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(54) Title: NANOPARTICULATE BENIDIPINE COMPOSITIONS

(57) Abstract: The present invention relates to nanoparticulate benidipine compositions having improved bioavailability. The compositions comprise benidipine particles having an effective average particle size of less than about 2000 nm and may be useful in the prevention and treatment of hypertension, renal parenchymal hypertension and angina pectoris.

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NANOPARTICULATE BENIDIPINE COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/687,145, filed on June 3, 2005, which is incorporated herein in its entirety.

FIELD

[0002] The invention relates generally to calcium channel blockers useful for treatment of hypertension, renal parenchymal hypertension, angina pectoris and related conditions, symptoms, and diseases. More specifically, the invention relates to nanoparticulate benidipine compositions having an effective average particle size of less than about 2000 nm. The invention also relates to methods of formulating and manufacturing nanoparticulate benidipine compositions and to methods of treatment using the compounds.

BACKGROUND

A. Background Regarding Benidipine

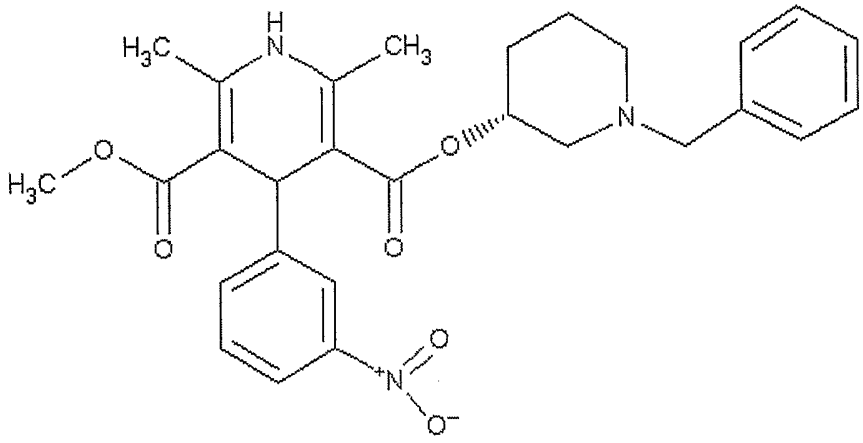
[0003] Hypertension, or high blood pressure, is known as "the silent killer" for two reasons. First, there are no specific symptoms. Estimates suggest that about one in three Americans has high blood pressure but is unaware. Second high blood pressure can lead to serious medical conditions that kill. Such medical conditions include heart arrhythmias, heart attack, stroke and organ failure.

[0004] Unfortunately, the precise cause of hypertension in more than 90 percent of cases is unknown. Factors often associated with this type of "primary" or "essential" hypertension have been shown to include race, heredity, sex, age, obesity, drug use, physical activity and diet. Occasionally, (*e.g.*, in the remaining 10 percent of cases), hypertension is caused by some other physical problem such as atherosclerosis or cancer. This is termed "secondary" hypertension. Blood pressure may be restored to non-hypertensive levels if the primary problem is treated.

[0005] There are numerous classes of medication used to treat high blood pressure including centrally acting drugs, diuretics, angtiotensin converting enzyme ("ACE") inhibitors, beta-blockers and calcium channel blockers ("CCBs"). CCBs work by blocking calcium channels and inhibiting the entry of calcium into the blood vessels and the heart tissue. The lowered calcium levels in the blood vessels and heart cause the blood vessels to dilate and the heart to

beat more slowly, thereby lowering blood pressure. Some commercially available calcium channel blockers include Verapamil, Diltiazem, Nifedipine, Nicardipine, Bepridil, and Mibefradil.

[0006] Another calcium channel blocker, benidipine, chemically known as 3-(1-benzyl-3-piperidinyloxycarbonyl)-2,6-dimethyl-5-- methoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine or its hydrochloride salt being (±)-(R*)-3-[(R*)-1-benzyl-3-piperidinyl]methyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride, has the empirical formula of $C_{28}H_{31}N_3O_6 \bullet HCl$ and molecular weight of 542.03. The structural formula of benidipine is:



[0007] Benidipine is a calcium channel blockers useful for treatment of hypertension, renal parenchymal hypertension and angina pectoris. Benidipine is commercially available under the tradename Coniel® Tablets as the hydrochloride salt of benidipine in strengths of 2 mg, 4 mg and 8 mg, and generally prescribed in regimes of once or twice daily.

[0008] Benidipine hydrochloride is an odorless yellow crystalline powder. It is very soluble in formic acid, freely soluble in dimethylformamide, soluble in methanol or ethanol, slightly soluble in acetic anhydride and relatively insoluble in water.

[0009] Benidipine has been disclosed, for example, in United States Patent No. 4,501,748 for "1,4-dihydropyridine derivatives" and United States Patent Application No. 2003/0073670 for "Stabilized pharmaceutical composition containing a calcium channel blocker".

[0010] Benidipine has high therapeutic value for the treatment of patients suffering from hypertension, renal parenchymal hypertension and angina pectoris. However, given the need to take benidipine daily after meals, such as breakfast, strict patient compliance is a critical factor in the efficacy of benidipine in the treatment of hypertension, renal parenchymal hypertension

and angina pectoris. Moreover, it is desirable for increased dissolution rate for faster onset of the benidipine. Thus, there is a need in the art for benidipine compositions which overcome these and other problems associated with their use in the treatment of hypertension, renal parenchymal hypertension and angina pectoris.

[0011] The present invention fulfills such a need by providing nanoparticulate benidipine compositions which overcome the poor bioavailability of benidipine and eliminate the requirement to take the product with food.

