Title: COMBINATION OF (S)-AMLODIPINE AND AN ACE INHIBITOR, AND METHODS FOR REDUCING HYPERTENSION

Abstract: The present invention generally relates to pharmaceutical compositions comprising optically pure (S)-amlodipine and an ACE inhibitor. In a preferred embodiment the (S)-amlodipine is (S)-amlodipine-L-malate, or a polymorph, pseudopolymorph or solvate thereof. In a preferred embodiment, the ACE inhibitor is ramipril. The pharmaceutical compositions of the invention are useful in the treatment of hypertension. The present invention also relates to a method of treating a patient suffering from hypertension or a cardiac disorder, comprising co-administering a therapeutically effective amount of optically pure (S)-amlodipine and an ACE inhibitor. In a preferred embodiment the (S)-amlodipine is (S)-amlodipine-L-malate, or a polymorph, pseudopolymorph or solvate thereof. In a preferred embodiment, the ACE inhibitor is ramipril.
COMBINATION OF (S)-AMLODIPINE AND AN ACE INHIBITOR, AND METHODS FOR REDUCING HYPERTENSION

Related Applications

This application claims the benefit of priority to United States Provisional Patent Application serial number 60/545,451, filed February 18, 2004; United States Provisional Patent Application serial number 60/554,030, filed March 16, 2004; and United States Provisional Patent Application serial number 60/xxx,xxx, filed February 3, 2005. The contents of all of them are incorporated by reference.

Background of the Invention

Treatments for cardiovascular disease have evolved rapidly over the last few decades from the early diuretics and natural products, such as rauwolfia serpentina, to the new agents, such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and calcium-channel blockers (CCB). In efforts to achieve improved treatments for hypertension and related cardiovascular diseases, a number of agents in each of these classes have been developed. Some of the conditions for which ACE inhibitors or calcium-channel blockers have been used or are believed useful include hypertension, angina, myocardial infarction, atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache.

The renin-angiotensin-aldosterone system ("RAAS") is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension, a precursor condition implicated in the progression of more serious cardiovascular diseases, such as congestive heart failure. Activation of the renin-angiotensin-aldosterone system begins with secretion of the enzyme renin from the juxtaglomerular cells in the kidney. The enzyme renin acts on a naturally-occurring substrate, angiotensinogen, to release a decapeptide, angiotensin I. This decapeptide is cleaved by angiotensin-converting enzyme ("ACE") to provide an octapeptide, angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects, such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing positive cardiac inotropic effect and modulating other hormonal systems.
ACE inhibitors inhibit angiotensin-converting enzyme, thereby blocking conversion of angiotensin I to angiotensin II. The principal pharmacological and clinical effects of ACE inhibitors arise from suppression of the synthesis of angiotensin II. Inhibition of the biosynthesis of angiotensin II can result in lower blood pressure levels, especially in animals and humans whose hypertension is angiotensin II related. ACE inhibitors are effective antihypertensive agents in a variety of animal models and they are clinically useful for the treatment of hypertension and heart conditions, such as angina in humans.

Calcium-channel blockers are a chemically diverse class of compounds having important therapeutic value in the control of a variety of diseases including several cardiovascular disorders, such as hypertension, angina, and cardiac arrhythmias. See Fleckenstein in *Experimental Facts and Therapeutic Prospects*, John Wiley, New York (1983); and D. McCall *Curr. Pract. Cardiol.* 1985, 10, 1-11. Calcium-channel blockers prevent or slow the entry of calcium into cells by regulating cellular calcium channels. (Remington, *The Science and Practice of Pharmacy*, Nineteenth Edition, Mack Publishing Company, Eaton, Pa., p. 963 (1995)). The regulation of calcium entry into the cells of the cardiovascular system is of paramount importance to the proper functioning of this system. Cardiac and vascular smooth muscle cells have calcium channels within the cell membrane. Calcium influx through these channels initiates a process of electromechanical coupling which ultimately leads to muscle contraction. The ability to regulate the entry of calcium into cardiac and vascular smooth muscle cells is a powerful therapeutic approach in the treatment of angina and hypertension, respectively. Likewise, blocking calcium influx into cardiac tissues and conduction systems provides a useful approach to control certain types of arrhythmia.

