NANOPARTICULATE CARVEDILOL FORMULATIONS

FIELD OF THE INVENTION

This invention is directed to nanoparticulate carvedilol formulations and methods of making and using the formulations. The formulations of the invention are particularly useful in treating high blood pressure (hypertension), congestive heart failure, cancer, viral infections, psychosis-related conditions, and similar conditions.

BACKGROUND OF THE INVENTION

A. Background Regarding Carvedilol

High blood pressure adds to the workload of the heart and arteries. If it continues for a long time, the heart and arteries may not function properly. This can damage the blood vessels of the brain, heart, and kidneys, resulting in a stroke, heart failure, or kidney failure. High blood pressure may also increase the risk of heart attacks. These problems may be less likely to occur if blood pressure is controlled.

Heart failure can be defined as a state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues. Symptoms are generally non-specific and include fatigue, dyspnoea, swollen ankles, and exercise intolerance. The overall prevalence of chronic heart failure (CHF) is estimated at 10-20 per 1000 population, with an annual incidence of 1-5 per 1000. Both prevalence and incidence rise with advancing age. McDonagh et al., "Epidemiology and Pathophysiology of Heart Failure," *Medicine*, *26*:111-5 (1998). Heart failure is a major cause of morbidity and mortality. *Id.* CHF is considered to impair the quality of life more than any other chronic medical disorder. *Id.* Prognosis in patients with CHF depends on severity (as indicated by symptoms and exercise capacity), age and sex, with a poorer prognosis in male patients. *Id.* Patients with heart failure require life-long treatment. Pharmacological treatment aims to improve both patients' quality of life and survival. Diuretics and angiotensin converting enzyme (ACE) inhibitors, combined with non-pharmacological measures, form the basis of initial treatment. Davies et al., "ABC of Heart Failure: Management: Diuretics, ACE

Inhibitors, and Nitrates," *BMJ, 320*:428-31 (2000). Digoxin may be added in selected patients.

There is now substantial clinical data demonstrating the effectiveness of using beta-blockers in patients with CHF resulting from left ventricular systolic dysfunction. Sharpe N., "Benefits of Beta-Blockers for Heart Failure: Proven in 1999," *Lancet, 353*:1988-9 (1999); Califf et al., "Beta-Blocker Therapy for Heart Failure," *JAMA, 283*:1335-7 (2000).

Carvedilol belongs to a group of medicines called beta-adrenergic blocking agents, beta-blocking agents, or, more commonly, beta-blockers. Beta-blockers work by affecting the response to some nerve impulses in certain parts of the body. As a result, they decrease the heart's need for blood and oxygen by reducing its workload. They also help the heart to beat more regularly. Beta-blockers can also reduce some heart arrhythmias.

Carvedilol is used to treat high blood pressure (hypertension). Carvedilol also is used to prevent further worsening of congestive heart failure in combination with other therapies, such as diuretics, digoxin, and ACE inhibitors. Carvedilol appears to act in heart failure by reducing the effects of the sympathetic nervous system. Carvedilol increases left ventricular ejection fraction, decreases intracardiac and pulmonary vascular pressures, decreases heart rate and prevents progressive enlargement of the left ventricle with continued use. Carvedilol is used to treat left ventricular dysfunction after a heart attack. Left ventricular dysfunction occurs when the left ventricle (the main pumping chamber of the heart) stiffens and enlarges and can cause the lungs to fill with blood. Beta-blockers approved by the U.S. Food and Drug Administration for heart failure include metoprolol (Toprol®-XL) and carvedilol (COREG®). Metoprolol blocks beta-1 receptors. Carvedilol blocks beta-1, beta-2, and alpha-receptors. Both drugs are good for heart failure, although carvedilol lowers blood pressure more.

Carvedilol may also be used for treating other conditions. For example, recently carvedilol has been reported to have anticancer activity. See U.S. Patent No. 6,632,832 for "Anti-cancer activity of carvedilol and its isomers," describing the inhibition of epidermal growth factor and platelet-derived growth factor-dependent proliferation of cancer cells utilizing carvedilol and its isomers. Exemplary cancers treated included cancers of the colon, ovary, breast, prostate, pancreas, lung, melanoma, glioblastoma, oral

cancer, and leukemias. In addition, WO 98/38986 describes the use of carvedilol for treating and preventing viral infections, and U.S. Patent No. 6,365,618 for "Novel methods of treating or preventing tardive dyskinesia, tardive dystonia and tardive akathisia using the antipsychotic agent, carvedilol" describes the use of carvedilol in treating psychoses. This reference also teaches that carvedilol is useful for improving the treatment of mental disorders in which dopamine blocking medications are used, such as manic episodes, major depressive episodes and psychoses, particularly schizophrenia and schizoaffective disorder.

U.S. patents describing non-nanoparticulate carvedilol include, but are not limited to, U.S. Patent No. 4,503,067 for "Carbazolyl-(4)-oxypropanolamine compounds and therapeutic compositions," U.S. Patent No. 5,760,069 for "Method of treatment for decreasing mortality resulting from congestive heart failure," and U.S. Patent No. 5,902,821 for "Use of carbazole compounds for the treatment of congestive heart failure."

Reported adverse events with carvedilol therapy in clinical trials include dizziness (about 1 in 3 patients on carvedilol), bradycardia, hypotension, oedema, upper respiratory infections, fatigue, lightheadedness, shortness of breath, chest pain (about 1 in 7 patients on carvedilol), low heart rate and low blood pressure, diarrhea (about 1 in 7 patients on carvedilol), high blood sugar (resulting in weight gain), impotence (1-2 out of every 50 men in COREG® clinical trials became impotent; the real-life number may be as high as 15% (*Am. J. Hypertens., 14*:27-31,70-73 (2001)), depression, nausea, vomiting, back pain, insomnia, or headache.

In the U.S., carvedilol is marketed under the trade name COREG® (GlaxoSmithKline) (in other countries carvedilol is marketed under other trade names, such as Dilitrend™, Dimitone™, Eucardic™, and Kredex™). COREG® is a white, oval, film-coated tablet containing 3.125 mg, 6.25 mg, 12.5 mg, or 25 mg of carvedilol. The 6.25 mg, 12.5 mg, and 25 mg tablets are TILTAB® tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

The dose of carvedilol will be different for different patients. The following information includes only the average doses of carvedilol. For oral dosage form (tablets): (a) Congestive heart failure: Adults—3.125 mg two times a day, taken with food; (b)

Hypertension or left ventricular dysfunction after a heart attack: Adults—6.25 mg two times a day, taken with food. For congestive heart failure, the maximum recommended dose is 25 mg twice daily in patients <85 kg and 50 mg twice daily in patients > 85 kg. For hypertension, the recommended initial doses of carvedilol is 6.25 mg twice daily. The maximum daily dose is 50 mg.

Pharmacokinetics: COREG® (carvedilol) is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism. Following oral administration, the apparent mean terminal elimination half-life of carvedilol generally ranges from 7 to 10 hours. Plasma concentrations achieved are proportional to the oral dose administered. When administered with food, the rate of absorption is slowed, as evidenced by a delay in the time to reach peak plasma levels, with no significant difference in extent of bioavailability. It is advised that patients take COREG® (carvedilol) with food to minimize the risk of orthostatic hypotension.

Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)-carvedilol approximately 2 to 3 times higher than S(-)-carvedilol following oral administration in healthy subjects. The mean apparent terminal elimination half-lives for R(+)-carvedilol range from 5 to 9 hours compared with 7 to 11 hours for the S(-)-enantiomer.

B. Background Regarding Nanoparticulate Active Agent Compositions

Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting 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 does not describe nanoparticulate compositions of carvedilol.

Methods of making nanoparticulate active agent compositions are described in, for example, U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate active agent compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;".5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray

Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using

Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" 6,431,478 for "Small Scale Mill;" and 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,582,285 for "Apparatus for sanitary wet milling;" 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;" and 7,101,576 for "Nanoparticulate Megestrol Formulation," all of which are specifically incorporated by reference.

In addition, U.S. Patent Publication No. 20070015719 for "Nanoparticulate clarithromycin formulations," U.S. Patent Publication No. 20070003628 for "Nanoparticulate clopidogrel formulations," U.S. Patent Publication No. 20070003615 for "Nanoparticulate clopidogrel and aspirin combination

formulations," U.S. Patent Publication No. 20060292214 for "Nanoparticulate acetaminophen formulations," U.S. Patent Publication No. 20060275372 for "Nanoparticulate imatinib mesylate formulations," U.S. Patent Publication No. 20060246142 for "Nanoparticulate quinazoline derivative formulations," U.S. Patent Publication No. 20060246141 for "Nanoparticulate lipase inhibitor formulations," U.S. Patent Publication No. 20060216353 for "Nanoparticulate corticosteroid and antihistamine formulations," U.S. Patent Publication No. 20060210639 for" Nanoparticulate bisphosphonate compositions," U.S. Patent Publication No. 20060210638 for "Injectable compositions of nanoparticulate immunosuppressive compounds," U.S. Patent Publication No. 20060204588 for "Formulations of a nanoparticulate finasteride, dutasteride or tamsulosin hydrochloride, and mixtures thereof," U.S. Patent Publication No. 20060198896 for "Aerosol and injectable formulations of nanoparticulate benzodiazepine," U.S. Patent Publication No. 20060193920 for "Nanoparticulate Compositions of Mitogen-Activated (MAP) Kinase Inhibitors," U.S. Patent Publication No. 20060188566 for "Nanoparticulate formulations of docetaxel and analogues thereof," U.S. Patent Publication No. 20060165806 for "Nanoparticulate candesartan formulations," "U.S. Patent Publication No. 20060159767 for "Nanoparticulate bicalutamide formulations," U.S. Patent Publication No. 20060159766 for "Nanoparticulate tacrolimus formulations," U.S. Patent Publication No. 20060159628 for "Nanoparticulate benzothiophene formulations," U.S. Patent Publication No. 20060154918 for "Injectable nanoparticulate olanzapine formulations," U.S. Patent Publication No. 20060121112 for "Topiramate pharmaceutical composition," U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticulate Compositions," U.S. Patent Publication No. 20040195413 A1, for "Compositions and method for milling materials," U.S. Patent Publication No. 20040173696 A1 for "Milling microgram quantities of nanoparticulate candidate compounds," 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. 20040156895 for "Solid Dosage Forms Comprising Pullulan"; 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.

Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

There is a need in the art for carvedilol compositions having greater bioavailability, decreased incidence, frequency, or severity of adverse events, decreased dosage quantity, and other improved dosage characteristics. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

The present invention relates to nanoparticulate compositions comprising carvedilol. The compositions comprise carvedilol and at least one surface stabilizer adsorbed on or associated with the surface of the carvedilol particles. The nanoparticulate

carvedilol particles have an effective average particle size of less than about 2000 nm. A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate carvedilol formulation of the invention. The pharmaceutical compositions comprise carvedilol, at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.

Another aspect of the invention is directed to a nanoparticulate carvedilol composition having improved pharmacokinetic profiles as compared to conventional microcrystalline or solubilized carvedilol formulations.

In yet another embodiment, the invention encompasses carvedilol compositions wherein administration of the composition to a subject in a fasted state as compared to administration of the composition to a subject in a fed state produces similar, or bioequivalent rates of absorption, as measured by AUC, C_{max}, T_{max}, or any combination thereof.

Another embodiment of the invention is directed to nanoparticulate carvedilol compositions additionally comprising one or more compounds useful in treating hypertension, congestive heart failure, or related conditions.

This invention further discloses a method of making a nanoparticulate carvedilol composition according to the invention. Such a method comprises contacting carvedilol and at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate carvedilol composition. The one or more surface stabilizers can be contacted with carvedilol either before, during, or after size reduction of carvedilol.

The present invention is also directed to methods of using the nanoparticulate carvedilol compositions of the invention for treating or preventing conditions such as hypertension, congestive heart failure, cancer, viral inventions, psychosis-related conditions such as tardive dyskinesia, tardive dystonia and tardive akathisia, and related conditions.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation 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 OF THE INVENTION

A. Introduction

The invention is directed to nanoparticulate compositions comprising carvedilol. The compositions comprise carvedilol and preferably at least one surface stabilizer adsorbed on or associated with the surface of the drug. The nanoparticulate carvedilol particles have an effective average particle size of less than about 2000 nm.

Advantages of the nanoparticulate carvedilol formulations of the invention as compared to conventional non-nanoparticulate or solubilized dosage forms of carvedilol include, but are not limited to: (1) smaller tablet or other solid dosage form size, or less frequent administration of the formulation; (2) smaller doses of drug required to obtain the same pharmacological effect as compared to conventional microcrystalline or solubilized forms of carvedilol; (3) increased bioavailability; (4) improved pharmacokinetic profiles, such as T_{max}, C_{max}, and/or AUC profiles; (5) substantially similar or bioequivalent pharmacokinetic profiles of the nanoparticulate carvedilol compositions when administered in the fed versus the fasted state; (6) an increased rate of dissolution for the nanoparticulate carvedilol compositions as compared to conventional microcrystalline or solubilized forms of carvedilol; (7) decreased incidence, frequency, or severity of adverse events as compared to conventional microcrystalline or solubilized forms of carvedilol; and (8) use of the nanoparticulate carvedilol compositions in conjunction with other active agents useful in treating hypertension, congestive heart failure, and related conditions.

The present invention also includes nanoparticulate carvedilol 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 oral administration in solid, liquid, or aerosol form, parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like. A preferred dosage form of the invention is a solid dosage form for oral administration,

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.

The dosage forms of the invention, including solid dosage forms, 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. A solid dose tablet formulation is preferred.

B. Definitions

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

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

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.

As used herein with reference to a "stable" carvedilol particle, this term connotes, but is not limited to, one or more of the following parameters: (1) that the carvedilol 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 carvedilol particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the carvedilol particles are chemically stable; and/or (4) where carvedilol has not been subject to a heating step at or above the melting point of carvedilol in the preparation of the nanoparticles of the invention.