B. Background Regarding Nanoparticulate Compositions

[0012] Nanoparticulate active agent compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), comprise particles of a poorly soluble therapeutic or diagnostic agent having adsorbed onto or associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent also describes methods of making such nanoparticulate active agent compositions but does not describe compositions comprising calcium channel blockers such as benidipine in nanoparticulate form. Methods of making nanoparticulate active agent compositions are described, for example, in U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0013] Nanoparticulate active agent compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. Nos. 5,399,363 and 5,494,683, both for "Surface Modified Anticancer

Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium

Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract;" U.S. Pat. No. 6,582,285 for "Apparatus for Sanitary Wet Milling;" and U.S. Pat. No. 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,656,504 for "Nanoparticulate Compositions Comprising Amorphous Cyclosporine;" 6,742,734 for "System and Method for Milling Materials;" 6,745,962 for "Small Scale Mill and Method Thereof;" 6,811,767 for "Liquid droplet aerosols of nanoparticulate drugs;" 6,908,626 for "Compositions having a combination of immediate

release and controlled release characteristics;" 6,969,529 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" 6,976,647 for "System and Method for Milling Materials;" 6,991,191 for "Method of Using a Small Scale Mill;" all of which are specifically incorporated by reference. In addition, U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticulate Compositions;" U.S. Patent Publication No. 20050276974 for "Nanoparticulate Fibrate Formulations;" U.S. Patent Publication No. 20050238725 for "Nanoparticulate compositions having a peptide as a surface stabilizer;" U.S. Patent Publication No. 20050233001 for "Nanoparticulate megestrol formulations;" U.S. Patent Publication No. 20050147664 for "Compositions comprising antibodies and methods of using the same for targeting nanoparticulate active agent delivery;" U.S. Patent Publication No. 20050063913 for "Novel metaxalone compositions;" U.S. Patent Publication No. 20050042177 for "Novel compositions of sildenafil free base;" U.S. Patent Publication No. 20050031691 for "Gel stabilized nanoparticulate active agent compositions;" U.S. Patent Publication No. 20050019412 for " Novel glipizide compositions;" U.S. Patent Publication No. 20050004049 for "Novel griseofulvin compositions;" U.S. Patent Publication No. 20040258758 for "Nanoparticulate topiramate formulations;" U.S. Patent Publication No. 20040258757 for " Liquid dosage compositions of stable nanoparticulate active agents;" U.S. Patent Publication No. 20040229038 for "Nanoparticulate meloxicam formulations;" U.S. Patent Publication No. 20040208833 for "Novel fluticasone formulations;" U.S. Patent Publication No. 20040195413 for " Compositions and method for milling materials;" U.S. Patent Publication No. 20040156895 for "Solid dosage forms comprising pullulan;" U.S. Patent Publication No. U.S. Patent Publication No. U.S. Patent Publication No. 20040156872 for "Novel nimesulide compositions;" U.S. Patent Publication No. 20040141925 for "Novel triamcinolone compositions;" U.S. Patent Publication No. 20040115134 for "Novel nifedipine compositions;" U.S. Patent Publication No. 20040105889 for "Low viscosity liquid dosage forms;" U.S. Patent Publication No. 20040105778 for "Gamma irradiation of solid nanoparticulate active agents;" U.S. Patent Publication No. 20040101566 for "Novel benzoyl peroxide compositions;" U.S. Patent Publication No. 20040057905 for "Nanoparticulate beclomethasone dipropionate compositions;" U.S. Patent Publication No. 20040033267 for "Nanoparticulate compositions of angiogenesis inhibitors;" U.S. Patent Publication No. 20040033202 for "Nanoparticulate sterol formulations and novel sterol combinations;" U.S. Patent Publication No. 20040018242 for "Nanoparticulate nystatin formulations;" U.S. Patent Publication No. 20040015134 for "Drug delivery systems and methods;" U.S. Patent

Publication No. 20030232796 for "Nanoparticulate polycosanol formulations & novel polycosanol combinations;" U.S. Patent Publication No. 20030215502 for "Fast dissolving dosage forms having reduced friability;" U.S. Patent Publication No. 20030185869 for "Nanoparticulate compositions having lysozyme as a surface stabilizer;" U.S. Patent Publication No. 20030181411 for "Nanoparticulate compositions of mitogen-activated protein (MAP) kinase inhibitors;" U.S. Patent Publication No. 20030137067 for "Compositions having a combination of immediate release and controlled release characteristics;" U.S. Patent Publication No. 20030108616 for "Nanoparticulate compositions comprising copolymers of vinyl pyrrolidone and vinyl acetate as surface stabilizers;" U.S. Patent Publication No. 20030095928 for "Nanoparticulate insulin;" U.S. Patent Publication No. 20030087308 for "Method for high through put screening using a small scale mill or microfluidics;" U.S. Patent Publication No. 20030023203 for "Drug delivery systems & methods;" U.S. Patent Publication No. 20020179758 for "System and method for milling materials; and U.S. Patent Publication No. 20010053664 for "Apparatus for sanitary wet milling," describe nanoparticulate active agent compositions and are specifically incorporated by reference. None of these references describe compositions of nanoparticulate benidipine.

[0014] Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter" all of which are specifically incorporated herein by reference.

[0015] There is a need for compositions of calcium channel blockers, such as benidipine, that have enhanced bioavailability, increased dissolution rate, reduced drug dosage, and reduced adverse side effects. The present invention satisfies these needs.

SUMMARY

[0016] The compositions and methods disclosed herein relate to compositions comprising at least one calcium channel blocker, such as benidipine or a derivative or salt thereof (referred to herein collectively as benidipine), having an effective average particle size of less than about 2000 nm. The compositions may be used to treat diseases or disorders such as, but not limited

to hypertension, renal parenchymal hypertension, angina pectoris and combinations thereof. In general, the compositions comprise particles of a nanoparticulate calcium channel blocker, such as benidipine, and at least one surface stabilizer adsorbed on or associated with the surface of the calcium channel blocker particles.

[0017] Additionally, the compositions may comprise at least one primary and at least one secondary surface stabilizer. Exemplary surface stabilizers may include one or more of an anionic surface stabilizer, a cationic surface stabilizers, a non-ionic surface stabilizers, a zwitterionic surface stabilizers, and an ionic surface stabilizers.

[0018] In some embodiments, the compositions may additionally include one or more pharmaceutically acceptable excipients, carriers, active agents or combinations thereof. In other embodiments, active agents may include agents useful for the treatment of hypertension, renal parenchymal hypertension, angina pectoris and related diseases or disorders. By way of example but not by way of limitation, active agents may include prostaglandins and derivatives thereof, thrombolytic agents, anticoagulants, calcium-entry blocking agents, antianginal agents, cardiac glycosides, vasodilators, antihypertensive agents, blood lipid-lowering agents and combinations thereof.