Calcium-channel blockers are also believed to be useful in the treatment of other disorders in which the regulation of calcium plays a role in normal hemostasis. Such disorders include, for example, pulmonary hypertension, peripheral vascular disease, mild congestive heart failure, hypertrophic subaortic stenosis, protection against ischemic injury, stroke, migraine, tumor resistance to anti-neoplastic drugs, achalasia, esophageal spasms, bronchial asthma, premature labor, dysmenorrhea, and enhancement of success in renal transplantation. (Remington, *The Science and Practice of Pharmacy*, Nineteenth Edition, Mack Publishing Company, Eaton, Pa., p. 963 (1995)).

Cellular calcium flux is regulated by receptor-operated and voltage-dependent channels, which are sensitive to inhibition by calcium entry blockers. The term calcium
antagonist was introduced by Fleckenstein when two drugs, prenylamine and verapamil, originally found as coronary dilators in the LANGENDORFF-experiment, were shown to mimic the cardiac effects of simple Ca$^{2+}$-withdrawal, diminishing Ca$^{2+}$-dependent high energy phosphate utilization, contractile force, and oxygen requirement of the beating heart without impairing the Na$^+$-dependent action potential parameters. These effects were clearly distinguishable from β-receptor blockade and could promptly be neutralized by elevated Ca$^{2+}$, β-adrenergic catecholamines, or cardiac glycosides, measures that restore the Ca$^{2+}$ supply to the contractile system. In the following years many Ca$^{2+}$-antagonists were introduced to therapy. Specific Ca$^{2+}$-antagonists interfere with the uptake of Ca$^{2+}$ into the myocardium and prevent myocardial necrotization arising from deleterious intracellular Ca$^{2+}$ overload. They act basically as specific inhibitors of the slow transsarcolemmal Ca$^{2+}$ influx, but do not or only slightly affect the fast Na$^+$ current that initiates normal myocardial excitation.

Amlodipine is a dihydropyridine calcium-channel blocker that is used to treat hypertension. Amlodipine is known to exist in two chiral forms designated (S)-amlodipine and (R)-amlodipine. The S-enantiomer is known to be much more active than the R-enantiomer. Importantly, administration of only (S)-amlodipine avoids the adverse effects including headache and edema, dizziness, flushing, palpitation, fatigue, nausea, abdominal pain and somnolence which are associated with administration of racemic amlodipine. (S)-Amlodipine is useful in treating cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, heart failure, coronary vasospasm, myocardial infarction, renal impairment, viral infection, thrombosis, atherosclerosis, peripheral vascular disease, migraine headache, restenosis following vascular surgery or injury and acute renal failure while avoiding the above-described adverse effects associated with the administration of the racemic mixture of amlodipine.

More effective treatments are needed for hypertension and related cardiovascular disorders. In particular, new therapeutic treatments are needed which cause a more substantial reduction in blood pressure while minimizing the negative side effects associated with taking such agents. Therapeutic compositions comprising optically pure (S)-amlodipine and an ACE inhibitor will fulfill this need and provide other related advantages.
Summary of the Invention

The present invention generally relates to pharmaceutical compositions comprising optically pure (S)-amlodipine and an ACE inhibitor. In a preferred embodiment the (S)-amlodipine is (S)-amlodipine-L-malate, or a polymorph, pseudopolymorph or solvate thereof. In a preferred embodiment, the ACE inhibitor is ramipril. The pharmaceutical compositions of the invention are useful in the treatment of hypertension.

The present invention also relates to a method of treating a patient suffering from hypertension or a cardiac disorder, comprising co-administering a therapeutically effective amount of optically pure (S)-amlodipine and an ACE inhibitor. In a preferred embodiment the (S)-amlodipine is (S)-amlodipine-L-malate, or a polymorph, pseudopolymorph or solvate thereof. In a preferred embodiment, the ACE inhibitor is ramipril.

Brief Description of Figures

Figure 1 depicts a procedure for the preparation of (S)-amlodipine-L-malate. If the free base of (S)-amlodipine is used as the starting material, then the first step (NaOH/MTBE) may be omitted.

Figure 2 depicts a procedure for the preparation of (S)-amlodipine hemi-D-tartrate DMAC solvate.

Figure 3 depicts a procedure for the preparation of (S)-amlodipine free base from (S)-amlodipine hemi-D-tartrate DMAC solvate.

Figure 4 depicts a procedure for the preparation of (S)-amlodipine-L-malate from (S)-amlodipine free base.