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.

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, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml.

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.

C. Preferred Characteristics of the Nanoparticulate Carvedilol Compositions

There are a number of enhanced pharmacological characteristics of nanoparticulate carvedilol compositions of the invention.

1. Increased Bioavailability

In one embodiment of the invention, the carvedilol formulations of the invention exhibit increased bioavailability at the same dose relative to conventional, non-nanoparticulate carvedilol formulations (e.g., COREG®), and therefore require administration of smaller doses of the drug to achieve equivalent pharmacokinetic profiles.

2. Improved Pharmacokinetic Profiles

The invention also provides carvedilol compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the carvedilol compositions preferably includes, but is not

limited to: (1) a C_{max} for carvedilol, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate carvedilol formulation (*e.g.*, COREG®), administered at the same dosage; and/or (2) an AUC for carvedilol, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate carvedilol formulation (*e.g.*, COREG®), administered at the same dosage; and/or (3) a T_{max} for carvedilol, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the T_{max} for a non-nanoparticulate carvedilol formulation (*e.g.*, COREG®), administered at the same dosage. The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of carvedilol.

In one embodiment, the nanoparticulate carvedilol composition exhibits in comparative pharmacokinetic testing with a non-nanoparticulate carvedilol formulation (*e.g.*, COREG®), 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 carvedilol formulation.

In another embodiment, the nanoparticulate carvedilol composition exhibits in comparative pharmacokinetic testing with a non-nanoparticulate carvedilol formulation of (*e.g.*, COREG®), 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 carvedilol formulation.

In yet another embodiment, the nanoparticulate carvedilol composition exhibits in comparative pharmacokinetic testing with a non-nanoparticulate carvedilol formulation (*e.g.*, COREG®), 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 carvedilol formulation (*e.g.*, COREG®).

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

In another embodiment of the invention, the pharmacokinetic profile of the carvedilol in the nanoparticulate carvedilol compositions is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is little or no appreciable difference in the quantity of drug absorbed (as measured by AUC) or the rate of drug absorption (as measured by T_{max} and/or C_{max}) when the nanoparticulate carvedilol compositions are administered in the fed versus the fasted state. The difference in the AUC, C_{max}, and/or T_{max} (or any combination thereof) of the compositions comprising the nanoparticulate carvedilol when administered in the fed versus the fasted state, is preferably less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, 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%.

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 a worsening of the medical condition for which the drug is being prescribed may be observed.

In one embodiment of the invention, the invention encompasses a composition comprising nanoparticulate carvedilol in which 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 and current European EMEA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and C_{max} are between 80% to 125% (T_{max} measurements are not relevant to bioequivalence for regulatory purposes). Previously, to show bioequivalency between two compounds or administration conditions pursuant to Europe's EMEA guidelines, the 90% CI for AUC had to be between 80% to 125% and the 90% CI for C_{max} had to be between 70% to 143%.

4. Dissolution Profiles of the Carvedilol Compositions of the Invention

In another embodiment of the invention, the carvedilol compositions of the invention have unexpectedly rapid dissolution profiles. Rapid dissolution of carvedilol following administration is preferable, as faster dissolution may lead to faster onset of action and greater bioavailability.

The carvedilol compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the carvedilol is dissolved. In other embodiments of the invention, at least about 30% or at least about 40% of the carvedilol 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 carvedilol 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 carvedilol is dissolved within about 20 minutes.

Dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium is intended to produce different *in vitro* dissolution profiles for two products having different *in vivo* dissolution profiles in gastric juices, *i.e.*, the dissolution behavior of the products in the dissolution medium is intended to be predictive of the dissolution behavior within the body. An exemplary dissolution medium is an aqueous

medium containing the surfactant sodium lauryl sulfate at a concentration of 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

5. Redispersibility Profiles of the Carvedilol Compositions of the Invention

In one embodiment of the invention, the nanoparticulate carvedilol compositions are formulated into a solid dosage form, and the solid dosage form redisperses such that the effective average particle size of the redispersed carvedilol particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate carvedilol compositions of the invention did not redisperse to a nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating carvedilol into a nanoparticulate particle size.

Indeed, the nanoparticulate carvedilol compositions of the invention benefit from the small particle size of carvedilol; if carvedilol does not redisperse into a small particle size upon administration, then "clumps" or agglomerated carvedilol 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 carvedilol particles, the bioavailability of the carvedilol dosage form can drop significantly below that observed when the nanoparticulate active agent is well dispersed.

Moreover, the nanoparticulate carvedilol compositions of the invention are believed to exhibit extensive redispersibility of the nanoparticulate carvedilol particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersibility in a biorelevant aqueous medium such that the effective average particle size of the redispersed carvedilol 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.

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 0.14M. *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). 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.*

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 N 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.

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.

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.

In other embodiments of the invention, the redispersed carvedilol particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable medium) 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 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less

than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

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."

6. Other Pharmaceutical Excipients

Pharmaceutical compositions according to the invention 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.

Examples of filling agents are 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™). Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel. 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.

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. 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.

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. Examples of effervescent agents are 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.

7. Combination Pharmacokinetic Profile Compositions

In yet another embodiment of the invention, a first nanoparticulate carvedilol composition providing a desired pharmacokinetic profile is co-administered, sequentially administered, or combined with at least one other carvedilol composition that generates a desired different pharmacokinetic profile. More than two carvedilol compositions can be co-administered, sequentially administered, or combined. While the first carvedilol composition has a nanoparticulate particle size, the additional one or more carvedilol compositions can be nanoparticulate, solubilized, or have a microparticulate particle size.

The second, third, fourth, *etc.*, carvedilol composition can differ from the first and from each other, for example: (1) in the effective average particle sizes of carvedilol; or (2) in the dosage of carvedilol. Such a combination composition can reduce the dose frequency required. If the second carvedilol composition has a nanoparticulate particle size, then preferably the carvedilol particles of the second composition have at least one surface stabilizer associated with the surface of the drug particles. The one or more

surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first carvedilol composition.

Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

8. Controlled Release Nanoparticulate Carvedilol Compositions

In one embodiment of the invention, the nanoparticulate carvedilol compositions are formulated into a controlled release dosage form. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release carvedilol compositions allow delivery of carvedilol to a subject over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of carvedilol for an extended period of time and thereby provide a longer period of pharmacologic or diagnostic response as compared to conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations.

Controlled release dosage forms of nanoparticulate active agents are described in U.S. Patent Application No. 20020012675 A1 for "Controlled Release Nanoparticulate Compositions," which is specifically incorporated by reference. Typically, a controlled release carvedilol composition comprises nanoparticulate carvedilol, at least one surface stabilizer, and at least one rate controlling polymer. The type of rate controlling polymer depends upon the type of rate controlling dosage form utilized.

