A, at least 45 wt% of the enteric polymer, and at least 20 wt% sodium caseinate, wherein the enteric polymer is hydroxypropyl methylcellulose acetate succinate.

Dosage Forms

The nanoparticles may be administered using any known dosage form. The nanoparticles may be formulated for administration via oral, subdermal, intranasal, buccal, intrathecal, ocular, intraaural, intraarticular, subcutaneous spaces, vaginal tract, arterial and venous blood vessels, pulmonary tract or intramuscular tissue of an animal, such as a mammal and particularly a human. Oral dosage forms include: powders or granules; tablets; chewable tablets; capsules; unit dose packets, sometimes referred to in the art as "sachets" or "oral powders for constitution" (OPC); syrups; and suspensions.

In one embodiment, the compositions of the present invention are capable of improving the concentration of dissolved Compound A in a use environment relative to a control composition consisting essentially of Compound A alone without the polymer. In order to determine concentration enhancement *in vitro*, the amount of "free" Compound A, or solvated Compound A is measured. By "free" Compound A is meant Compound A which is dissolved or present in micelles, but which is not in the nanoparticles or any solid particles larger than 500 nm, such as precipitate. A composition of the invention provides concentration enhancement if, when administered to an aqueous use environment, it provides a free Compound A concentration that is at least 1.25-fold the free Compound A concentration

provided by the control composition. Preferably, the free Compound A concentration provided by the compositions of the invention are at least about 1.5-fold, more preferably at least about 2-fold, and most preferably at least about 3-fold that provided by the control composition.

Alternatively, the compositions of the present invention, when dosed orally to a mammalian subject such as a human, provide an AUC in Compound A concentration in the blood plasma or serum (or relative bioavailability) that is at least 1.25-fold that observed in comparison to the control composition. Preferably, the blood AUC is at least about 2-fold, more preferably at least about 3-fold, even more preferably at least about 4-fold, still more preferably at least about 6-fold, yet more preferably at least about 10-fold, and most preferably at least about 20-fold that of the control composition. The determination of AUCs is a well-known procedure and is described, for example, in Welling, "Pharmacokinetics Processes and Mathematics," ACS Monograph 185 (1986).

Alternatively, the compositions of the present invention, when dosed orally to a human or other animal, provide a maximum Compound A concentration in the blood plasma or serum (C_{max}) that is at least 1.25-fold that observed in comparison to the control composition. Preferably, the C_{max} is at least about 2-fold, more preferably at least about 3-fold, even more preferably at least about 4-fold, still more preferably at least about 6-fold, yet more preferably at least about 10-fold, and most preferably at least about 20-fold that of the control composition. Thus, compositions that meet the *in vitro* or *in vivo* performance criteria, or both, are considered to be within the scope of the invention.

Without further elaboration, it is believed that one of ordinary skill in the art can, using the foregoing description, utilize the present invention to its fullest extent. Therefore, the following specific embodiments are to be construed as merely illustrative and not restrictive of the scope of the invention. Those of ordinary skill in the art will understand that variations of the conditions and processes of the following examples can be used.

Examples

Polymers Used in Examples

The following enteric polymers were used in the examples: hydroxypropyl methylcellulose acetate succinate (HPMCAS-L, AQOAT-L from Shin Etsu, Tokyo, Japan), and carboxymethyl ethylcellulose (CMEC, available from Freund Industrial Co., Ltd., Japan).

