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(54) Title: NANOPARTICLES COMPRISING DRUG, A NON-IONIZABLE CELLULOSIC POLYMER AND TOCOPHERYL POLYETHYLENE GLYCOL SUCCINATE

(57) Abstract: A pharmaceutical composition comprises nanoparticles comprising a poorly water soluble drug, a non-ionizable cellulosic polymer, and TPGS.

NANOPARTICLES COMPRISING DRUG, A NON-IONIZABLE CELLULOSIC POLYMER AND TOCOPHERYL POLYETHYLENE GLYCOL SUCCINATE

BACKGROUND OF THE INVENTION

5 The present invention relates to nanoparticles comprising a poorly water-soluble drug, a poorly aqueous soluble non-ionizable cellulosic polymer having an ether- or ester- linked alkyl substituent, and tocopheryl polyethylene glycol succinate (TPGS).

10 It is known that poorly water-soluble drugs may be formulated as nanoparticles. Nanoparticles are of interest for a variety of reasons, such as to improve the bioavailability of poorly water-soluble drugs, to provide targeted drug delivery to specific areas of the body, to reduce side effects, or to reduce pharmacokinetic variability *in vivo*.

15 A variety of approaches have been taken to formulate drugs as nanoparticles. One approach is to decrease the size of crystalline drug by grinding or milling the drug in the presence of a surface modifier. See, e.g., U.S. Patent No. 5,145,684. Another approach to forming nanoparticles is to precipitate the drug in the presence of a film forming material such as a polymer. See, e.g., U.S. Patent No. 5,118,528.

20 While these methods of forming nanoparticles are functional, nevertheless there remain a number of problems associated with the use of nanoparticles to deliver pharmaceutical compounds to the body. First, it is difficult to form very small particles. Second, once particles of the target size are formed, they must remain stable over time in a variety of different environments. Often, the 25 nanoparticles are formed in a liquid environment. The nanoparticles must be stabilized so that they do not aggregate in solution into larger particles. In addition, the drug in the nanoparticles must be stabilized so that it does not crystallize in the use environment.

30 Third, the nanoparticles must be well tolerated in the body. Often surface modifiers such as surfactants are used to stabilize the nanoparticles, but such materials can have adverse physiological effects when administered *in vivo*. In addition, such materials are often labile, dissolving into the aqueous use environment, resulting in undesirable agglomeration of nanoparticles. Ionizable stabilizers are often

-2-

not ionized in the low pH of a gastric environment, resulting in agglomeration of the nanoparticles in the stomach. In addition, without a surface modifier present, the surface of the nanoparticles is unprotected, leading to a decrease in performance and stability.

5 Finally, the nanoparticles must be formulated to provide optimum delivery. The nanoparticles should provide good bioavailability of the poorly water-soluble drug. In some applications, it is desired that the nanoparticles provide reduced differences in exposure when administered orally to subjects in the fed state versus in the fasted state. Alternatively, it may be desired to provide controlled or sustained
10 release of the drug below pre-determined dissolved drug concentrations *in vivo*. It may be desired to administer the nanoparticles through non-oral routes, such as by parenteral, topical, or ocular delivery.

 The use of TPGS as a component of nanoparticles is known in the art. See, for example, Mu and Feng (*J. Controlled Release*, 80 (2002) 129-144 and
15 *Pharmaceutical Research*, Vol. 20, No. 11 2003, 1864-1872). In these studies, nanoparticles consisting of paclitaxel, poly(lactic-co-glycolic acid) [PLGA], and TPGS were formed wherein the paclitaxel was in an amorphous form. However, such formulations are not ideal for commercial dosage forms.

 Accordingly, there is still a continuing need for nanoparticles that are
20 stable, in the sense of not forming crystalline drug over time or aggregating into larger particles, and that improve the bioavailability of poorly water-soluble drugs.

BRIEF SUMMARY OF THE INVENTION

 In a first aspect, a pharmaceutical composition comprises nanoparticles,
25 the nanoparticles comprising: (a) a poorly water soluble drug having an aqueous solubility of about 5 mg/mL or less over the pH range of 6.5 to 7.5 at 25°C, at least 90 wt% of the drug in the nanoparticles being non-crystalline; (b) a poorly aqueous soluble non-ionizable cellulosic polymer having an ether- or ester-linked alkyl substituent; and (c) tocopheryl polyethylene glycol succinate (TPGS); wherein the
30 nanoparticles have an average size of less than 500 nm, and the drug, the non-ionizable cellulosic polymer, and the TPGS collectively constitute at least 60 wt% of the nanoparticles.

-3-

In one embodiment, the non-ionizable cellulosic polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose propionate, cellulose butyrate, and cellulose acetate butyrate.

Because the nanoparticles are formed from a blend of a poorly aqueous soluble non-ionizable cellulosic polymer and TPGS, the stability of the non-crystalline drug and the suspension stability of the nanoparticle can be addressed independently, resulting in nanoparticles with improved performance and stability.

First, the poorly aqueous soluble non-ionizable cellulosic polymer used in the nanoparticles stabilizes the poorly water soluble drug in the sense of reducing the rate of crystallization of the drug in the solid state and while in suspension *in vivo*. The non-ionizable cellulosic polymer is chosen so that a portion of the drug is soluble in the polymer. This helps prevent or reduce the rate of crystallization of the non-crystalline drug in the nanoparticle. It is well known that the non-crystalline form of a low-solubility drug provides a greater aqueous concentration of drug relative to the crystalline form of the drug when administered to an aqueous use environment. However, it is also well known that when the drug is not stabilized in the non-crystalline form, the drug rapidly converts to the crystalline form in the use environment. See, for example, Hancock and Parks (*Pharmaceutical Research*, Vol. 17, No. 4, 2000). Thus, the poorly aqueous soluble non-ionizable cellulosic polymer is selected to maintain the stability of the non-crystalline drug in the nanoparticle and while suspended in an aqueous solution, resulting in an enhanced concentration of free drug when the nanoparticle is administered to an aqueous use environment.

In addition, because the non-ionizable cellulosic polymer is poorly aqueous soluble at physiological pH, the nanoparticles maintain the drug within a solid (or at least undissolved) polymer matrix when the nanoparticles are suspended in an aqueous solution, further preventing or reducing crystallization of the drug.

Second, the TPGS provides suspension stability to the nanoparticles. The TPGS reduces or eliminates agglomeration of the nanoparticles when in an aqueous suspension.

Finally, nanoparticles formed using TPGS may provide improved toleration relative to conventional nanoparticles that incorporate a substantial amount of surfactant to stabilize the nanoparticles.

-4-

The combination of the two different materials—the poorly aqueous soluble non-ionizable cellulosic polymer and the TPGS—provides a synergistic effect that cannot be obtained when using only one material, resulting in improved stability and re-suspendability of the nanoparticles.

5 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.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

10 FIG. 1 is a powder X ray diffraction (PXR) diffractogram of the solid composition containing nanoparticles of Example 6.

 FIG. 2 is a powder X ray diffraction (PXR) diffractogram of the solid composition containing nanoparticles of Example 7.

15 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

 The nanoparticles of the present invention comprise a poorly water soluble drug, a poorly aqueous soluble non-ionizable cellulosic polymer, and TPGS. At least 90 wt% of the drug in the nanoparticle is non-crystalline. The nature of the nanoparticles, TPGS, suitable polymers and drugs, and methods for making
20 nanoparticles are described in detail below.

Nanoparticles

 The nanoparticles are small particles of drug, the poorly aqueous soluble non-ionizable cellulosic polymer, and TPGS, with each particle containing the drug, the
25 non-ionizable cellulosic polymer and TPGS. By “nanoparticles” is meant a plurality of small particles in which the average size of the particles is less than about 500 nm. In suspension, by “average size” is meant the effective cumulant diameter as measured by dynamic light scattering (DLS), using for example, Brookhaven Instruments’ 90Plus particle sizing instrument. By “size” is meant the diameter if the particles were
30 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, more preferably less than 200 nm, more preferably less than 150 nm, and most preferably less than 100 nm.

-5-

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. Fiskens, "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 still another embodiment, the average size of the nanoparticles is less than 200 nm with a polydispersity of 0.5 or less. In yet another embodiment, the average size of the nanoparticles is less than 200 nm with a polydispersity of 0.3 or less.

While the drug in its pure form may be either crystalline or non-crystalline, at least 90 wt% of the drug in the nanoparticles is non-crystalline. 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. As previously discussed, the non-crystalline form of a low-solubility drug is preferred as it provides a greater aqueous concentration of drug relative to the crystalline form of the drug in an aqueous use environment. Preferably at least about 95 wt% of the drug in the nanoparticle is non-crystalline; in other words, the amount of drug in crystalline form does not exceed about 5 wt%. Amounts of crystalline drug 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.

The nanoparticles can exist in a number of different configurations. In one embodiment, the nanoparticles comprise a core, the core comprising the non-crystalline drug and the poorly aqueous soluble non-ionizable cellulosic polymer. As used herein, the term "core" refers to the interior portion of the nanoparticle. The

-6-

nanoparticles also have a "surface portion," meaning the outside or exterior portion of the nanoparticle. Thus, the nanoparticles consist of a core (i.e., the interior portion) and a surface portion. In some embodiments, described herein below, materials may be adsorbed to the surface portion of the nanoparticle. Materials adsorbed to the surface portion of the nanoparticle 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 portion of the nanoparticle 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, the non-crystalline drug and the poorly aqueous soluble non-ionizable cellulosic polymer constitute at least 60 wt% of the core, more preferably at least 80 wt% of the core. In another embodiment, the core consists essentially of the non-crystalline drug and the poorly aqueous soluble non-ionizable cellulosic polymer.

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

In yet another embodiment, the core comprises the non-crystalline drug, the poorly aqueous soluble non-ionizable cellulosic polymer, and TPGS. In this

-7-

embodiment, the drug, the non-ionizable cellulosic polymer, and the TPGS constitute at least 60 wt% of the core, more preferably at least 80 wt% of the core.

