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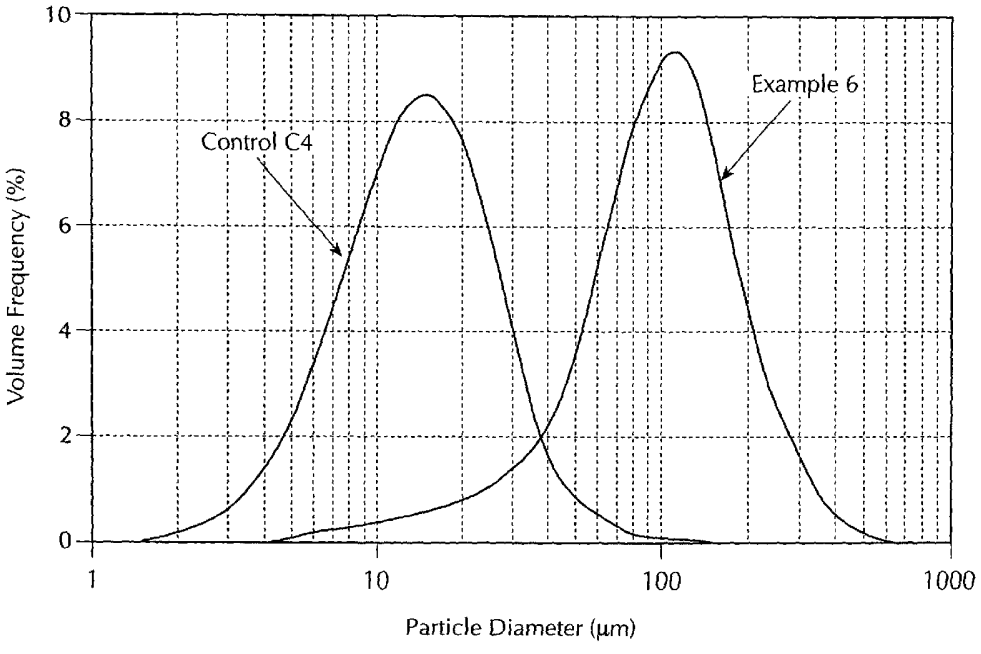
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(54) Title: METHOD FOR MAKING HOMOGENEOUS SPRAY-DRIED SOLID AMORPHOUS DRUG DISPERSIONS USING PRESSURE NOZZLES



(57) Abstract: Homogeneous solid amorphous dispersions of drugs in concentration-enhancing polymers are formed in desirable larger particle sizes with minimal fines by using an atomizer and process conditions capable of producing droplets having an average diameter of at least 50 microns and a D_{10} of at least 10 microns.

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METHOD FOR MAKING HOMOGENEOUS SPRAY-DRIED SOLID AMORPHOUS DRUG DISPERSIONS USING PRESSURE NOZZLES

BACKGROUND OF THE INVENTION

The use of spray-drying to produce powders from fluid feed stocks is well known, with applications ranging from powdered milk to bulk chemicals and pharmaceuticals. See U.S. Patent No. 4,187,617 and Mujumbar et al., *91 Drying*, pages 56-73 (1991). The use of spray-drying to form solid amorphous dispersions of drugs and concentration-enhancing polymers is also known. See commonly owned European Patent Applications Nos. 0 901 786, 1 027 886, 1 027 887, 1 027 888, and commonly owned PCT Applications Nos. WO 00/168092 and WO 00/168055.

A typical spray-drying apparatus comprises a drying chamber, atomizing means for atomizing a solvent-containing liquid feed into the drying chamber, a source of heated drying gas directed into the drying chamber and dried product collection means for separating the dried product from the cooled drying gas and vaporized solvent stream following its exit from the drying chamber. Examples of such apparatus include Niro Models PSD-1, PSD-2 and PSD-4 (Niro A/S, Soeborg, Denmark). When used for forming solid amorphous dispersions by spray-drying, conventional wisdom suggests that to achieve the rapid removal of solvent required to form a homogeneous solid amorphous dispersion, the droplets of atomized solvent-containing feed should be small. The prior art therefore uses spray-drying apparatus equipped with a two-fluid nozzle for atomizing the solvent-containing feed, which produces droplets of solvent-containing feed with diameters of about 50 μm or less, resulting in a spray-dried product with median particle diameters of about 30 μm or less. In some cases such spray-drying apparatus are reported to be effective in forming substantially amorphous and substantially homogeneous solid

amorphous dispersions of drug and polymer that exhibit concentration enhancement when introduced to an environment of use. In other cases, less than satisfactory results are achieved, thereby requiring undue experimentation to attempt to identify suitable process conditions. However, even when solid amorphous dispersion particles are successfully achieved, the spray-dried particles produced in such apparatus often have small median particle sizes (less than about 30 μm) and a large amount of "fines" (particles with diameters of less than about 10 μm). In addition, such particles often have high specific volumes--that is, the volume of the spray-dried powder divided by its mass--typically reported in units of cm^3/g. Generally, the higher the specific volume of a powder, the poorer its flow characteristics. As a result, solid amorphous dispersions produced using a spray-drying apparatus equipped with a two-fluid nozzle have relatively poor flow characteristics and poor collection efficiency. In addition, downstream handling and processing of such small diameter, high specific volume products is often difficult.

Thus, there is a need in the art for an improved spray-drying process that results in solid amorphous dispersions with improved flow characteristics and improved collection efficiency.

BRIEF SUMMARY OF THE INVENTION

According to the present invention homogeneous spray-dried solid amorphous dispersions of drugs in a concentration-enhancing polymer are formed that have far greater median particle sizes and dramatically reduced proportions of fines present while still achieving the same degree of concentration enhancement as that achieved by conventional spray-drying techniques. Such improved drug dispersions are formed by the use of atomizing means that produces droplets with a median droplet diameter of 50 μm or larger, with less than about 10 vol% of the droplets having a diameter less than 10 μm, for atomization of the solution of polymer and drug. Such an atomizing means is referred to

herein as a "pressure nozzle." The pressure nozzle may be employed with a wide range of spray-dryer designs, including both conventional and custom-designed dryers.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIG. 1 is a cross-sectional schematic of a prior art spray-drying apparatus.

FIG. 2 is a schematic of a typical two-fluid spray nozzle shown atomizing solvent-containing feed.

FIG. 3 is a schematic of a pressure nozzle shown spraying solvent-containing feed.

FIGS. 4-7 are graphs showing a comparison of median particle sizes and particle size distributions of spray-dried drug dispersions made using a two-fluid nozzle and using various pressure nozzles.

DETAILED DESCRIPTION OF THE INVENTION

Turning to the drawings, wherein the same numerals refer to like elements, there is shown in FIG. 1 a typical spray-drying apparatus 10 comprising a drying chamber 20, a drying chamber top 21, a collection cone 22, a connecting duct 26 connected to the distal end 23 of the collection cone, a cyclone 28 and a collection vessel 29. An atomizer 30 is shown spraying a solvent-bearing feed 32. The arrows in FIG. 1 show the direction and flow of drying gas from a drying gas source (not shown). As the drying gas contacts the solvent-bearing feed 32, solvent evaporates from the feed and particles of the feedstock are formed and are entrained by the drying gas through the collection cone 22 to the connecting duct 26, and then to the cyclone 28. In the cyclone, the particles are separated from the drying gas and evaporated solvent, allowing the particles to be collected in collection vessel 29. Alternatively, a filter can be used to separate and collect the particles from the drying gas and evaporated solvent instead of a cyclone.

The drying gas may be virtually any gas, but to minimize the risk of fire or explosions due to ignition of

flammable vapors, and to minimize undesirable oxidation of the drug, concentration-enhancing polymer, or other materials in the dispersion, an inert gas such as nitrogen, nitrogen-enriched air, or argon is utilized. The temperature of the drying gas at the gas inlet of apparatus 10 is typically from about 60° to about 300°C. The temperature of the product particles, drying gas and evaporated solvent at the outlet or distal end 23 of the collection cone 22 typically ranges from about 0° to about 100°C.

As noted above, conventional wisdom is that the formation of a homogeneous solid amorphous dispersion comprising a low-solubility drug and a concentration-enhancing polymer requires the use of a two-fluid nozzle, of the type shown in FIG. 2, to produce an atomized solvent-containing feed with relatively small droplets. In two-fluid nozzles, the solvent-containing feed 32 is mixed with an atomizing gas 36, such as air or nitrogen, resulting in atomization of the solvent-containing feed into small droplets. The atomized droplets of solvent-containing feed produced by a two-fluid nozzle typically have a diameter of 50 μm or less. Often, most droplets have diameters of 30 μm or less. This small droplet size results in a large surface area that facilitates rapid evaporation of the solvent from the droplets. Conventional wisdom suggests that this rapid drying is required to obtain solid dispersions that are homogeneous. However, the resulting dried dispersion particles generally have median diameters of 30 μm or less, typically averaging 10 to 20 μm in diameter. This small particle size leads to relatively poor flow characteristics for the dispersion particles. In addition, the use of a two-fluid nozzle results in the formation of a very large proportion of fines, as noted above. These fines not only generally lead to poor flow characteristics for the product, but are sufficiently small that the static electrical charge they often incur is large relative to their mass due to their large surface-to-mass ratio. This allows the particles to stick to each other or to the spray dryer surfaces. Such small charged particles

exhibit poor collection efficiencies in both cyclone- and filter-based collection schemes.

Pressure nozzles, of the type shown in FIG. 3, are known to produce larger droplets than two-fluid nozzles, typically having diameters of 100 to 250 μm. The time required for removal of solvent from such larger droplets is longer than that from smaller droplets, such as those produced by a two-fluid nozzle. Despite this longer time for solvent removal, the inventors have discovered that by proper choice of solution composition and processing conditions, homogeneous spray-dried dispersions can nevertheless be formed using a pressure nozzle. In addition, dispersions obtained by use of a pressure nozzle have substantially larger median particle sizes, with minimal fines present. Preferably, at least 80 vol% of the dispersion particles, and more preferably at least 90 vol% have diameters larger than 10 μm. The resulting dispersions therefore have improved flow characteristics and improved collection efficiencies, yet still achieve the same degree of drug concentration enhancement as achieved with conventional two-fluid nozzles.

THE DRUG

The present invention is useful in the formation of solid amorphous dispersions of a drug and a concentration-enhancing polymer. The term "drug" is conventional, denoting a compound having beneficial prophylactic and/or therapeutic properties when administered to an animal, especially humans. The drug does not need to be a low-solubility drug in order to benefit from this invention, although low-solubility drugs represent a preferred class for use with the invention. Even a drug that nonetheless exhibits appreciable solubility in the desired environment of use can benefit from the increased solubility/bioavailability made possible by this invention if the addition of the concentration-enhancing polymer can reduce the size of the dose needed for therapeutic efficacy or

increase the rate of drug absorption in cases where a rapid onset of the drug's effectiveness is desired.

The present invention is particularly suitable for preparing a solid dispersion of and enhancing the solubility of a "low-solubility drug," meaning that the drug may be either "substantially water-insoluble," which means that the drug has a minimum aqueous solubility at physiologically relevant pH (*e.g.*, pH 1-8) of less than 0.01 mg/mL, "sparingly water-soluble," that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous solubility, having an aqueous solubility from about 1 mg/mL to as high as about 20 to 40 mg/mL. The invention finds greater utility as the solubility of the drug decreases. Thus, compositions of the present invention are preferred for low-solubility drugs having a solubility of less than 10 mg/mL, more preferably less than 1 mg/mL, and even more preferably less than 0.1 mg/mL. In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than 10 mL, and more typically greater than 100 mL, where the drug solubility (mg/mL) is the minimum value observed in any physiologically relevant aqueous solution (those with pH values between 1 and 8), including USP simulated gastric and intestinal buffers, and the dose is in mg. Thus, a dose-to-aqueous-solubility ratio may be calculated by dividing the dose (in mg) by the solubility (in mg/mL).

Preferred classes of drugs include, but are not limited to, antihypertensives, antianxiety 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, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, antiviral agents, glycogen

phosphorylase inhibitors, and cholesterol ester transfer protein (CETP) inhibitors.