Detailed Description of the Invention

1. Overview

The present invention relates generally to pharmaceutical compositions containing two or more active agents that when taken together reduce hypertension. In certain embodiments, the present invention relates to a pharmaceutical composition comprising optically pure (S)-amlodipine and an ACE inhibitor. Another aspect of the present invention relates to a method of treating a patient suffering from hypertension, comprising the step of co-administering to said patient a therapeutically effective amount of optically pure (S)-amlodipine and an ACE inhibitor. In a preferred embodiment the (S)-amlodipine is (S)-amlodipine-L-malate, or a polymorph, pseudopolymorph or solvate thereof. In a preferred embodiment, the ACE inhibitor is ramipril.
2. Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (d)-isomers, (l)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as ACE inhibitors), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in binding to sigma receptors. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

As used herein, the term “optically pure” means that an active ingredient (e.g., (S)-amlodipine) for use in the compositions or methods of the present invention contains a significantly greater proportion of the specified enantiomer in relation to the non-specified enantiomer. For example, optically pure (S)-amlodipine contains a significantly greater proportion of the (S)-enantiomer in relation to the (R)-enantiomer. In a preferred
embodiment, compositions including the optically pure active ingredients contain at least 90% by weight of the specified enantiomer and 10% by weight or less of the non-specified enantiomer. More preferably, such compositions contain at least 95% by weight of the specified enantiomer and 5% by weight or less of the non-specified enantiomer. Even more preferably, such compositions contain at least 99% by weight of the specified enantiomer and 1% by weight or less of the non-specified enantiomer. These percentages are based upon the total amount of the active ingredient.

The terms “co-administration” and “co-administering” refer to both concurrent administration (administration of two or more therapeutic agents at the same time) and time varied administration (administration of one or more therapeutic agents at a time different from that of the administration of an additional therapeutic agent or agents), as long as the therapeutic agents are present in the patient to some extent at the same time.

The term “antagonist” refers to a compound that binds to a receptor site, but does not cause any physiological changes.

The terms “inverse agonist” and “negative antagonist” and “neutral antagonist” refer to compounds that inhibit an unoccupied, but active receptor.

The term “patient” refers to a mammal in need of a particular treatment. In a preferred embodiment, a patient is a primate, canine, feline, or equine. In another preferred embodiment, a patient is a human.

The term “solvate” refers to a pharmaceutically acceptable form of a specified compound, with one or more solvent molecules, that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with solvents such, for example, water (to form the hydrate), isopropanol, ethanol, methanol, dimethyl sulfoxide, ethyl acetate, acetic acid, ethanolamine, or acetone. Also included are formulations of solvate mixtures such as a compound of the invention in combination with two or more solvents.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

3. (S)-Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine is known to exist in two chiral forms
designated (S)-amlodipine and (R)-amlodipine. The S-enantiomer is known to be much more active than the R-enantiomer. Methods of treatment using (S)-amlodipine are described in U.S. Patent 6,476,058. See Burges et al. Cardiovas Drug Dev. 1990, 8, 25-44 for a review of amlodipine. Amlodipine, its pharmaceutically acceptable salts, routes of administration, dosages, and formulations are described in U.S. Patents 4,572,909 and 4,879,303. The chemical name of (S)-amlodipine is (S)-3-Ethyl-5-1-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate and the structure is presented below.

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&\text{O} \\
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&\text{NH}_2 \\
&\text{O} \\
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\end{align*}
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(S)-Amlodipine can be prepared by separation of the R- and S-enantiomers via fractional crystallization of diastereomeric mixtures formed by basic resolving agents and racemic carboxylic-acid-containing precursors of amlodipine. See T. Shibanuma et al. Chem. Pharm. Bull. 1980, 28(9), 2809-2812 and M. Eltze et al. Chirality 1990, 2, 233-240. In particular, (S)-amlodipine may be obtained by resolution of the corresponding racemic 4-aryl-1-ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethylpyridine-3-carboxylic acids followed by subsequent alkylation and esterification as described in WO 88/07524 and WO 88/07525. Optically pure cinchonine and cinchonidine salts are basic resolving agents that have proven useful in the resolution of amlodipine. In fact, a technique for separation of the (S)-amlodipine isomer from the racemic mixture has been illustrated schematically by J. E. Arrowsmith in EP 331,315. See also U.S. Published Patent Application 20020010200. Procedures for synthesis of racemic amlodipine can be found in Arrowsmith, J. E. et al. J. Med. Chem. 1986, 29, 1696 and U.S. Patents 4,572,909 and 5,438,145.

Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The (S) isomer has been reported to be more active than the (R) isomer.
Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

The metabolites of amlodipine apparently do not possess significant calcium-channel blocking activity, while the parent drug offers a biological half-life of some 35-40 hours, prompting a once-daily dosage regimen (Lorimer, A. R. et al. J. Hum. Hypertens. 1989, 3, 191-96; Glasser, S. F. et al. A.J.H. 1989, 2, 154-57). Its ability to block calcium channels in smooth muscle produces peripheral vasodilation resulting in decreases in both systolic and diastolic blood pressure.


After oral administration of therapeutic doses of racemic amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

Patients with renal failure may therefore receive the usual initial dose. Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose may be required.
Following administration of therapeutic doses to patients with hypertension, racemic amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina. With chronic once daily oral administration of racemic amlodipine, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg). As with other calcium-channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to-man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects. In a double-blind, placebo-controlled clinical trial involving 118 patients with well compensated heart failure (NYHA Class II and Class III), treatment with racemic amlodipine did not lead to worsened heart failure, based on measures of exercise tolerance, left ventricular ejection fraction and clinical symptomatology. Studies in patients with NYHA Class IV heart failure have not been performed and, in general, all calcium-channel blockers should be used with caution in any patient with heart failure. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.
The size of a prophylactic or therapeutic dose of (S)-amlodipine, or one of its salts, in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 0.5 mg to about 50 mg. Preferably, a daily dose range should be between about 1 mg to about 25 mg. Most preferably, a daily dose range should be between about 1 mg to about 10 mg. In certain embodiments, the daily dose range should be about 2, 4, 6, or 8 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 0.05 mg to about 1 mg and increased up to about 5 mg or higher depending on the patient’s global response.

(S)-Amlodipine may be useful in the treatment of cerebral ischemia. Cerebral ischemia, often the result of atherosclerotic disease or hypertension, results from insufficient cerebral circulation. Under normal circumstances, an extensive collateral circulation ensures adequate blood flow. However, cerebral ischemia may result from either an intra- or extracranial interruption of arterial blood flow. If interruption is transient, the cerebral tissues recover, and neurologic symptoms disappear. If the ischemia lasts for a somewhat more extended period, infarction results and the resulting neurologic damage is permanent. In the case of extended ischemia resulting in infarction, treatment is directed to the underlying vascular disease, to blood platelet aggregation inhibitors, and anticoagulant therapy.

Because of its activity as a calcium channel antagonist, (S)-amlodipine may also be useful in treating cardiac arrhythmias. Cardiac arrhythmias represent a broad, complex group of electrophysiologic disorders that affect the mechanical properties of the heart and vasculature, altering normal cardiac rhythm, function and output. Normal cardiac rhythm originates with the sinoatrial node, which possesses high intrinsic automaticity. Adequate automaticity and conduction lead to activation of atrial and ventricular fibers, producing in sequence the elements of normal functional heart beat. Calcium antagonists may be of value in conditions where calcium-related changes in membrane potential and conduction alter normal rhythm. In the absence of treatment, symptoms vary with individual arrhythmias, but are often the consequence of inadequate cardiac filling and output and often include fatigue, decreased exercise tolerance, syncope, shortness of breath, nausea, lightheadedness and the like.
(S)-Amlodipine may be useful to treat cardiac hypertrophy. Cardiac hypertrophy can result from excessive workload either due to an obstruction to outflow, termed systolic overload, or to excessive volumes presented to the heart in diastole, termed diastolic overload. Systolic overload results in concentric ventricular hypertrophy, in which there is an increased thickness in the walls of the heart not associated with increased volume. Diastolic overload causes dilation and hypertrophy with an increased blood volume. An inadequate cardiac output results from the heart's failure in systolic or diastolic overload, leading to fatigue, shortness of breath, pulmonary congestion, edema and the like. Calcium channel antagonists effect workload and, as such, may be useful in treating cardiac hypertrophy due to the effect of the calcium antagonist on cardiac and vascular smooth muscle in reducing blood pressure.

(S)-Amlodipine could be used to treat coronary arterial spasm. Coronary arterial spasm can occur in the absence of significant coronary atherosclerosis and is thought to be an initiating event in variant angina and in myocardial infarction. Coronary spasm may occur without the patient feeling any significant discomfort. In an electrically unstable heart, diverse neural impulses to the heart may provoke coronary vascular spasm. This may result in enhanced myocardial ischemia and arrhythmia, which in turn may culminate in ventricular fibrillation and sudden cardiac death. As in variant or vasospastic angina, the calcium channel antagonists may be of particular usefulness due to their effect on cardiac and vascular smooth muscle.