The core may be (1) a homogeneous molecular mixture of drug, non-ionizable cellulosic polymer, and TPGS, (2) domains of pure drug, domains of pure non-ionizable cellulosic polymer, and domains of pure TPGS distributed throughout the core, or (3) any combination of these states or those states that lie between them. In one embodiment, the drug, non-ionizable cellulosic polymer, and TPGS are homogeneously distributed throughout the core as a supersaturated solid solution. In another embodiment, the surface portion of the nanoparticle has a higher concentration of TPGS relative to the nanoparticle as a whole.

In still another embodiment, the core comprises the non-crystalline drug and the poorly aqueous soluble non-ionizable cellulosic polymer, with the TPGS adsorbed to the surface portion of the nanoparticle.

In yet another embodiment, the core comprises the non-crystalline drug, the poorly aqueous soluble non-ionizable cellulosic polymer, and a portion of the TPGS. The remaining portion of the TPGS is adsorbed to the surface portion of the nanoparticle. In this embodiment, a portion of the TPGS is integral to the core, while the remaining portion of the TPGS is adsorbed to the surface portion of the nanoparticle.

The drug, polymer, and TPGS are collectively present in the nanoparticle in an amount ranging from about 60 wt% to 100 wt%. Preferably, the drug polymer, and TPGS collectively constitute at least 70 wt%, more preferably at least 80 wt%, and even more preferably at least 90 wt% of the nanoparticle. In one embodiment, the nanoparticles consist essentially of the drug, the non-ionizable cellulosic polymer and the TPGS. 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 effect on the performance or properties of the nanoparticle.

The amount of drug in the nanoparticle may range from 0.1 wt% to 90 wt%. Preferably the amount of drug in the nanoparticle ranges from about 1 wt% to about 80 wt%, more preferably from about 5 wt% to about 75 wt%, and most preferably from about 10 wt% to about 67 wt%.

To minimize the total mass of the formulation, high drug loadings are desired. However, if the amount of drug in the nanoparticle is too high, the

-8-

nanoparticle suspension becomes unstable, resulting in crystallization of the drug in the suspension. Additionally, high amounts of drug in the nanoparticle can lead to crystalline drug formation when the nanoparticles are isolated from suspension in solid form. Therefore, it is generally preferred that the amount of drug in the nanoparticle be less than about 90 wt%, more preferably less than about 80 wt%, even more preferably less than about 75 wt% the total mass of the nanoparticle.

The amount of poorly aqueous soluble non-ionizable cellulosic polymer may range from 10 wt% to 75 wt%. The physical stability of the non-crystalline drug in the nanoparticle tends to improve with increasing amounts of the poorly aqueous soluble non-ionizable cellulosic polymer. Accordingly, it is preferred that the amount of poorly aqueous soluble non-ionizable cellulosic polymer in the nanoparticle is at least 15 wt%, more preferably at least 20 wt%, and most preferably at least 25 wt%. However, too much non-ionizable cellulosic polymer will lead to low drug loading in the nanoparticle and low amounts of TPGS. Thus, it is preferred that the amount of poorly aqueous soluble non-ionizable cellulosic polymer in the nanoparticle is 75% or less, and most preferably 70 wt% or less.

The amount of TPGS may range from 5 wt% to 80 wt%. Preferably, the TPGS is present in a sufficient amount so that the nanoparticles do not agglomerate into larger particles in solution. Preferably the amount of TPGS in the nanoparticle is at least 10 wt%, more preferably at least 15 wt%, and most preferably at least 20 wt%. However, too much TPGS will lead to low drug loading and low amounts of the non-ionizable polymer. Thus, it is preferred that the amount of TPGS be 75 wt% or less, and most preferably 70 wt% or less.

In one embodiment, the mass ratio of non-ionizable cellulosic polymer to TPGS ranges from 1:8 to 15:1, more preferably from 1:6 to 9:1, even more preferably from 1:4 to 4:1, and most preferably from 1:3 to 3:1. Preferably, there is a sufficient amount of non-ionizable cellulosic polymer to stabilize the drug in the nanoparticle, and a sufficient amount of TPGS to stabilize the nanoparticles in solution.

Preferred embodiments of nanoparticles have the following amount of drug, poorly aqueous soluble non-ionizable cellulosic polymer and TPGS:

1 to 80 wt%, preferably 5 to 75 wt%, more preferably 5 to 50 wt% drug;
10 to 75 wt%, preferably 20 to 60 wt%, more preferably 30 to 60 wt% poorly aqueous soluble non-ionizable cellulosic polymer; and

-9-

5 to 60 wt%, preferably 5 to 40 wt%, more preferably 10 to 40 wt%

TPGS.

The nanoparticle is preferably substantially free from ionizable surfactants. By a "surfactant" is meant a surface-active material with a molecular weight of less than about 2000 daltons having a hydrophobic portion and a hydrophilic portion, and which is soluble in the use environment. By "ionizable" is meant the surfactant has at least one ionizable group covalently attached to the surfactant. By substantially "free from" is meant that the amount of ionizable surfactant present in the composition is less than about 0.1 wt%. Preferably, the amount of ionizable surfactant present in the nanoparticles is less than the detection limit.

Non-ionizable Cellulosic Polymers

The nanoparticles of the present invention comprise a poorly aqueous soluble non-ionizable cellulosic polymer having an ether- or ester-linked alkyl substituent. 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 the drug in an adverse manner, and should be pharmaceutically acceptable.

The polymer is a poorly aqueous soluble non-ionizable cellulosic polymer. By "poorly aqueous soluble" is meant that the polymer has a solubility of less than 0.1 mg/mL when administered alone at a concentration of 0.2 mg/mL to a phosphate buffered saline solution (PBS) at pH 6.5. An appropriate PBS solution is an aqueous solution comprising 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. A test to determine whether the polymer is insoluble may be performed as follows. The polymer is initially present in bulk powder form with average particle sizes of greater than about 1 micron. The polymer alone is administered at a concentration of 0.2 mg/mL to the PBS solution and stirred for approximately 1 hour at room temperature. Next, a nylon 0.45 μm filter is weighed, and the polymer solution is filtered. The filter is dried overnight at 40°C, and weighed the following morning. The amount of polymer dissolved is calculated from the amount of polymer added to the

-10-

PBS solution minus the amount of polymer remaining on the filter (mg). The non-ionizable cellulosic polymer is considered to be poorly aqueous soluble if it has a solubility of less than 0.1 mg/mL in this test. Preferably, when administered at a concentration of 0.2 mg/mL to the pH 6.5 PBS, a poorly aqueous soluble non-ionizable cellulosic polymer has a solubility of less than 0.07 mg/mL, more preferably less than 0.05 mg/mL, and most preferably less than 0.01 mg/mL.

To ease processing, it is preferred that the poorly aqueous soluble non-ionizable cellulosic polymer be soluble in an organic solvent. Preferably the 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 polymer is not crosslinked.

The polymer is "non-ionizable," meaning that the polymer possesses substantially no ionizable functional groups. By "substantially no ionizable functional groups" is meant that the number of ionizable groups covalently attached to the polymer is less than about 0.05 milliequivalents per gram of polymer. Preferably, the number is less than about 0.02 milliequivalents per gram of polymer. By "ionizable groups" is meant functional groups that are at least about 10% ionized over at least a portion of the physiologically relevant pH range of 1 to 8. Such groups have pK_a values of about 0 to 9.

The polymer is a poorly aqueous soluble non-ionizable cellulosic polymer having an ether- or ester-linked alkyl substituent. Suitable alkyl substituents include C_1 to C_4 alkyl groups. Exemplary ether-linked alkyl substituents include methyl, ethyl, propyl, and butyl groups. Exemplary ester-linked alkyl substituents include acetate, propionate, and butyrate groups.

Exemplary non-ionizable cellulosic polymers include methylcellulose, ethylcellulose, propylcellulose, butylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose acetate butyrate, cellulose acetate propionate, methyl cellulose acetate, methyl cellulose propionate, methyl cellulose butyrate, ethyl cellulose acetate, ethyl cellulose propionate, ethyl cellulose butyrate, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose propionate, and hydroxypropyl methylcellulose butyrate. Preferably the poorly aqueous soluble non-ionizable cellulosic polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose propionate, cellulose butyrate, and cellulose acetate butyrate. Preferably, the non-ionizable polymer is ethylcellulose.

-11-

TPGS

The nanoparticles of the present invention comprise TPGS. By "TPGS" is meant "tocopheryl polyethylene glycol succinate." TPGS is a family of compounds that have polyethylene glycol ester linked to tocopheryl succinate. By "tocopheryl succinate" is meant a succinate ester of tocopherol. By "tocopherol" is meant the chemical compounds collectively known as Vitamin E. Isomers of tocopherol include α -tocopherol, β -tocopherol, γ -tocopherol, and δ -tocopherol. In a preferred embodiment, TPGS is α -tocopheryl polyethylene glycol succinate.

The polyethylene glycol (PEG) that is ester linked to tocopheryl succinate can be any molecular weight. Preferably the molecular weight of the PEG group ranges from about 100 to about 20,000 Daltons. More preferably, the molecular weight of the PEG group ranges from about 200 to about 10,000 Daltons. Most preferably, the molecular weight of the PEG group ranges from about 400 to about 5000 Daltons. In another embodiment, the molecular weight of the PEG group is about 1000 Daltons.

In a preferred embodiment, the TPGS is Vitamin E TPGS, also known as d- α -tocopheryl polyethylene glycol 1000 succinate, available from Eastman Chemical Company (Kingsport, TN).