Each named drug should be understood to include the neutral form of the drug, pharmaceutically acceptable salts thereof and prodrugs thereof. Specific examples of antihypertensives include prazosin, nifedipine, amlodipine besylate, trimazosin and doxazosin; specific examples of a blood glucose-lowering agent are glipizide and chlorpropamide; a specific example of an anti-impotence agent is sildenafil and sildenafil citrate; specific examples of antineoplastics include chlorambucil, lomustine and echinomycin; a specific example of an imidazole-type antineoplastic is tubulazole; a specific example of an anti-hypercholesterolemic is atorvastatin calcium; specific examples of anxiolytics include hydroxyzine hydrochloride and doxepin hydrochloride; specific examples of anti-inflammatory agents include betamethasone, prednisolone, aspirin, piroxicam, valdecoxib, carprofen, celecoxib, flurbiprofen and (+)-N-{4-[3-(4-fluorophenoxy)phenoxy]-2-cyclopenten-1-yl}-N-hyroxyurea; a specific example of a barbiturate is phenobarbital; specific examples of antivirals include acyclovir, nelfinavir, and virazole; specific examples of vitamins/nutritional agents include retinol and vitamin E; specific examples of beta blockers include timolol and nadolol; a specific example of an emetic is apomorphine; specific examples of a diuretic include chlorthalidone and spironolactone; a specific example of an anticoagulant is dicumarol; specific examples of cardiotonics include digoxin and digitoxin; specific examples of androgens include 17-methyltestosterone and testosterone; a specific example of a mineral corticoid is desoxycorticosterone; a specific example of a steroidal hypnotic/anesthetic is alfaxalone; specific examples of anabolic agents include fluoxymesterone and methanstenolone; specific examples of antidepression agents include sulpiride, [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethylpropyl)-amine, 3,5-dimethyl-4-(3'-pentoxy)-2-(2',4',6'-trimethylphenoxy)pyridine, pyroxidine, fluoxetine, paroxetine,

venlafaxine and sertraline; specific examples of antibiotics include carbenicillin indanylsodium, bacampicillin hydrochloride, troleandomycin, doxycyline hyclate, ampicillin and penicillin G; specific examples of anti-infectives include benzalkonium chloride and chlorhexidine; specific examples of coronary vasodilators include nitroglycerin and mioflazine; a specific example of a hypnotic is etomidate; specific examples of carbonic anhydrase inhibitors include acetazolamide and chlorzolamide; specific examples of antifungals include econazole, terconazole, fluconazole, voriconazole, and griseofulvin; a specific example of an antiprotozoal is metronidazole; specific examples of anthelmintic agents include thiabendazole and oxfendazole and morantel; specific examples of antihistamines include astemizole, levocabastine, cetirizine, decarboethoxyloratadine, and cinnarizine; specific examples of antipsychotics include ziprasidone, olanzepine, thiothixene hydrochloride, fluspirilene, risperidone and penfluridole; specific examples of gastrointestinal agents include loperamide and cisapride; specific examples of serotonin antagonists include ketanserin and mianserin; a specific example of an anesthetic is lidocaine; a specific example of a hypoglycemic agent is acetohexamide; a specific example of an anti-emetic is dimenhydrinate; a specific example of an antibacterial is cotrimoxazole; a specific example of a dopaminergic agent is L-DOPA; specific examples of anti-Alzheimer's Disease agents are THA and donepezil; a specific example of an anti-ulcer agent/H2 antagonist is famotidine; specific examples of sedative/hypnotic agents include chlordiazepoxide and triazolam; a specific example of a vasodilator is alprostadil; a specific example of a platelet inhibitor is prostacyclin; specific examples of ACE inhibitor/antihypertensive agents include enalaprilic acid, quinapril and lisinopril; specific examples of tetracycline antibiotics include oxytetracycline and minocycline; specific examples of macrolide antibiotics include erythromycin, clarithromycin, and spiramycin; a specific example of an azalide antibiotic is azithromycin; specific examples of

glycogen phosphorylase inhibitors include [R-(R*S*)]-5-chloro-N-[2-hydroxy-3-{methoxymethylamino}-3-oxo-1-(phenylmethyl)propyl-1H-indole-2-carboxamide and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl-)-3-oxypropyl]amide; 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,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester and [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

SOLID DRUG-CONTAINING DISPERSION

The compositions produced by the inventive method comprise dispersions of a drug and at least one concentration-enhancing polymer. At least a major portion of the drug in the dispersion is amorphous. As used herein, the term "a major portion" of the drug means that at least 60% of the drug in the dispersion is in the amorphous, as opposed to the crystalline form. By "amorphous" is meant simply that the drug is in a non-crystalline state. Preferably, the drug in the dispersion is "substantially amorphous," meaning that the amount of the drug in crystalline form does not exceed about 25%. More preferably, the drug in the dispersion is "almost completely amorphous," meaning that the amount of drug in the crystalline form does not exceed about 10%. Amounts of crystalline drug may be measured by Powder X-Ray Diffraction (PXRD), Scanning Electron Microscope (SEM) analysis, Differential Scanning Calorimetry (DSC) or any other standard quantitative measurement.

The composition may contain from about 1 to about 80 wt% drug, depending on the dose of the drug and the effectiveness of the concentration-enhancing polymer. Enhancement of aqueous drug concentrations and relative

bioavailability are typically best at low drug levels, typically less than about 25 to 40 wt%. However, due to the practical limit of the dosage form size, higher drug levels are often preferred and in many cases perform well.

The amorphous drug can exist within the solid amorphous dispersion as a pure phase, as a solid solution of drug homogeneously distributed throughout the polymer or any combination of these states or those states that lie intermediate between them. The dispersion is preferably substantially homogeneous so that the amorphous drug is dispersed as homogeneously as possible throughout the polymer. As used herein, "substantially homogeneous" means that the fraction of drug present in relatively pure amorphous domains within the solid dispersion is relatively small, on the order of less than 20%, and preferably less than 10% of the total amount of drug.

While the dispersion may have some drug-rich domains, it is preferred that the dispersion itself have a single glass transition temperature (T_g), which confirms that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous drug particles and pure amorphous polymer particles, which generally display two distinct T_gs, one being that of the drug and one that of the polymer. T_g as used herein is the characteristic temperature where a glassy material, upon gradual heating, undergoes a relatively rapid (*i.e.*, in 10 to 100 seconds) physical change from a glassy state to a rubbery state. The T_g of an amorphous material such as a polymer, drug or dispersion can be measured by several techniques, including by a Dynamic Mechanical Analyzer (DMA), by a dilatometer, by a dielectric analyzer or by DSC. The exact values measured by each technique can vary somewhat but usually fall within 10° to 30°C of each other. Regardless of the technique used, when an amorphous dispersion exhibits a single T_g, this indicates that the dispersion is substantially homogenous. Dispersions of the present invention that are substantially homogeneous generally are more physically stable and have improved

concentration-enhancing properties and in turn, improved bioavailability relative to nonhomogeneous dispersions.

CONCENTRATION-ENHANCING POLYMERS

Concentration-enhancing polymers suitable for use in the compositions of the present invention should be inert in the sense that they do not chemically react with the drug in an adverse manner. The polymer can be neutral or ionizable, and should have an aqueous solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8.

The concentration-enhancing polymer should meet at least one, and more preferably both, of the following conditions. The first condition is that the concentration-enhancing polymer increases the maximum drug concentration (MDC) of the drug in the environment of use relative to a control composition consisting of an equivalent amount of the undispersed drug but no concentration-enhancing polymer. That is, once the composition is introduced into an environment of use, the polymer increases the aqueous concentration of drug relative to the control composition. Preferably, the polymer increases the MDC of the drug in aqueous solution by at least 1.25-fold relative to a control composition, more preferably by at least 2-fold, and most preferably by at least 3-fold. The second condition is that the concentration-enhancing polymer increases the area under the concentration versus time curve (AUC) of the drug in the environment of use relative to a control composition consisting of undispersed drug but no polymer as described above. That is, in the environment of use, the composition comprising the drug and the concentration-enhancing polymer provides an AUC for any period of 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold that of a control composition comprising an equivalent quantity of drug but no polymer. More preferably, the AUC provided by the composition is at least 2-fold, and most preferably at least 3-fold that of the control composition.

As used herein, a "use environment" can be either the *in vivo* environment of the GI tract of a mammal, particularly a human, or the *in vitro* environment of a test solution, such as Phosphate Buffered Saline (PBS) or Model Fasted Duodenal (MFD) solution.

Concentration-enhancing polymers suitable for use with the present invention may be cellulosic or non-cellulosic. The polymers may be neutral or ionizable in aqueous solution. Of these, ionizable and cellulosic polymers are preferred, with ionizable cellulosic polymers being more preferred.

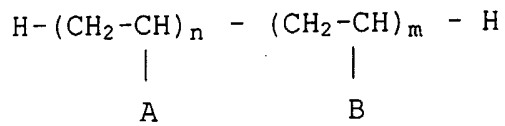
It is preferred that the concentration-enhancing polymer be "amphiphilic" in nature, meaning that the polymer has hydrophobic and hydrophilic portions. Amphiphilic polymers are preferred because it is believed that such polymers tend to have relatively strong interactions with the drug and may promote the formation of various types of polymer/drug assemblies in solution. A particularly preferred class of amphiphilic polymers are those that are ionizable, the ionizable portions of such polymers, when ionized, constituting at least a portion of the hydrophilic portions of the polymer. For example, while not wishing to be bound by a particular theory, such polymer/drug assemblies may comprise hydrophobic drug clusters surrounded by the concentration-enhancing polymer with the polymer's hydrophobic regions turned inward towards the drug and the hydrophilic regions of the polymer turned outward toward the aqueous environment. Alternatively, depending on the specific chemical nature of the drug, the ionized functional groups of the polymer may associate, for example, via ion-pairing or hydrogen bonds, with ionic or polar groups of the drug. In the case of ionizable polymers, the hydrophilic regions of the polymer would include the ionized functional groups. In addition, the repulsion of the like charges of the ionized groups of such polymers (where the polymer is ionizable) may serve to limit the size of the polymer/drug assemblies to the nanometer or submicron scale. Such drug/concentration-enhancing polymer

assemblies in solution may well resemble charged polymeric micellar-like structures. In any case, regardless of the mechanism of action, the inventors have observed that such amphiphilic polymers, particularly ionizable cellulosic polymers such as those listed below, have been shown to interact with drug so as to maintain a higher concentration of drug in an aqueous use environment.

One class of polymers suitable for use with the present invention comprises non-ionizable (neutral) non-cellulosic polymers. Exemplary polymers include: vinyl polymers and copolymers having at least one substituent selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido; polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form; polyvinyl alcohol polyvinyl acetate copolymers; polyvinyl pyrrolidone; and polyethylene polyvinyl alcohol copolymers; and polyoxyethylene-polyoxypropylene copolymers.

A preferred class of neutral non-cellulosic polymers are comprised of vinyl copolymers of at least one hydrophilic, hydroxyl-containing repeat unit and at least one hydrophobic, alkyl- or aryl-containing repeat unit. Such neutral vinyl copolymers are termed "amphiphilic hydroxyl-functional vinyl copolymers." Amphiphilic hydroxyl-functional vinyl copolymers are believed to provide high concentration enhancements due to the amphiphilicity of these copolymers which provide both sufficient hydrophobic groups to interact with the hydrophobic, low-solubility drugs and also sufficient hydrophilic groups to have sufficient aqueous solubility for good dissolution. The copolymeric structure of the amphiphilic hydroxyl-functional vinyl copolymers also allows their hydrophilicity and hydrophobicity to be adjusted to maximize performance with a specific low-solubility drug.

The preferred copolymers have the general structure:



where A and B represent "hydrophilic, hydroxyl-containing" and "hydrophobic" substituents, respectively, and n and m represent the average number of hydrophilic vinyl repeat units and average number of hydrophobic vinyl repeat units respectively per polymer molecule. Copolymers may be block copolymers, random copolymers or they may have structures anywhere between these two extremes. The sum of n and m is generally from about 50 to about 20,000 and therefore the polymers have molecular weights from about 2,500 to about 1,000,000 daltons.

The hydrophilic, hydroxyl-containing repeat units "A" may simply be hydroxyl (-OH) or it may be any short-chain, 1 to 6 carbon, alkyl with one or more hydroxyls attached thereto. The hydroxyl-substituted alkyl may be attached to the vinyl backbone via carbon-carbon or ether linkages. Thus, exemplary "A" structures include, in addition to hydroxyl itself, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxymethoxy, hydroxyethoxy and hydroxypropoxy.

The hydrophobic substituent "B" may simply be: hydrogen (-H), in which case the hydrophobic repeat unit is ethylene; an alkyl or aryl substituent with up to 12 carbons attached via a carbon-carbon bond such as methyl, ethyl or phenyl; an alkyl or aryl substituent with up to 12 carbons attached via an ether linkage such as methoxy, ethoxy or phenoxy; an alkyl or aryl substituent with up to 12 carbons attached via an ester linkage such as acetate, propionate, butyrate or benzoate. The amphiphilic hydroxyl-functional vinyl copolymers of the present invention may be synthesized by any conventional method used to prepare substituted vinyl copolymers. Some substituted vinyl copolymers such as polyvinyl alcohol/polyvinyl acetate are well known and commercially available.

A particularly convenient subclass of amphiphilic hydroxyl-functional vinyl copolymers to synthesize are those where the hydrophobic substituent "B" comprises the hydrophilic substituent "A" to which an alkylate or arylate group is attached via an ester linkage to one or more of the

hydroxyls of A. Such copolymers may be synthesized by first forming the homopolymer of the hydrophobic vinyl repeat unit having the substituent B, followed by hydrolysis of a portion of the ester groups to convert a portion of the hydrophobic repeat units to hydrophilic, hydroxyl-containing repeat units having the substituent A. For example, partial hydrolysis of the homopolymer, polyvinylbutyrate, yields the copolymer, vinylalcohol/vinylbutyrate copolymer for which A is hydroxyl (-OH) and B is butyrate (-OOC-CH_2-CH_2-CH_3).

For all types of copolymers, the value of n must be sufficiently large relative to the value of m that the resulting copolymer is at least partially water soluble. Although the value of the ratio, n/m varies depending on the identity of A and B, it is generally at least about 1 and more commonly about 2 or more. The ratio n/m can be as high as 200. When the copolymer is formed by hydrolysis of the hydrophobic homopolymer, the relative values of n and m are typically reported in "percent hydrolysis," which is the fraction (expressed as a percent) of the total repeat units of the copolymer that are in the hydrolyzed or hydroxyl form. The percent hydrolysis, H, is given as

$$H = 100 \times \left(\frac{n}{n+m} \right)$$

Thus, vinylbutyrate/vinylalcohol copolymer (formed by hydrolysis of a portion of the butyrate groups) having a percent hydrolysis of 75% has an n/m ratio of 3.

A particularly preferred family of amphiphilic hydroxyl-functional vinyl copolymers are those where A is hydroxyl and B is acetate. Such copolymers are termed vinylacetate/vinylalcohol copolymers. Some commercial grades are also sometimes referred to simply as polyvinylalcohol. However, the true homopolymer polyvinylalcohol is not amphiphilic and is almost entirely water-insoluble. Preferred vinylacetate/vinylalcohol copolymers are those where H is between about 67% and 99.5%, or n/m has a value between about 2 and 200. The preferred average molecular weight is between

about 2500 and 1,000,000 daltons and more preferably between about 3000 and about 100,000 daltons.