Example 1

The nanoparticles of Example 1 were made containing Compound A, hydroxypropyl methylcellulose acetate succinate (HPMCAS-L, AQOAT-L from Shin Etsu, Tokyo, Japan), and sodium caseinate as a surface stabilizer. First, 150 mg Compound A and 150 mg HPMCAS were dissolved in 5 mL 3:1 ethyl acetate:methylene chloride to form an organic solution. Next, 100 mg sodium caseinate was added to 20 mL deionized water to form an aqueous solution. The organic solution was then poured into the aqueous solution and emulsified for 3 min using a Kinematica Polytron 3100 rotor/stator (Kinematica AG, Lucerne, Switzerland) at 10,000 rpm (high-shear mixing). The solution was further emulsified using a Microfluidizer (Microfluidics [Newton, MA] model M-110S F12Y with ice bath and cooling coil), for 6 minutes (high-pressure homogenization). The ethyl acetate and methylene chloride were removed from

the emulsion using a rotary evaporator to a combined concentration of less than about 3 wt%, resulting in an aqueous suspension of nanoparticles, with a mass ratio of 37.5:37.5:25 Compound A:HPMCAS:caseinate.

Light Scattering Analysis

The particle size of the nanoparticles in the aqueous suspension was determined using dynamic light scattering (DLS) as follows. First, the aqueous suspension was filtered using a 1 μm glass membrane filter (Anotop filter, Whatman), and poured into a cuvette. Light-scattering was measured using a Brookhaven Instruments (Holtsville, NY) BI-200SM particle size analyzer with a BI-9000AT correlator. The sums of exponentials from the autocorrelation functions are analyzed to extract size distributions from the samples, and the size is reported as the cumulant value. The average diameter was found to be 100 nm, with a polydispersity of 0.25.

The aqueous suspension of Example 1 was allowed to stand unmixed for 24 hours at ambient conditions to measure stability. DLS analysis showed that the average cumulant diameter of the nanoparticles in suspension was 119 nm, with a polydispersity of 0.26. These results demonstrate that the nanoparticles of Example 1 in suspension were stable during storage with no significant particle agglomeration.

Isolation of Solid Compositions

The nanoparticle suspension of Example 1 was spray-dried as follows. The suspension was added to a reservoir and pumped to a two fluid nozzle located in a spray-drying chamber, using an HPLC pump (model 515, Waters Corp., Milford, MA) at a flow rate of about 0.15 g/min. The spray-drying chamber consisted of two sections: a straight-side section (top), and a cone section (bottom). The top of the straight-side section was equipped with a spray-solution inlet. The spray solution was sprayed through the spray-solution inlet using the two-fluid nozzle, into the straight-side section of the spray-drying chamber. The straight-side section had a diameter of 10 cm and a length of 19 cm.

Drying gas (nitrogen) entered the cone section through a drying-gas inlet at a flow of about 1.0 SCFM and an inlet temperature of about 120°C. The flow rate of drying gas and spray solution were selected such that the atomized spray solution was sufficiently dry by the time it reached the walls of the spray-drying chamber that it did not stick to the walls. The diameter of the cone section at the top was 10 cm, and the distance from the top of the cone section to the bottom was 19 cm. At the bottom of the cone section was a 4.7-cm diameter outlet port, fitted with a 0.8 μm nylon filter (Magna, GE Osmonics, Minnetonka, MN) supported by a metal screen. The spray dried composition was collected on the filter, and evaporated solvent and drying gas were removed from the spray-drying chamber through the outlet port.

Nanoparticle Resuspension

The solid composition of Example 1 was resuspended by adding 8.7 mg of sample to 2 mL deionized water. DLS analysis showed that the average cumulant diameter of the nanoparticle suspension was 144 nm, with a polydispersity of 0.44. This demonstrates that a small particle size was maintained after isolation of the solid composition of Example 1, followed by resuspension.

Filter Potency

Filter potency was used to characterize the resuspended nanoparticles of Example 1. First, a 50 μL sample of the aqueous nanoparticle suspension was added to 1 mL methanol, and the

concentration of Compound A in solution was analyzed by HPLC. Next, the suspension was filtered using a 0.45 µm filter and diluted in methanol for HPLC analysis.

Potencies of the nanoparticle suspensions are shown in Table 2. The results in Table 2 show that 82% of the nanoparticle suspension potency is maintained following filtration of Example 1 using a 0.45 µm filter. This indicates that the nanoparticles in suspension remain small and unagglomerated.