There are several different types of rate controlling dosage forms. In a first aspect of the invention, the nanoparticulate carvedilol, at least one surface stabilizer, and one or more auxiliary excipient materials are compressed into a tablet form followed by coating with a rate controlling polymer material. In a second aspect, the nanoparticulate carvedilol, at least one surface stabilizer, a rate controlling polymer material, and one or more auxiliary excipients are compressed together to form a controlled release matrix. The controlled release matrix may optionally be coated with a rate controlling polymer to provide additional controlled release properties. In a third aspect, the nanoparticulate

carvedilol, at least one surface stabilizer, and one or more auxiliary excipient materials are compressed into the form of a multilayer tablet prior to coating with a rate controlling polymer material. In a fourth aspect, the nanoparticulate carvedilol and at least one surface stabilizer are dispersed in a rate controlling polymer material and compressed into a multilayer tablet. The multilayer tablet may optionally be coated with a rate controlling polymer material to provide additional controlled release properties. In an alternative aspect, a first layer in such a multilayer tablet comprises a controlled release composition according to the invention and a second layer comprises a conventional active agent containing composition (e.g., carvedilol or a different active agent), such as an instant release composition. In a fifth aspect, the nanoparticulate carvedilol and at least one surface stabilizer are incorporated into a single layer or multilayer tablet comprising osmagent surrounded by a semi-permeable membrane, with the semi-permeable membrane defining an orifice. In this embodiment the semi-permeable membrane is permeable to aqueous media, such as gastrointestinal fluids, but it is not permeable to the poorly soluble carvedilol when in solution or when in other form. Such osmotic delivery systems are well known in the art, wherein infusion of fluid through the semi-permeable membrane causes the osmagent to swell thus driving the carvedilol through the orifice defined by the semi-permeable membrane. In a sixth aspect, the nanoparticulate carvedilol, at least one surface stabilizer, one or more auxiliary excipients, and a rate controlling polymer material are combined into a multiparticulate form. The multiparticulate form preferably comprises discrete particles, pellets, mini-tablets, or combinations thereof. In a final oral dosage form the multiparticulate form may be encapsulated, for example in hard or soft gelatin capsules. Alternatively, a multiparticulate form may be incorporated into other final dosage forms such as a sachet. In the case of a multiparticulate form comprising discrete particles or pellets, the multiparticulate form may be compressed, optionally with additional auxiliary excipients, into the form of tablets. The compressed multiparticulate tablet may optionally be coated with rate controlling polymer material so as to provide additional controlled release properties.

The choice of a rate controlling polymer first depends upon the type of controlled release system to be utilized: *i.e.*, a coating system or a matrix system. A rate controlling

composition utilizing a coating system employs a polymer that forms a water insoluble backbone, such as poly(alkylmethacrylate), as a rate controlling polymer. Water soluble polymers, such as polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG), can also be used in coating systems, but they must be used in conjunction with a polymer that forms a water insoluble backbone to yield a controlled release composition. Thus, if the water soluble polymers PVP and PEG are utilized in a coating system in the absence of a polymer that forms a water insoluble backbone, the resulting composition is an immediate release composition.

Matrix controlled release systems can use as a rate controlling polymer a water soluble polymer having a molecular weight high enough to form a viscous hydrogel. Water soluble polymers such as hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC) have varying "grades" or molecular weights; high molecular weight polymers are very viscous, and strong, viscous gels resulting from such polymers control the diffusion of water and drug release, producing rate controlling properties. See "Formulating for Controlled Release with METHOCEL Premium Cellulose Ethers," The Dow Chemical Company (1995).

Exemplary rate-controlling polymers include but are not limited to hydrophilic polymers, hydrophobic polymers, and mixtures of hydrophobic and hydrophilic polymers that are capable of retarding the release of carvedilol from a composition or dosage form of the invention. Particularly useful rate-controlling polymers for causing an effective controlled release of carvedilol following administration include plant exudates (gum arabic), seaweed extracts (agar), plant seed gums or mucilages (guar gum), cereal gums (starches), fermentation gums (dextran), animal products (gelatin), hydroxyalkyl celluloses such as hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methylcelluose (HPMC), and sodium carboxymethylcellulose (CMC), guar, pectin, and carrageenan. Additional polymers include poly(ethylene) oxide, alkyl cellulose such as ethyl cellulose and methyl cellulose, carboxymethyl cellulose, hydrophilic cellulose derivatives, polyethylene glycol, polyvinylpyrrolidone, cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate,

opylmethyl cellulose acetate succinate, polyvinyl acetaldiethylamino acetate,

poly(alkylmethacrylate) and poly(vinyl acetate). Other suitable hydrophobic polymers include polymers and/or copolymers derived from acrylic or methacrylic acid and their respective esters, waxes, shellac, and hydrogenated vegetable oils. Two or more rate-controlling polymers can be used in combination. The polymers are commercially available and/or can be prepared by techniques known in the art.

9. Carvedilol Compositions Used in Conjunction with Other Active Agents

The carvedilol compositions of the invention can additionally comprise one or more non-carvedilol compounds useful in treating hypertension, congestive heart failure (or related conditions such as dyslipidemia, hyperlipidemia, hypercholesterolemia, and cardiovascular disorders), viral infections, cancer, psychoses, or related conditions. The compositions of the invention can be co-formulated with such other active agents, or the compositions of the invention can be co-administered or sequentially administered in conjunction with such active agents.

Examples of such compounds include, but are not limited to, digoxin, CETP (cholesteryl ester transfer protein) inhibitors (e.g., torcetrapib), cholesterol lowering compounds (e.g., ezetimibe (Zetia®)) antihyperglycemia agents, statins or HMG CoA reductase inhibitors, antihypertensives, ACE inhibitors, and nitrates.

Examples of antihypertensives include, but are not limited to diuretics ("water pills"), beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin receptor blockers (formal medical name angiotensin-2-receptor antagonists, known as "sartans" for short).

Examples drugs useful in treating hyperglycemia include, but are not limited to, (a) insulin (Humulin®, Novolin®), (b) sulfonylureas, such as glyburide (Diabeta®, Micronase®), acetohexamide (Dymelor®), chlorpropamide (Diabinese®), glimepiride (Amaryl®), glipizide (Glucotrol®), gliclazide, tolazamide (Tolinase®), and tolbutamide (Orinase®), (c) meglitinides, such as repaglinide (Prandin®) and nateglinide (Starlix®), (d) biguanides such as metformin (Glucophage®, Glycon,), (e) thiazolidinediones such as

rosiglitazone (Avandia®) and pioglitazone (Actos®), and (f) glucosidase inhibitors, such as acarbose (Precose®) and miglitol (Glyset®).

Examples of statins or HMG CoA reductase inhibitors include, but are not limited to, lovastatin (Mevacor®, Altocor®); pravastatin (Pravachol®); simvastatin (Zocor®); velostatin; atorvastatin (Lipitor®) and other 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives, as disclosed in U.S. Patent No. 4,647,576); fluvastatin (Lescol®); fluindostatin (Sandoz XU-62-320); pyrazole analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488; rivastatin (also known as cerivastatin, Baycol®) and other pyridyldihydroxyheptenoic acids, as disclosed in European Patent 491226A; Searle's SC-45355 (a 3-substituted pentanedioic acid derivative); dichloroacetate; imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393; 2,3-di-substituted pyrrole, furan, and thiophene derivatives, as disclosed in European Patent Application No. 0221025; naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237; octahydronaphthalenes, such as those disclosed in U.S. Patent No. 4,499,289; keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No. 0,142,146 A2; phosphinic acid compounds; rosuvastatin (Crestor®); pitavastatin (Pitava®), as well as other HMG CoA reductase inhibitors.