Another class of polymers suitable for use with the present invention comprises ionizable non-cellulosic polymers. Exemplary polymers include: carboxylic acid-functionalized vinyl polymers, such as the carboxylic acid functionalized polymethacrylates and carboxylic acid functionalized polyacrylates such as the EUDRAGIT® series manufactured by Rohm Tech Inc., of Malden, Massachusetts; amine-functionalized polyacrylates and polymethacrylates; proteins such as gelatin and albumin; and carboxylic acid functionalized starches such as starch glycolate.

Non-cellulosic polymers that are amphiphilic are copolymers of a relatively hydrophilic and a relatively hydrophobic monomer. Examples include acrylate and methacrylate copolymers. Exemplary commercial grades of such copolymers include the EUDRAGIT® series, which are copolymers of methacrylates and acrylates.

A preferred class of polymers comprises ionizable and neutral (or non-ionizable) cellulosic polymers with at least one ester- and/or ether-linked substituent in which the polymer has a degree of substitution of at least 0.05 for each substituent. It should be noted that in the polymer nomenclature used herein, ether-linked substituents are recited prior to "cellulose" as the moiety attached to the ether group; for example, "ethylbenzoic acid cellulose" has ethoxybenzoic acid substituents. Analogously, ester-linked substituents are recited after "cellulose" as the carboxylate; for example, "cellulose phthalate" has one carboxylic acid of each phthalate moiety ester-linked to the polymer and the other carboxylic acid unreacted.

It should also be noted that a polymer name such as "cellulose acetate phthalate" (CAP) refers to any of the family of cellulosic polymers that have acetate and phthalate groups attached via ester linkages to a significant fraction of the cellulosic polymer's hydroxyl groups. Generally, the degree of substitution of each substituent group can range

from 0.05 to 2.9 as long as the other criteria of the polymer are met. "Degree of substitution" refers to the average number of the three hydroxyls per saccharide repeat unit on the cellulose chain that have been substituted. For example, if all of the hydroxyls on the cellulose chain have been phthalate-substituted, the phthalate degree of substitution is 3. Also included within each polymer family type are cellulosic polymers that have additional substituents added in relatively small amounts that do not substantially alter the performance of the polymer.

Amphiphilic cellulosics comprise polymers in which the parent cellulosic polymer has been substituted at any or all of the 3 hydroxyl groups present on each saccharide repeat unit with at least one relatively hydrophobic substituent. Hydrophobic substituents may be essentially any substituent that, if substituted to a high enough level or degree of substitution, can render the cellulosic polymer essentially aqueous-insoluble. Examples of hydrophobic substitutents include ether-linked alkyl groups such as methyl, ethyl, propyl, butyl, etc.; or ester-linked alkyl groups such as acetate, propionate, butyrate, etc.; and ether- and/or ester-linked aryl groups such as phenyl, benzoate, or phenylate. Hydrophilic regions of the polymer can be either those portions that are relatively unsubstituted, since the unsubstituted hydroxyls are themselves relatively hydrophilic, or those regions that are substituted with hydrophilic substituents. Hydrophilic substituents include ether- or ester-linked nonionizable groups such as the hydroxy alkyl substituents hydroxyethyl, hydroxypropyl, and the alkyl ether groups such as ethoxyethoxy or methoxyethoxy. Particularly preferred hydrophilic substituents are those that are ether- or ester-linked ionizable groups such as carboxylic acids, thiocarboxylic acids, substituted phenoxy groups, amines, phosphates or sulfonates.

One class of cellulosic polymers comprises neutral polymers, meaning that the polymers are substantially non-ionizable in aqueous solution. Such polymers contain non-

ionizable substituents, which may be either ether-linked or ester-linked. Exemplary ether-linked non-ionizable substituents include: alkyl groups, such as methyl, ethyl, propyl, butyl, etc.; hydroxy alkyl groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, etc.; and aryl groups such as phenyl. Exemplary ester-linked non-ionizable substituents include: alkyl groups, such as acetate, propionate, butyrate, etc.; and aryl groups such as phenylate. However, when aryl groups are included, the polymer may need to include a sufficient amount of a hydrophilic substituent so that the polymer has at least some water solubility at any physiologically relevant pH of from 1 to 8.

Exemplary nonionizable cellulosic polymers that may be used as the polymer include: hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

A preferred set of neutral cellulosic polymers are those that are amphiphilic. Exemplary polymers include hydroxypropyl methyl cellulose and hydroxypropyl cellulose acetate, where cellulosic repeat units that have relatively high numbers of methyl or acetate substituents relative to the unsubstituted hydroxyl or hydroxypropyl substituents constitute hydrophobic regions relative to other repeat units on the polymer.

A preferred class of cellulosic polymers comprises polymers that are at least partially ionizable at physiologically relevant pH and include at least one ionizable substituent, which may be either ether-linked or ester-linked. Exemplary ether-linked ionizable substituents include: carboxylic acids, such as acetic acid, propionic acid, benzoic acid, salicylic acid, alkoxybenzoic acids such as ethoxybenzoic acid or propoxybenzoic acid, the various isomers of alkoxyphthalic acid such as ethoxyphthalic acid and ethoxyisophthalic acid, the various isomers of alkoxynicotinic acid such as ethoxynicotinic acid, and the various isomers of

picolinic acid such as ethoxypicolinic acid, etc.; thiocarboxylic acids, such as thioacetic acid; substituted phenoxy groups, such as hydroxyphenoxy, etc.; amines, such as aminoethoxy, diethylaminoethoxy, trimethylaminoethoxy, etc.; phosphates, such as phosphate ethoxy; and sulfonates, such as sulphonate ethoxy. Exemplary ester-linked ionizable substituents include: carboxylic acids, such as succinate, citrate, phthalate, terephthalate, isophthalate, trimellitate, and the various isomers of pyridinedicarboxylic acid, etc.; thiocarboxylic acids, such as thiosuccinate; substituted phenoxy groups, such as amino salicylic acid; amines, such as natural or synthetic amino acids, such as alanine or phenylalanine; phosphates, such as acetyl phosphate; and sulfonates, such as acetyl sulfonate. For aromatic-substituted polymers to also have the requisite aqueous solubility, it is also desirable that sufficient hydrophilic groups such as hydroxypropyl or carboxylic acid functional groups be attached to the polymer to render the polymer aqueous soluble at least at pH values where any ionizable groups are ionized. In some cases, the aromatic substituent may itself be ionizable, such as phthalate or trimellitate substituents.

Exemplary cellulosic polymers that are at least partially ionized at physiologically relevant pHs include: hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, carboxyethyl cellulose, carboxymethyl cellulose, carboxymethyl ethyl cellulose, ethyl carboxymethyl cellulose, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methyl cellulose

acetate succinate phthalate, hydroxypropyl methyl cellulose succinate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

Exemplary cellulosic polymers that meet the definition of amphiphilic, having hydrophilic and hydrophobic regions include polymers such as cellulose acetate phthalate and cellulose acetate trimellitate where the cellulosic repeat units that have one or more acetate substituents are hydrophobic relative to those that have no acetate substituents or have one or more ionized phthalate or trimellitate substituents.

A particularly desirable subset of cellulosic ionizable polymers are those that possess both a carboxylic acid functional aromatic substituent and an alkylate substituent and thus are amphiphilic. Exemplary polymers include cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxylpropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl

methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

Another particularly desirable subset of cellulosic ionizable polymers are those that possess a non-aromatic carboxylate substituent. Exemplary polymers include hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate and carboxymethyl ethyl cellulose. Of these cellulosic polymers that are at least partially ionized at physiologically relevant pHs, the inventors have found the following to be most preferred: hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethyl ethyl cellulose. The most preferred is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

Another preferred class of polymers consists of neutralized acidic polymers. By "neutralized acidic polymer" is meant any acidic polymer for which a significant fraction of the "acidic moieties" or "acidic substituents" have been "neutralized"; that is, exist in their deprotonated form. By "neutralized acidic cellulosic polymers" is meant any cellulosic "acidic polymer" in which a significant fraction of the "acidic moieties" or "acidic substituents" have been "neutralized." By "acidic polymer" is meant any polymer that possesses a significant number of acidic moieties. In general, a significant number of acidic moieties would be

greater than or equal to about 0.1 milliequivalents of acidic moieties per gram of polymer. "Acidic moieties" include any functional groups that are sufficiently acidic that, in contact with or dissolved in water, can at least partially donate a hydrogen cation to water and thus increase the hydrogen-ion concentration. This definition includes any functional group or "substituent," as it is termed when the functional group is covalently attached to a polymer, that has a pK_a of less than about 10. Exemplary classes of functional groups that are included in the above description include carboxylic acids, thiocarboxylic acids, phosphates, phenolic groups, and sulfonates. Such functional groups may make up the primary structure of the polymer such as for polyacrylic acid, but more generally are covalently attached to the backbone of the parent polymer and thus are termed "substituents." Neutralized acidic polymers are described in more detail in commonly assigned U.S. Patent Application Serial No. 60/300,255 filed June 22, 2001, the relevant disclosure of which is incorporated by reference.

While specific polymers have been discussed as being suitable for use in the dispersions formable by the present invention, blends of such polymers may also be suitable. Thus, the term "concentration-enhancing polymer" is intended to include blends of polymers in addition to a single species of polymer.

The amount of concentration-enhancing polymer relative to the amount of drug present in the spray-dried dispersions formed by the present invention depends on the drug and concentration-enhancing polymer and may vary widely from a drug-to-polymer weight ratio of 0.01 to 5. However, in most cases, except when the drug dose is quite low, *e.g.*, 25 mg or less, it is preferred that the drug-to-polymer ratio is greater than 0.05 and less than 2.5 and often the enhancement in drug concentration or relative bioavailability is observed at drug-to-polymer ratios of 1 or less or for some drugs even 0.2 or less. In cases where the drug dose is about 25 mg or less, the drug-to-polymer weight ratio may be

significantly less than 0.05. In general, regardless of the dose, enhancements in drug concentration or relative bioavailability increase with decreasing drug-to-polymer weight ratio. However, due to the practical limits of keeping the total mass of a tablet, capsule or suspension low, it is often desirable to use a relatively high drug-to-polymer ratio as long as satisfactory results are obtained. The maximum drug:polymer ratio that yields satisfactory results varies from drug to drug and is best determined in the *in vitro* and/or *in vivo* dissolution tests described below.

In general, to maximize the drug concentration or relative bioavailability of the drug, lower drug-to-polymer ratios are preferred. At low drug-to-polymer ratios, there is sufficient concentration-enhancing polymer available in solution to ensure the inhibition of the precipitation or crystallization of drug from solution and, thus, the average concentration of drug is much higher. For high drug/polymer ratios, not enough concentration-enhancing polymer may be present in solution and drug precipitation or crystallization may occur more readily. However, the amount of concentration-enhancing polymer that can be used in a dosage form is often limited by the maximum total mass of the dosage form that is acceptable. For example, when oral dosing to a human is desired, at low drug/polymer ratios the total mass of drug and polymer may be unacceptably large for delivery of the desired dose in a single tablet or capsule. Thus, it is often necessary to use drug/polymer ratios that are less than those which yield maximum drug concentration or relative bioavailability in specific dosage forms to provide a sufficient drug dose in a dosage form that is small enough to be easily delivered to a use environment.

CONCENTRATION ENHANCEMENT

The concentration-enhancing polymer is present in the spray-dried dispersions formed by the present invention in a sufficient amount so as to improve the concentration of the drug in a use environment relative to a control composition.

At a minimum, the compositions formed by the present invention provide concentration enhancement relative to a control of undispersed drug alone. Thus, the concentration-enhancing polymer is present in a sufficient amount so that when the composition is administered to a use environment, the composition provides improved drug concentration relative to a control consisting of an equivalent amount of crystalline drug, but with no concentration-enhancing polymer present.

The compositions comprising the drug and concentration-enhancing polymer provide enhanced concentration of the dissolved drug in *in vitro* dissolution tests. It has been determined that enhanced drug concentration in *in vitro* dissolution tests in MFD or PBS solution is a good indicator of *in vivo* performance and bioavailability. An appropriate PBS solution is an aqueous solution comprising 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. An appropriate MFD solution is the same PBS solution with the additions of 7.3 mM sodium taurocholic acid and 1.4 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine. In particular, a composition of the present invention can be dissolution-tested by adding it to MFD or PBS solution and agitating to promote dissolution. Generally, the amount of composition added to the solution in such a test is an amount that, if all the drug in the composition dissolved, would produce a drug concentration that is at least about 2-fold and preferably at least 10-fold the equilibrium solubility of the drug alone in the test solution. To demonstrate even higher levels of dissolved drug concentration, addition of even larger amounts of the composition are added to the test solution.

In one aspect, the compositions formed by the present invention provide an MDC that is at least 1.25-fold the equilibrium concentration of a control composition of an equivalent quantity of undispersed drug but free from the polymer. In other words, if the equilibrium concentration provided by the control composition is 1 μg/mL, then a composition of the present invention provides an MDC of at

least about 1.25 μg/mL. The comparison composition is conventionally the undispersed drug alone (typically, the crystalline drug alone in its most thermodynamically stable crystalline form, or in cases where a crystalline form of the drug is unknown, the control may be the amorphous drug alone) or the drug plus an amount of inert diluent equivalent to the weight of polymer in the test composition. Preferably, the MDC of drug achieved with the compositions of the present invention is at least about 2-fold, and more preferably at least about 3-fold, the equilibrium concentration of the control composition.

Alternatively, the compositions formed by the present invention provide in an aqueous use environment an AUC, for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment, that is at least 1.25-fold that of a control composition of an equivalent quantity of undispersed drug. Preferably, the compositions of the present invention provide in an aqueous use environment an AUC for the same period that is at least about 2-fold, and more preferably at least about 3-fold that of a control composition as described above.