Table 2

Sample	Potency Unfiltered (mg/mL)	Potency 0.45 µm filtered (mg/mL)	Potency Retained (%)
Example 1	1.7	1.4	82

Example 2

For Example 2, nanoparticles containing Compound A were prepared using a precipitation method as follows. First, a water-miscible organic solution was formed by dissolving 200 mg Compound A and 373.2 mg HPMCAS-L in 37 mL methanol. To form the nanoparticles, the stem of a glass funnel containing the organic solution was inserted under the surface of an aqueous solution consisting of 343 mL of filtered water, and delivered into the stirring vortex all at once, rapidly forming nanoparticles. The methanol was removed using a rotary evaporator to a concentration of less than about 0.1 wt%, resulting in an aqueous suspension of nanoparticles. DLS analysis showed that the average cumulant diameter of the nanoparticles in suspension was 109 nm, with a polydispersity of 0.26.

The aqueous suspension was concentrated using tangential flow filtration with a Millipore Biomax® 300 50 cm^2 polyethersulfone membrane (available from Millipore Corp., Billerica, MA). The feed solution, consisting of about 345 mL aqueous nanoparticle suspension, was concentrated to 24 mL final volume.

To form an aqueous suspension of the present invention, sodium caseinate was added to this concentrated suspension, resulting in a nanoparticle suspension consisting of 26.2:48.8:25 Compound A:HPMCAS-L:casein.

Isolation of Solid Compositions

The nanoparticle suspension of Example 2 was spray-dried using the procedures described in Example 1, resulting in the formation of a solid composition of the invention.

Nanoparticle Resuspension

The solid composition of Example 2 was resuspended by adding about 5 mg/mL sample to deionized water. DLS analysis showed that the average cumulant diameter of the resuspended nanoparticles was 157 nm, with a polydispersity of 0.26. This demonstrates that a small particle size can be maintained after isolation of the solid composition, followed by resuspension.

Filter Potency

A filter potency test was used to characterize resuspended nanoparticles of Example 2. A 50 µL sample of the aqueous nanoparticle resuspension of Example 2 was added to 1 mL methanol, and the concentration of Compound A in solution was analyzed by HPLC. Next, the suspension was filtered using a 0.2 µm filter, and diluted in methanol for HPLC analysis.

Potencies of the nanoparticle suspensions are shown in Table 3. The results in Table 3 show that 94% of the nanoparticle suspension potency is maintained following filtration by a 0.2 μm filter. This indicates that most of the nanoparticles in suspension remain small and unagglomerated.

Table 3

Sample	Potency Unfiltered (mg/mL)	Potency 0.2 μm filtered (mg/mL)	Potency Retained (%)
Example 2	2.47	2.33	94

Example 3

Nanoparticles containing Compound A and the enteric polymer carboxymethyl ethylcellulose (CMEC, available from Freund Industrial Co., Ltd., Japan) were prepared using the procedure outlined in Example 2 with the following exceptions. The water-miscible organic solution was formed by dissolving 93 mg Compound A and 181.2 mg CMEC in 20 mL methanol. The aqueous solution consisted of 180 mL of filtered water. The organic solution and aqueous solutions were then mixed rapidly to form nanoparticles. The methanol was removed using rotary evaporation to a concentration of less than 0.5 wt%, resulting in a nanoparticle suspension consisting of 34:66 (wt:wt) Compound A:CMEC. DLS analysis showed that the average cumulant diameter of the nanoparticles in suspension was 110 nm, with a polydispersity of 0.39. The aqueous suspension was concentrated as described in Example 2.

To form an aqueous suspension of the present invention, sodium caseinate was added to this concentrated suspension, resulting in a nanoparticle suspension consisting of 25.5:49.5:25 Compound A:CMEC:sodium caseinate.

Isolation of Solid Compositions

The nanoparticle suspension of Example 3 was spray-dried using the procedures described in Example 1, resulting in the formation of a solid composition of the invention.