The Drug

The drug is a "poorly water soluble drug," meaning that the drug has a solubility in water (over the pH range of 6.5 to 7.5 at 25 °C) of less than 5 mg/mL. The utility of the invention increases as the water solubility of the drug decreases. The drug may have an even lower solubility in water, such as less than about 1 mg/mL, less than about 0.1 mg/mL, and even less than about 0.01 mg/mL.

In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than about 10 mL, and more typically greater than about 100 mL, where the aqueous solubility (mg/mL) is the minimum value observed in any physiologically relevant aqueous solution (i.e., solutions with pH 1- 8), including USP simulated gastric and intestinal buffers, and dose is in mg. Thus, a dose-to-aqueous solubility ratio may be calculated by dividing the dose (in mg) by the aqueous solubility (in mg/mL).

-12-

Preferred classes of drugs include, but are not limited to, compounds for use in the following therapeutic areas: antihypertensives, antianxiety agents, antiarrhythmia agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, anti-atherosclerotic agents, cholesterol-reducing agents, triglyceride-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-angiogenesis agents, anti-glaucoma agents, anti-depressants, and antiviral agents.

Each named drug should be understood to include the nonionized form of the drug or pharmaceutically acceptable forms of the drug. By "pharmaceutically acceptable forms" is meant any pharmaceutically acceptable derivative or variation, including stereoisomers, stereoisomer mixtures, enantiomers, solvates, hydrates, isomorphs, polymorphs, pseudomorphs, neutral forms, salt forms and prodrugs.

Exemplary drugs suitable for use in the nanoparticles include, but are not limited to, phosphodiesterase inhibitors, such as sildenafil and sildenafil citrate; HMG-CoA reductase inhibitors, such as atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, itavastatin, nisvastatin, visastatin, atavastatin, bervastatin, compactin, dihydrocompactin, dalvastatin, flindostatin, pitivastatin, and velostatin (also referred to as synvinolin); vasodilator agents, such as amiodarone; antipsychotics, such as ziprasidone; calcium channel blockers, such as nifedipine, nicardipine, verapamil, and amlodipine; cholesteryl ester transfer protein (CETP) inhibitors; cyclooxygenase-2 inhibitors; microsomal triglyceride transfer protein (MTP) inhibitors; vascular endothelial growth factor (VEGF) receptor inhibitors; carbonic anhydrase inhibitors; and glycogen phosphorylase inhibitors. Other low-solubility drugs suitable for use in the nanoparticles are disclosed in US Published patent application 2005/0031692, herein incorporated by reference.

In one embodiment, the drug is ziprasidone or a pharmaceutically acceptable form thereof.

In another embodiment, the drug is a hydrophobic non-ionizable drug. By "hydrophobic non-ionizable drug" is meant a subclass of non-ionizable drugs that are essentially water insoluble and highly hydrophobic, and are characterized by a set

-13-

of physical properties, as described hereinafter. By "non-ionizable" is meant that the drug has substantially no ionizable groups. By "ionizable groups" is meant functional groups that are at least about 10% ionized over at least a portion of the physiologically relevant pH range of 1 to 8. Such groups have pKa values of about 0 to 9. Thus, hydrophobic non-ionizable drugs do not have a pKa value between 0 and 9.

The first property of hydrophobic drugs is that they are extremely hydrophobic. Log P, defined as the base 10 logarithm of the ratio of the drug solubility in octanol to the drug solubility in water, is a widely accepted measure of hydrophobicity. By "extremely hydrophobic" is meant that the Log P value of the drug is at least 4.0, preferably at least 4.5, and most preferably at least 5.0. Log P may be measured experimentally or calculated using methods known in the art. When using a calculated value for Log P, the highest value calculated using any generally accepted method for calculating Log P is used. Calculated Log P values are often referred to by the calculation method, such as Clog P, Alog P, and Mlog P. The Log P may also be estimated using fragmentation methods, such as Crippen's fragmentation method (27 J.Chem.Inf.Comput.Sci. 21 (1987)); Viswanadhan's fragmentation method (29 J.Chem.Inf.Comput.Sci. 163 (1989)); or Broto's fragmentation method (19 Eur.J.Med.Chem.-Chim.Theor. 71 (1984)). Preferably the Log P value is calculated by using the average value estimated using Crippen's, Viswanadhan's, and Broto's fragmentation methods.

The second property of hydrophobic drugs is that they have an extremely low solubility in water over the pH range of 6.5 to 7.5 at 25°C. By "extremely low solubility in water" is meant that the solubility of the drug in water is less than 100 µg/mL. Preferably, the hydrophobic drug has a water solubility of less than 50 µg/mL, and most preferably less than 10 µg/mL.

In another embodiment the drug is a cholesteryl ester transfer protein (CETP) inhibitor. CETP inhibitors are drugs that inhibit CETP activity. The effect of a drug on the activity of CETP can be determined by measuring the relative transfer ratio of radiolabeled lipids between lipoprotein fractions, essentially as previously described by Morton in J. Biol. Chem. 256, 11992, 1981 and by Dias in Clin. Chem. 34, 2322, 1988, and as presented in U.S. Patent No. 6,197,786, the disclosures of which are herein incorporated by reference. The potency of CETP inhibitors may be determined by performing the above-described assay in the presence of varying concentrations of

-14-

the test compounds and determining the concentration required for 50% inhibition of transfer of radiolabeled lipids between lipoprotein fractions. This value is defined as the "IC₅₀ value." Preferably, the CETP inhibitor has an IC₅₀ value of less than about 2000 nM, more preferably less than about 1500 nM, even more preferably less than about 1000 nM, and most preferably less than about 500 nM.

Specific examples of CETP inhibitors include [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester; (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol; S-[2-(((1-(2-ethylbutyl)cyclohexyl)carbonyl)amino)phenyl]2-methylpropanethioate; trans-4-[[[2-[[[3,5-bis(trifluoromethyl)phenyl]methyl](2-methyl-2H-tetrazol-5-yl)amino]methyl]-4-(trifluoromethyl)phenyl]ethylamino]methyl]-cyclohexaneacetic acid; trans-(4-[[N-(2-[[N'-(3,5-bis(trifluoromethyl)benzyl)-N'-(2-methyl-2H-tetrazol-5-yl)amino]methyl)-5-methyl-4-trifluoromethylphenyl)-N-ethylamino]methyl]cyclohexyl)acetic acid methanesulfonate; trans-(2R,4S)- 2-(4-{4-[(3,5-bis-trifluoromethyl-benzyl)-(2-methyl-2H-tetrazol-5-yl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carbonyl}-cyclohexyl)-acetamide; methyl N-(3-cyano-5-trifluoromethylbenzyl)-[6-(N'-cyclopentylmethyl-N'-ethylamino)indan-5-ylmethyl]-carbamate; methyl (3-cyano-5-trifluoromethylbenzyl)-[6-(N-cyclopentylmethyl-N-ethylamino)indan-5-ylmethyl]-carbamate; ethyl 4-((3,5-bis(trifluoromethyl)phenyl)(2-methyl-2H-tetrazol-5-yl)methyl)-2-ethyl-6-(trifluoromethyl)-3,4-dihydroquinoxaline-1(2H)-carboxylate; tert-butyl 5-(N-(3,5-bis(trifluoromethyl)benzyl)acetamido)-7-methyl-8-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b]azepine-1-carboxylate; (3,5-bis-trifluoromethyl-benzyl)-[2-(cyclohexyl-methoxy-methyl)-5-trifluoromethyl-benzyl]-[2-methyl-2H-tetrazol-5-yl)-amine; 1-[1-(2-[[3,5-bis-trifluoromethyl-benzyl)-(2-methyl-2H-tetrazol-5-yl)-amino]-methyl]-4-trifluoromethyl-phenyl)-2-methyl-propyl]-piperidine-4-carboxylic acid; (3,5-bis-trifluoromethyl-benzyl)-[2-(1-methoxy-cycloheptyl)-5-trifluoromethyl-benzyl]-[2-methyl-2H-tetrazol-5-yl)-amine; (3,5-bis-trifluoromethyl-benzyl)-[2-(1-cyclohexyl-1-methoxy-ethyl)-5-trifluoromethyl-benzyl]-[2-methyl-2H-tetrazol-5-yl)-amine; the drugs disclosed in commonly owned U.S. Patent Application Serial Nos. 09/918,127 and 10/066,091, the disclosures of both of which are incorporated herein by reference; and the drugs disclosed in the following patents and published applications, the disclosures of all of which are incorporated herein by reference: DE 19741400 A1; DE 19741399

-15-

A1; WO 9914215 A1; WO 9914174; DE 19709125 A1; DE 19704244 A1; DE 19704243 A1; EP 818448 A1; WO 9804528 A2; DE 19627431 A1; DE 19627430 A1; DE 19627419 A1; EP 796846 A1; DE 19832159; DE 818197; DE 19741051; WO 9941237 A1; WO 9914204 A1; JP 11049743; WO 0018721; WO 0018723; WO 0018724; WO 0017164; WO 0017165; WO 0017166; EP 992496; EP 987251; WO 9835937; JP 03221376; WO 04020393; WO 05095395; WO 05095409; WO 05100298; WO 05037796; WO 0509805; WO 03028727; WO 04039364; WO 04039453; WO 0633002; and U.S. Provisional Patent Application Numbers 60/781488 and 60/780993, both of which were filed on March 10, 2006.

10 Thus, in one embodiment, the CETP inhibitor is selected from the group of compounds mentioned above. In another embodiment, the CETP inhibitor is selected from the group consisting of (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol; trans-(2R,4S)- 2-(4-{4-[(3,5-bis-trifluoromethyl-benzyl)-(2-methyl-2H-tetrazol-5-yl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carbonyl}-cyclohexyl)-acetamide; (3,5-bis-trifluoromethyl-benzyl)-[2-(cyclohexyl-methoxy-methyl)-5-trifluoromethyl-benzyl]-(2-methyl-2H-tetrazol-5-yl)-amine; 1-[1-(2-[(3,5-bis-trifluoromethyl-benzyl)-(2-methyl-2H-tetrazol-5-yl)-amino]-methyl)-4-trifluoromethyl-phenyl]-2-methyl-propyl-piperidine-4-carboxylic acid; (3,5-bis-trifluoromethyl-benzyl)-[2-(1-methoxy-cycloheptyl)-5-trifluoromethyl-benzyl]-(2-methyl-2H-tetrazol-5-yl)-amine; (3,5-bis-trifluoromethyl-benzyl)-[2-(1-cyclohexyl-1-methoxy-ethyl)-5-trifluoromethyl-benzyl]-(2-methyl-2H-tetrazol-5-yl)-amine, and pharmaceutically acceptable forms thereof.