A typical *in vitro* test to evaluate enhanced drug concentration in aqueous solution can be conducted by (1) adding with agitation a sufficient quantity of control composition, typically the drug alone, to the *in vitro* test medium, typically MFD or PBS solution, to achieve equilibrium concentration of the drug; (2) adding with agitation a sufficient quantity of test composition (*e.g.*, the drug and polymer) in an equivalent test medium, such that if all the drug dissolved, the theoretical concentration of drug would exceed the equilibrium concentration of the drug by a factor of at least 2, and preferably a factor of at least 10; and (3) comparing the measured MDC and/or aqueous concentration AUC of the test composition in the test medium with the equilibrium concentration, and/or the aqueous concentration AUC of the control composition. In conducting such

dissolution tests, the amount of test composition or control composition used is an amount such that if all of the drug dissolved the drug concentration would be at least 2-fold and preferably at least 10-fold that of the equilibrium concentration. Indeed, for some extremely insoluble drugs, in order to identify the MDC achieved it may be necessary to use an amount of test composition such that if all of the drug dissolved, the drug concentration would be 100-fold or even more, that of the equilibrium concentration of the drug.

The concentration of dissolved drug is typically measured as a function of time by sampling the test medium and plotting drug concentration in the test medium vs. time so that the MDC can be ascertained. The MDC is taken to be the maximum value of dissolved drug measured over the duration of the test. The aqueous concentration AUC is calculated by integrating the concentration versus time curve over any 90-minute time period between the time of introduction of the composition into the aqueous use environment (time equals zero) and 270 minutes following introduction to the use environment (time equals 270 minutes). Typically, when the composition reaches its MDC rapidly, *i.e.*, in less than about 30 minutes, the time interval used to calculate AUC is from time equals zero to time equals 90 minutes. However, if the AUC over any 90-minute time period described above of a composition meets the criterion of this invention, then the composition formed by the inventive method is contemplated to be within the scope of this invention.

To avoid large drug particulates that would give an erroneous determination, the test solution is either filtered or centrifuged. "Dissolved drug" is typically taken as that material that either passes a 0.45 μm syringe filter or, alternatively, the material that remains in the supernatant following centrifugation. Filtration can be conducted using a 13 mm, 0.45 μm polyvinylidine difluoride syringe filter sold by Scientific Resources of Eatontown, New Jersey under the trademark TITAN®. Centrifugation is typically carried out in a polypropylene microcentrifuge tube by centrifuging at 13,000 G

for 60 seconds. Other similar filtration or centrifugation methods can be employed and useful results obtained. For example, using other types of microfilters may yield values somewhat higher or lower (±10-40%) than that obtained with the filter specified above but will still allow identification of preferred dispersions. It is recognized that this definition of "dissolved drug" encompasses not only monomeric solvated drug molecules but also a wide range of species such as polymer/drug assemblies that have submicron dimensions such as drug aggregates, aggregates of mixtures of polymer and drug, micelles, polymeric micelles, colloidal particles or nanocrystals, polymer/drug complexes, and other such drug-containing species that are present in the filtrate or supernatant in the specified dissolution test.

Alternatively, the compositions formed by the present invention, when dosed orally to a human or other animal, provide an AUC in drug concentration in the blood that is at least about 1.25-fold that observed when a control composition of an equivalent quantity of undispersed drug is dosed. It is noted that such compositions can also be said to have a relative bioavailability of about 1.25. To facilitate dosing, a dosing vehicle may be used to administer the dose. The dosing vehicle is preferably water, but may also contain materials for suspending the test or control composition, provided these materials do not dissolve the composition or change drug solubility *in vivo*. Preferably, the compositions, when dosed orally to a human or other animal, provide an AUC in drug concentration in the blood that is at least about 2-fold, more preferably at least about 3-fold, that observed when a control composition comprising an equivalent quantity of undispersed drug is dosed. Thus, the compositions formed by the present invention can be evaluated in either *in vitro* or *in vivo* tests, or both.

Relative bioavailability of drugs in the dispersions formed by the present invention can be tested *in vivo* in animals or humans using conventional methods for making such a

determination. An *in vivo* test, such as a crossover study, may be used to determine whether a composition of drug and concentration-enhancing polymer provides an enhanced relative bioavailability compared with a control composition of drug but no polymer as described above. In an *in vivo* crossover study a test composition of drug and polymer is dosed to half a group of test subjects and, after an appropriate washout period (*e.g.*, one week) the same subjects are dosed with a control composition of an equivalent quantity of drug as in the test composition but with no polymer present. The other half of the group is dosed with the control composition first, followed by the test composition. The relative bioavailability is measured as the concentration in the blood (serum or plasma) versus time AUC determined for the test group divided by the AUC in the blood provided by the control composition. Preferably, this test/control ratio is determined for each subject, and then the ratios are averaged over all subjects in the study. *In vivo* determinations of AUC can be made by plotting the serum or plasma concentration of drug along the ordinate (y-axis) against time along the abscissa (x-axis). The determination of AUCs is a well-known procedure and is described, for example, in Welling, "Pharmacokinetics Processes and Mathematics," ACS Monograph 185 (1986).

PREPARATION OF COMPOSITIONS

Dispersions of the drug and concentration-enhancing polymer are made via a spray-drying process, which results in at least a major portion, *i.e.*, at least 60% of the drug being in the amorphous state. Spray-drying processes and spray-drying equipment are described generally in Perry's *Chemical Engineers' Handbook* (Sixth Edition 1984), pages 20-54 to 20-57. More details on spray-drying processes and equipment are reviewed by Marshall, "Atomization and Spray-Drying," 50 *Chem. Eng. Prog. Monogr. Series* 2 (1954), and Masters, *Spray Drying Handbook* (Fourth Edition 1985).

The dispersions generally have their maximum bioavailability and stability when the drug is dispersed in the polymer such that it is substantially amorphous and substantially homogeneously distributed throughout the polymer. In general, as the degree of homogeneity of the dispersion increases, the enhancement in the aqueous concentration of the drug and relative bioavailability increases as well. Thus, most preferred are dispersions having a single glass transition temperature, which indicates a high degree of homogeneity.

In the spray-drying process, the drug and one or more concentration-enhancing polymers are dissolved in a common solvent. "Common" here means that the solvent, which can be a mixture of compounds, will dissolve the drug and the polymer(s). After both the drug and the polymer have been dissolved, the solvent is rapidly removed by evaporation in the spray-drying apparatus, resulting in the formation of a substantially homogeneous, solid amorphous dispersion. In such substantially homogeneous dispersions, the drug is dispersed as homogeneously as possible throughout the polymer and can be thought of as a solid solution of drug dispersed in the polymer. This generally requires that the atomized droplets be dried rapidly to obtain such homogeneous dispersions. The desire for rapid drying has generally led others to use atomizing means that generate extremely fine droplets, such as those obtained from two-fluid nozzles or rotary atomizers. While solid amorphous dispersions may be obtained using such atomizers, the inventors have found that atomizing the solution of polymer and drug using a pressure nozzle, which produces droplets with a average droplet diameter of about 50 μm or larger, with less than about 10 vol% of the droplets having a diameter of less than 10 μm, has numerous advantages, while still allowing sufficiently rapid drying that solid dispersions are obtained that are substantially amorphous and substantially homogeneous. When the resulting dispersion constitutes a solid solution of drug in polymer, the dispersion may be thermodynamically stable,

meaning that the concentration of drug in the polymer is at or below its equilibrium value, or it may be considered a supersaturated solid solution where the drug concentration in the dispersion polymer(s) is above its equilibrium value.

The solvent is removed by the spray-drying process. The term spray-drying is used conventionally and broadly refers to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixture in a spray-drying apparatus where there is a strong driving force for evaporation of solvent from the droplets. Such a strong driving force for solvent evaporation is generally provided by maintaining the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature of the drying droplets. This is accomplished by either (1) maintaining the pressure in the spray-drying apparatus at a partial vacuum (*e.g.*, 0.01 to 0.50 atm); (2) mixing the liquid droplets with a warm drying gas; or (3) both (1) and (2). In addition, at least a portion of the heat required for evaporation of solvent may be provided by heating the spray solution.

Solvents suitable for spray-drying can be any organic compound in which the drug and polymer are mutually soluble. Preferably, the solvent is also volatile with a boiling point of 150°C or less. In addition, the solvent should have relatively low toxicity and be removed from the dispersion to a level that is acceptable according to The International Committee on Harmonization (ICH) guidelines. Removal of solvent to this level may require a processing step such as tray-drying subsequent to the spray-drying process. Preferred solvents include alcohols such as methanol, ethanol, n-propanol, iso-propanol, and butanol; ketones such as acetone, methyl ethyl ketone and methyl iso-butyl ketone; esters such as ethyl acetate and propylacetate; and various other solvents such as acetonitrile, methylene chloride, toluene, and 1,1,1-trichloroethane. Lower volatility solvents such as dimethylacetamide or dimethylsulfoxide can also be used. Mixtures of solvents, such as 50% methanol and 50%

acetone, can also be used, as can mixtures with water as long as the polymer and drug are sufficiently soluble to make the spray-drying process practicable.

The composition of the solvent-bearing feed will depend on the desired ratio of drug-to-polymer in the dispersion and the solubility of the drug and polymer in the solvent. Generally, it is desirable to use as high a combined drug and polymer concentration in the solvent-bearing feed as possible, provided the drug and polymer are dissolved in the solvent, to reduce the total amount of solvent that must be removed to form the solid amorphous dispersion. Thus, the solvent-bearing feed will generally have a combined drug and polymer concentration of at least about 0.1 wt%, preferably at least about 1 wt%, and more preferably at least about 10 wt%. However, solvent-bearing feeds with lower combined drug and polymer concentrations can be used to form suitable solid amorphous dispersions.

The solvent-bearing feed comprising the drug and polymer is atomized through a pressure nozzle. By "pressure nozzle" is meant an atomizing means that produces droplets with an average droplet diameter of 50 μm or larger, with less than about 10 vol% of the droplets having a size less than about 10 μm. Generally, an appropriately sized and designed pressure nozzle is one that will produce droplets within this size range when the spray solution is pumped through the nozzle at the desired rate. Thus, for example, when it is desired to deliver 400 g/min of a spray solution to a PSD-1 dryer, a nozzle must be chosen that is matched to the viscosity and flow rate of the solution to achieve the desired average droplet size. Too large a nozzle will deliver too large a droplet size when operated at the desired flow rate. This is particularly true the higher the viscosity of the spray solution. Too large droplets result in the rate of drying being too slow, which can yield nonhomogeneous dispersions or, if still fluid when they reach the spray-dryer wall, the droplets may stick to or even coat the dryer wall, resulting in low or no yield of the desired product. In such

cases, the height of the spray-drying chamber can be increased to provide an increased minimum distance that a droplet travels before impinging on the walls of the drying chamber or collection cone. Such modified spray-drying apparatus allow for use of atomizing means that produce larger droplets. Details of such a modified spray-drying apparatus are provided in commonly owned U.S. Provisional Application No. 60/354,080 (Attorney Docket PC23195), filed February 1, 2002 and incorporated herein by reference. Use of too small a nozzle can yield droplets that are undesirably small or may require an unacceptably high pump pressure to achieve the desired flow rate, particularly for high viscosity feed solutions.

The vast majority of atomizers atomize the liquid feed into droplets with a distribution of sizes. The size distribution of droplets produced by an atomizing means can be measured by several techniques, including mechanical techniques, such as the molten-wax and frozen-drop techniques; electrical techniques, such as charged-wire and hot-wire techniques; and optical techniques, such as photography and light-scattering techniques. One of the more common methods for determining the droplet size distribution produced by an atomizer is with the use of a Malvern Particle Size Analyzer, available from Malvern Instruments Ltd. of Framingham, Massachusetts. Further details about the principles used to determine droplet size and droplet size distribution using such instruments can be found in Lefebvre, *Atomization and Sprays* (1989).

The data obtained using a droplet size analyzer can be used to determine several characteristic diameters of the droplets. One of these is D_{10}, the diameter corresponding to the diameter of droplets that make up 10% of the total liquid volume containing droplets of equal or smaller diameter. In other words, if D_{10} is equal to 10 μm, 10 vol% of the droplets have a diameter less than or equal to 10 μm. Thus, it is preferred that the atomizing means produce droplets such that D_{10} is greater than about 10 μm, meaning that 90 vol% of the

droplets have a diameter of greater than 10 μm. This requirement ensures the number of fines in the solidified product (*i.e.*, particles with diameters of less than 10 μm) is minimized. Preferably, D_{10} is greater than about 15 μm, more preferably greater than about 20 μm.

Another useful characteristic diameter of the droplets produced by an atomizing means is D_{90}, the diameter corresponding to the diameter of droplets that make up 90% of the total liquid volume containing droplets of equal or smaller diameter. In other words, if D_{90} is equal to 100 μm, 90 vol% of the droplets have a diameter less than or equal to 100 μm. For producing substantially homogeneous, substantially amorphous dispersions using the technology of the present invention, the inventors have found that D_{90} should be less than about 300 μm, preferably less than 250 μm. If D_{90} is too high, the rate of drying of the larger droplets may be too slow, which can yield nonhomogeneous dispersions or, if still fluid when they reach the spray dryer wall, the larger droplets may stick to or coat the dryer wall, as noted above.