Nanoparticle Resuspension

The solid composition of Example 3 was resuspended by adding 38 mg of sample to 2 mL deionized water. DLS analysis showed that the average cumulant diameter of the nanoparticle suspension was 165 nm, with a polydispersity of 0.38. This demonstrates that a small particle size can be maintained after isolation of the solid composition, followed by resuspension.

Example 4

For Example 4, nanoparticles containing Compound A were prepared using a precipitation method as follows. First, a water-miscible organic solution was formed containing 0.62 wt% Compound A, 1.15 wt% HPMCAS-L, and 98.23 wt% methanol. The methanol solution was pumped through a tube having an inside diameter of 0.01 inches (0.25 mm) at a flow rate of 10 mL/min. The tube was located inside another tube having an inside diameter of 0.22 inches (5.6 mm), through which was fed purified water at a flow rate of 90 mL/min. This resulted in the formation of a suspension of nanoparticles in the water/methanol liquid. An aqueous solution containing 8 wt% sodium caseinate was added to this suspension to form a Compound A/polymer/sodium caseinate nanoparticle suspension (0.051 wt% Compound A, 0.094 wt% HPMCAS-L, 0.048 wt% sodium caseinate, 8.026 wt% methanol, and 91.781 wt% water). The pH of the suspension was adjusted to a pH of 7 with an aqueous solution

containing 1 wt% sodium hydroxide. The resulting nanoparticle suspension consisted of 26.4:48.6:25.0 Compound A:HPMCAS-L:sodium caseinate.

Filter Potency and Suspension Stability

A filter potency test was used to characterize the nanoparticle suspension of Example 4. A sample of the aqueous suspension of Example 4 was diluted in methanol (to obtain a target concentration of 0.5 to 50 µgA/mL), and the concentration of Compound A in solution was analyzed by HPLC. The suspension was filtered through 0.45 µm and 0.2 µm filters, and the filtrate collected and diluted in methanol for HPLC analysis. Filter potency was performed for the nanoparticle suspension before and after storage for 14 days in a glass vial at 5°C.

Potencies of the nanoparticle suspensions are shown in Table 4. The results show that concentration of Compound A in the filtrate was high for both filters, indicating that the nanoparticles retained a small particle size during the test.

Table 4

Sample	Amount Passed Through Filter (% of unfiltered)	
	0.45-µm Filter	0.2-µm Filter
Initial	96	97
14 days at 5°C	97	93

Isolation of Solid Compositions

The pH-adjusted nanoparticle suspension was spray-dried to form a solid powder as follows. The suspension was pumped using a high-pressure pump to a spray drier (a Niro type XP Portable Spray-Dryer with a Liquid-Feed Process Vessel ("PSD-1")), equipped with a Schlick #1.5 pressure nozzle (available from Dusen Schlick GmbH of Untersiemau, Germany). The PSD-1 was equipped with 6-foot, 4-inch, and 9-inch chamber extensions to increase the vertical length of the dryer. A high-pressure pump was used to deliver liquid to the nozzle. The suspension was pumped to the spray drier at about 40 g/min at a pressure of 500 psig. Drying gas (e.g., nitrogen) at a flow rate of 1200 g/min was circulated at an inlet temperature of 160°C, and the evaporated solvent and drying gas exited the spray drier at a temperature of 50°C. The resulting solid composition was collected in a cyclone.

Nanoparticle Resuspension and Filter Potency

The solid composition of Example 4 was resuspended by adding about 2 mgA/mL of the solid sample to filtered deionized water, and vortexing for 30 seconds.

A filter potency test was used to characterize the resuspended nanoparticles, using the procedures described above. Potencies of the nanoparticle resuspensions are shown in Table 5. The results in Table 5 show that 93% passed through a 0.2-µm filter. Additionally, the resuspension was stored at 5°C for 8 hours and filter potency was repeated and 90% of the particles passed through the filter. Based on these data, most of the nanoparticles in suspension remain small and unagglomerated, indicating that the resuspension has acceptable stability.