[0019] Additionally disclosed are methods related to making nanoparticulate benidipine compositions having an effective average particle size of less than about 2000 nm. By way of example, but not by way of limitation, methods may include contacting particles of the benidipine with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate benidipine composition having an effective average particle size of less than about 2000 nm. In some methods, contacting may include, for example, grinding, wet grinding, homogenization, freezing, template emulsion, precipitation, or combinations thereof.

[0020] The nanoparticulate benidipine compositions described herein may be formulated for dosage or administration in a variety of forms. Although any pharmaceutically acceptable dosage form may be utilized, dosage forms contemplated include but are not limited to formulations for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, and topical administration. Dosage forms may include bioadhesives, liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, and capsules, and dosage forms may also include controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled

release formulations. Combinations of these dosage forms are also contemplated. In some embodiments, solid dosage forms may be preferred.

[0021] The nanoparticulate benidipine compositions disclosed herein are also contemplated to exhibit improved pharmacokinetic properties as compared to a non-nanoparticulate composition of the same benidipine.

[0022] In further embodiments, the pharmacokinetic profiles of the nanoparticulate benidipine compositions may be substantially similar when administered to a fed or fasted subject; in other embodiments, the nanoparticulate benidipine compositions may be bioequivalent when administered to a fed or fasted subject.

[0023] Also disclosed are methods of using the nanoparticulate benidipine formulations, for example, to treat or prevent diseases, disorders, symptoms or conditions in a subject. Exemplary methods may include administering to a subject a stable nanoparticulate bendipine composition including at least one benidipine or derivative or salt thereof and at least one surface stabilizer having an effective average particle size of less than about 200 nm. In some embodiments, the subject may have been diagnosed with hypertension, renal parenchymal hypertension, angina pectoris, a hypertension related disease or disorder, or a combination thereof. In other embodiments, the compositions may be used to treat symptoms indicative of hypertension, renal parenchymal hypertension, angina pectoris, a hypertension related disease or disorder or combinations thereof.

[0024] Both the foregoing summary of the invention and the following detailed description of the invention are exemplary and explanatory and are intended to provide further details of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

DETAILED DESCRIPTION

A. Nanoparticulate Benidipine Compositions

[0025] The invention is directed to compositions comprising a nanoparticulate calcium channel blocker such as benidipine. The compositions comprise a benidipine and preferably at least one surface stabilizer adsorbed on or associated with the surface of the drug. The benidipine particles may have an effective average particle size of less than about 2000 nm.

[0026] Advantages of the nanoparticulate benidipine formulation of the invention as compared to non-nanoparticulate benidipine compositions (e.g., microcrystalline or solubilized

dosage forms) include, but are not limited to: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) improved pharmacokinetic profiles; (4) increased bioavailability; (5) substantially similar pharmacokinetic profiles of the benidipine compositions when administered in the fed versus the fasted state; (6) bioequivalency of the benidipine compositions when administered in the fed versus the fasted state; (7) an increased rate of dissolution for the benidipine compositions; and (8) the benidipine compositions can be used in conjunction with other active agents useful in the prevention and treatment of hypertension, renal parenchymal hypertension and angina pectoris.

[0027] The invention also relates to nanoparticulate benidipine compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions may be formulated for parental injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments, or drops), buccal, intracisternal, intraperitoneal, or topical administrations, and the like.

[0028] In some embodiments, a preferred dosage form may be a solid dosage form such as a tablet, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof.

[0029] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0030] The term "effective average particle size of less than about 2000 nm," as used herein, means that at least about 50% of the nanoparticulate benidipine particles have a size of less than about 2000 nm (by weight or by other suitable measurement technique, such as by number or by volume) when measured by, for example, sedimentation flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

[0031] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0032] As used herein with reference to stable nanoparticulate benidipine "stable" connotes, but is not limited to one or more of the following parameters: (1) the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) that the physical structure of the particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the particles are chemically stable; and/or (4) where the benidipine has not been subject to a heating step at or above the melting point of the benidipine in the preparation of the nanoparticles of the present invention.

[0033] The term "conventional" or "non-nanoparticulate" active agent shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2000 nm. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000 nm.

[0034] The phrase "poorly water soluble drugs" as used herein refers to those drugs that have a solubility in water of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, or less than about 1 mg/ml.

[0035] As used herein, the phrase "therapeutically effective amount" shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

[0036] The term "particulate" as used herein refers to a state of matter which is characterized by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology. The term "multiparticulate" as used herein means a plurality of discrete or aggregated particles, pellets, beads, granules or mixtures thereof irrespective of their size, shape or morphology.

B. Characteristics of the Nanoparticulate Benidipine Compositions

1. Increased Bioavailability

[0037] The nanoparticulate benidipine formulations of the invention are proposed to exhibit increased bioavailability, and require smaller doses as compared to prior conventional benidipine formulations.

[0038] In one embodiment, the nanoparticulate benidipine composition, upon administration to a mammal, produces therapeutic results at a dosage which is less than that of a non-nanoparticulate dosage form of the same benidipine.

2. Improved Pharmacokinetic Profiles

[0039] The benidipine compositions described herein may also exhibit a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the benidipine compositions preferably includes, but is not limited to: (1) a C_{max} for benidipine or a derivative or salt thereof, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate formulation of the same benidipine, administered at the same dosage; and/or (2) an AUC for benidipine or a derivative or a salt thereof, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate formulation of the same benidipine, administered at the same dosage; and/or (3) a T_{max} for benidipine or a derivative or a salt thereof, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the T_{max} for a non-nanoparticulate formulation of the same benidipine, administered at the same dosage. The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of the benidipine or derivative or a salt thereof.

[0040] In one embodiment, a composition comprising at least one nanoparticulate benidipine or a derivative or salt thereof exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same benidipine (*e.g.*, CONIEL®), administered at the same dosage, a T_{max} not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the T_{max} exhibited by the non-nanoparticulate benidipine formulation.