Another useful parameter is "Span," defined as

$$Span = \frac{D_{90} - D_{10}}{D_{50}},$$

where D_{50} is the diameter corresponding to the diameter of drops that make up 50% of the total liquid volume containing drops of equal of smaller diameter, and D_{90} and D_{10} are defined as above. Span, sometimes referred to in the art as the Relative Span Factor or RSF, is a dimensionless parameter indicative of the uniformity of the drop size distribution. Generally, the lower the Span, the more narrow the droplet size distribution produced by the atomizing means, which in turn generally leads to a narrower particle size distribution for the dried particles, resulting in improved flow characteristics. Preferably, the Span of the droplets produced by the atomizing means of the present invention is

less than about 3, more preferably less than about 2, and most preferably less than about 1.5.

The size of the solid dispersion particles formed in the spray dryer are generally somewhat smaller than the size of the droplets produced by the atomizing means. Typically, the characteristic diameter of the dispersion particles is about 80% the characteristic diameter of the droplets. Thus, in one aspect, the process of the present invention produces particulates of a solid amorphous dispersion with an average diameter of about 40 μm or larger, with less than about 10 vol% of the particles having a size less than about 8 μm.

When selecting an atomizing means for use in forming a homogeneous solid amorphous dispersion, several factors should be considered, including the desired flow rate, the maximum allowable liquid pressure, and the viscosity and surface tension of the solvent-bearing feed. The relationship between these factors and their influence on droplet size and droplet size distribution are well known in the art.

As indicated above, the selection of atomizing means will depend upon the scale of the spray-drying apparatus used. For smaller scale apparatus such as the Niro PSD-1 that can spray about 10-400 g/min of a solvent-bearing feed, examples of suitable atomizers include the SK and TX spray dry nozzle series from Spraying Systems of Wheaton, Illinois; the WG series from Delavan LTV of Widnes, Cheshire, England; and the Model 121 nozzle from Dusen Schlick GmbH of Untersiemau, Germany. For larger scale apparatus such as the Niro PSD-4 that can spray about 25-600 kg/hr of a solvent-bearing feed, exemplary atomizers include the SDX and SDX III nozzles from Delavan LTV.

In many cases, the solvent-bearing feed is delivered to the atomizing means under pressure. The pressure required is determined by the design of the atomizer, the size of the nozzle orifice, the viscosity and other characteristics of the solvent-bearing feed, and the desired droplet size and size distribution. Generally, feed pressures should range from 2 to 200 atm or more, with 4 to 150 atm being more typical.

The temperature and flow rate of the drying gas is chosen so that sufficient heat for drying the solvent-bearing feed is delivered to the drying chamber, while allowing sufficient residence time for the droplets to solidify before they impinge on the walls of the spray-drying apparatus. Generally, the higher the feed rate of the solvent-bearing feed, the higher the temperature and/or flow rate of the drying gas. Typically, the temperature of the drying gas at the inlet to the spray dryer will be at least about 60°C and less than about 300°C.

The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to rapid solidification times for the droplets. Solidification times should be less than about 20 seconds, preferably less than about 10 seconds, and more preferably less than 1 second. This rapid solidification is often critical to the formation of particles having uniform, homogeneous dispersion instead of separating into drug-rich and polymer-rich phases. As noted above, to get large enhancements in concentration and bioavailability it is often necessary to obtain as homogeneous a dispersion as possible.

Following solidification, the solid powder typically stays in the spray-drying chamber for about 5 to 60 seconds, further evaporating solvent from the solid powder. The final solvent content of the solid dispersion as it exits the dryer should be low, since solvent in the dispersion lowers the glass transition temperature of the dispersion, tending to cause it to be kinetically unstable. This can lead to phase separation or even crystallization of the drug in the dispersion, which can dramatically reduce the concentration enhancement obtained compared with a homogeneous solid amorphous dispersion. Generally, the solvent content of the dispersion as it leaves the spray-drying chamber should be less than about 10 wt% and preferably less than about 3 wt% and most preferably less than about 1 wt%. As indicated above, a subsequent processing step, such as tray-drying, may be used to remove the solvent to this level.

EXCIPIENTS AND DOSAGE FORMS

Although the key ingredients present in the solid amorphous dispersion are simply the drug and the concentration-enhancing polymer, other excipients may be included in the dispersion to improve performance, handling, or processing of the dispersion. Optionally, once formed, the dispersion may be mixed with other excipients in order to formulate the composition into tablets, capsules, suppositories, suspensions, powders for suspension, creams, transdermal patches, depots, and the like. The dispersion may be added to other dosage form ingredients in essentially any manner that does not substantially alter the drug. The excipients may be either separate from the dispersion and/or included within the dispersion.

Generally, excipients such as surfactants, pH modifiers, fillers, matrix materials, complexing agents, solubilizers, pigments, lubricants, glidants, flavorants, and so forth may be used for customary purposes and in typical amounts without adversely affecting the properties of the compositions. See for example, *Remington's Pharmaceutical Sciences* (18th ed. 1990).

One very useful class of excipients is surfactants, preferably present from 0 to 10 wt%. Suitable surfactants include fatty acid and alkyl sulfonates; commercial surfactants such as benzalkonium chloride (HYAMINE® 1622, available from Lonza, Inc., Fairlawn, New Jersey); dioctyl sodium sulfosuccinate (DOCUSATE SODIUM, available from Mallinckrodt Spec. Chem., St. Louis, Missouri); polyoxyethylene sorbitan fatty acid esters (TWEEN®, available from ICI Americas Inc., Wilmington, Delaware; LIPOSORB® O-20, available from Lipochem Inc., Patterson New Jersey; CAPMUL® POE-0, available from Abitec Corp., Janesville, Wisconsin); and natural surfactants such as sodium taurocholic acid, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, lecithin, and other phospholipids and mono- and diglycerides. Such materials can advantageously be employed to increase the rate

of dissolution by, for example, facilitating wetting, or otherwise increase the rate of drug release from the dosage form.

The addition of pH modifiers such as acids, bases, or buffers may be beneficial, retarding the dissolution of the composition (*e.g.*, acids such as citric acid or succinic acid when the concentration-enhancing polymer is anionic) or, alternatively, enhancing the rate of dissolution of the composition (*e.g.*, bases such as sodium acetate or amines when the polymer is cationic).

Conventional matrix materials, complexing agents, solubilizers, fillers, disintegrating agents (disintegrants), or binders may also be added as part of the composition itself or added by granulation via wet or mechanical or other means. These materials may comprise up to 90 wt% of the composition.

Examples of matrix materials, fillers, or diluents include lactose, mannitol, xylitol, microcrystalline cellulose, dibasic calcium phosphate (anhydrous and dihydrate) and starch.

Examples of disintegrants include sodium starch glycolate, sodium alginate, carboxy methyl cellulose sodium, methyl cellulose, and croscarmellose sodium, and crosslinked forms of polyvinyl pyrrolidone such as those sold under the trade name CROSPOVIDONE (available from BASF Corporation).

Examples of binders include methyl cellulose, microcrystalline cellulose, starch, and gums such as guar gum, and tragacanth.

Examples of lubricants include magnesium stearate, calcium stearate, and stearic acid.

Examples of preservatives include sulfites (an antioxidant), benzalkonium chloride, methyl paraben, propyl paraben, benzyl alcohol and sodium benzoate.

Examples of suspending agents or thickeners include xanthan gum, starch, guar gum, sodium alginate, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, polyacrylic acid, silica gel, aluminum silicate, magnesium silicate, and titanium dioxide.

Examples of anti-caking agents or fillers include silicon oxide and lactose.

Examples of solubilizers include ethanol, propylene glycol or polyethylene glycol.

Other conventional excipients may be employed in the compositions of this invention, including those well-known in the art. Generally, excipients such as pigments, lubricants, flavorants, and so forth may be used for customary purposes and in typical amounts without adversely affecting the properties of the compositions.

Compositions of the present invention may be delivered by a wide variety of routes, including, but not limited to, oral, nasal, rectal, vaginal, subcutaneous, intravenous, and pulmonary. Generally, the oral route is preferred.

Compositions of the invention may also be used in a wide variety of dosage forms for administration of drugs. Exemplary dosage forms are powders or granules that may be taken orally either dry or reconstituted by addition of water or other liquids to form a paste, slurry, suspension or solution; tablets; capsules; multiparticulates; and pills. Various additives may be mixed, ground, or granulated with the compositions of this invention to form a material suitable for such dosage forms.

The compositions of the present invention may be formulated in various forms so that they are delivered as a suspension of particles in a liquid vehicle. Such suspensions may be formulated as a liquid or paste at the time of manufacture, or they may be formulated as a dry powder with a liquid, typically water, added at a later time but prior to oral administration. Such powders that are constituted into a suspension are often referred to as a sachet or an oral powder for constitution (OPC). Such dosage forms can be formulated and reconstituted via any known procedure. The simplest approach is to formulate the dosage form as a dry powder that is reconstituted by simply adding water and agitating. Alternatively, the dosage form may be formulated as a liquid

and a dry powder that are combined and agitated to form the oral suspension. In yet another embodiment, the dosage form can be formulated as two powders that are reconstituted by first adding water to one powder to form a solution to which the second powder is combined with agitation to form the suspension.

Generally, it is preferred that the dispersion of drug be formulated for long-term storage in the dry state as this promotes the chemical and physical stability of the drug.

Compositions of the present invention may be used to treat any condition that is subject to treatment by administering a drug.

Example 1

Multiparticulates of a solid amorphous dispersion of the poorly water-soluble drug 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Drug 1) and the amphiphilic polymer hydroxypropyl methyl cellulose acetate succinate (HPMCAS) were prepared by a spray-drying process using a pressure nozzle as follows. Drug 1 was mixed in an acetone solvent together with a medium fine grade of HPMCAS (AQUOT-MF manufactured by Shin Etsu) to form a feed solution comprising 2.5 wt% Drug 1, 7.5 wt% HPMCAS, and 90 wt% acetone. The feed solution was pumped by a high-pressure gear pump (Z-Drive 2000 from Zenith, Inc. of Sanford, North Carolina) to a Niro PSD-1 Spray-Dryer with a liquid feed process vessel and a pressure nozzle of the type shown in FIG. 3 (Model SK 71-16 from Spraying Systems, Inc.). The droplet size produced by this pressure nozzle was determined using a Malvern Particle Size Analyzer with the following results: the mean droplet diameter was 125 μm, D_{10} was 64 μm, D_{50} was 110 μm and D_{90} was 206 μm, resulting in a Span of 1.3.

The dryer was also equipped with a 9-inch drying chamber extension to increase the length and volume of the dryer's drying chamber. The added length increased the particle residence time within the dryer. The dryer was also

equipped with gas-dispersing means for introduction of the drying gas to the drying chamber. The gas-dispersing means consisted of a plate coextensive with the interior of the drying chamber (about 0.8 m diameter) and bearing a multiplicity of 1.7 mm perforations occupying about 1% of the surface area of the plate. The perforations were uniformly distributed across the plate, except that the density of perforations at the center 0.2 m of the diffuser plate was about 25% of the density of perforations in the outer part of the diffuser plate. The use of the diffuser plate resulted in organized plug flow of drying gas through the drying chamber and dramatically decreased product recirculation within the spray drier. The pressure nozzle was arranged flush with the gas disperser plate during operation. The spray solution was pumped to the spray drier at 180 g/min at a pressure of 19 atm (262 psig). Nitrogen drying gas was delivered to the gas disperser plate at an inlet temperature of 103°C. The evaporated solvent and drying gas exited the dryer at a temperature of 51±4°C. The dispersion formed by this process was collected in a cyclone and then dried in a solvent tray dryer by spreading the spray-dried particles onto polyethylene-lined trays to a depth of not more than 1 cm and then drying them at 40°C for 25 hours. After drying, the solid dispersion contained 25 wt% Drug 1.

Control 1 (C1) consisted of a solid amorphous dispersion of Drug 1 with HPMCAS-MF, but prepared by spray-drying in the same Niro PSD-1 dryer equipped with a Niro two-fluid external mix spray nozzle of the type shown in FIG. 2. The spray-drying conditions and feed makeup for Example 1 and Control 1 are summarized in Table 1.

Table 1

Ex. No.	Drug Mass (g)	Polymer Mass (g)	Solvent Mass (g)	Nozzle Type	Nozzle Pressure (psi/atm)	Feed Rate (g/min)	T_{in} (°C)	T_{out} (°C)
1	138	416	991	SK 79-16	262/19	180	103	51
C1	24	72	855	Niro 2-fluid	42/4	190	135	50

Samples of Example 1 were analyzed to determine the degree of crystallinity of the dispersion. First, powder X-ray diffraction (PXRD) analysis was performed on Example 1 using an AXS D8 Advance PXRD measuring device (Bruker, Inc. of Madison, Wisconsin). This analysis showed no crystalline peaks in the diffractogram, indicating that the drug in the dispersion was almost completely amorphous.

The degree of concentration enhancement of the dispersion made by the process of Example 1 was demonstrated in a dissolution test. For this test, samples containing 7.2 mg of the Example 1 dispersion were added to microcentrifuge tubes, in duplicate. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL PBS at pH 6.5 and having an osmotic pressure of 290 mOsm/kg was added. The samples were mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solutions were then sampled and diluted 1:6 by volume with methanol and then analyzed by high-performance liquid chromatography (HPLC) at a UV absorbance of 256 nm using a Waters Symmetry C8 column and a mobile phase consisting of 15% (0.2% H_3PO_4)/85% methanol. The contents of the tubes were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Collections of the samples were made at 4, 10, 20, 40, 90, and 1200 minutes and the AUC was calculated for each elapsed time period. Control 1 and crystalline Drug 1 alone were tested using the same procedure. The results are shown in Table 2.