D. Compositions

The invention provides compositions comprising nanoparticulate carvedilol particles and at least one surface stabilizer. The surface stabilizers are preferably adsorbed to or associated with the surface of the carvedilol particles. Surface stabilizers useful herein do not chemically react with the carvedilol particles or itself. Preferably, individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages. The compositions can comprise two or more surface stabilizers.

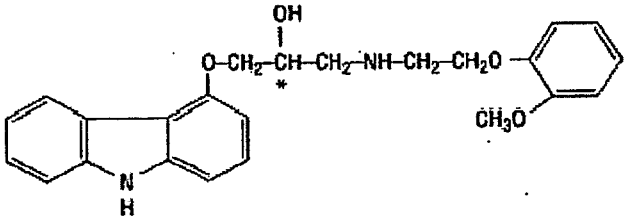
The present invention also includes nanoparticulate carvedilol compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for injection (*e.g.*, intravenous, intramuscular, or subcutaneous), 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. For example, the compositions of the invention can be formulated: (a) for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, otic, and topical administration; (b) into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, tablets, and capsules; (c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or (d) any combination thereof.

1. Carvedilol

Carvedilol can be in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixtures thereof. As used herein, the term "carvedilol" encompasses a racemic mixture, isomers of carvedilol, such as R(+)-carvedilol and/or S(-)-carvedilol, including optically active isomers, hydroxy carbazole derivatives of carvedilol, pharmaceutically acceptable salts of carvedilol, and derivatives thereof.

Carvedilol is a nonselective b-adrenergic blocking agent with a_1-blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy) ethyl]amino]-2-propanol. It is a racemic mixture with the following structure:



Carvedilol is a white to off-white powder with a molecular weight of 406.5 and a molecular formula of $C_{24}H_{26}N_2O_4$. It is freely soluble in dimethylsulfoxide; soluble in methylene chloride and methanol; sparingly soluble in 95% ethanol and isopropanol;

slightly soluble in ethyl ether; and practically insoluble in water, gastric fluid (simulated, TS, pH 1.1), and intestinal fluid (simulated, TS without pancreatin, pH 7.5).

Carvedilol, isomers thereof, or derivatives thereof can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,503,067; 5,760,069; 5,902,821; 6,699,997, and 6,730,326, all of which are specifically incorporated by reference.

2. Surface Stabilizers

Preferably, the nanoparticulate carvedilol compositions of the invention comprise at least one surface stabilizer. Combinations of more than one surface stabilizer can be used in the invention.

Useful surface stabilizers that can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Exemplary surface stabilizers include nonionic, ionic, anionic, cationic, and zwitterionic surfactants.

Representative examples of surface stabilizers include albumin, including but not limited to human serum albumin and bovine albumin, 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, such as Plasdone® S630,, and the like.

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.

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_{12-15}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_{12-18})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 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.

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).

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 $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(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;

(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;

(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 $n>1$;

(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;

(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;

(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;

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

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

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.

Particularly preferred surface stabilizers include, but are not limited to, polymeric surface stabilizers, particularly when in combination with sodium lauryl sulfate and/or dioctyl sodium sulfosuccinate (DOSS), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), polyvinylpyrrolidone, Plasdone® S-630, which is a random copolymer of vinyl acetate and vinyl pyrrolidone, and combinations thereof.

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

3. Nanoparticulate Carvedilol Particle Size

The compositions of the invention comprise nanoparticulate carvedilol particles which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns), 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 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about

130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the carvedilol particles have a particle size of less than the effective average, by weight or by other suitable measurement techniques (i.e., by volume, number, etc.), *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.* (as listed above), 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 carvedilol particles (e.g., D60, D70, D80, D90, D95, and D99 particle size, respectively), by weight or by other suitable measurement techniques (i.e., by volume, number, etc.), have a particle size of less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, *etc.* In another embodiment of the invention, the "effective average particle size" as described above is the mean particle size of the composition (i.e., the invention encompasses a composition having a mean particle size of less than about 2000 nm, . . . less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, etc.).

In the invention, the value for D50 of a nanoparticulate carvedilol composition is the particle size below which 50% of the carvedilol particles fall, by weight or by other suitable measurement techniques (i.e., by volume, number, etc.). Similarly, D90 is the particle size below which 90% of the carvedilol particles fall, by weight or by other suitable measurement techniques (i.e., by volume, number, etc.), and D99 is the particle size below which 99% of the carvedilol particles fall, by weight or by other suitable measurement techniques (i.e., by volume, number, etc.).

4. Concentration of Carvedilol and Surface Stabilizers

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

In one embodiment, the concentration of carvedilol 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 weight of carvedilol and at least one surface stabilizer, not including other excipients.

In another embodiment, the concentration of 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 carvedilol and at least one surface stabilizer, not including other excipients.

5. Exemplary Nanoparticulate Carvedilol Tablet Formulations

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

Exemplary Nanoparticulate Carvedilol Tablet Formulation #1	
Component	**g/kg**
Carvedilol	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 Carvedilol Tablet Formulation #2	
Component	**g/kg**
Carvedilol	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 Carvedilol Tablet Formulation #3	
Component	**g/kg**
Carvedilol	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

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Exemplary Nanoparticulate Carvedilol Tablet Formulation #4	
Component	**g/kg**
Carvedilol	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

E. Methods of Making Carvedilol Formulations

In another aspect of the invention there is provided a method of preparing the nanoparticulate carvedilol formulations of the invention. The compositions of the invention can be made using, for example, milling (including but not limited to wet milling), homogenization, precipitation, evaporation, freezing, template emulsion techniques, supercritical fluid techniques, nano-electrospray techniques, or any combination thereof. Exemplary methods of making nanoparticulate active agent compositions are described in U.S. Patent No. 5,145,684. Methods of making nanoparticulate active agent 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.

Following preparation of a nanoparticulate carvedilol composition by any suitable method, the resultant carvedilol composition can be utilized in a suitable dosage form for administration.

For milling and homogenization, preferably the dispersion medium used for the size reduction process is aqueous. However, any medium in which carvedilol is poorly soluble and dispersible can be used as a dispersion medium. Non-aqueous examples of dispersion medium include, but are not limited to, aqueous salt solutions, safflower oil and solvents such as ethanol, t-butanol, hexane, and glycol.

Carvedilol can be added to a liquid medium in which it is essentially insoluble to form a premix. The surface stabilizer can be present in the premix, it can be during particle size reduction, or it can be added to the drug dispersion following particle size reduction.

The premix can be used directly by subjecting it to mechanical means to reduce the average carvedilol particle size in the dispersion to the desired size, preferably less than about 5 microns. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, carvedilol and a surface stabilizer can be dispersed in the liquid medium 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 premilling dispersion step when a recirculating media mill is used for attrition.