Table 5

Sample	Unfiltered (% of theoretical)	Amount Passed Through Filter (% of unfiltered)	
		0.45-µm Filter	0.2-µm Filter
Initial	95	93	93
8 hours at 5°C	97	93	90

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

We claim:

1. A pharmaceutical composition comprising nanoparticles, said nanoparticles comprising:
   (a) the compound (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol;
   (b) an enteric polymer;
   (c) an optional surface stabilizer;

wherein said nanoparticles have an average size of less than 500 nm, and said nanoparticles comprise a core, wherein said compound and said enteric polymer, collectively constitute at least 80 wt% of said core.

2. The composition of claim 1 wherein said optional surface stabilizer is adsorbed to the surface of said core.

3. The composition of claim 1 wherein said compound and said enteric polymer collectively constitute at least 90 wt% of said core.

4. The composition of claim 1 wherein said core consist essentially of said compound and said enteric polymer.

5. The composition of claim 1 wherein said nanoparticles have the following composition: from 5 wt% to 80 wt% of said compound and from 20 wt% to 95 wt% of said enteric polymer.

6. The composition of claim 1 wherein said nanoparticles have an average size of less than 300 nm.

7. The composition of claim 1 wherein said enteric polymer has a glass-transition temperature of at least 100°C when measured at a relative humidity of less than 5%.

8. The composition of claim 1 wherein said enteric polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethyl ethylcellulose, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, polyvinyl acetate phthalate, vinyl acetate-maleic anhydride copolymer, polyacrylates, methyl acrylate-methacrylic acid copolymers, ethyl acrylate-methacrylic acid copolymers, styrene-maleic acid copolymers, shellac, and mixtures thereof.

9. The composition of claim 8 wherein said enteric polymer is hydroxypropyl methylcellulose acetate succinate.

10. The composition of claim 9 wherein said nanoparticles comprise at least 20 wt% said compound and at least 40 wt% said enteric polymer and wherein said enteric polymer is hydroxypropyl methylcellulose acetate succinate.

11. The composition of claim 1 wherein said optional surface stabilizer constitutes from 0.1 to 40 wt% of said nanoparticles.

12. The composition of claim 11 wherein said surface stabilizer is selected from the group consisting of casein, caseinates, polyvinyl pyrrolidone, polyoxyethylene alkyl ethers, polyoxyethylene stearates, polyoxyethylene castor oil derivatives, poly(ethylene oxide-propylene oxide), tragacanth, gelatin, polyethylene glycol, sodium and potassium salts of cholic acid, glycocholic acid, and taurocholic acid, phospholipids (such as phosphatidyl cholines, including 1,2-diacylphosphatidylcholine also referred to as PPC or lecithin), sodium dodecylsulfate (also known as sodium lauryl sulfate), benzalkonium chloride, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (polysorbates), polyoxyethylene stearates, triethanolamine, sodium docusate, sodium stearyl fumarate, sodium cyclamate, and pharmaceutically acceptable forms and mixtures thereof.

13. A composition comprising the nanoparticles of claim 1 and a matrix material, wherein a mass ratio of said nanoparticles to said matrix material ranges from 9:1 to 1:9.

14. The composition of claim 13 wherein said matrix material is casein or a pharmaceutically acceptable form thereof.

15. A process for forming nanoparticles, comprising:

(a) forming an organic solution comprising the compound (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol and an enteric polymer dissolved in a solvent;

(b) forming an aqueous solution;

(c) mixing said organic solution with said aqueous solution to form a first mixture;

(d) removing said solvent from said first mixture to form a suspension comprising said nanoparticles and said aqueous solution, wherein

(i) said nanoparticles have an average size of less than 500 nm, and

(ii) said nanoparticles comprising a core, wherein said compound and said enteric polymer, collectively constitute at least 80 wt% of said core.