Table 2

Sample	Time (min)	Drug 1 Concentration (μg/mL)	AUC (min•μg/mL)
Example 1	0	0	0
	4	259	500
	10	671	3,300
	20	704	10,200
	40	717	24,400
	90	666	59,000
	1200	161	518,000
Control C1	0	0	0
	4	223	400
	10	513	2,600
	20	657	8,500
	40	675	21,800
	90	711	56,500
	1200	387	665,900
Crystalline Drug 1	0	0	0
	4	<1	<2
	10	<1	<8
	20	<1	<18
	40	<1	<38
	90	<1	<88
	1200	<1	<1,200

The concentrations of drug obtained in these samples were used to determine the values of the maximum concentration of drug in the first ninety minutes (C_{max90}) and the area under the curve of drug concentration versus time in the first ninety minutes (AUC_{90}). The results are shown in Table 3. These data show that the dispersion of Example 1 provided a C_{max90} that was greater than 717-fold that of the crystalline control, while the AUC_{90} was greater than 670-fold that of the crystalline control. The data also show that the degree of concentration enhancement of the dispersion of Example 1, made using the pressure nozzle, was essentially equivalent to that of the dispersion of Control 1, made using a two-fluid nozzle.

Table 3

Sample	C_{max90} (μg/mL)	AUC_{90} (min•μg/mL)
Example 1	717	59,000
Control C1	711	56,500
Crystalline Drug 1	<1	<88

The particle size distribution of the dispersion of Example 1 was determined by light scattering analysis of each dry solid dispersion using an LA-910 Particle Size Analyzer (Horiba Co. of Irvine, California), as was the dispersion of Control C1. FIG. 4 is a plot of volume frequency (%) versus particle diameter (μm) for Example 1 and Control C1. From these data, the mean particle diameter (the peak of the curve) and the percent fines (area under the curve less than about 10 μm in diameter divided by the total area under the curve) were calculated and are summarized in Table 4. These data show that the mean diameter of the dispersion particles formed by a pressure nozzle (Example 1) were more than three times larger than that of the dispersion particles formed by a two-fluid nozzle (Control C1). In addition, the number of fines in the dispersion of Example 1 was reduced by more than 90% relative to those for Control C1.

Table 4

Sample	Mean Particle Diameter (μm)	Particles Having a Diameter of Less than 10 μm (%)
Example 1	53	2.9
Control C1	15	42

The bulk and tapped specific volume of the dispersion of Example 1 was determined using the following procedure. A sample of the dispersion of Example 1 was poured into a 100-mL graduated cylinder, the tare weight of which had been measured, and the volume and weight of the sample recorded. The volume divided by the weight yielded the bulk specific volume of 4.8 mL/g. Next, the cylinder containing the dispersion was tapped 1000 times using a VanKel tap density instrument, model 50-1200. The tapped volume divided by the same weight of dispersion yielded a tapped specific volume of 3.1 mL/g. Similar tests were performed with the dispersion of Control C1. The results, reported in Table 5, indicate that the dispersion made with the pressure nozzle (Example 1) had a lower specific volume (both bulk and tapped) than the dispersion made using a two-fluid nozzle (Control C1). The lower specific volume results in improved flow characteristics for the dispersion.

Table 5

Sample	Bulk Specific Volume (mL/g)	Tapped Specific Volume (mL/g)
Example 1	4.8	3.1
Control C1	5.7	3.3

Examples 2-3

Spray-dried dispersions comprising 25 wt% Drug 1 and HPMCAS were prepared as in Example 1 except that alternative pressure nozzles from Spray Systems, Inc. and spray-drying conditions were used, as indicated in Table 6.

Table 6

Ex. No.	Drug Mass (g)	Polymer Mass (g)	Solvent Mass (g)	Nozzle Type	Nozzle Pressure (psi/atm)	Feed Rate (g/min)	T_{in} (°C)	T_{out} (°C)
2	150	450	5400	SK 76-16	190/14	204	105	45
3	150	450	5400	SK 71-16	97/7.6	205	107	44

The properties of the dispersions of Examples 2 and 3 were determined as in Example 1. The results, together with those for Example 1 and Control C1, are summarized in Table 7 and graphically displayed in FIG. 4 and show that the dispersions made using pressure nozzles (Examples 1 to 3) have much larger particle diameters and virtually no fines as compared to the dispersion made using a two-fluid nozzle (Control C1), while providing essentially equivalent dissolution performance. In addition, the dispersions of Examples 1-3 had lower specific volumes than that of Control C1, resulting in improved flow characteristics.

Table 7

Example No.	C_{max90} (µg/mL)	AUC_{90} (min•µg/mL)	Mean Particle Diameter (µm)	Particles With Diameters <10 µm (%)	Specific Volume (mL/g)	
					Bulk	Tapped
1	717	59,000	53	2.9	4.8	3.1
2	470	60,200	63	3.5	5.1	3.1
3	730	57,300	89	1.5	5.1	3.2
C1	711	56,500	15	42	5.7	3.3

Example 4

A solid amorphous dispersion comprising the poorly water-soluble drug 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl -3 -((3R, 4S) -dihydroxypyrroldin-1-yl-) - (2R) - hydroxy-3-oxypropyl] amide (Drug 2) with HPMCAS was made by an SK 80-16 pressure nozzle (Spraying Systems, Inc.) as in Example 1 but with a solvent mixture comprising 5 wt% water in acetone with the conditions given in Table 8. The dispersion of Example 4 contained 50 wt% Drug 2.

Control C2 (C2) consisted of a solid dispersion of Drug 2 with HPMCAS, spray-dried using a Niro two-fluid external mix spray nozzle of the type shown in FIG. 2, and containing 50 wt% drug. The spray conditions and feed makeup were as noted in Table 8.

Table 8

Ex. No.	Drug Mass (g)	Polymer Mass (g)	Solvent Mass (g)	Nozzle Type	Nozzle Pressure (psi/atm)	Feed Rate (g/min)	T_{in} (°C)	T_{out} (°C)
4	200	200	2263	SK 80-16	145/11	165	110	44
C2	250	250	2831	Niro 2-fluid	39/3.7	180	113	43

The solubility and physical properties of the dispersions of Example 4 and Control C2 were determined as in Example 1 with the following exceptions. For measurement of concentration enhancement, sufficient quantities of the dispersion were added to the microcentrifuge tubes such that the concentration if all of the drug had dissolved would be 2000 µg/mL. Samples were analyzed by HPLC, with absorbance at 297 nm (Hewlett Packard 1100 HPLC, Zorbax SB C18 column, 35% acetonitrile/65% H_2O). The same properties of a control of crystalline Drug 2 (CD2) alone were also determined.

The results of these tests are summarized in Table 9 and graphically displayed in FIG. 5 and show that the dispersion made using the pressure nozzle (Example 4) had a larger mean particle diameter, and fewer fines than the dispersion made using a two-fluid nozzle (Control C2). FIG. 5 is a plot of volume frequency versus particle diameter for the dispersions of Example 4 and Control C2. The dissolution performance of the dispersion of Example 4 was slightly better than that of the C2 dispersion made using a two-fluid nozzle. The dispersion of Example 4 provided a C_{max90} that was 4.9-fold that of the crystalline control, and an AUC_{90} that was 4.1-fold that of the crystalline control. The Example 4 dispersion also had a lower specific volume than that of the crystalline control.

Table 9

Sample	C_{max90} (µg/mL)	AUC_{90} (min•µg/mL)	Mean Particle Diameter (µm)	Particles With Diameters <10 µm (%)	Specific Volume (mL/g)	
					Bulk	Tapped
Ex. 4	730	52,200	70	2.4	4.2	3.0
C2	580	49,600	20	17	5.0	3.2
CD2	149	12,800	--	--	--	--

Example 5

A solid amorphous dispersion comprising 50 wt% Drug 2 with HPMCAS was made using a Model WG-256 pressure nozzle (Delavan LTV) as in Example 4 with the conditions given in Table 10, except that the spray dryer was a standard Niro PSD-1 spray drier that did not have a chamber extension or a gas disperser plate.

Control C3 (C3) consisted of multiparticulates of a solid dispersion of 50 wt% Drug 2 with HPMCAS, spray-dried with a Niro two-fluid external mix spray nozzle in the same dryer as for Example 5 with the spray conditions and feed makeup noted in Table 10.

Table 10

Ex. No.	Drug Mass (g)	Polymer Mass (g)	Solvent Mass (g)	Nozzle Type	Nozzle Pressure (psi/atm)	Feed Rate (g/min)	T_{in} (°C)	T_{out} (°C)
5	75	75	850	WG-256	100/7.8	195	108	28
C3	250	250	2231	Niro 2-fluid	30/3	180	113	43

The solubility and physical properties of the dispersions of Example 5 and Control C3 were determined as in Example 4. The results of these tests are summarized in Table 11 and graphically displayed in FIG. 6 and show that the

dispersion made using the pressure nozzle (Example 5) had a much larger mean particle diameter and far fewer fines than the dispersion made using a two-fluid nozzle (Control C3). FIG. 6 is a plot of volume frequency versus particle diameter for the dispersions of Example 5 and Control C3. The dissolution performance of the dispersion of Example 5 was substantially the same as the dispersion made using a two-fluid nozzle. The dispersion of Example 5 provided a C_{max90} that was 4.2-fold that of the crystalline control (CD2), and an AUC_{90} that was 4.0-fold that of the crystalline control.

Table 11

Sample	C_{max90} (µg/mL)	AUC_{90} (min•µg/mL)	Mean Particle Diameter (µm)	Particles With Diameters <10 µm (%)
Ex.5	620	51,600	152	1.2
C3	610	52,000	38	18
CD2	149	12,800	-	-

Example 6

A solid amorphous dispersion comprising 25 wt% Drug 1 with HPMCAS was made using a Model WG-256 pressure nozzle as in Example 1 with the conditions given in Table 12, except that the spray dryer was a standard Niro PSD-1 spray drier that did not have a chamber extension or gas dispenser plate.

Control C4 (C4) consisted of a solid dispersion of 25 wt% Drug 1 with HPMCAS, spray-dried using a Niro two-fluid external mix spray nozzle using the same dryer as for Example 6. The spray conditions and feed makeup are noted in Table 12.

Table 12

Ex. No.	Drug Mass (g)	Polymer Mass (g)	Solvent Mass (g)	Nozzle Type	Nozzle Pressure (psi/atm)	Feed Rate (g/min)	T_{in} (°C)	T_{out} (°C)
6	10	30	360	WG-256	58/4.9	115	135	50
C4	8	24	288	Niro 2-Fluid	35/3.4	150	135	50

The solubility and physical properties of the dispersions of Example 6 and Control C4 were determined as in Example 1. The results of these tests are summarized in Table 13 and graphically displayed in FIG. 7 and show that the dispersion made using the pressure nozzle (Example 6) had a larger mean particle diameter and a dramatically reduced proportion of fines than the dispersion made using a two-fluid nozzle (Control C4). FIG. 7 is a plot of volume frequency versus particle diameter for Example 6 and Control C4. The dissolution performance of the dispersion of Example 6 was about the same as the dispersion made using a two-fluid nozzle, but provided a C_{max90} that was greater than 709-fold that of the crystalline control Drug 1 alone (CD1), and an AUC_{90} that was greater than 611-fold that of the crystalline control.

Table 13

Sample	C_{max90} (μg/mL)	AUC_{90} (min•μg/mL)	Mean Particle Diameter (μm)	Particles With Diameters <10 μm (%)
Ex.6	709	53,800	107	1.5
C4	625	55,400	15	34
CD1	<1	<88	-	-

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.

CLAIMS

1. A process for producing a pharmaceutical composition comprising the steps:

(a) forming a feed solution comprising a drug, a concentration-enhancing polymer and a solvent;

(b) directing said feed solution to a spray-drying apparatus comprising a drying chamber, atomizing means for atomizing said feed solution into droplets in said drying chamber, a source of heated drying gas for drying said droplets and dried product collection means;

(c) atomizing said feed solution into droplets in said drying chamber by said atomizing means, said droplets having an average diameter of at least 50 μm and a D_{10} of at least 10 μm;

(d) contacting said droplets with said heated drying gas to form particulates of a solid amorphous dispersion of said drug and said concentration-enhancing polymer; and

(e) collecting said particulates

wherein said concentration-enhancing polymer is present in said solution in a sufficient amount so that said solid amorphous dispersion provides concentration enhancement of said drug in a use environment relative to a control composition consisting essentially of an equivalent amount of said drug alone.

2. The process of claim 1 wherein said droplets have a Span of less than 3.

3. The process of claim 1 wherein said drug in said dispersion is substantially amorphous and said dispersion is substantially homogeneous.

4. The process of claim 1 wherein said composition provides

(a) a maximum concentration of said drug in said use environment that is at least 1.25-fold the concentration of said drug provided by said control composition; or

(b) an area under a concentration versus time curve for any 90-minute period in said use environment from the time of introduction to about 270 minutes following introduction to said use environment that is at least about 1.25-fold that of said control composition.

5. The process of claim 1 wherein said composition provides a relative bioavailability of said drug that is at least 1.25-fold that of said control composition.

6. The process of claim 1 wherein said concentration-enhancing polymer is selected from the group consisting of ionizable cellulosic polymers, non-ionizable cellulosic polymers, ionizable non-cellulosic polymers, non-ionizable non-cellulosic polymers, neutralized acidic polymers and blends thereof.

7. The process of claim 6 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxymethyl ethyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl alcohols that have at least a portion of their repeat units in hydrolyzed form, polyvinyl pyrrolidone, poloxamers and blends thereof.

8. The process of claim 1 wherein said drug is selected from the group consisting of antihypertensives, antianxiety 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, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial agents, antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, antiviral agents, glycogen phosphorylase inhibitors, and cholesterol ester transfer protein inhibitors.

9. The process of claim 1 wherein said drug is selected from the group consisting of [R-(R*S*)]-5-chloro-N-[2-hydroxy-3-{methoxymethylamino}-3-oxo-1-(phenylmethyl)propyl-1H-indole-2-carboxamide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl-)-3-oxypropyl]amide, [2R,4S]-4-[acetyl-(3,5-bis-trifluoromethyl-benzyl)-amino]-

2-ethyl-6-trifuloromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester, [2R,4S]-4-[3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester and [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

10. The process of claim 1 wherein said atomizing means is a pressure nozzle that atomizes said feed solution at a pressure of from about 2 to about 200 atm.