25 In still another embodiment, the CETP inhibitor is (2R)-3-[[3-(4-chloro-3-ethylphenoxy)phenyl][3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol.

 In still another embodiment, the CETP inhibitor is trans-(2R,4S)- 2-(4-{4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-methyl-2H-tetrazol-5-yl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carbonyl}-cyclohexyl)-acetamide.

30 In another embodiment, the drug is an inhibitor of cyclooxygenase-2 (COX-2). COX-2 inhibitors are nonsteroidal anti-inflammatory drugs that exhibit anti-inflammatory, analgesic and antipyretic effects. Preferably, the COX-2 inhibitor is a selective COX-2 inhibitor, meaning that the drug is able to inhibit COX-2 without significant inhibition of cyclooxygenase-1 (COX-1). Preferably, the COX-2 inhibitor has

-16-

a potency such that the concentration of drug that inhibits 50% of COX-2 enzyme in an *in vitro* test (i.e., the IC₅₀ value) is less than about 10 μM, preferably less than 5 μM, more preferably less than 2 μM. In addition, it is also preferable that the COX-2 inhibitor be selective relative to COX-1. Thus, preferably, the ratio of the IC_{50,COX-2} to IC_{50,COX-1} ratio for the compound is less than 0.5, more preferably less than 0.3, and most preferably less than 0.2.

Specific examples of COX-2 inhibitors include 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (celecoxib); 4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (valdecoxib); N-(4-(5-methyl-3-phenylisoxazol-4-yl)phenylsulfonyl)propionamide (paracoxb); sodium (S)-6,8-dichloro-2-(trifluoromethyl)-2H-chromene-3-carboxylate; sodium (S)-7-tert-butyl-6-chloro-2-(trifluoromethyl)-2H-chromene-3-carboxylate; 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl benzeneacetic acid (lumiracoxib); 4-(3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (deracoxib); 4-(4-(methylsulfonyl)phenyl)-3-phenylfuran-2(5H)-one (rofecoxib); 5-chloro-2-(6-methylpyridin-3-yl)-3-(4-(methylsulfonyl)phenyl)pyridine (etoricoxib); 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-(4-(methylsulfonyl)phenyl)pyridazin-3(2H)-one; (Z)-3-((3-chlorophenyl)(4-(methylsulfonyl)phenyl)methylene)-dihydrofuran-2(3H)-one; N-(2-(cyclohexyloxy)-4-nitrophenyl)methanesulfonamide; 4-Methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoyl-phenyl)-1H-pyrrole; 6-((5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl)methyl)pyridazin-3(2H)-one; 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide (tilmacoxib); 2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-1H-pyrrole; 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (meloxicam); 4-(4-chloro-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide(cimicoxib), and pharmaceutically acceptable forms thereof; and the compounds disclosed in the following patents and published applications, the disclosures of which are incorporated herein by reference: US 5,466,823, US 5,633,272, US 5,932,598, US 6,034,256, US 6,180,651, US 5,908,858, US 5,521,207, US 5,691,374, WO 99/11605, WO 98/03484, and WO 00/24719.

Preferably the COX-2 inhibitor is selected from the group consisting of celecoxib; valdecoxib; paracoxb; sodium (S)-6,8-dichloro-2-(trifluoromethyl)-2H-chromene-3-carboxylate; sodium (S)-7-tert-butyl-6-chloro-2-(trifluoromethyl)-2H-

-17-

chromene-3-carboxylate; and pharmaceutically acceptable forms thereof. In one embodiment, the COX-2 inhibitor is celecoxib or pharmaceutically acceptable forms thereof.

5 Process for Making Nanoparticles

The nanoparticles may be formed by any process that results in formation of nanoparticles of non-crystalline drug, a non-ionizable cellulosic polymer, and TPGS. The drug used to form the nanoparticles may be in a crystalline or non-crystalline form; however, at least 90 wt% of the drug in the resulting nanoparticles is
10 in non-crystalline form.

One process for forming nanoparticles is an emulsification process. In this process, the drug and the non-ionizable cellulosic polymer are dissolved in an organic solvent that is immiscible with an aqueous solution in which the drug and non-ionizable cellulosic polymer are poorly soluble, forming an organic solution. Solvents
15 suitable for forming the solution of dissolved drug and polymer can be any compound or mixture of compounds in which the drug and the polymer are mutually soluble and which is immiscible with the aqueous solution. As used herein, the term "immiscible" means that the 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%.
20 Preferably, the solvent is also volatile with a boiling point of 150°C or less. Exemplary organic solvents include methylene chloride, trichloroethylene, trichlorotrifluoroethylene, tetrachloroethane, trichloroethane, dichloroethane, dibromoethane, ethyl acetate, phenol, chloroform, toluene, xylene, ethyl-benzene, benzyl alcohol, creosol, methyl-ethyl ketone, methyl-isobutyl ketone, hexane, heptane, ether, and
25 mixtures thereof. Preferred organic solvents are methylene chloride, ethyl acetate, benzyl alcohol, and mixtures thereof.

The TPGS is added to the aqueous solution. Generally, the amount of TPGS added to the aqueous solution will be at least 0.1 mg/mL organic solvent used in the process, but will generally be less than about 100 mg/mL organic solvent used in
30 the process. Preferably, the amount of TPGS will range from 1 mg/mL to 50 mg/mL of organic solvent used in the process.

The organic solution is mixed with the aqueous solution and homogenized to form an emulsion of fine droplets of the organic solution distributed

-18-

throughout the aqueous solution. The volume ratio of organic solution to aqueous solution used in the process will generally range from 1:100 (organic solution:aqueous solution) to 2:3 (organic solution:aqueous solution). Preferably, the organic solution:aqueous solution volume ratio ranges from 1:9 to 1:2 (organic solution:aqueous solution). The emulsion is generally formed by a two-step homogenization procedure. The organic solution and aqueous solution are first mixed 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 organic solvent is then removed forming a suspension of the nanoparticles in the aqueous solution. 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 The International Committee on Harmonization (ICH) guidelines. Preferably, the concentration of 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%.

Alternatively, the TPGS may be added to the organic solution. The nanoparticles are then formed using the above emulsification procedure.

An alternative process to form the nanoparticles is a precipitation process. In this process, the drug and non-ionizable cellulosic polymer are first dissolved in an organic solvent that is miscible with an aqueous solution in which the drug and non-ionizable cellulosic polymer are poorly soluble. The resulting organic solution is mixed with the aqueous solution which contains the TPGS, causing the nanoparticles to precipitate. Solvents suitable for forming the solution of dissolved drug and non-ionizable cellulosic polymer can be any compound or mixture of compounds in which the drug and polymer are mutually soluble and which is miscible in the aqueous solution. Preferably, the organic solvent is also volatile with a boiling point of 150°C or less. Exemplary organic solvents include acetone, methanol, ethanol, tetrahydrofuran (THF), and dimethylsulfoxide (DMSO). Mixtures of organic solvents, such as 50% methanol and 50% acetone, can also be used, so long as the

-19-

drug and polymer are sufficiently soluble to dissolve the drug and polymer. Preferred organic solvents are methanol, acetone, and mixtures thereof.

The aqueous solution may be any compound or mixture of compounds in which the drug and polymer are sufficiently insoluble so as to precipitate to form
5 nanoparticles. The aqueous solution preferably comprises TPGS and water.

The organic 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 solution to a stirring container of the aqueous solution. Alternately a stream or jet of organic solution can be mixed with a moving
10 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 drug and polymer in the organic solution depends on the solubility of each in the organic solvent and the desired ratios of drug to polymer to TPGS in the resulting nanoparticles. The organic
15 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 solution:aqueous solution volume ratio should be selected such that there is sufficient aqueous solution in the nanoparticle suspension that the nanoparticles solidify and do not rapidly agglomerate. However, too much aqueous
20 solution will result in a very dilute suspension of nanoparticles, which may require further processing for ultimate use. Generally, the organic solution:aqueous solution volume ratio should be at least 1:100, but generally should be less than 1:2 (organic solution:aqueous solution). Preferably, the organic solution:aqueous solution volume ratio ranges from about 1:20 to about 1:3.

25 Alternatively, the drug, non-ionizable cellulosic polymer, and TPGS are dissolved in the solvent that is miscible with the aqueous solution. The nanoparticles are then formed using the above precipitation procedure.

Once the nanoparticle suspension is made, a portion of the organic solvent may be removed from the suspension using methods known in the art.
30 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

-20-

10 wt%, 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) forming an organic solution comprising a poorly water soluble drug and a poorly aqueous soluble non-ionizable cellulosic polymer dissolved in an organic solvent, wherein the drug has a solubility in water of less than 5 mg/ml over the pH range of 6.5 to 7.5, and the non-ionizable cellulosic polymer has an ether- or ester-linked alkyl substituent; (b) forming an aqueous solution, wherein the drug and the non-ionizable cellulosic polymer are poorly soluble in the aqueous solution; (c) adding TPGS to at least one of the organic solution and the aqueous solution; (d) mixing the organic solution with the aqueous solution to form a first mixture; (e) 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, (ii) at least 90 wt% of the drug in the nanoparticles is non-crystalline, and (iii) the drug, the non-ionizable cellulosic polymer, and the TPGS collectively constitute at least 60 wt% of the nanoparticles.