[0041] In another embodiment, the composition comprising at least one nanoparticulate benidipine or a derivative or salt thereof, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same benidipine (*e.g.*, CONIEL®), administered at the same dosage, a C_{max} which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least

about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by the non-nanoparticulate benidipine formulation.

[0042] In yet another embodiment, the composition comprising at least one nanoparticulate benidipine or a derivative or salt thereof, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same benidipine (*e.g.*, CONIEL®), administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate benidipine formulation.

3. The Pharmacokinetic Profiles of the Benidipine Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

[0043] In one embodiment of the invention, the pharmacokinetic profile of the nanoparticulate benidipine compositions is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there would be little or no appreciable difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate benidipine compositions are administered in the fed versus the fasted state.

[0044] For conventional benidipine formulations, *i.e.*, CONIEL®, the absorption of benidipine is increased when administered with food. This difference in absorption observed with conventional benidipine formulations is undesirable. The nanoparticulate benidipine formulations of the invention are proposed to overcome this problem, as the benidipine formulations are likely to reduce or preferably substantially eliminate significantly different absorption levels when administered under fed as compared to fasting conditions.

[0045] Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed.

4. Bioequivalency of Benidipine Compositions When Administered in the Fed Versus the Fasted State

[0046] In one embodiment of the invention, administration of a nanoparticulate benidipine composition of the invention to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state. The difference in absorption of the nanoparticulate benidipine compositions when administered in the fed versus the fasted state, is preferably less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

[0047] In some embodiments, the invention encompasses compositions comprising at least one nanoparticulate benidipine, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by C_{max} and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and C_{max} are between 0.80 to 1.25 (T_{max} measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMEA guidelines, the 90% CI for AUC must be between 0.80 to 1.25 and the 90% CI for C_{max} must between 0.70 to 1.43

5. Dissolution Profiles of Nanoparticulate Benidipine Compositions

[0048] The nanoparticulate benidipine compositions are proposed to have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of benidipine, it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

[0049] The benidipine compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is dissolved. In other embodiments of the invention, at least about 30% or at least about 40% of benidipine composition is dissolved within about 5 minutes. In yet other embodiments of the invention, at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the benidipine composition is dissolved within about 10 minutes. Finally, in another embodiment of the invention, at least about 70%, at least about 80%, at least about 90%, or at least about 100% of the benidipine composition is dissolved within about 20 minutes.

[0050] Dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; *i.e.*, the dissolution medium is predictive of *in vivo* dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. For example, the rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

6. Redispersibility Profiles of the Benidipine Compositions of the Invention

[0051] An additional feature of the benidipine compositions of the invention may include redispersion such that the effective average particle size of the redispersed benidipine particles is less than about 2 microns. This is significant, as if upon administration the benidipine compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating the benidipine into a nanoparticulate particle size.

[0052] Not wishing to be bound by any theory, it is proposed that nanoparticulate active agent compositions benefit from the small particle size of the active agent; if the active agent does not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

[0053] Moreover, the nanoparticulate benidipine compositions of the invention exhibit dramatic redispersion of the nanoparticulate benidipine particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed benidipine particles is less than about 2 microns. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength. Such redispersion in a biorelevant media is predictive of in vivo efficacy of the benidipine dosage form.

[0054] Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," Pharm. Res., 14 (4): 497-502 (1997).

[0055] It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, etc.

[0056] Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 N, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 N HCl or less, about 0.01 N HCl or less, about 0.001 N HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

[0057] Electrolyte concentrations of 0.001 N HCl, 0.01 N HCl, and 0.1 N HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 N HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

[0058] Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

[0059] In other embodiments of the invention, the redispersed benidipine particles of the invention (redispersed in water, a biorelevent media, or any other suitable dispersion media)

have an effective average particle size of less than about less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods. Such methods suitable for measuring effective average particle size are known to a person of ordinary skill in the art.

[0060] Redispersibility can be tested using any suitable means known in the art. *See e.g.*, the example sections of U.S. Patent No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

7. Benidipine Compositions Used in Conjunction with Other Active Agents

[0061] The nanoparticulate benidipine compositions can additionally comprise one or more compounds useful in treating hypertension, renal parenchymal hypertension and angina pectoris, or the benidipine compositions can be administered in conjunction with such a compound. Examples of such compounds include, but are not limited to, prostaglandins and derivatives thereof, thrombolytic agents, anticoagulants, calcium-entry blocking agents, antianginal agents, cardiac glycosides, vasodilators, antihypertensive agents, and blood lipid-lowering agents.

C. Nanoparticulate Benidipine Compositions

[0062] The invention provides compositions comprising benidipine particles and at least one surface stabilizer. The surface stabilizers preferably are adsorbed on, or associated with, the surface of the benidipine particles. In some embodiments, surface stabilizers preferably physically adhere on, or associate with, the surface of the nanoparticulate benidipine particles, but do not chemically react with the benidipine particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

[0063] The invention also includes benidipine compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal,

nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

1. Benidipine Particles

The compositions of the invention comprise particles of benidipine or a salt or derivative thereof. The particles can be in a crystalline phase, semi-crystalline phase, amorphous phase, semi-amorphous phase, or a combination thereof.

2. Surface Stabilizers

[0064] Combinations of more than one surface stabilizers may be used in the invention. Suitable surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients may include various polymers, low molecular weight oligomers, natural products, and surfactants. Exemplary surface stabilizers include nonionic, ionic, anionic, cationic, and zwitterionic surfactants or compounds.