(S)-Amlodipine may be useful in the treatment of myocardial infarction, ischemic myocardial necrosis, and ischemia reperfusion injury. Myocardial infarction or ischemic myocardial necrosis generally results from the abrupt reduction of coronary blood flow to a portion of the myocardium. The condition likely originates from atherosclerosis of the coronary arteries. Either coronary artery vasospasm or acute coronary thrombosis precipitates the condition, although the etiology is the subject of continuing research. Myocardial infarction is predominantly a disease of the left ventricle. Precordial pain and left ventricular dysfunction characterize the disease. The pain, which can be severe aching or pressure, leads to apprehension. Symptoms include left ventricular heart failure, pulmonary edema, shock or significant cardiac arrhythmia. Calcium channel antagonists may find utility in the management of myocardial infarction patients due to their effects on coronary artery vasospasm, blood pressure or other effects on cardiac function or vascular smooth muscle.
(S)-Amlodipine may be used to treat congestive heart failure. Congestive heart failure can be caused by hypertension, cardiomyopathy, coronary artery disease or valvular heart disease. Congestive failure results in poor cardiac output and elevated left-ventricular diastolic pressure, leading to dyspnea, fatigue, peripheral edema, and coughing. The ability of some calcium antagonists to lower afterload by dilating peripheral arteries without having a significant inotropic effect may increase their use in treating congestive heart failure.

(S)-Amlodipine may be of use in treating migraine. Classic migraine typically begins with visual auras followed by severe headaches, often accompanied by nausea and vomiting. Common migraine has similar symptoms without the preceding visual aura. The causes of migraine have been studied intensely, and are still a matter of debate. The most generally accepted cause is hypoxia due to reduced cerebral blood flow. Calcium channel antagonists have been used for migraine prophylaxis since they can increase cerebral blood flow.

(S)-Amlodipine may be useful for treating Raynaud's phenomenon, which is characterized by vascular spasm of the extremities. These vasospasms can be caused by cold or stress. A pallor or cyanosis is usually present due to severe constriction of the digital arteries. The phenomenon is often seen as a secondary disorder with arterial diseases or connective tissue diseases such as scleroderma, arthritis or lupus erythematosus. Calcium channel antagonists have been shown to be effective in treating Raynaud's phenomenon.

(S)-Amlodipine salts

A variety of amlodipine salts have been reported. The besylate salt of amlodipine was first disclosed in EP 0 244 944 and has since been used worldwide in the treatment of ischaemic heart disease and hypertension. Amlodipine maleate has been described in U.S. Patent 4,572,909 and J. Med. Chem. 1986, 29, 1696. It has been observed that amlodipine maleate is very sensitive to moisture and interacts with certain excipients leading to degradation. In addition, amlodipine maleate is a sticky material which poses problems during manufacturing of tablets. Procedures for the preparation of various amlodipine salts, e.g., tosylate, mesylate, succinate, acetate, and nitrate, are described in U.S. Patents 4,879,303; 5,270,323; 5,750,707; and 6,451,826. However, these compositions relates to racemic mixtures of amlodipine or relate to salt forms of (S)-amlodipine that have limited utility as pharmaceutical agents owing to their limited solubility, poor thermal stability, or unsuitability for processing into a tablet.
In one embodiment, the present invention relates to (S)-amlodipine malate. In a preferred embodiment, the compound is (S)-amlodipine-L-malate in one of its polymorphic or solvated forms (A-G; see Example 6).

It has been discovered that (S)-amlodipine-L-malate has unexpectedly superior properties as a pharmaceutical agent. (S)-Amlodipine-L-malate has excellent solubility, high thermal stability, and can be easily processed into a tablet. For example, results from adhesion tests to metal surfaces, e.g., solid-dosage-form manufacturing equipment, reveal that the (S)-amlodipine-L-malate, when blended at typical levels of 5% and 25% with a typical excipient Avicel, showed decreased adhesion to solid dosage form manufacturing equipment compared to blends made with other salts. Importantly, even low-level adhesion becomes significant when manufacturing dosage forms at a typical production rate of 50,000 or more tablets or capsules per hour. Further, results from adhesion tests to metal surfaces, e.g., solid-dosage-form manufacturing equipment, reveal that adhesion of the malate salt is less than for the succinate, maleate, (D)-tartrate, and (L)-tartrate salts of (S)-amlodipine.