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 liquid from the suspension. Exemplary processes for removing at least a portion of the liquid include spray drying, spray coating, spray layering, lyophilization, evaporation, vacuum evaporation, filtration, ultrafiltration, reverse osmosis, and other processes known in the art. Preferably, the liquids are removed by a process selected from spray drying, evaporation, and lyophilization. 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 lyophilization. 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, lyophilization, evaporation, vacuum evaporation, filtration, ultrafiltration, and reverse osmosis. For example, a portion of the liquids may be removed by filtration to concentrate the nanoparticles, followed by spray-drying to remove most of the remaining liquids, followed by a further drying step such as tray-drying.

-21-

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 liquids. The matrix material functions to help slow or prevent agglomeration of the nanoparticles as the liquids are being removed, as well as to help re-suspend the nanoparticles when the solid composition is added to an aqueous solution (e.g., an aqueous environment of use). 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, pharmaceutically acceptable forms thereof, and other matrix materials known in the art.

In one embodiment of the invention, a solid composition comprises (a) a plurality of nanoparticles comprising a poorly water-soluble drug, a non-ionizable cellulosic polymer, and TPGS, and (b) a matrix material. As used herein, the term "solid pharmaceutical 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.

The presence of nanoparticles in the solid composition can be determined using the following procedure. A sample of the solid composition is embedded in a suitable material, such as an epoxy or polyacrylic acid (e.g., LR White from London Resin Co., London, England). The sample is then microtomed to obtain a cross-section of the solid composition that is about 100 to 200 nm thick. This sample is then analyzed using transmission electron microscopy (TEM) with energy dispersive X-ray (EDX) analysis. TEM-EDX analysis quantitatively measures the concentration and type of atoms larger than boron over the surface of the sample. From this analysis, regions that are rich in drug can be distinguished from regions that are rich in the matrix material. The size of the regions that are rich in drug will have an average diameter of less than 500 nm in this analysis, demonstrating that the solid composition comprises nanoparticles of drug in the matrix material. See, for example, *Transmission Electron Microscopy and Diffractometry of Materials* (2001) for further details of the TEM-EDX method.

Another procedure that demonstrates the solid composition contains nanoparticles is to administer a sample of the solid composition to water to form a suspension of the nanoparticles. The suspension is then analyzed by dynamic DLS as

-22-

described herein. A solid composition of the invention will form nanoparticles having an average cumulant diameter of less than 500 nm.

A specific procedure for demonstrating the solid composition contains nanoparticles is as follows. A sample of the solid composition is added to water at ambient temperature such that the concentration of solids is less than about 1 mg/mL. The so-formed suspension is then analyzed by DLS. The solid composition contains nanoparticles if the DLS analysis results in particles having an average cumulant diameter of less than 500 nm.

A solid composition of the invention will show the presence of nanoparticles in at least one, and preferably both of the above tests.

Dosage Forms

The compositions of the present invention may be administered using any known dosage form. The nanoparticles may be formulated for administration via oral, topical, subdermal, intranasal, buccal, intrathecal, ocular, intraaural, subcutaneous spaces, intraarticular, 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. Parenteral dosage forms include reconstitutable powders or suspensions. Topical dosage forms include creams, pastes, suspensions, powders, foams and gels. Ocular dosage forms include suspensions, emulsions, powders, gels, creams, pastes, solid inserts, depots, and implants.

In one embodiment, the compositions of the present invention are capable of improving the concentration of dissolved drug in a use environment relative to a control composition consisting essentially of the drug alone without the polymer or TPGS. In order to determine concentration enhancement *in vitro*, the amount of "free" drug, or solvated drug is measured. By "free" drug is meant drug which is in the form of dissolved drug 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 drug concentration that is at least 1.25-fold the free

-23-

drug concentration provided by the control composition. Preferably, the free drug 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.

5 Alternatively, the compositions of the present invention, when administered to a human or other animal, provide an AUC in drug 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
10 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).

15 Alternatively, the compositions of the present invention, when administered to a human or other animal, provide a maximum drug 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
20 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.

25 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
30 examples can be used.

-24-

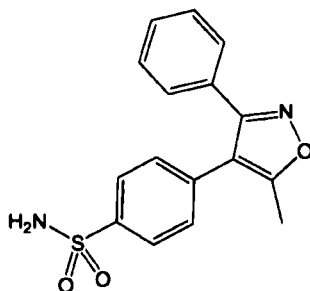
Examples

Drugs Used in Examples

The following drugs were used in the examples as described below.

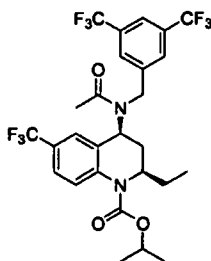
Drug 1 was 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide, also

5 known as valdecoxib, having the structure:



Drug 1 has a solubility in water of about 10 µg/mL, and a Log P value of about 3.0. The T_g of non-crystalline Drug 1 was determined by DSC analysis to be 55°C, while the T_m of crystalline Drug 1 was 170°C.

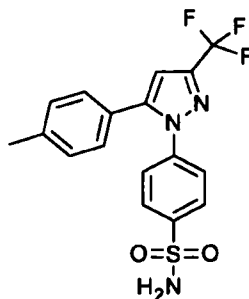
10 Drug 2 was [2R,4S] 4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, having the structure:



15 Drug 2 has a solubility in model fasted duodenal (MFD) solution of about 11 µg/mL, and a CLogP value of about 6.6. The T_g of amorphous Drug 2 was determined by DSC analysis to be about 45°C, and the T_m is about 111°C.

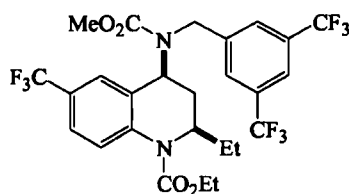
Drug 3 was 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, also known as celecoxib, having the structure:

-25-



Drug 3 has a solubility in MFD solution of about 40 $\mu\text{g/mL}$, and a LogP value of 3.75. The T_g of amorphous Drug 3 was determined by DSC analysis to be 54°C.

Drug 4 was [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, also known as torcetrapib, having the structure:



Torcetrapib has a solubility in water of less than 0.1 $\mu\text{g/mL}$, and an Alog P value of 7.4. The T_g of amorphous Drug 4 was determined by DSC analysis to be 29°C.

Polymers Used in Examples

The following non-ionizable cellulosic polymers were used in the examples: ethylcellulose (ETHOCEL® Viscosity 4, Dow Chemical Co., Midland, MI); cellulose acetate (CA-398-10, available from Eastman Chem. Co., Kingsport, TN); cellulose acetate butyrate (CAB-551-0.01, available from Eastman Chem. Co.).

These polymers were evaluated using the following procedure to determine their aqueous solubility. First, 0.2 mg/mL of the polymer is added to a PBS solution consisting of 20 mM Na_2HPO_4 , 47 mM KH_2PO_4 , 87 mM NaCl, and 0.2 mM KCl, adjusted to pH 6.5 with NaOH. The polymer is stirred in the PBS solution for approximately 1 hour at room temperature. Next, the polymer solution is filtered through a nylon 0.45 μm filter that had been weighed dry prior to filtration. The filter is dried overnight at 40°C, and weighed the following morning. The amount of soluble polymer is calculated from amount of polymer added to form the polymer solution

-26-

minus the amount of polymer remaining on the filter. The results of these tests are shown in Table 1 and show that all of the polymers tested are poorly aqueous soluble.

Table 1

Example Polymer	Soluble at pH 6.5 (mg/mL)	Observations
Ethylcellulose	<0.001	Fine particle suspension
Cellulose Acetate	0.03	Fine particle suspension
Cellulose Acetate Butyrate	0.01	Fine particle suspension

5

Example 1

Nanoparticles containing Drug 1 were prepared as follows. For the nanoparticles of Example 1, 160 mg Drug 1 and 160 mg ethyl cellulose (ETHOCEL® Viscosity 4, Dow Chemical Co., Midland, MI) were dissolved in 5 mL ethyl acetate to form an organic solution. This organic solution was poured into 20 mL of deionized water containing 80 mg d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS, available from Eastman Chemical Co., Kingsport, Tennessee) and emulsified for 4 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), with an inlet pressure of 80 psi, for 6 minutes (high-pressure homogenization). The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 40:40:20 Drug 1:ethyl cellulose:TPGS.

20

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 (25 mm Pall Acrodisc®), and added to a cuvette filled with deionized water. Dynamic light-scattering was measured using a Brookhaven Instruments (Holtville, 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,

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-27-

and the size is reported as the cumulant value. Dynamic light-scattering analysis showed that the average cumulant diameter was 104 nm, with a polydispersity of 0.16.

The aqueous nanoparticle suspension was allowed to stand unmixed for 3 days (ambient conditions) to measure stability. DLS analysis showed that the
5 average cumulant diameter of the nanoparticle suspension after 3 days was 104 nm, with a polydispersity of 0.19. This demonstrates that the nanoparticle suspension of Example 1 was stable for at least 3 days with no significant particle agglomeration.

Control 1

10 As a control nanoparticles were made containing Drug 1, TPGS, and poly(DL-lactide-co-glycolide) 50:50 (PLGA), which is not a cellulosic polymer. The nanoparticles of Control 1 were prepared as follows. First, 20 mg Drug 1 and 20 mg PLGA were dissolved in 5 mL ethyl acetate to form an organic solution. The aqueous
15 solution consisted of 10 mg TPGS dissolved in 20 mL deionized water. The organic solution was poured into the aqueous solution and emulsified as described for Example 1. The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 40:40:20 Drug 1:PLGA:TPGS. After 2 hours, optical microscopy was used to analyze the nanoparticle suspension, and crystals were observed.