Effective methods of providing mechanical force for particle size reduction of carvedilol include but are not limited to ball milling, media milling, and homogenization, for example, with a Microfluidizer® (Microfluidics Corp.).

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.

Preferably, the carvedilol particles are reduced in size at a temperature which does not significantly degrade carvedilol. 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 with a cooling liquid, 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.

1. Milling to Obtain Nanoparticulate Carvedilol Dispersions

Milling carvedilol to obtain a nanoparticulate dispersion comprises dispersing the carvedilol particles in a liquid dispersion medium in which the carvedilol is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the carvedilol to the desired effective average particle size. The grinding media may homogeneous or heterogeneous with respect to media size and composition depending on the desired size range and particle stabilizer(s) selected. The term milling is defined to include any method where there is an input force to a particle system to generate shearing forces within said system resulting in a reduction of the particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. A preferred dispersion medium is water.

The carvedilol particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the carvedilol particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the carvedilol/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

In one embodiment of the invention, a mixture of a carvedilol and one or more

surface stabilizers is heated during the milling process. If a polymeric surface stabilizer is utilized, the temperature is raised to above the cloud point of the polymeric surface stabilizer but below the actual or depressed melting point of carvedilol. The utilization of heat may be important for scale up of the milling process, as it can aid in the solubilization of the one or more active agents.

The mechanical means applied to reduce the carvedilol particle size conveniently 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. 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 but are in no way limiting.

Media milling is a high energy milling process. Carvedilol, surface stabilizer, and liquid are placed in a reservoir and recirculated in a chamber containing media and a rotating shaft/impeller. The rotating shaft agitates the media which subjects carvedilol to impaction and sheer forces, thereby reducing the carvedilol particle size.

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.

Grinding Media

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, and glass grinding media are exemplary grinding materials.

The grinding media can comprise particles that are preferably substantially spherical in shape, *e.g.*, beads, consisting essentially of polymeric resin or glass or Zirconium Silicate or other suitable compositions. Alternatively, the grinding media can comprise a core having a coating of a polymeric resin adhered thereon.

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. The polymeric resin can have a density from about 0.8 to about 3.0 g/cm^3.

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.

In one embodiment of the invention, the carvedilol particles are made continuously. Such a method comprises continuously introducing carvedilol into a milling chamber, contacting the carvedilol with grinding media while in the chamber to

reduce the carvedilol particle size, and continuously removing the nanoparticulate carvedilol from the milling chamber.

The grinding media can be separated from the milled nanoparticulate carvedilol 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. Alternatively, a screen can be utilized during the milling process to remove the grinding media following completion of particle size reduction.

2. Precipitation to Obtain Nanoparticulate Carvedilol Compositions

Another method of forming the desired nanoparticulate carvedilol 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 carvedilol 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.

3. Homogenization to Obtain Nanoparticulate Carvedilol Compositions

Homogenization is a technique that does not use milling media. Carvedilol, surface stabilizer, and liquid (or carvedilol and liquid with the surface stabilizer added after carvedilol particle size reduction) constitute a process stream propelled into a process zone, which in the Microfluidizer® is called the Interaction Chamber. 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 carvedilol 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. U.S. Patent No. 5,510,118, which is specifically incorporated by reference, refers to a process using a Microfluidizer® resulting in nanoparticulate active agent particles. Other compounds, such as a diluent, can be added to the carvedilol/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

4. Cryogenic Methodologies to Obtain Nanoparticulate Carvedilol Compositions

Another method of forming the desired nanoparticulate carvedilol compositions is by spray freezing into liquid ("SFL"). This technology comprises an organic or organoaqueous solution of carvedilol with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the carvedilol solution freeze at a rate sufficient to minimize crystallization and particle growth, thus formulating nanostructured carvedilol particles. Depending on the choice of solvent system and processing conditions, the nanoparticulate carvedilol 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 carvedilol particles.

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

5. Emulsion Methodologies to Obtain Nanoparticulate Carvedilol Compositions

Another method of forming the desired nanoparticulate carvedilol composition is by template emulsion. Template emulsion creates nanostructured carvedilol 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 carvedilol and stabilizers. The particle size distribution of the carvedilol particles is a direct result of the size of the emulsion droplets prior to loading with the carvedilol 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 carvedilol particles are recovered. Various carvedilol particles morphologies can be achieved by appropriate control of processing conditions.

6. Supercritical Fluid Techniques Used to Obtain Nanoparticulate Carvedilol Compositions

Published International Patent Application No. WO 97/14407 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. A "supercritical fluid" is any substance at a temperature and pressure above its thermodynamic critical point. Common examples of supercritical fluids include, but are not limited to, carbon dioxide, ethane, ethylene, propane, propylene, trifluoromethane (fluoroform), chlorotrifluoromethane, trichlorofluoromethane, ammonia, water, cyclohexane, n-pentane and toluene.

7. Nano-Electrospray Techniques Used to Obtain Nanoparticulate Carvedilol Compositions

In electrospray ionization a liquid is pushed through a very small charged, usually metal, capillary. This liquid contains the desired substance, e.g., carvedilol (or "analyte"),

dissolved in a large amount of solvent, which is usually much more volatile than the analyte. Volatile acids, bases or buffers are often added to this solution as well. The analyte exists as an ion in solution either in a protonated form or as an anion. As like charges repel, the liquid pushes itself out of the capillary and forms a mist or an aerosol of small droplets about 10 μm across. This jet of aerosol droplets is at least partially produced by a process involving the formation of a Taylor cone and a jet from the tip of this cone. A neutral carrier gas, such as nitrogen gas, is sometimes used to help nebulize the liquid and to help evaporate the neutral solvent in the small droplets. As the small droplets evaporate, suspended in the air, the charged analyte molecules are forced closer together. The drops become unstable as the similarly charged molecules come closer together and the droplets once again break up. This is referred to as Coulombic fission because it is the repulsive Coulombic forces between charged analyte molecules that drive it. This process repeats itself until the analyte is free of solvent and is a lone ion.

In nanotechnology the electrospray method may be employed to deposit single particles on surfaces, e.g., particles of carvedilol. This is accomplished by spraying colloids and making sure that on average there is not more than one particle per droplet. Consequent drying of the surrounding solvent results in an aerosol stream of single particles of the desired type. Here the ionizing property of the process is not crucial for the application but may be put to use in electrostatic precipitation of the particles.

F. Method of Treatment

The present invention is also directed to methods treatment or prevention using the nanoparticulate carvedilol compositions of the invention for conditions such as hypertension, congestive heart failure, cancer, viral infections, psychosis-related conditions such as tardive dyskinesia, tardive dystonia and tardive akathisia, and related conditions. In addition, the nanoparticulate carvedilol compositions of the invention are useful for improving the treatment of mental disorders in which dopamine blocking medications are used, such as manic episodes, major depressive episodes and psychoses, particularly schizophrenia and schizoaffective disorder.