The adhesion test reflects the improved manufacturability of pharmaceutical dosage forms, i.e., tablets and capsules, that are made using the malate salt compared to other salts of (S)-amlodipine. Importantly, none of the previously reported salt forms of (S)-amlodipine have these critical properties. U.S. patent 6,608,206 discloses the besylate, succinate, maleate, oxalate, and tosylate salts of (S)-amlodipine. These salts were prepared by mixing (S)-amlodipine with the conjugate acid of the besylate, succinate, maleate, oxalate, and tosylate anion. See the following for previously reported salt forms of racemic amlodipine and (S)-amlodipine: U.S. Patents 4,572,909; 4,879,303; 5,155,120; 5,270,323; 5,438,145; 5,750,707; 6,046,337; 6,046,338; 6,057,344; 6,262,092; and 6,451,826; U.S. Published Patent Applications 20030119883; 20030225143; and 20040001886; European Patent Applications EP 0 599 200; EP 0 089 167; EP 0 024 494; and EP 0 313 154; PCT Patent Applications WO 93/10779; WO 95/25722; and WO 99/52873; and Canadian Patent CA 2,188,071.

(S)-Amlodipine-L-malate has been found to be unexpectedly bioavailable in mammals (in particular humans). Analysis of plasma levels (AUC is Area Under the Curve and indicates the total amount of the drug in plasma over a period of time) of humans dosed with (S)-amlodipine-malate showed increased levels of (S)-amlodipine compared to humans dosed with equivalent amounts of amlodipine maleate. This increased bioavailability
increases the effectiveness of the drug without increasing the dosage. This allows an improved effectiveness for the compound with an equivalent dose or the use of a lower dose to achieve the same efficacy.

One aspect of the present invention relates to a pharmaceutical composition comprising (S)-amlodipine malate. In a preferred embodiment, the pharmaceutical composition comprises (S)-amlodipine L-malate. Another aspect of the present invention relates to a method of preparing (S)-amlodipine malate comprising admixing (S)-amlodipine with malic acid (see Exemplification). In a preferred embodiment, said malic acid is L-malic acid.

4. ACE Inhibitors

ACE inhibitors are compounds that inhibit the angiotensin-converting enzyme. Inhibition of the angiotensin-converting enzyme prevents or slows the conversion of angiotensin I to angiotensin II. A large number of ACE inhibitors are known and are amenable to the present invention. ACE inhibitors are effective antihypertensive agents in a variety of animal models and are clinically useful for the treatment of hypertension. In general, a dose of the ACE inhibitor or a pharmaceutically acceptable salt thereof suitable for administration to a human will be in the range of 0.01 to 50 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 3 mg per kilogram body weight per day. Unless otherwise stated all weights of active ingredients are calculated in terms of drug per se. In certain embodiments, the desired dose is presented as two, three, four, five or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing about 5 to 50 mg.

Alacepril

Alacepril is an antihypertensive that has the chemical name (S)-N-[1-[3-(Acetylthio)-2-methyl-1-oxopropyl]-L-prolyl]-L-phenylalanine. Procedures for the preparation of alacepril are described in U.S. Patent 4,248,883. The pharmacological and antihypertensive properties of alacepril are described in Arzneimittell-Forsch. 1986, 36, 47 and K. Mizuno et al. Res. Commun. Chem. Pathol. Pharmacol. 1985, 49, 175. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 900 mg. Preferably, a daily dose range should
be between about 10 mg to about 200 mg. The chemical structure of alacepril is presented below.

Benazepril

Benazepril is an antihypertensive disclosed in U.S. patent 4,410,520. Benazepril has been characterized as the free amine and the hydrochloride. Benazeprilat is the diacid derivative of Benazepril. As used herein, the term “Benazepril” refers to the free base and any pharmaceutically acceptable salt of the free base. Benazepril has the chemical name \( [S-(R^*,R^*)]-3-[(1-(Ethoxycarbonyl)-3-phenylpropyl)amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benazepine-1-acetic acid. \) The structure of benazepril is presented below.

The size of a prophylactic or therapeutic dose of benazepril, or one of its salts, in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 80 mg. Preferably, a daily dose range should be between about 2 mg to about 25 mg. Most preferably, a daily dose range should be between about 2 mg to about 5 mg. In certain embodiments, the daily dose range should be about 5, 10, 15, or 20 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 0.5 mg to about 1 mg and increased up to about 10 mg or higher depending on the patient's global response.