20

Filter Potency

Filter potency was used to characterize the nanoparticle suspension of Control 1. Filter potency tests are used to examine changes in nanoparticle suspension potencies due to particle agglomeration. As nanoparticles agglomerate, the larger particles are removed via filtration, and the concentration of suspended drug
25 is reduced.

To measure nanoparticle potency, the Control 1 suspension was filtered using a 1 μ m filter, and a 250 μ L sample was added to 1 mL acetonitrile. The concentration of drug in solution was analyzed by high-performance liquid chromatography (HPLC). Next, the suspension was allowed to stand unmixed at room
30 temperature for 1 day. The nanoparticles were filtered using a 1 μ m filter, diluted in acetonitrile, and analyzed using HPLC.

-28-

HPLC analysis of Drug 1 was performed using a Zorbax SB C₈ column. The mobile phase consisted of 55% acetonitrile/ 45% 10 mM ammonium acetate, adjusted to pH 4. UV absorbance was measured at 254 nm.

Potencies of the nanoparticle suspensions are shown in Table 2, and show that only 17% of the potency of the nanoparticle suspension of Control 1 is retained after 1 day following filtration by a 1 µm filter. This indicates that most of the nanoparticles of Control 1 had agglomerated. Control 1 demonstrates that nanoparticles containing PLGA (a polymer outside the scope of the invention) are not stable in solution.

10

Table 1

Sample	Initial Potency (mg/mL)	1 day Potency (mg/mL)	Potency Retained (%)
Control 1	0.79	0.13	17

Control 2

As a control, nanoparticles were prepared containing Drug 1 and the poorly aqueous soluble non-ionizable cellulosic polymer ethylcellulose, but without TPGS. To form Control 1 nanoparticles, 40.6 mg Drug 1 and 123.8 mg ethylcellulose were dissolved in 5 mL methylene chloride to form an organic solution. The organic solution was then poured into 20 mL deionized water, and emulsified as described in Example 1. The methylene chloride was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles. The aqueous suspension was analyzed using DLS as described in Example 1. The cumulant diameter of the nanoparticles was 815 nm, with a polydispersity of 0.41. Visual observation of the aqueous suspension confirmed large agglomerated and stringy material. These results show that nanoparticles made without TPGS do not provide a stable formulation.

25

Control 3

As a control, nanoparticles were prepared containing Drug 1 and TPGS, but without a poorly aqueous soluble non-ionizable cellulosic polymer. The nanoparticles of Control 3 were made using a precipitation process as follows. First, 40.3 mg Drug 1 and 24.5 mg TPGS were added to 10 mL acetone and stirred to form a clear organic solution. The aqueous solution consisted of 9 mL deionized water. To

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-29-

form the nanoparticles, a 1-mL sample of the organic solution was rapidly added into the stirring vortex of the aqueous solution. The acetone was removed using a rotary evaporator, resulting in an aqueous suspension of nanoparticles. The aqueous suspension was analyzed using DLS as described in Example 1. The cumulant diameter of the nanoparticles was 1494 nm, with a polydispersity of 0.39. Visual observation of the aqueous suspension confirmed large agglomerated material. These results show that nanoparticles made without a poorly aqueous soluble non-ionizable cellulosic polymer do not provide a stable formulation.

10

Example 2

Nanoparticles containing Drug 2 were prepared as follows. First, 100 mg Drug 2, 200 mg ethylcellulose, and 100 mg TPGS were added to 5 mL ethyl acetate to form an organic solution. The organic solution was poured into the 20 mL of deionized water and emulsified as described for Example 1. The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 25:50:25 Drug 2:ethylcellulose:TPGS.

15

Light Scattering Analysis

The aqueous suspension of Example 2 was filtered using a 1 μ m glass membrane filter and added to a cuvette filled with deionized water. Dynamic light-scattering analysis showed that the average cumulant diameter was 176 nm, with a polydispersity of 0.41.

20

Example 3

Nanoparticles containing Drug 2 were prepared as follows. First, 20 mg Drug 2 and 60 mg ethyl cellulose were dissolved in 5 mL ethyl acetate to form an organic solution. The organic solution was poured into the aqueous solution consisting of 20 mL deionized water containing 20 mg TPGS and emulsified as described for Example 1, except that high-pressure homogenization time was 4 minutes. The ethyl acetate was removed from the emulsions using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 20:60:20 Drug 2:ethyl cellulose:TPGS.

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-30-

Light Scattering Analysis

The aqueous suspension of Example 3 was analyzed using DLS, and the average cumulant diameter was 124 nm, with a polydispersity of 0.13.

5 The aqueous suspension above was allowed to stand unmixed for 2 days (ambient conditions) to measure stability. DLS analysis showed that the average cumulant diameter of the nanoparticle suspension after 2 days was 134 nm, with a polydispersity of 0.27. This demonstrates that the nanoparticle suspension of Example 3 was stable for at least 2 days with no significant particle agglomeration.

10

Example 4

Nanoparticles containing Drug 3 were prepared as follows. First, 2.04 g Drug 3, 2.07 g ethyl cellulose, and 1.01 g TPGS, were added to 50 mL ethyl acetate to form an organic solution. The organic solution was poured into 250 mL deionized water and emulsified for 10 min using high-shear mixing, then further emulsified using high-pressure homogenization for 21 minutes. The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 40:40:20 Drug 3:ethylcellulose:TPGS. The aqueous suspension of Example 4 was filtered using a 1 μ m glass membrane filter and analyzed using DLS, and the average cumulant diameter was 90 nm, with a polydispersity of 0.25.

20

Evaluation of Example 4 *In Vivo*

The nanoparticles of Example 4 were evaluated *in vivo*. Samples were dosed orally as a suspension to 6 male beagle dogs. Animals were fasted overnight through at least 4 hours postdose. Approximately 40 mL of 5 mg/mL suspension (20 mgA/kg) was administered to each dog. The dose was administered via oral gavage, followed by approximately 5 mL water. Whole-blood samples (3-mL red-top Vacutainer tubes without serum separators) were taken from the jugular vein predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose. Serum was harvested into tubes containing K₂EDTA anticoagulant. Blood was maintained on wet ice prior to centrifugation to obtain plasma. Centrifugation began within 1 hour of collection, and samples were centrifugation at 2500 rpm for 15 minutes. Plasma was maintained on dry ice prior to storage at approximately -70°C. Plasma was analyzed using liquid chromatography with tandem mass spectrometry (LC/MS/MS). A

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-31-

marketed Drug 3 capsule (200 mg dose) was tested for comparison. The results are shown in Table 3. The nanoparticles of Example 4 provided a C_{max} that was 6.4-fold that provided by the marketed capsule.

Table 3

Parameter	Marketed Capsule	Example 4 Drug 3:ethylcellulose:TPGS
C_{max} (ng/mL)	1,460	9,404
T_{max} (hours)	1.75	0.92
AUC_{0-t} (ng/mL-hr)	not determined	59,548

5

Example 5

Nanoparticles containing Drug 3 were prepared as follows. First, 20 mg Drug 3, 60 mg ethylcellulose, and 20 mg TPGS were added to 5 mL ethyl acetate to form an organic solution. The organic solution was poured into 20 mL deionized water and emulsified for 4 minutes of high-shear mixing and 4 minutes of high-pressure homogenization. The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 20:60:20 Drug 3:ethylcellulose:TPGS. The aqueous suspension of Example 5 was analyzed using DLS, and the average cumulant diameter was 146 nm, with a polydispersity of 0.12.

The aqueous suspension above was allowed to stand unmixed for 5 days (ambient conditions) to measure stability. DLS analysis showed that the average cumulant diameter of the nanoparticle suspension after 5 days was 149 nm, with a polydispersity of 0.06. This demonstrates that the nanoparticle suspension is stable for at least 5 days with no measurable particle agglomeration.

Example 6

Nanoparticles containing Drug 3 were prepared as described in Example 1 with the following exceptions. The organic solution consisted of 184 mg Drug 3, 184 mg ethyl cellulose, and 32 mg TPGS in 5 mL ethyl acetate; the solution consisted of 20 mL deionized water. The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 46:46:8 Drug 3:ethylcellulose:TPGS. The aqueous suspension of Example 6 was analyzed using DLS, and the average cumulant diameter was 157 nm, with a polydispersity of 0.09.

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-32-

Isolation of Solid Composition

A solid composition comprising the nanoparticles of Example 6 was prepared as follows. Approximately 100 mg casein was added to 15 mL of the aqueous suspension of Example 6 (which contained 300 mg nanoparticles). The suspension was pumped into a small-scale spray-drying apparatus at a rate of 0.15 ml/min. The heated gas entered the chamber at an inlet temperature of 120°C, with a flow of 1 standard ft³/min. The resulting solid composition was collected on a 0.8 µm nylon filter.

PXRD Analysis

The solid composition was examined using powder x-ray diffraction (PXRD) with a Bruker AXS D8 Advance diffractometer to determine the crystalline character of the drug in the formulation. A sample (approximately 100 mg) was packed in a Lucite sample cup fitted with Si(511) plate as the bottom of the cup to give no background signal. The sample was spun in the ϕ plane at a rate of 30 rpm to minimize crystal orientation effects. The x-ray source (KCu α , $\lambda = 1.54 \text{ \AA}$) was operated at a voltage of 45 kV and a current of 40 mA. Data were collected in continuous detector scan mode at a scan speed of 2 seconds/step and a step size of 0.04°/step. Diffractograms were collected over the 2θ range of 4° to 40°. FIG. 1 is the diffraction pattern of the composition containing the nanoparticles of Example 6, which showed only an amorphous halo, with no sharp peaks characteristic of crystalline drug. These data indicate that the drug in the nanoparticles of Example 6 is in a non-crystalline form.