[0065] Representative examples of surface stabilizers include hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.,* Tween® 20 and Tween® 80 (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs® 3550 and 934 (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.,* Pluronics® F68 and F108, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic® 908, also known as Poloxamine™ 908, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic® 1508 (T-1508)

(BASF Wyandotte Corporation), Tritons® X-200, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas™ F-110, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin®-lOG or Surfactant™ 10-G (Olin Chemicals, Stamford, CT); Crodestas™ SL-40 (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

[0066] Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

[0067] Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, $C_{12\text{-}15}$dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride or bromide, N-alkyl $(C_{12\text{-}18})$dimethylbenzyl ammonium chloride, N-alkyl $(C_{14\text{-}18})$dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and $(C_{12\text{-}14})$ dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt,

dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

[0068] Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

[0069] Nonpolymeric surface stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

[0070] (i) none of R_1-R_4 are CH_3;

[0071] (ii) one of R_1-R_4 is CH_3;

[0072] (iii) three of R_1-R_4 are CH_3;

[0073] (iv) all of R_1-R_4 are CH_3;

[0074] (v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

[0075] (vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

[0076] (vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

[0077] (viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

[0078] (ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

[0079] (x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

[0080] (xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

[0081] (xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

[0082] Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

[0083] Most of these surface stabilizers are known pharmaceutical excipients are commercially available and/or can be prepared by techniques known in the art. *See e.g.*, *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

a. Povidone Polymers

[0084] Povidone polymers are exemplary surface stabilizers for use in formulating an injectable nanoparticulate benidipine compositions. Povidone polymers, also known as polyvidon(e), povidonum, PVP, and polyvinylpyrrolidone, are sold under the trade names Kollidon® (BASF Corp.) and Plasdone® (ISP Technologies, Inc.). They are polydisperse macromolecular molecules, with a chemical name of 1-ethenyl-2-pyrrolidinone polymers and 1-vinyl-2-pyrrolidinone polymers. Povidone polymers are produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000 daltons. To be useful as a surface modifier for a drug compound to be administered to a mammal, the povidone polymer must have a molecular weight of less than about 40,000 daltons, as a molecular weight of greater than 40,000 daltons would have difficulty clearing the body.

[0085] Povidone polymers are prepared by, for example, Reppe's process, comprising: (1) obtaining 1,4-butanediol from acetylene and formaldehyde by the Reppe butadiene synthesis; (2) dehydrogenating the 1,4-butanediol over copper at 200° to form γ-butyrolactone; and (3) reacting γ-butyrolactone with ammonia to yield pyrrolidone. Subsequent treatment with acetylene gives the vinyl pyrrolidone monomer. Polymerization is carried out by heating in the presence of H_2O and NH_3. *See* The Merck Index, 10th Edition, pp. 7581 (Merck & Co., Rahway, NJ, 1983).

[0086] The manufacturing process for povidone polymers produces polymers containing molecules of unequal chain length, and thus different molecular weights. The molecular weights of the molecules vary about a mean or average for each particular commercially available grade. Because it is difficult to determine the polymer's molecular weight directly, the most widely used method of classifying various molecular weight grades is by K-values, based on viscosity measurements. The K-values of various grades of povidone polymers represent a function of the average molecular weight, and are derived from viscosity measurements and calculated according to Fikentscher's formula.

[0087] The weight-average of the molecular weight, Mw, is determined by methods that measure the weights of the individual molecules, such as by light scattering. Table 1 provides

molecular weight data for several commercially available povidone polymers, all of which are soluble.

TABLE 1

Povidone	K-Value	Mv (Daltons)**	Mw (Daltons)**	Mn (Daltons)**
Plasdone C-15®	17 ± 1	7,000	10,500	3,000
Plasdone C-30®	30.5 ± 1.5	38,000	62,500*	16,500
Kollidon 12 PF®	11-14	3,900	2,000-3,000	1,300
Kollidon 17 PF®	16-18	9,300	7,000-11,000	2,500
Kollidon 25®	24-32	25,700	28,000-34,000	6,000

*Because the molecular weight is greater than 40,000 daltons, this povidone polymer is not useful as a surface stabilizer for a drug compound to be administered parenterally (*i.e.*, injected).

**Mv is the viscosity-average molecular weight, Mn is the number-average molecular weight, and Mw is the weight average molecular weight. Mw and Mn were determined by light scattering and ultra-centrifugation, and Mv was determined by viscosity measurements.

[0088] Based on the data provided in Table 1, exemplary useful commercially available povidone polymers include, but are not limited to, Plasdone C-15®, Kollidon 12 PF®, Kollidon 17 PF®, and Kollidon 25®.

3. Other Pharmaceutical Excipients

[0089] Pharmaceutical compositions including at least one nanoparticulate benidipine may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[0090] Typical bonding agents or binders may include starch paste or methyl cellulose.

[0091] Examples of filling agents include lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

[0092] Suitable lubricants, including agents that act on the flowability of the powder to be compressed, may include colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0093] Aqueous suspensions comprising the nanoparticulate benidipine can be in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acadia.

[0094] Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

[0095] Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

[0096] Examples of buffers include phosphate buffers, citrate buffers and buffers made from other organic acids.

[0097] Examples of wetting or dispersing agents include a naturally-occurring phosphatide, for example, lecithin or condensation products of n-alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate.

[0098] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

[0099] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0100] Examples of effervescent agents include effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

4. Nanoparticulate Benidipine Particle Size

[0101] The compositions disclosed herein comprise benidipine particles having an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns). In other embodiments, the benidipine particles have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0102] By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the benidipine particles have a particle size of less than the effective average, by weight (or by other suitable measurement technique, such as by volume, number, etc.), *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, etc., when measured by the above-noted techniques. In other embodiments of the invention, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the benidipine particles have a particle size of less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, etc.

[0103] In the present invention, the value for D50 of a nanoparticulate benidipine composition is the particle size below which 50% of the benidipine particles fall, by weight (or by other suitable measurement technique, such as by volume, number, etc.). Similarly, D90 is the particle size below which 90% of the benidipine particles fall, by weight (or by other suitable measurement technique, such as by volume, number, etc.).

5. Concentration of Benidipine and Surface Stabilizers

[0104] The relative amounts of benidipine and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the particular benidipine selected, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, etc.

[0105] The concentration of benidipine can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of benidipine and at least one surface stabilizer, not including other excipients.

[0106] The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of benidipine and at least one surface stabilizer, not including other excipients.

6. Exemplary Nanoparticulate Benidipine Tablet Formulations

[0107] Several exemplary benidipine tablet formulations are given below. These examples are not intended to limit the claims in any respect, but rather to provide exemplary tablet formulations of benidipine which can be utilized in the methods of the invention. Such exemplary tablets can also comprise a coating agent.