Cilazapril

Cilazapril is an antihypertensive that has the chemical name \( [1S-[1α,9α,(R^*)]]-9-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid monohydrate. \) Procedures for the preparation of cilazapril are described in U.S. Patent 4,512,924 and J. Chem. Soc. Perkin Trans. I 1986, 1011. The pharmacological and antihypertensive properties of cilazapril are described in I.
L. Natoff et al. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 569 and A. A. Ajayi et al. *Brit J. Clin. Pharmacol.* **1986**, *22*, 167. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 900 mg. Preferably, a daily dose range should be between about 10 mg to about 200 mg. The chemical structure of cilazapril is presented below.

![Chemical structure of cilazapril](image)

**Delapril**

Delapril is an antihypertensive that has the chemical name (S)-N-(2,3-Dihydro-1H-

![Chemical structure of delapril](image)

The size of a prophylactic or therapeutic dose of Delapril, or one of its salts, in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 120 mg. Preferably, a daily dose range should be between about 20 mg to about 80 mg. Most preferably, a daily dose range should be between about 50 mg to about 70 mg. In certain embodiments, the daily dose range should be about 55, 60, 65, or 70 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 10 mg to about 15 mg and increased up to about 30 mg or higher depending on the patient's global response.
Fosinopril

Fosinopril is an antihypertensive agent that has the chemical name [1(S*(R*)),2α,4β]-4-Cyclohexyl-1-[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-L-proline. Fosinopril is generally administered in the form of its sodium salt known as monopril. Procedures for the preparation of fosinopril can be found in U.S. Patent 4,337,201. The pharmacology and antihypertensive activity of fosinopril is described in Drug Invest. 1991, 3 (Suppl. 4), 1-53 and P. A. Sullivan et al. Am. J. Hypertension 1988, 1, 280S. U.S. Patent 5,162,543 describes the preparation and interconversion of two polymorphs of fosinopril. Fosinopril polymorph A is thought to be more thermodynamically stable than polymorph B. The structure of fosinopril is described below.

The size of a prophylactic or therapeutic dose of fosinopril, or one of its salts, in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 120 mg. Preferably, a daily dose range should be between about 10 mg to about 80 mg. Most preferably, a daily dose range should be between about 20 mg to about 40 mg. In certain embodiments, the daily dose range should be about 10, 15, 20, 25, 30, or 35 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 1 mg to about 5 mg and increased up to about 15 mg or higher depending-on the patient's global response.

Imidapril

Imidapril is an antihypertensive that has the chemical name [4S-[3[R*(R*)],4R*]]-3-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-4-imidazolidinedicarboxylic acid. Procedures for the preparation of imidapril are described in Eur. Pat. Appl. 95,163 and U.S. Patent 4,508,727. The pharmacological and antihypertensive properties of imidapril are described in Arzneimittel-Forsch. 1992, 42, 446.
and M. J. Vandenbarg et al. *Brit J. Clin. Pharmacol.* **1994**, *37*, 265. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 900 mg. Preferably, a daily dose range should be between about 10 mg to about 200 mg. The chemical structure of imidapril is presented below.

![Chemical structure of imidapril]

**Lisinopril**


![Chemical structure of lisinopril]

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there is a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. On multiple dosing lisinopril has an effective half-life of accumulation of about 12.6 hours. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to
dose. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80 mg). Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine. Lisinopril is currently sold under the trademark ZESTRIL® or PRINIVIL®.

Several different forms of lisinopril monohydrate have been reported. Lisinopril monohydrate Form I was reported by Ip et al., (Lisinopril, in Analytical Profiles of Drug Substances and Excipients (Ed., Brittain, H. G.), Academic Press, Volume 21, pp 233-276, 1992). The only characterising data of the monohydrate in this publication is an X-ray powder diffraction (XRPD) pattern shown as a plot of intensity of diffracted x-rays. (FIG. 12, p257). No other analytical data or description of the monohydrate is given, nor is its preparation described.