Example 7

Nanoparticles containing Drug 3 were prepared using the procedures of Example 1 with the following exception. The organic solution consisted of 141.2 mg Drug 3 and 141.2 mg ethylcellulose dissolved in 5 mL ethyl acetate. The aqueous solution consisted of 20 mL deionized water containing 117.6 mg casein (spray dried sodium caseinate, available from American Casein Company, Burlington, NJ.). The organic solution was poured into the aqueous solution and emulsified as described for Example 1. Following the emulsification step, 1.5 mL of deionized water containing 30 mg TPGS was added to 8.5 mL of the emulsion, and stirred for 3 hours in a scintillation vial. The ethyl acetate was removed from the emulsion using a rotary

-33-

evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 30:30:25:15 Drug 3:ethyl cellulose:casein:TPGS. The aqueous suspension of Example 7 was analyzed using DLS, and the average cumulant diameter was 111 nm, with a polydispersity of 0.21.

5 Isolation of Solid Nanoparticles

The nanoparticles of Example 7 were spray-dried using the spray-drier, as described in Example 6, except that no additional casein was added.

PXRD Analysis

10 The solid composition was examined using PXRD as described in Example 6. FIG. 2 is a diffraction pattern of the nanoparticles of Example 7 showing only an amorphous halo, with no sharp peaks characteristic of crystalline drug. These data indicate that the drug in the nanoparticles of Example 7 is in a non-crystalline form.

15 Example 8

Nanoparticles containing Drug 3 were prepared as described in Example 1 with the following exceptions. The organic solution consisted of 320 mg Drug 3, 320 mg ethylcellulose, and 160 mg TPGS in 12 mL ethyl acetate. The aqueous solution consisted of 40 mL deionized water. The organic solution was
20 poured into the aqueous solution and emulsified for 3 minutes of high-shear mixing followed by high-pressure homogenization. The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 40:40:20 Drug 3:ethylcellulose:TPGS. Approximately 200 mg casein was added to the aqueous suspension. The aqueous
25 suspension of Example 8 was filtered using a 1 μm filter, and analyzed using DLS. The average cumulant diameter was 106 nm, with a polydispersity of 0.09.

Potency

A filter potency test was used to characterize the nanoparticle suspension of Example 8. First, a 25 μL sample of the aqueous nanoparticle
30 suspension was added to 1 mL acetonitrile, and the concentration of drug in solution was analyzed by high-performance liquid chromatography (HPLC). Next, the suspension was filtered using a 1 μm , 0.45 μm , or 0.2 μm filter and diluted in acetonitrile for HPLC analysis.

-34-

HPLC analysis of Drug 3 in the filtrate was performed using a Zorbax SB C₈ column. The mobile phase consisted of 55% acetonitrile/ 45% 10 mM ammonium acetate, adjusted to pH 4. UV absorbance was measured at 254 nm.

Potencies of the nanoparticle suspensions are shown in Table 4. The results in Table 4 show that 94% of the potency of the nanoparticle suspension of Example 8 is maintained following filtration by a 0.2 μm filter. This indicates that most of the nanoparticles of the invention remain small and unagglomerated.

Table 4

Sample	Potency Unfiltered (mg/mL)	Potency 1 μm filtered (mg/mL)	Fraction Retained (%)	Potency 0.45 μm filtered (mg/mL)	Fraction Retained (%)	Potency 0.2 μm filtered (mg/mL)	Fraction Retained (%)
Example 8	9.4	9.4	100	9.1	97	8.8	94

10

Example 9

Nanoparticles containing Drug 4 were prepared as follows. For the nanoparticles of Example 9, 80 mg Drug 4 and 80 mg ethylcellulose were dissolved in 5 mL ethyl acetate to form an organic solution. The aqueous solution consisted of 20 mL deionized water containing 40 mg TPGS. The organic solution was poured into the aqueous solution and emulsified with 3 minutes of high-shear mixing followed by 6 minutes of high-pressure homogenization. The ethyl acetate was removed from the emulsion using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a composition ratio of 40:40:20 Drug 4:ethyl cellulose:TPGS. The aqueous suspension of Example 9 was filtered using a 1 μm glass filter, and analyzed using DLS. The average cumulant diameter was 130 nm, with a polydispersity of 0.14.

20

Example 10

Nanoparticles comprising Drug 3, ethylcellulose, and TPGS were made using a precipitation process using the following procedure. First, 40 mg of Drug 3 and 40 mg ethylcellulose were added to 10 mL of acetone and sonicated for 30 minutes to dissolve the drug and polymer. This solution was filtered through a 1-μm Anodisc glass membrane filter to form the organic solution. Next, 22.2 mg of TPGS was placed into a beaker and heated to 80°C to melt. A 100 mL sample of purified water at 80°C was then added to the melted TPGS while stirring and the solution allowed to cool to

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-35-

room temperature to form the aqueous solution. A 1-mL sample of the organic solution was then rapidly added to 9 mL of the aqueous solution, resulting in the formation of nanoparticles in suspension, with a composition mass ratio of 40:40:20 Drug 3:ethylcellulose:TPGS.

5

Light Scattering Analysis

The nanoparticle suspension of Example 10 was analyzed by DLS using the procedures outlined in Example 1. The cumulant diameter of the nanoparticles was 64 nm, with a polydispersity of 0.29.

10 The aqueous suspension of Example 10 was stored at ambient conditions for 6 days and again analyzed by DLS. The cumulant diameter was 70 nm, with a polydispersity of 0.29. These data indicate that the nanoparticle suspension of Example 10 remained stable and unagglomerated after 6 days storage at ambient conditions.

Filter Potency

15 Filter potency was used to characterize the nanoparticle suspension of Example 10 after storage 6 days at ambient conditions. First, a 25 μ L sample of the nanoparticle suspension was added to 975 μ L of 80%acetonitrile:20%methanol, and the concentration of drug in solution was analyzed by HPLC. Next, the suspension was filtered using a 0.2 μ m polytetrafluoroethylene (PTFE) filter and diluted 1:40 using
20 80%acetonitrile:20%methanol.

Potencies of the nanoparticle suspensions are shown in Table 5. The results in Table 5 show that 92% of the nanoparticle suspension potency is maintained following filtration of Example 10 using a 0.2 μ m filter. This indicates that the nanoparticles in suspension remain small and unagglomerated.

25

Table 5

Sample	Potency Unfiltered (mg/mL)	Potency 0.2 μ m filtered (mg/mL)	Potency Retained (%)
Example 10	0.37	0.34	92

Example 11

Nanoparticles comprising Drug 3, ethylcellulose, and TPGS were made using a precipitation process as outlined in Example 10 except that the organic
30 solution consisted of 40 mg Drug 3, 40 mg ethylcellulose, and 20 mg TPGS dissolved in acetone, while the aqueous solution was distilled water. The nanoparticles were

-36-

made by rapidly adding 1 mL of the organic solution to 9 mL of the aqueous solution. DLS analysis of the nanoparticles showed that cumulant diameter was 64 nm, with a polydispersity of 0.36.

The nanoparticle suspension of Example 11 was stored at ambient conditions for 6 days and again analyzed by DLS. The results of this test showed the nanoparticles to have a cumulant diameter of 72 nm and a polydispersity of 0.35.

Filter Potency

Filter potency was used to characterize the nanoparticle suspension of Example 11 after storage 6 days at ambient conditions. First, a 25 μ L sample of the nanoparticle suspension was added to 975 μ L of 80%acetonitrile:20%methanol, and the concentration of drug in solution was analyzed by HPLC. Next, the suspension was filtered using a 0.2 μ m polytetrafluoroethylene (PTFE) filter and diluted 1:40 using 80%acetonitrile:20%methanol.

Potencies of the nanoparticle suspensions are shown in Table 6. The results in Table 6 show that 87% of the nanoparticle suspension potency is maintained following filtration of Example 11 using a 0.2 μ m filter. This indicates that the nanoparticles in suspension remain small and unagglomerated.

Table 6

Sample	Potency Unfiltered (mg/mL)	Potency 0.2 μ m filtered (mg/mL)	Potency Retained (%)
Example 11	0.39	0.34	87

20

Example 12

Nanoparticles containing Drug 2 were prepared using a precipitation process as described above. The organic solution consisted of 39.8 mg Drug 2, 47.1 mg of the poorly aqueous soluble non-ionizable cellulosic polymer cellulose acetate (CA 398-10NF, Eastman Chemical Co., Kingsport, TN), and 20.4 mg TPGS. A 1-mL sample of the organic solution was rapidly added into the stirring vortex of 9 mL aqueous solution. The acetone was removed using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a mass ratio of 40:40:20 Drug 2: cellulose acetate:TPGS. DLS analysis showed an average cumulant diameter of 97 nm, with a polydispersity of 0.29.

30

The aqueous nanoparticle suspension was allowed to stand unmixed for 1 day (ambient conditions) to measure stability. DLS analysis showed that the

-37-

average cumulant diameter of the nanoparticle suspension after 1 day was 87 nm, with a polydispersity of 0.29. This demonstrates that the nanoparticle suspension of Example 12 was stable for at least 1 day with no significant particle agglomeration.

5

Example 13

Nanoparticles containing Drug 2 were prepared using a precipitation process as described above. The organic solution consisted of 41.8 mg Drug 2, 44.7 mg of the poorly aqueous soluble non-ionizable cellulosic polymer cellulose acetate butyrate (CAB-551-0.01, Eastman Chemical Co.), and 24.1 mg TPGS. A 1-mL
10 sample of the organic solution was rapidly added into the stirring vortex of 9 mL aqueous solution. The acetone was removed using a rotary evaporator, resulting in an aqueous suspension of nanoparticles, with a mass ratio of about 40:40:20 Drug 2: cellulose acetate butyrate:TPGS. DLS analysis showed that the average cumulant diameter was 45 nm, with a polydispersity of 0.09.

15

The aqueous nanoparticle suspension was allowed to stand unmixed for 1 day (ambient conditions) to measure stability. DLS analysis showed that the average cumulant diameter of the nanoparticle suspension after 1 day was 48 nm, with a polydispersity of 0.09. This demonstrates that the nanoparticle suspension of Example 13 was stable for at least 1 day with no significant particle agglomeration.