11. The process of claim 1 wherein the temperature of said drying gas at an inlet to said apparatus is from about 60° to about 300°C.

12. The process of claim 11 wherein the temperature of said drying gas at an outlet from said apparatus is from about 0° to about 100°C.

13. The process of claim 1 wherein said particulates have an average diameter of at least 40 μm and less than 10 vol% of said particulates have a diameter of less than about 8 μm.

14. The process of claim 1 wherein at least 80 vol% of said particulates have diameters greater than 10 μm.

15. The product of the process of any of claims 1-14.

FIG. 1

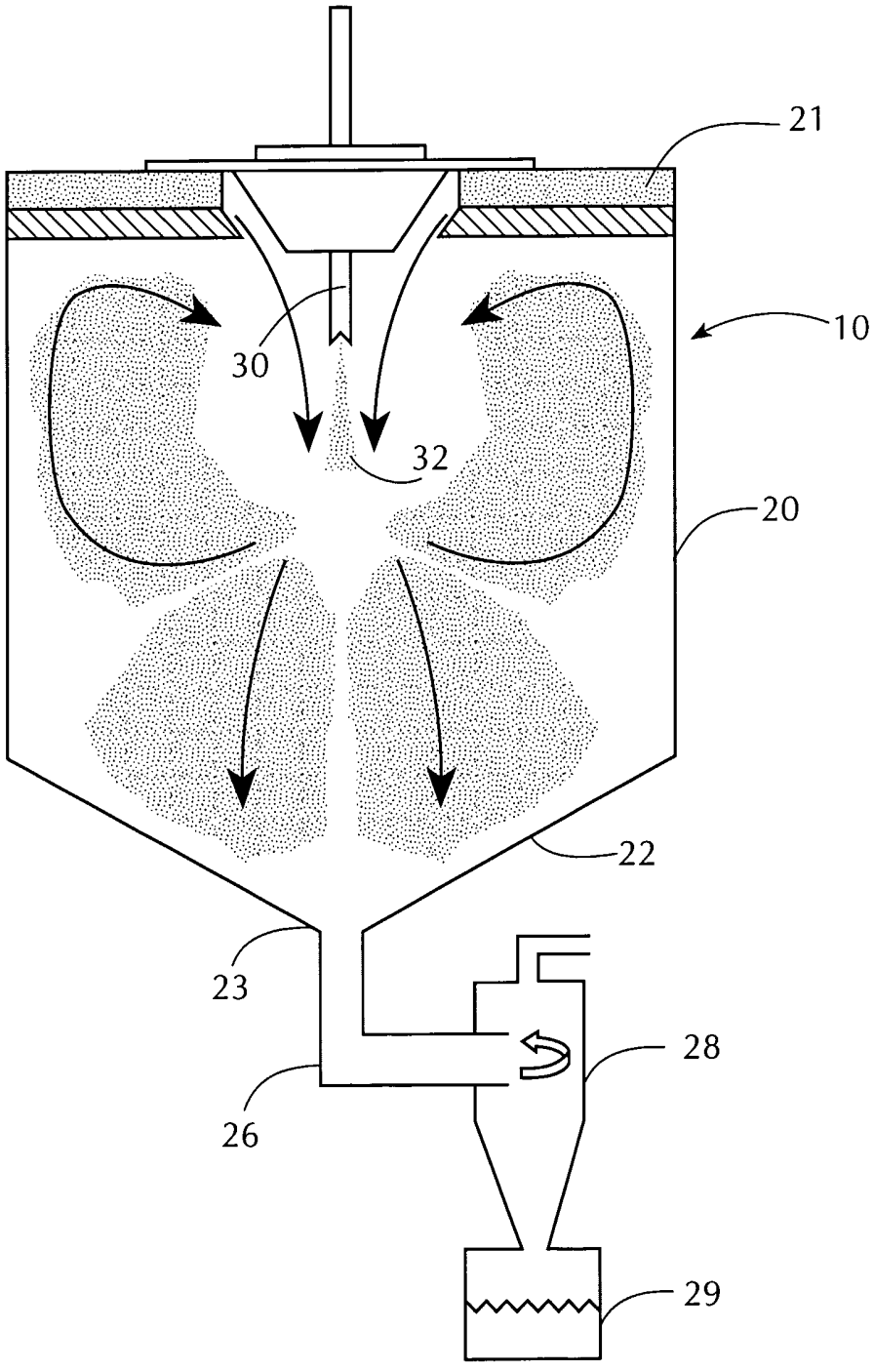


FIG. 2

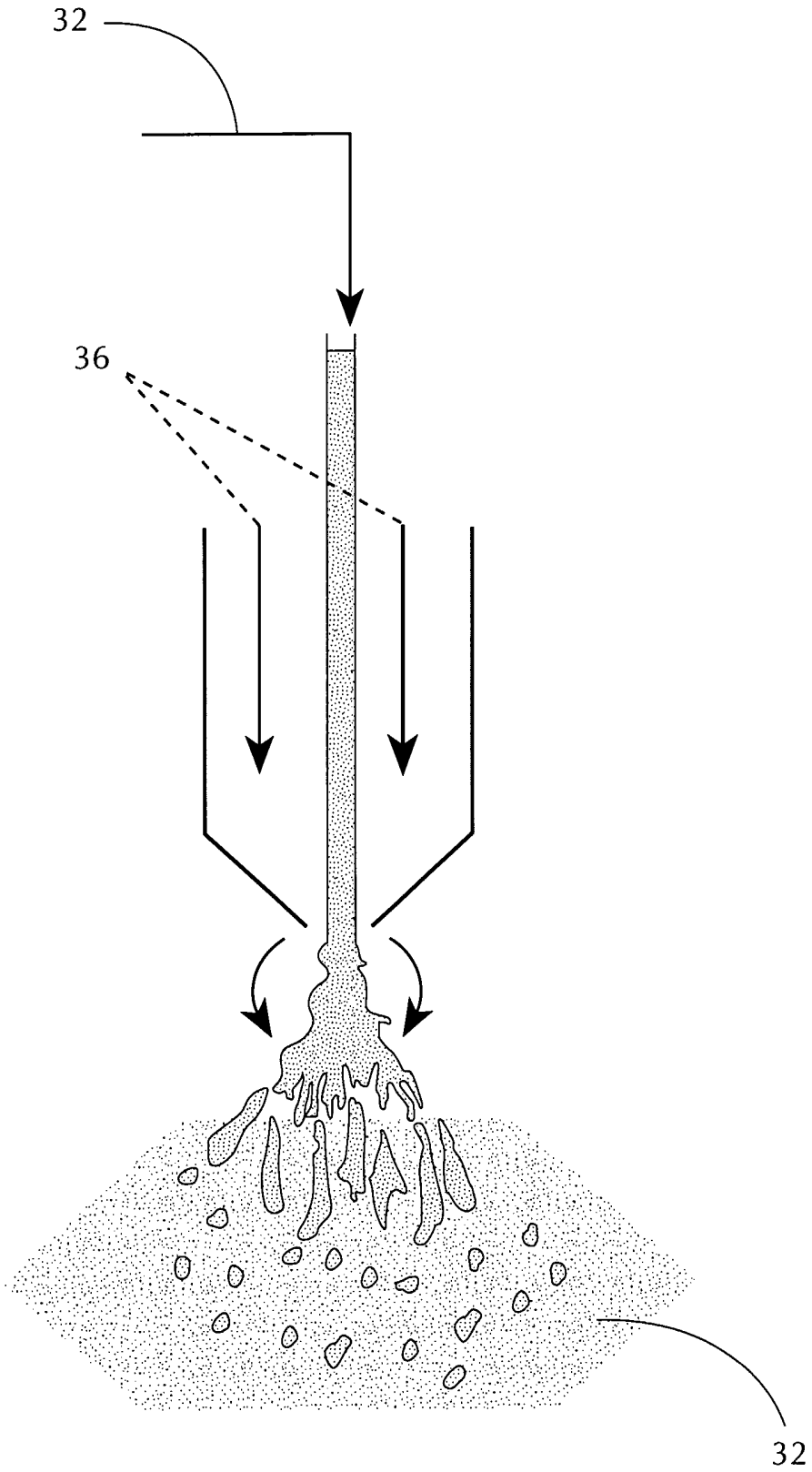


FIG. 3

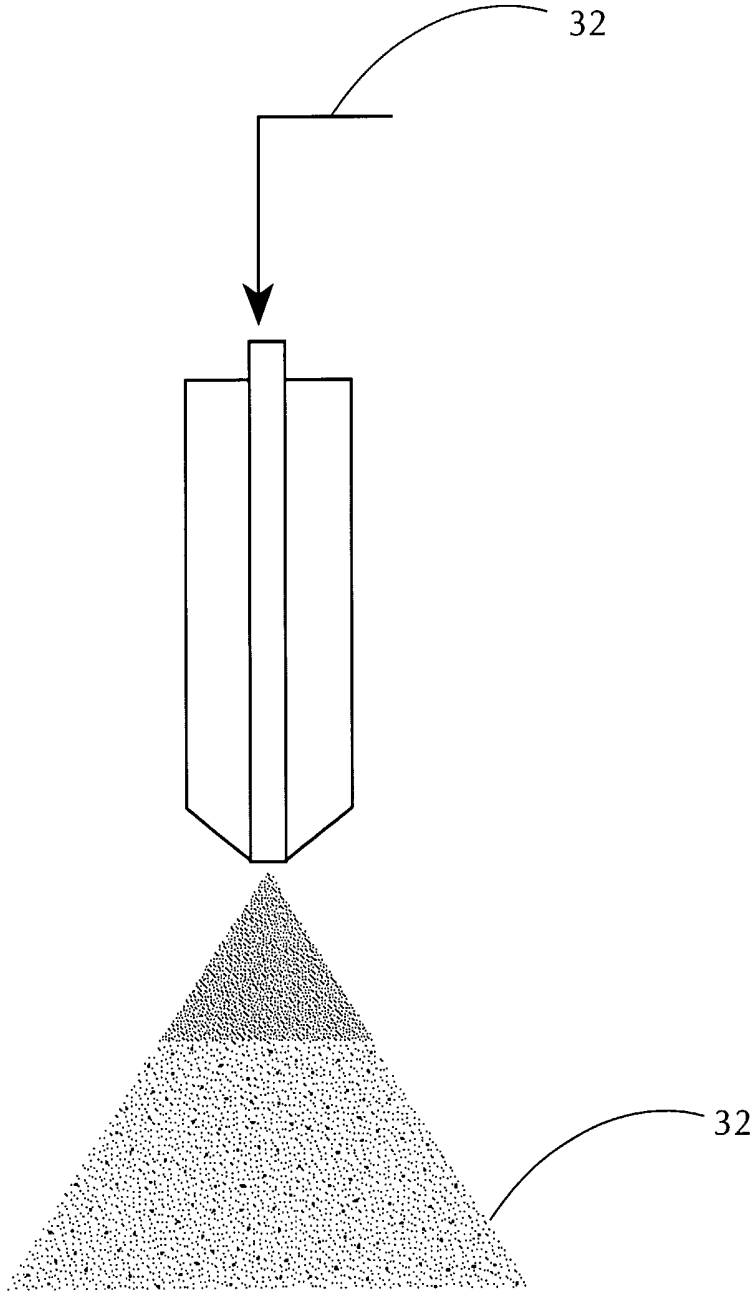


FIG. 4

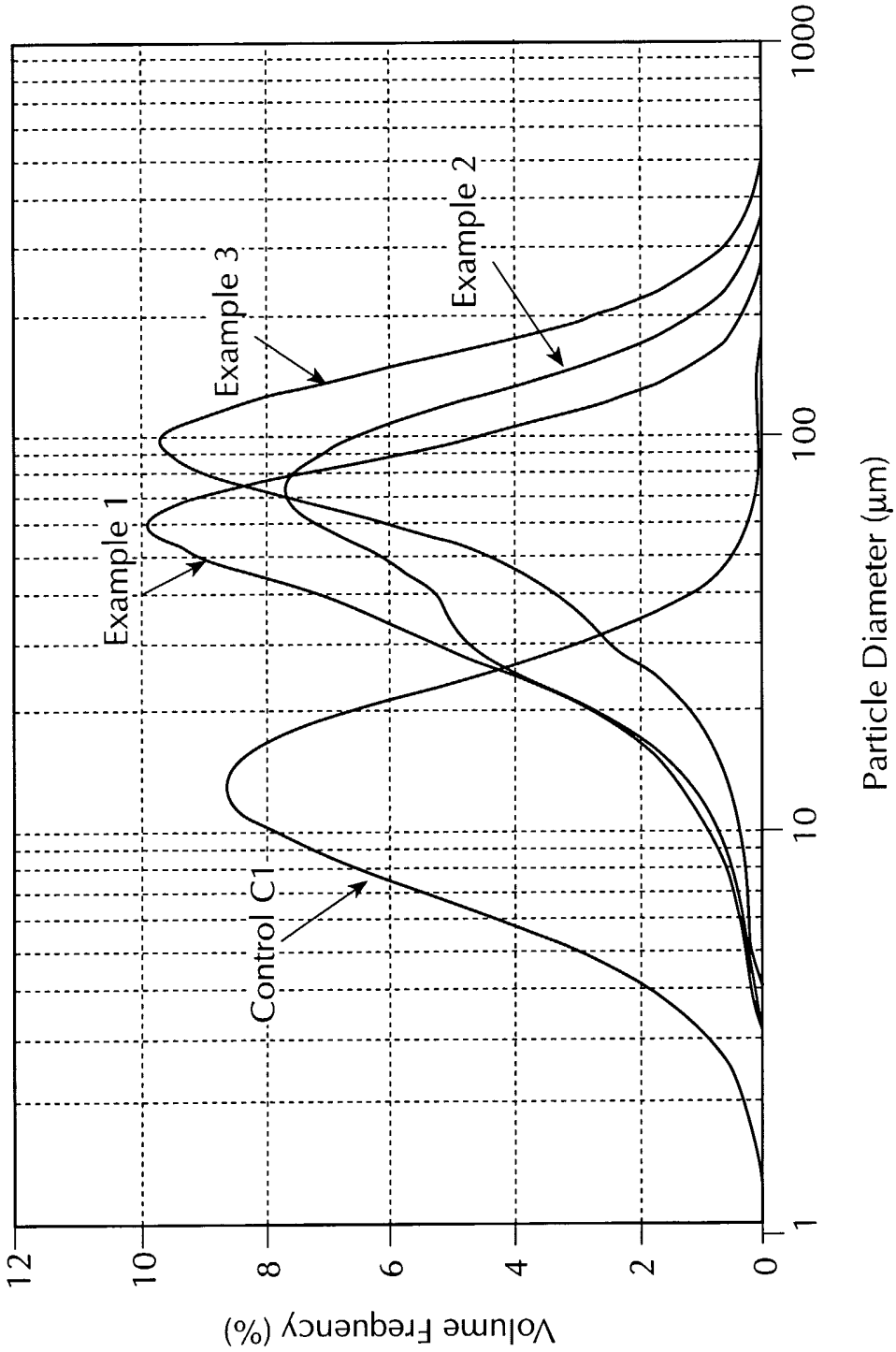

Volume Frequency (%)
0
2
4
6
8
10
12
1
10
100
1000
Particle Diameter (µm)
Example 1
Example 2
Example 3
Control C1