Exemplary Nanoparticulate Benidipine Tablet Formulation #1	
Component	**g/Kg**
Benidipine	about 50 to about 500
Hypromellose, USP	about 10 to about 70
Docusate Sodium, USP	about 1 to about 10
Sucrose, NF	about 100 to about 500
Sodium Lauryl Sulfate, NF	about 1 to about 40
Lactose Monohydrate, NF	about 50 to about 400
Silicified Microcrystalline Cellulose	about 50 to about 300
Crospovidone, NF	about 20 to about 300
Magnesium Stearate, NF	about 0.5 to about 5

Exemplary Nanoparticulate Benidipine Tablet Formulation #2	
Component	**g/Kg**
Benidipine	about 100 to about 300
Hypromellose, USP	about 30 to about 50
Docusate Sodium, USP	about 0.5 to about 10
Sucrose, NF	about 100 to about 300
Sodium Lauryl Sulfate, NF	about 1 to about 30
Lactose Monohydrate, NF	about 100 to about 300
Silicified Microcrystalline Cellulose	about 50 to about 200
Crospovidone, NF	about 50 to about 200
Magnesium Stearate, NF	about 0.5 to about 5

Exemplary Nanoparticulate Benidipine Tablet Formulation #3	
Component	**g/Kg**
Benidipine	about 200 to about 225
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 200 to about 225
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 200 to about 205
Silicified Microcrystalline Cellulose	about 130 to about 135
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

Exemplary Nanoparticulate Benidipine Tablet Formulation #4	
Component	**g/Kg**
Benidipine	about 119 to about 224
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 119 to about 224
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 119 to about 224
Silicified Microcrystalline Cellulose	about 129 to about 134
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

D. Methods of Making Nanoparticulate Benidipine Compositions

[0108] The nanoparticulate benidipine compositions can be made using any suitable method known in the art, for example, milling, homogenization, precipitation, freezing, or template emulsion techniques.

[0109] Exemplary methods of making nanoparticulate compositions are described in the '684 patent. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

[0110] The resultant nanoparticulate benidipine compositions or dispersions can be utilized in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, etc.

1. Milling to Obtain Nanoparticulate Benidipine Dispersions

[0111] Milling benidipine to obtain a nanoparticulate dispersion comprises dispersing the benidipine particles in a liquid dispersion media in which benidipine is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the benidipine to the desired effective average particle size (*e.g.*, less than about 2000 nm). The dispersion media can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. A preferred dispersion media is water.

[0112] A surface stabilizer can be added to the dispersion media either before, during, or after particle size reduction of benidipine. The liquid dispersion media can be maintained at a physiologic pH, for example, within the range of from about 3.0 to about 8.0 during the size reduction process; more preferably within the range of from about 5.0 to about 7.5 during the size reduction process.

[0113] Other compounds, such as a diluent, can be added to the benidipine/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

[0114] Using a particle size reduction method, the particle size of the benidipine composition is reduced to an effective average particle size of less than about 2000 nm. Effective methods of providing mechanical force for particle size reduction of the benidipine can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, and media mills such as a sand mill and a bead mill, and homogenization, for example, with a Microfluidizer® (Microfluidics Corp.).

[0115] Ball milling is a low energy milling process that uses milling media, drug, stabilizer, and liquid. The materials are placed in a milling vessel that is rotated at optimal speed such that the media cascades and reduces the drug particle size by impaction. The media used must have a high density as the energy for the particle reduction is provided by gravity and the mass of the attrition media.

[0116] Media milling is a high energy milling process. Benidipine, surface stabilizer, and liquid are placed in a reservoir and re-circulated in a chamber comprising grinding media and a rotating shaft/impeller. The rotating shaft agitates the grinding media which subjects benidipine to impaction and sheer forces, thereby reducing the benidipine particle size. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix is preferably from about 100 to about 1000 centipoise, and for ball milling the apparent viscosity of the premix is preferably from about 1 up to about 100 centipoise. Such ranges tend to afford an optimal balance between efficient particle size reduction and media erosion.

[0117] Benidipine can be added to a liquid media in which it is essentially insoluble to form a premix. The surface stabilizer can be present in the premix or it can be added to the benidipine dispersion following particle size reduction. The premix can be used directly by subjecting it to mechanical means to reduce the average benidipine particle size in the dispersion to less than about 2000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, benidipine and at least one surface stabilizer can be dispersed in the liquid media using suitable agitation, e.g., a Cowles type mixer, until a homogeneous dispersion is observed in which there are no large agglomerates visible to the naked eye. It is preferred that the premix be subjected to such a pre-milling dispersion step when a re-circulating media mill is used for attrition.

[0118] The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For ball mills, processing times of up to five days or longer may be required. Alternatively, processing times of less than 1 day (residence times of one minute up to several hours) are possible with the use of a high shear media mill.

[0119] The benidipine particles can be reduced in size at a temperature which does not significantly degrade the benidipine molecule. Processing temperatures of less than about 30 to less than about 40°C are ordinarily preferred. If desired, the processing equipment can be cooled with conventional cooling equipment. Control of the temperature, e.g., by jacketing or immersion of the milling chamber in ice water, is contemplated. Generally, the method of the invention is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process. Ambient processing pressures are typical of ball mills, attritor mills, and vibratory mills.

a. Grinding Media

[0120] The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of material for the grinding media is not believed to be critical. Zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, ceramic, stainless steel, titania, alumina, 95% ZrO stabilized with yttrium, glass grinding media, and polymeric grinding media are exemplary grinding materials.

[0121] The grinding media can comprise particles that are preferably substantially spherical in shape, e.g., beads, consisting essentially of polymeric resin or other suitable material. Alternatively, the grinding media can comprise a core having a coating of a polymeric resin adhered thereon. The polymeric resin can have a density from about 0.8 to about 3.0 g/cm3.