For example, the nanoparticulate carvedilol compositions may be used to treat or prevent high blood pressure, congestive heart failure, and related conditions. In addition, the nanoparticulate carvedilol compositions may be used to treat a cancer, such as cancers of the colon, ovary, breast, prostate, pancreas, lung, melanoma, glioblastoma, oral cancer, and leukemias. The compositions of the invention are particularly useful in treating cancers mediated by epidermal growth factor and/or platelet derived growth of cancer cells, Protein kinase C (PKC) activity, and/or cyclooxygenase 2 enzyme.

Such treatment comprises administering to the subject the nanoparticulate carvedilol formulation of the invention. 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.

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 nanoparticulate compositions 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.

One of ordinary skill will appreciate that effective amounts of carvedilol 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 carvedilol in the nanoparticulate compositions of the invention may be varied to obtain an

amount of carvedilol 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 carvedilol the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily or other suitable dosing period (e.g., such as every other day, weekly, bi-weekly, monthly, etc.) 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.

* * * *

The following examples are 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 these examples 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

The purpose of this example was to prepare a nanoparticulate carvedilol formulation.

An aqueous dispersion of 5% (w/w) carvedilol (Verion, Inc. (Lionville, PA)) was combined with 1.25% (w/w) hydroxypropyl cellulose (HPC-SL) and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS). This mixture was then milled in a roller mill (U.S. Stoneware, Mahwah, NJ) using a 50% media load with 0.8 mm Yittium treated zirconia media (Tosoh, Ceramics Division) for 46 hours at 170 rpm.

Microscopy of the milled carvedilol sample, using a Lecia DM5000B and Lecia CTR 5000 light source (Laboratory Instruments and Supplies Ltd., Ashbourne Co.,

Meath, Ireland), showed well dispersed discrete particles. The sample appeared acceptable.

Following milling, the particle size of the milled carvedilol particles was measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The mean milled carvedilol particle size was 160 nm, with a D90 of less than 228 nm. The pH of the nanoparticulate carvedilol dispersion was 9.6.

Following three days of storage at room temperature, the carvedilol particles remained in dispersion (i.e., no precipitation or crystal growth observed), with no visible particle size growth or agglomeration observed. After the three day period, the mean carvedilol particle size was 163 nm, with a D90 of less than 229 nm.

Stability of the nanoparticulate carvedilol dispersion was then measured in simulated biological fluids. For testing in simulated biological fluids, the composition was incubated at 40°C for 1 hour in simulated gastric fluid (sodium chloride and pepsin in HCl and water), 0.01 N HCl (which simulates typical acidic conditions found in the stomach), and simulated intestinal fluid (Monobasic potassium phosphate, water, sodium hydroxide, and pancreatin). The results are show in Table 1, below.

Table 1: Stability of the Nanoparticulate Carvedilol Composition in Simulated Biological Fluids

Composition	Simulated Gastric Fluid	0.01 N HCl	Simulated Intestinal Fluid
5% carvedilol 1.25% HPC-SL 0.05% DOSS	particle growth	acceptable	slight agglomeration

The results demonstrate that the nanoparticulate carvedilol composition is stable at room temperature. Moreover, the composition does not exhibit significant particle size growth when incubated in simulated biological fluids. These results are predictive of excellent *in vivo* bioavailability.

Example 2

The purpose of this example was to prepare a nanoparticulate carvedilol formulation.

An aqueous dispersion of 5% (w/w) carvedilol (Verion, Inc. (Lionville, PA)) was combined with 1.25% (w/w) hydroxypropylmethyl cellulose (HPMC) and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS). This mixture was then milled on a roller mill (U.S. Stoneware, Mahwah, NJ), using 0.8 mm Yittrium treated zirconia attrition media (Tosoh, Ceramics Division) (50% media load). The mixture was milled at a speed of 170 rpms for 46 hours.

Microscopy of the nanoparticulate carvedilol sample, using a Lecia DM5000B and Lecia CTR 5000 light source (Laboratory Instruments and Supplies Ltd., Ashbourne Co., Meath, Ireland), showed well dispersed discrete particles. The sample appeared acceptable.

Following milling, the particle size of the milled carvedilol particles was measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The mean milled carvedilol particle size was 160 nm, with a D90 of less than 235 nm. The pH of the milled carvedilol dispersion was 9.8.

Following three days of storage at room temperature, the carvedilol particles remained in dispersion (i.e., no precipitation or crystal growth observed), with no visible particle size growth or agglomeration observed. After the three day period, the mean carvedilol particle size was 157 nm, with a D90 of less than 223 nm.

Stability of the nanoparticulate carvedilol dispersion was then measured in simulated biological fluids. For testing in simulated biological fluids, the composition was incubated at 40°C for 1 hour in simulated gastric fluid (sodium chloride and pepsin in HCl and water), 0.01 N HCl (which simulates typical acidic conditions found in the stomach), and simulated intestinal fluid (Monobasic potassium phosphate, water, sodium hydroxide, and pancreatin). The results are show in Table 2, below.

Table 2: Stability of the Nanoparticulate Carvedilol Composition in Simulated Biological Fluids

Composition	Simulated Gastric Fluid	0.01 N HCl	Simulated Intestinal Fluid
5% carvedilol 1.25% HPMC 0.05% DOSS	particle growth	acceptable	agglomeration

The results demonstrate that the nanoparticulate carvedilol composition is stable at room temperature. Moreover, the composition does not exhibit significant particle size growth when incubated in simulated biological fluids, although the formulation prepared in Example 1 demonstrated less agglomeration when incubated in simulated intestinal fluid. These results are predictive of good *in vivo* bioavailability.

Example 3

The purpose of this example was to prepare a nanoparticulate carvedilol formulation.

An aqueous dispersion of 5% (w/w) carvedilol (Verion, Inc. (Lionville, PA)) was combined with 1.25% (w/w) polyvinylpyrrolidone (PVP) and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS). This mixture was then milled on a roller mill (U.S. Stoneware, Mahwah, NJ) using 0.8 mm Yittrium treated zirconia attrition media (Tosoh, Ceramics Division) (50% media load). The mixture was milled at a speed of 170 rpms for 5 days.

Microscopy of the milled carvedilol sample, using a Lecia DM5000B and Lecia CTR 5000 light source (Laboratory Instruments and Supplies Ltd., Ashbourne Co., Meath, Ireland), showed well dispersed discrete particles. The sample appeared acceptable.

Following milling, the particle size of the milled carvedilol particles was measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The mean milled carvedilol particle size was 107 nm, with a D90 of less than 167 nm. The pH of the milled carvedilol dispersion was 9.2.

Stability of the nanoparticulate carvedilol dispersion was then measured in simulated biological fluids. For testing in simulated biological fluids, the composition was incubated at 40°C for 1 hour in simulated gastric fluid (sodium chloride and pepsin in HCl and water), 0.01 N HCl (which simulates typical acidic conditions found in the stomach), and simulated intestinal fluid (Monobasic potassium phosphate, water, sodium hydroxide, and pancreatin). The results are show in Table 3, below.