20

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
25 the invention is defined and limited only by the claims which follow.

-38-

We claim:

1. A pharmaceutical composition comprising nanoparticles, said nanoparticles comprising:
 - (a) a poorly water soluble drug having a solubility in water of less than 5 mg/mL over the pH range of 6.5 to 7.5 at 25°C, at least 90 wt% of said drug in said nanoparticles being non-crystalline;
 - (b) a poorly aqueous soluble non-ionizable cellulosic polymer having an ether- or ester-linked alkyl substituent; and
 - (c) tocopheryl polyethylene glycol succinate (TPGS);
- 10 wherein said nanoparticles have an average size of less than 500 nm; and said drug, said non-ionizable cellulosic polymer, and said TPGS collectively constitute at least 60 wt% of said nanoparticles.
2. The composition of claim 1 wherein said nanoparticles comprise a core, said core comprising said drug and said non-ionizable cellulosic polymer.
3. The composition of claim 2 wherein said core further comprises said TPGS.
4. The composition of any one of the preceding claims wherein said drug, said non-ionizable cellulosic polymer, and said TPGS collectively constitute at least 90 wt% of said nanoparticles.
5. The composition of any one of the preceding claims wherein said nanoparticles consist essentially of said drug, said non-ionizable cellulosic polymer, and said TPGS.
6. The composition of any one of the preceding claims wherein said nanoparticles have the following composition: from 1 wt% to 80 wt% said drug, from 10 wt% to 75 wt% said non-ionizable cellulosic polymer, and from 5 wt% to 40 wt% said TPGS.
7. The composition of any one of the preceding claims wherein said nanoparticles have the following composition: from 5 wt% to 50 wt% said drug, from 30 wt% to 70 wt% said non-ionizable cellulosic polymer, and from 5 wt% to 30 wt% said TPGS.

-39-

8. The composition of any one of the preceding claims wherein said nanoparticles have an average size of less than 300 nm.

9. The composition of any one of the preceding claims wherein said non-ionizable
5 cellulosic polymer is selected from the group consisting of methylcellulose,
ethylcellulose, propylcellulose, butylcellulose, cellulose acetate, cellulose propionate,
cellulose butyrate, cellulose acetate butyrate, cellulose acetate propionate, methyl
cellulose acetate, methyl cellulose propionate, methyl cellulose butyrate, ethyl
cellulose acetate, ethyl cellulose propionate, ethyl cellulose butyrate, hydroxypropyl
10 methylcellulose acetate, hydroxypropyl methylcellulose propionate, and hydroxypropyl
methylcellulose butyrate.

10. The composition of any one of the preceding claims wherein said non-ionizable
cellulosic polymer is selected from the group consisting of ethyl cellulose, cellulose
15 acetate, cellulose propionate, cellulose butyrate, and cellulose acetate butyrate.

11. The composition of any one of the preceding claims wherein said TPGS is d- α -
tocopheryl polyethylene glycol 1000 succinate.

20 12. A pharmaceutical composition comprising an aqueous suspension of the
nanoparticles of any one of claims 1 to 11.

13. A process for forming nanoparticles, comprising:

- 25 (a) forming an organic solution comprising a poorly water soluble drug and a
poorly aqueous soluble non-ionizable cellulosic polymer dissolved in a
solvent, wherein said drug has a solubility in water of less than 5 mg/ml
over the pH range of 6.5 to 7.5 at 25°C and said non-ionizable cellulosic
polymer has an ether- or ester-linked alkyl substituent;
- (b) forming an aqueous solution, wherein said drug and said non-ionizable
30 cellulosic polymer are poorly soluble in said non-solvent;
- (c) adding tocopheryl polyethylene glycol succinate (TPGS) to at least one of
said organic solution and said aqueous solution;

-40-

- (d) mixing said organic solution with said aqueous solution to form a first mixture;
- (e) removing said solvent from said first mixture to form a suspension comprising said nanoparticles and said aqueous solution, wherein
- 5 (i) said nanoparticles have an average size of less than 500 nm;
- (ii) at least 90 wt% of said drug in said nanoparticles is non-crystalline; and
- (iii) said drug, said non-ionizable cellulosic polymer, and said TPGS collectively constitute at least 60 wt% of said nanoparticles.

10

14. The process of claim 13 comprising the additional step

- (f) adding a matrix material to said suspension.

15. The process of claim 11 wherein said matrix material is selected from the group
15 consisting of polyvinyl pyrrolidone, trehalose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, casein, caseinate, albumin, gelatin, acacia, lactose, mannitol, pharmaceutically acceptable forms thereof, and mixtures thereof.

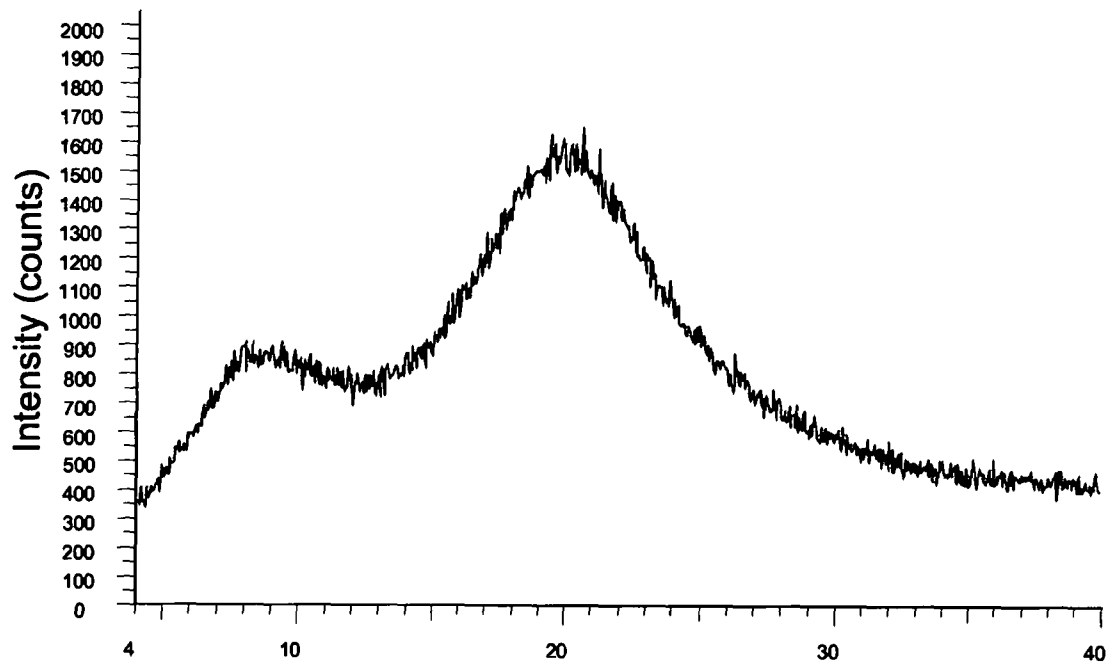
16. The process of any one of claims 13-15 further comprising

- 20 (g) removing liquid from said suspension to form a solid composition comprising said nanoparticles.

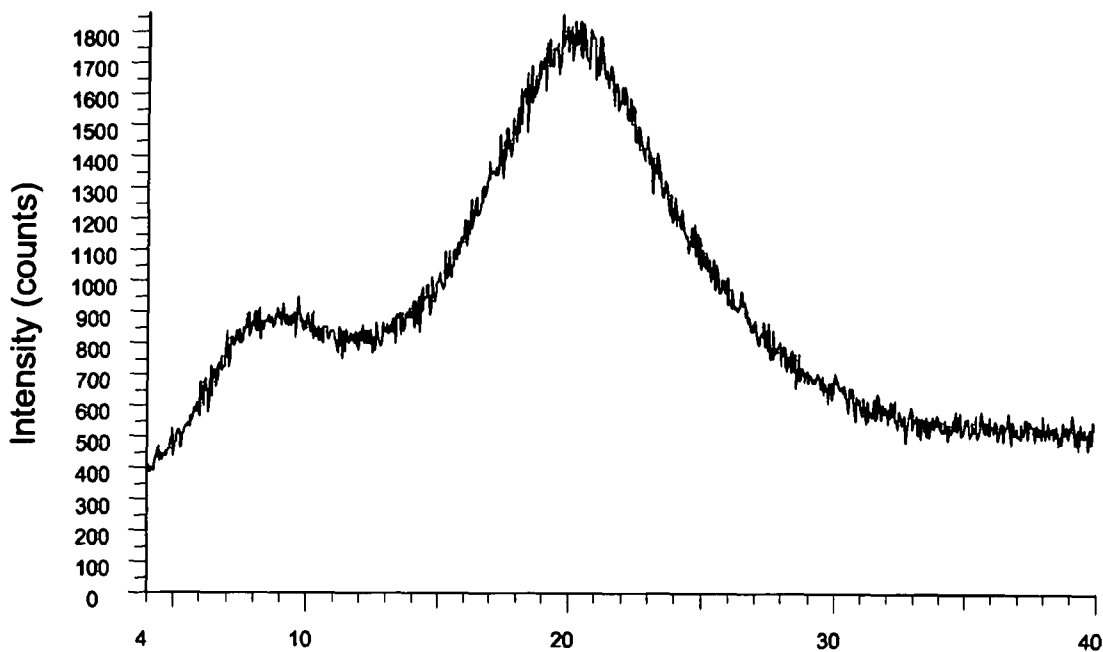
17. The process of claim 16 wherein said liquid is removed by one or more
25 processes selected from the group consisting of spray drying, spray coating, spray layering, lyophilization, evaporation, vacuum evaporation, and filtration.

18. The process of claim 17 wherein said liquid is removed by spray drying.

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2-Theta - Scale
FIG. 1



2-Theta - Scale
FIG. 2