[0122] In general, suitable polymeric resins are chemically and physically inert, substantially free of metals, solvent, and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric resins include crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene; styrene copolymers; polycarbonates; polyacetals, such as Delrin® (E.I. du Pont de Nemours and Co.); vinyl chloride polymers and copolymers; polyurethanes; polyamides; poly(tetrafluoroethylenes), e.g., Teflon®(E.I. du Pont de Nemours and Co.), and other

fluoropolymers; high density polyethylenes; polypropylenes; cellulose ethers and esters such as cellulose acetate; polyhydroxymethacrylate; polyhydroxyethyl acrylate; and silicone-containing polymers such as polysiloxanes and the like. The polymer can be biodegradable. Exemplary biodegradable polymers include poly(lactides), poly(glycolide) copolymers of lactides and glycolide, polyanhydrides, poly(hydroxyethyl methacylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes). For biodegradable polymers, contamination from the media itself advantageously can metabolize in vivo into biologically acceptable products that can be eliminated from the body.

[0123] The grinding media preferably ranges in size from about 0.01 to about 3 mm. For fine grinding, the grinding media is preferably from about 0.02 to about 2 mm, and more preferably from about 0.03 to about 1 mm in size.

[0124] In some grinding process the benidipine particles are made continuously. Such a method comprises continuously introducing the benidipine into a milling chamber, contacting the compounds with grinding media while in the chamber to reduce the particle size, and continuously removing the nanoparticulate benidipine from the milling chamber.

[0125] The grinding media is separated from the milled nanoparticulate benidipine using conventional separation techniques, in a secondary process such as by simple filtration, sieving through a mesh filter or screen, and the like. Other separation techniques such as centrifugation may also be employed.

b. Sterile Product Manufacturing

[0126] Development of injectable compositions requires the production of a sterile product. The manufacturing process of the present invention is similar to typical known manufacturing processes for sterile suspensions. A typical sterile suspension manufacturing process flowchart is as follows:

(Media Conditioning)

↓

Compounding

↓

Particle Size Reduction

↓

Vial Filling

↓

(Lyophilization) and/or (Terminal Sterilization)

[0127] As indicated by the optional steps in parentheses, some of the processing is dependent upon the method of particle size reduction and/or method of sterilization. For example, media conditioning is not required for a milling method that does not use media. If terminal sterilization is not feasible due to chemical and/or physical instability, aseptic processing can be used.

2. Precipitation to Obtain Nanoparticulate Benidipine Compositions

[0128] Another method of forming the desired nanoparticulate benidipine composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving benidipine in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means. The resultant nanoparticulate benidipine composition may then be utilized in a pharmaceutically acceptable dosage form.

3. Homogenization to Obtain Nanoparticulate Benidipine Compositions

[0129] Exemplary homogenization methods of preparing nanoparticulate active agent compositions are described, for example in U.S. Patent No. 5,510,118, which is specifically incorporated by reference. Such a method comprises dispersing particles of benidipine in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of benidipine to the desired effective average particle size. The benidipine particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the benidipine particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the benidipine/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

[0130] Homogenization is a technique that does not use milling media. In some embodiments, benidipine, surface stabilizer, and liquid (or drug and liquid with the surface stabilizer added after particle size reduction) constitute a process stream propelled into a process zone, which in the Microfluidizer® is called the Interaction Chamber (*see e.g*, U.S. Patent No. 5,510,118). The product to be treated is inducted into the pump, and then forced out. The priming valve of the Microfluidizer® purges air out of the pump. Once the pump is filled with product, the priming valve is closed and the product is forced through the interaction chamber. The geometry of the interaction chamber produces powerful forces of sheer, impact, and cavitation which are responsible for particle size reduction. Specifically, inside the interaction chamber, the pressurized product is split into two streams and accelerated to extremely high velocities. The formed jets are then directed toward each other and collide in the interaction zone. The resulting product has very fine and uniform particle or droplet size. The Microfluidizer® also provides a heat exchanger to allow cooling of the product.

4. Cryogenic Methodologies to Obtain Nanoparticulate Benidipine Compositions

[0131] Another method of forming the desired nanoparticulate benidipine composition is by spray freezing into liquid ("SFL"). This technology comprises an organic or organoaqueous solution of benidipine with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the benidipine solution freeze at a rate sufficient to minimize crystallization and particle growth, thus formulating nanostructured benidipine particles. Depending on the choice of solvent system and processing conditions, the nanoparticulate benidipine particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under conditions that avoid agglomeration or ripening of the benidipine particles.

[0132] As a complementary technology to SFL, ultra rapid freezing (URF) may also be used to created equivalent nanostructured benidipine particles with greatly enhanced surface area. URF comprises an organic or organoaqueous solution of benidipine with stabilizers onto a cryogenic substrate.

5. Emulsion Methodologies to Obtain Nanoparticulate Benidipine Compositions

[0133] Another method of forming the desired nanoparticulate benidipine composition is by template emulsion. Template emulsion creates nanostructured benidipine particles with

controlled particle size distribution and rapid dissolution performance. The method comprises an oil-in-water emulsion that is prepared, then swelled with a non-aqueous solution comprising the benidipine and stabilizers. The particle size distribution of the benidipine particles is a direct result of the size of the emulsion droplets prior to loading with the benidipine a property which can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald ripening. Subsequently, the solvent and water are removed, and the stabilized nanostructured benidipine particles are recovered. Various benidipine particles morphologies can be achieved by appropriate control of processing conditions.

[0134] Published International Patent Application No. WO 97/144407 to Pace *et al.*, published April 24, 1997, discloses particles of water insoluble biologically active compounds with an average size of 100 nm to 300 nm that are prepared by dissolving the compound in a solution and then spraying the solution into compressed gas, liquid or supercritical fluid in the presence of appropriate surface modifiers.

E. Methods of Using the Nanoparticulate Benidipine Compositions

[0135] The invention provides a method of increasing bioavailability (*e.g,* plasma levels) of a benidipine in a subject. Such a method comprises orally administering to a subject an effective amount of a nanoparticulate benidipine composition according to the invention.

[0136] In one embodiment of the invention, the benidipine composition, in accordance with standard pharmacokinetic practice, has a bioavailability that is about 50% greater, about 40% greater, about 30% greater, about 20% greater, or about 10% greater than a conventional, non-nanoparticulate benidipine dosage form,. In other embodiments, the nanoparticulate benidipine compositions, in accordance with standard pharmacokinetic practice, preferably produce a maximum blood plasma concentration profile in less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after the initial dose of the composition.