Table 3: Stability of the Nanoparticulate Carvedilol Composition in Simulated Biological Fluids

Composition	Simulated Gastric Fluid	0.01 N HCl	Simulated Intestinal Fluid
5% carvedilol 1.25% PVP 0.05% DOSS	particle growth	acceptable	slight agglomeration

The results demonstrate that the nanoparticulate carvedilol composition does not exhibit significant particle size growth when incubated in simulated biological fluids. These results are predictive of excellent *in vivo* bioavailability.

Example 4

The purpose of this example was to prepare a nanoparticulate carvedilol formulation.

An aqueous dispersion of 5% (w/w) carvedilol (Verion, Inc. (Lionville, PA)) was combined with 1.25% (w/w) Pluronic® S-630 (a random copolymer of vinyl acetate and vinyl pyrrolidone) and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS). This mixture was then milled on a roller mill (U.S. Stoneware, Mahwah, NJ) using 0.8 mm Yittrium treated zirconia attrition media (Tosoh, Ceramics Division) (50% media load). The mixture was milled at a speed of 170 rpms for 46 hours.

Microscopy of the nanoparticulate carvedilol sample, using a Lecia DM5000B and Lecia CTR 5000 light source (Laboratory Instruments and Supplies Ltd., Ashbourne Co., Meath, Ireland), showed well dispersed discrete particles. The sample appeared acceptable.

Following milling, the particle size of the milled carvedilol particles was measured, in deionized distilled water, using a Horiba LA 910 particle size analyzer. The mean milled carvedilol particle size was 189 nm, with a D90 of less than 279 nm. The pH of the milled carvedilol dispersion was 8.9.

Following three days of storage at room temperature, the carvedilol particles remained in dispersion (i.e., no precipitation or crystal growth observed), with no visible

particle size growth or agglomeration observed. After the three day period, the mean carvedilol particle size was 160 nm, with a D90 of less than 224 nm.

Stability of the nanoparticulate carvedilol dispersion was then measured in simulated biological fluids. For testing in simulated biological fluids, the composition was incubated at 40°C 1 hour in simulated gastric fluid (sodium chloride and pepsin in HCl and water), 0.01 N HCl (which simulates typical acidic conditions found in the stomach), and simulated intestinal fluid (Monobasic potassium phosphate, water, sodium hydroxide, and pancreatin). The results are show in Table 4, below.

Table 4: Stability of the Nanoparticulate Carvedilol Composition in Simulated Biological Fluids

Composition	Simulated Gastric Fluid	0.01 N HCl	Simulated Intestinal Fluid
5% carvedilol 1.25% S-630 0.05% DOSS	particle growth	acceptable	agglomeration

The results demonstrate that the nanoparticulate carvedilol composition is stable at room temperature. Moreover, the composition does not exhibit significant particle size growth when incubated in simulated biological fluids, although the formulation prepared in Examples 1 and 3 demonstrated less agglomeration when incubated in simulated intestinal fluid. These results are predictive of good *in vivo* bioavailability.

* * * * *

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 invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

WE CLAIM:

1. A stable nanoparticulate carvedilol composition comprising:
   (a) particles of a carvedilol, a salt thereof, or an optically active isomer 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 carvedilol 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, wherein the effective average particle size of the nanoparticulate carvedilol particles 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 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450

nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm.

4. The composition of claim 3, wherein the "effective average particle size" is selected from the group consisting of a mean, D50, D60, D70, D80, D90, D95, and a D99 particle size.

5. The composition of claim 1, wherein the composition is formulated:

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

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

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

(d) any combination thereof.

6. The composition of claim 5, wherein the carvedilol composition is formulated into a controlled release dosage form.

7. The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

8. The composition of claim 1, wherein:

(a) carvedilol 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 weight of carvedilol and at least one surface stabilizer, not including other excipients;

(b) at least one surface stabilizer is present in an amount selected from the group consisting of from 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 carvedilol and at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

9. The composition of claim 1, wherein at least one surface stabilizer is selected from the group consisting of a non-ionic surface stabilizer, an ionic surface stabilizer, an anionic surface stabilizer, a cationic surface stabilizer, and a zwitterionic surface stabilizer.

10. The composition of claim 1, wherein at least one surface stabilizer is selected from the group consisting of albumin, human serum albumin, bovine albumin, 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, 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 (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

11. The composition of claim 1, wherein the AUC of carvedilol, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate carvedilol formulation, administered at the same dosage;

12. The composition of claim 1, wherein the C_{max} of carvedilol, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a non-nanoparticulate carvedilol formulation, administered at the same dosage.

13. The composition of claim 1, wherein the T_{max} of carvedilol, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a non-nanoparticulate carvedilol formulation, administered at the same dosage.

14. The composition of claim 1, wherein the composition has a similar rate of absorption when administered to a human under fed conditions as compared to fasting conditions.

15. The composition of claim 1, wherein the composition exhibits bioequivalence upon administration to a human subject in a fed state as compared to administration to a human subject in a fasted state. .

16. The composition of claim 15, wherein bioequivalency is established by:

(a) a 90% Confidence Interval for AUC which is between 80% and 125%; and

(b) a 90% Confidence Interval for C_{max}, which is between 80% and 125%.

17. The composition of claim 1 formulated into a solid dosage form, wherein upon administration the carvedilol particles redisperse to an effective average particle size of less than about 2 microns.

18. The composition of claim 17, wherein the redispersed carvedilol particle size 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 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than

about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm.

19. The composition of claim 1 formulated into a solid dosage form, wherein the carvedilol particles redisperses in a biorelevant medium such that the redispersed particles of carvedilol have an effective average particle size of less than about 2000 nm.

20. The composition of claim 19, wherein the redispersed particles of carvedilol have an effective average particle size 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 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than

about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm.

21. The composition of claim 1, additionally comprising one or more non- carvedilol active agents.

22. The composition of claim 21, wherein the one or more non-carvedilol active agents is selected from the group consisting of antihypertensives, active agents useful in treating congestive heart failure, and active agents useful in treating cardiovascular disorders.

23. The composition of claim 22, wherein the one or more non-carvedilol active agents is selected from the group consisting of digoxin, nitrates, diuretics, beta blockers,

alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers.

24. A method of making a nanoparticulate carvedilol composition comprising:

contacting particles of carvedilol, an optically active isomer thereof, or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a carvedilol composition having an effective average particle size of less than about 2 microns.

25. The method of claim 24, wherein the contacting comprises milling, wet milling, homogenizing, precipitation, evaporation, freezing, supercritical fluid particle generation, template emulsion techniques, nano-electrospray techniques, or a combination thereof.

26. A method for treating or preventing hypertension comprising administering to a subject in need an effective amount of a composition comprising:

(a) carvedilol nanoparticles having an effective average particle size of less than about 2 microns;

(b) at least one surface stabilizer; and

(c) at least one pharmaceutically acceptable carrier.

27. A method for treating congestive heart failure comprising administering to a subject in need an effective amount of a composition comprising:

(a) carvedilol nanoparticles having an effective average particle size of less than about 2 microns;

(b) at least one surface stabilizer; and

(c) at least one pharmaceutically acceptable carrier.