FIG. 5

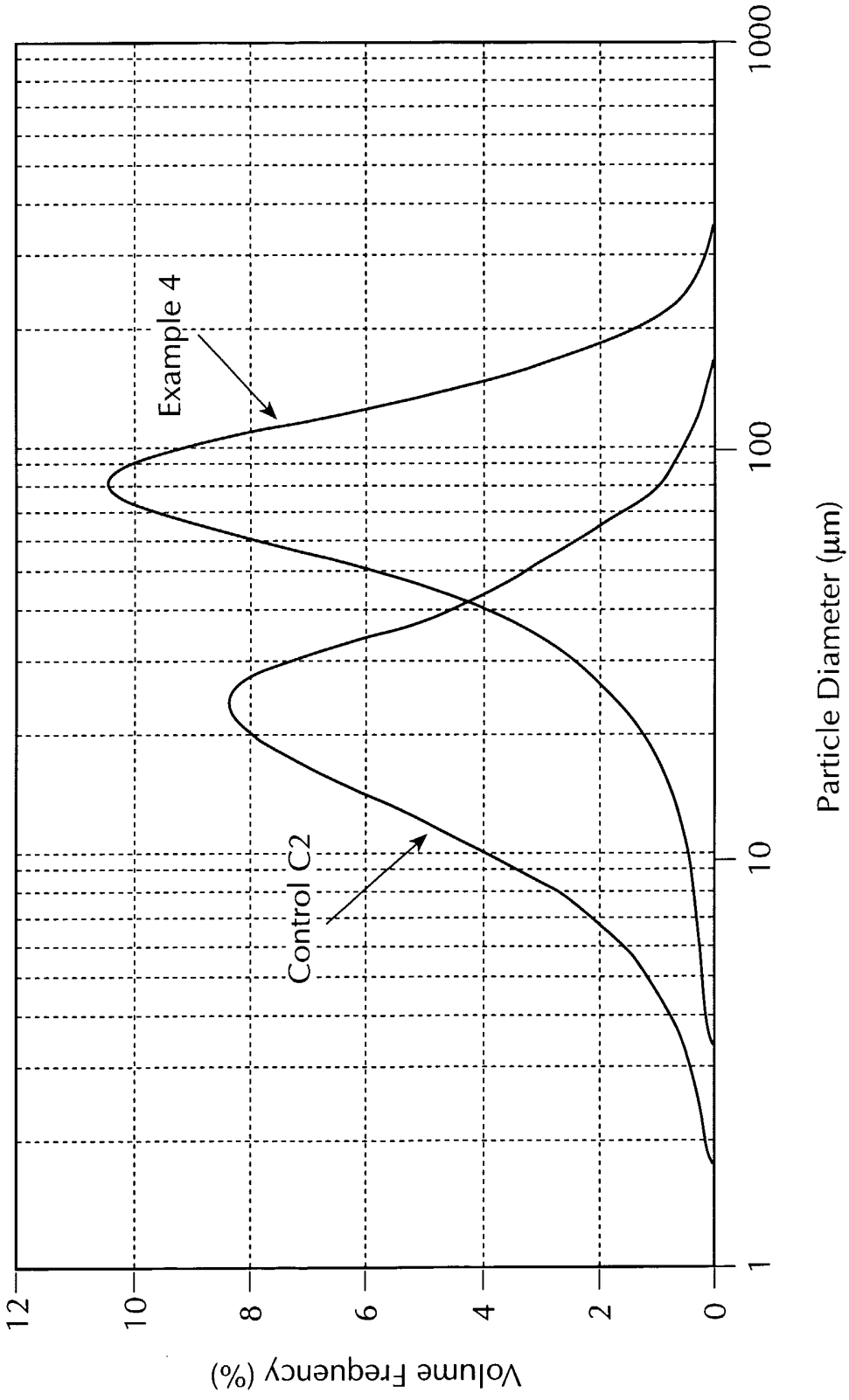

Example 4
Control C2
Volume Frequency (%)
0
2
4
6
8
10
12
1
10
100
1000
Particle Diameter (µm)

FIG. 6

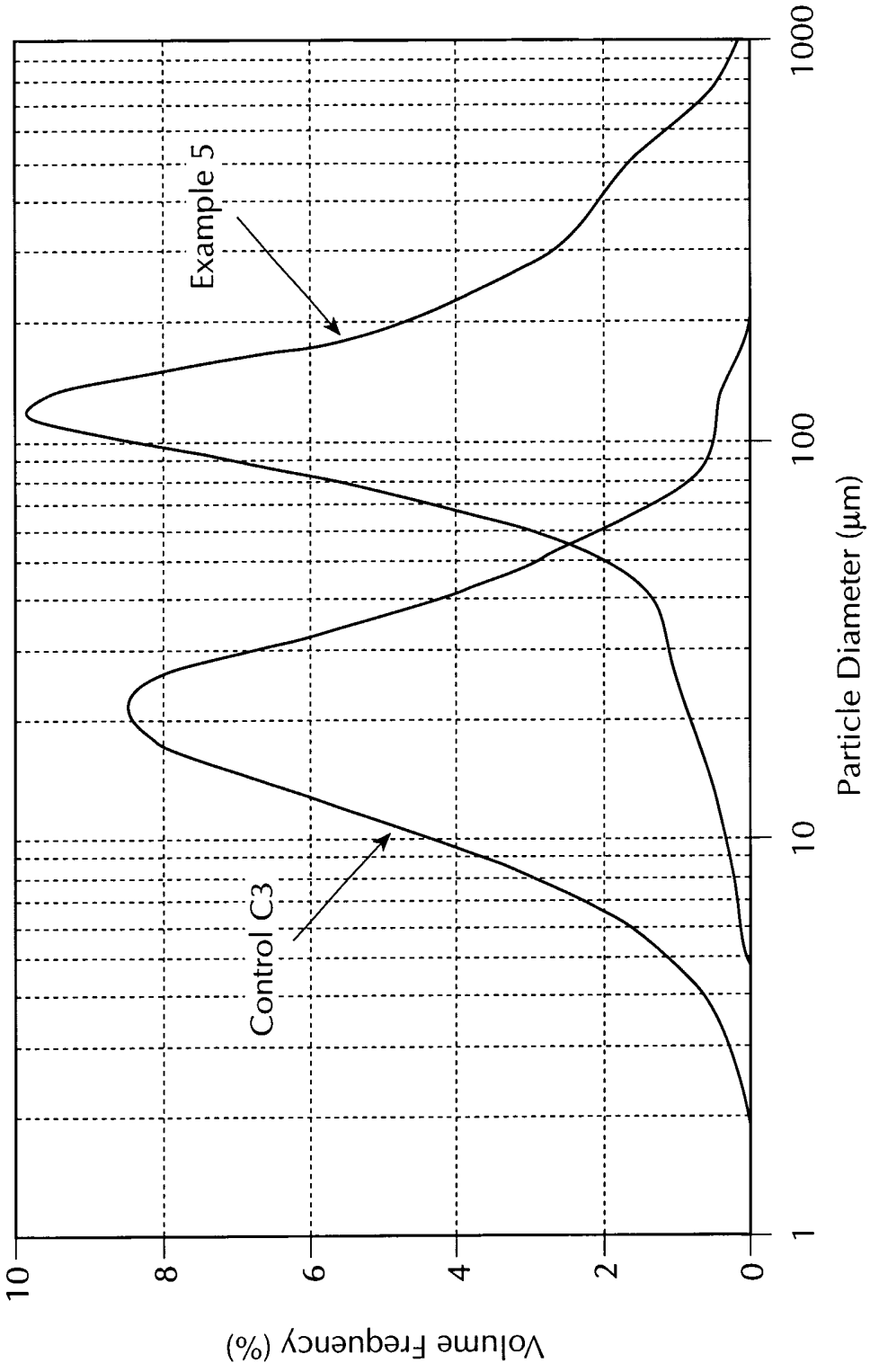
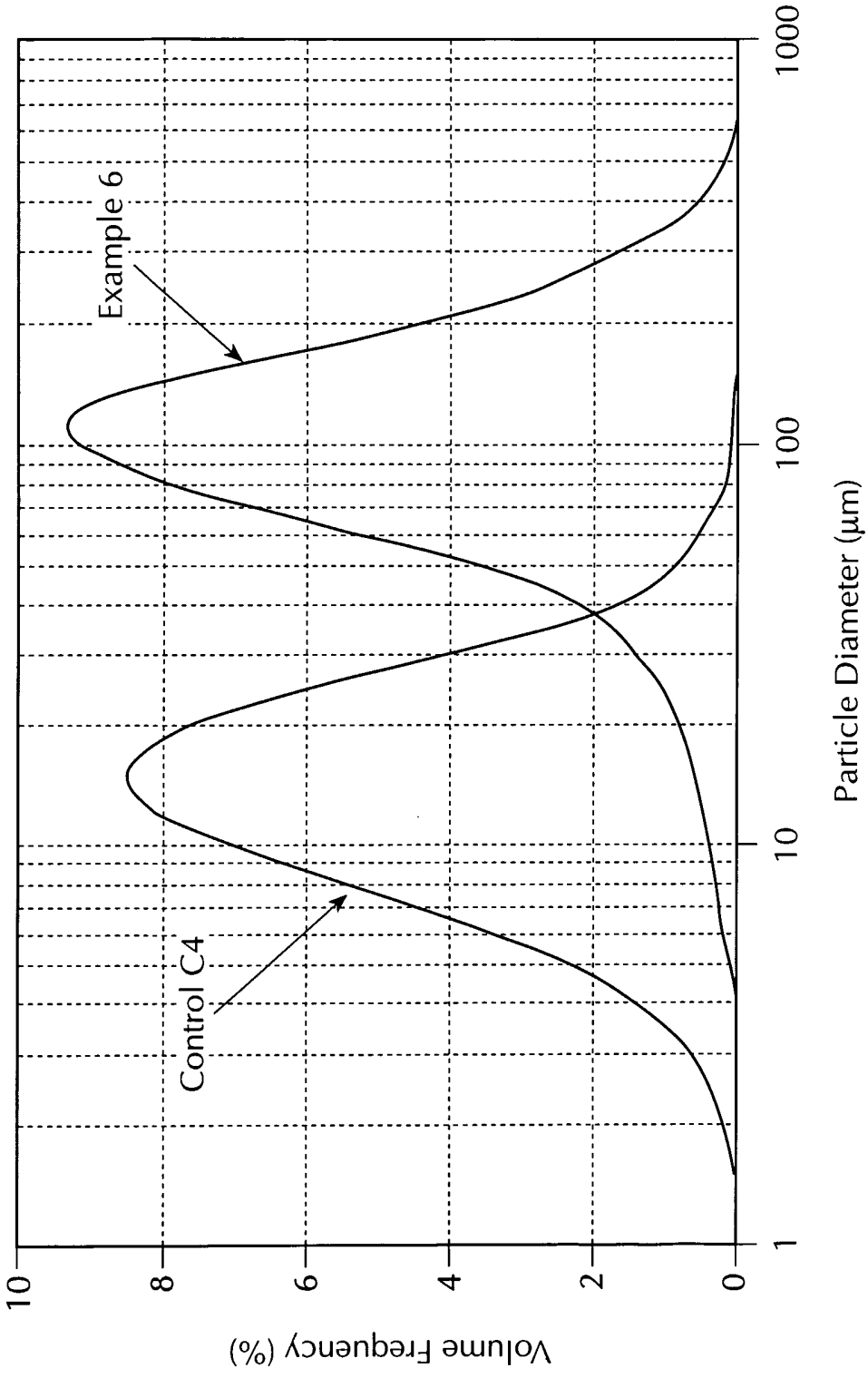

Volume Frequency (%)
0
2
4
6
8
10
1
10
100
1000
Particle Diameter (µm)
Example 5
Control C3

FIG. 7


Example 6
Control C4
Volume Frequency (%)
0
2
4
6
8
10
1
10
100
1000
Particle Diameter (µm)