[0137] The compositions of the invention are useful in the prevention and treatment of disorders including but not limited to hypertension, renal parenchymal hypertension and angina pectoris.

[0138] The benidipine compounds of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally,

intraperitoneally, locally (*e.g.*, powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[0139] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. The compositions and formulations may also include biodegradable polymers and lipid complexes.

[0140] The injectable formulations may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0141] The nanoparticulate benidipine compositions may also comprise adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0142] Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol;

(e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0143] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to a benidipine, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0144] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0145] 'Therapeutically effective amount' as used herein with respect to a benidipine dosage shall mean that dosage that provides the specific pharmacological response for which a benidipine is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that benidipine dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

[0146] One of ordinary skill will appreciate that effective amounts of a benidipine can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of a benidipine in the nanoparticulate compositions of the invention may be varied to obtain an amount of a benidipine that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired

therapeutic effect, the route of administration, the potency of the administered benidipine, the desired duration of treatment, and other factors.

[0147] Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies.

[0148] The following prophetic example is given to illustrate the present invention. It should be understood, however, that the spirit and scope of the invention is not to be limited to the specific conditions or details described in this example but should only be limited by the scope of the claims that follow. All references identified herein, including U.S. patents, are hereby expressly incorporated by reference.

Example 1

[0149] The purpose of this example was to prepare a composition comprising a nanoparticulate benidipine or a salt or derivative thereof.

[0150] An aqueous dispersion of 5% (w/w) benidipine, combined with one or more surface stabilizers, such as hydroxypropyl cellulose (HPC-SL) and dioctylsulfosuccinate (DOSS), could be milled in a 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see e.g., U.S. Patent No. 6,431,478), along with 500 micron PolyMill® attrition media (Dow Chemical Co.) (e.g., at an 89% media load). In an exemplary process, the mixture could be milled at a speed of 2500 rpms for 60 minutes.

[0151] Following milling, the particle size of the milled benidipine particles can be measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. For a successful composition, the initial mean and/or D50 milled benidipine particle size is expected to be less than 2000 nm.

[0152] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present inventions without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modification and variations of the invention provided they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A stable nanoparticulate benidipine composition comprising:

(a) particles of at least one benidipine or a derivative or a salt thereof having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer.

2. The composition of claim 1, wherein the benidipine particle is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

3. The composition of claim 1 or claim 2, wherein the effective average particle size of the benidipine particle is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

4. The composition of any one of claims 1 to 3, wherein the composition is formulated:

(a) for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or

(d) any combination of (a), (b), and (c).

5. The composition of any one of claims 1 to 4, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

6. The composition of any one of claims 1 to 5, wherein:

(a) benidipine is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of benidipine and at least one surface stabilizer, not including other excipients;

(b) the surface stabilizer is present in an amount selected from the group consisting of about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of benidipine and at least one surface stabilizer, not including other excipients; or

(c) a combination thereof.

7. The composition of any one of claims 1 to 6, further comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

8. The composition of any one of claims 1 to 7, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a non-ionic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

9. The composition of c any one of claims 1 to 8, wherein the surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose,

magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, a cationic phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride, lauryl dimethyl $(ethenoxy)_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium

chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

10. The composition of any one of claims 1 to 9, wherein the composition is bioadhesive.

11. The composition of any one of claims 1 to 10, wherein the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

12. The composition of any one of claims 1 to 11, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

13. The composition of any one of claims 1 to 12, additionally comprising one or more active agents useful for the treatment of hypertension, renal parenchymal hypertension and angina pectoris.

14. The composition of claim 13, wherein the active agents is selected from a group consisting of prostaglandins and derivatives thereof, thrombolytic agents, anticoagulants, calcium-entry blocking agents, antianginal agents, cardiac glycosides, vasodilators, antihypertensive agents, blood lipid-lowering agents and combinations thereof.

15. A benidipine composition comprising at least one benidipine or derivative or a salt thereof, wherein upon administration to a human the at least one benidipine or derivative or salt thereof does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

16. The composition of claim 15, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state.

17. A stable nanoparticulate benidipine composition comprising:

(a) particles of at least one benidipine or a salt or derivative thereof having an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer,

wherein upon administration to a mammal the composition produces therapeutic results at a dosage which is less than that of a non-nanoparticulate dosage form of the same benidipine.

18. A nanoparticulate benidipine composition comprising at least one benidipine or derivative or a salt thereof, wherein the composition has:

(a) a C_{max} for the benidipine when assayed in the plasma of a mammalian subject following administration that is greater than the C_{max} for a non-nanoparticulate formulation of the same benidipine, administered at the same dosage;

(b) an AUC for the benidipine when assayed in the plasma of a mammalian subject following administration that is greater than the AUC for a non-nanoparticulate formulation of the same benidipine, administered at the same dosage;

(c) a T_{max} for the benidipine when assayed in the plasma of a mammalian subject following administration that is less than the T_{max} for a non-nanoparticulate formulation of the same benidipine, administered at the same dosage; or

(d) any combination thereof.

19. Use of a composition according to any one of claims 1 to 18 for the manufacture of a medicament, wherein the medicament is useful in the treatment of a hypertension, renal parenchymal hypertension, angina pectoris or a combination thereof.

20. A method for the preparation of a nanoparticulate benidipine or a derivative or salt thereof comprising contacting particles of the benidipine with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate benidipine composition having an effective average particle size of less than about 2000 nm.

21. The method of claim 20, wherein the contacting comprises grinding, wet grinding, homogenization, freezing, template emulsion, precipitation, or a combination thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/021655

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4545 A61P9/10 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/110448 A (KYOWA HAKKO KOGYO CO., LTD; GOTO, TOMOHIKO; HAYAKAWA, EIJI; TAKESHIGE,) 23 December 2004 (2004-12-23) abstract	1-21
P,X	PATENT ABSTRACTS OF JAPAN & JP 2005 263816 A (KYOWA HAKKO KOGYO CO., LTD;), 29 September 2005 (2005-09-29) abstract	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2006	02/10/2006

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/021655

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004110448 A	23-12-2004	CN 1794993 A	28-06-2006
		JP 3786287 B2	14-06-2006
JP 2005263816 A	29-09-2005	NONE	