Lisinopril monohydrate Form II is described in U.S. Patent 6,468,976. Lisinopril monohydrate Form II was reported to be substantially more soluble than the dihydrate of lisinopril (Zestril), and in view of this increased solubility, it may prove more suitable pharmaceutical usages in some cases. Monohydrate lisinopril form 2 is also different from the "monohydrate" that is disclosed in Wang, S-L. et al. Chem. Pharm. Bull. 2000, 48, 1890-93. Wang et al. describes the generation of a lisinopril "monohydrate" by heating lisinopril dihydrate until weight loss corresponding to one mole of H₂O per mole of lisinopril was observed. J. Brown reports having performed the identical experiment as Wang et al. and have found that the resulting "monohydrate" is strongly hygroscopic, i.e., the evolved water is quickly reabsorbed from the atmospheric water when the crystals are returned to room temperature. By contrast, both form 1 and form 2 monohydrates of the invention are stable at a standard room temperature and humidity.

The size of a prophylactic or therapeutic dose of lisinopril in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 0.5 mg to about 120 mg. Preferably, a daily dose range should be between about 1 mg to about 80 mg. Most preferably, a daily dose range should be between about 2 mg to about 40 mg. In certain embodiments, the daily dose range should be about 5, 10, 15, 20, 25, 30, or 35 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 1 mg to
about 2 mg and increased up to about 5 mg or higher depending on the patient's global response.

**Moexipril**

Moexipril is an orally active antihypertensive that has the chemical name [3S-

\[2[[R^*(R^*)],3R^*]]-2-[2-[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-

tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid. Procedures for the synthesis of

moexipril and its acid salts are described in U.S. Pat. No. 4,344,949. Moexipril is generally

administered in the form of its hydrochloride salt marked as UNIVASC®. Moexipril

hydrochloride is a fine white powder that is soluble in water. The pharmacological and

antihypertensive properties of moexipril are described by Song, J. C. and White, C. M. in


![Chemical Structure of Moexipril]

In certain instances, improved stability is achieved by producing a moexipril dosage

form which comprises moexipril magnesium. B.C. Sherman reports that the magnesium

salt of moexipril (i.e. moexipril magnesium) is sufficiently stable to enable stable solid

compositions, without the presence of an alkaline stabilizing compound in the final

composition. It has also been found that stable solid compositions comprising moexipril

magnesium can be made using moexipril or an acid addition salt thereof, by reacting the

moexipril or acid addition salt with an alkaline magnesium compound, so as to convert

most or all (i.e. more than half) of the moexipril or acid addition salt to moexipril


The size of a prophylactic or therapeutic dose of moexipril in the acute or chronic

management of disease will vary with the severity of the condition to be treated and the

route of administration. The dose, and perhaps the dose frequency, will also vary according

to the age, body weight, and response of the individual patient. In general, the total daily

dose ranges, for the conditions described herein, is from about 1 mg to about 120 mg.

Preferably, a daily dose range should be between about 1 mg to about 40 mg. Most

preferably, a daily dose range should be between about 5 mg to about 20 mg. In certain

embodiments, the daily dose range should be about 8, 10, 12, or 15 mg. In managing the
patient, the therapy may be initiated at a lower dose, perhaps about 4 mg to about 6 mg and increased up to about 10 mg or higher depending on the patient's global response.

**Perindopril**

Perindopril is an antihypertensive that has the chemical name \((2S,1R)-1\)\-[2α,3αβ,7αβ]-1-\-[2-[(1-(Ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid. Procedures for the preparation of perindopril are described in U.S. Patents 4,508,729 and 4,914,214. Perindopril has been isolated as various acid and base salts. The pharmacological and antihypertensive properties of perindopril have been described in T. Morgan et al. *J. Cardiovasc. Pharmacol.* **1987**, *10* (Suppl. 7), S116 and P. A. Todd et al. *Drugs* **1991**, *42*, 90. The structure of perindopril is presented below.

One preferred form of perindopril is its tert-butylamine salt. The tert-butylamine salt demonstrates good stability compared to many other forms. However, in view of the intrinsic fragility of perindopril, the tert-butylamine salt has not been capable of providing a complete solution to the problems of the product's stability to heat and humidity. Often times, tablets of perindopril tert-butylamine salt must be protected with additional packaging measures. However, the arginine salt of perindopril has been reported to have superior properties. The arginine salt of perindopril, its hydrates, and pharmaceutical compositions thereof are described in U.S. Patent Application 20030199568.

The size of a prophylactic or therapeutic dose of perindopril in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 60 mg.

Preferably, a daily dose range should be between about 2 mg to about 40 mg. Most preferably, a daily dose range should be between about 4 mg to about 16 mg. In certain embodiments, the daily dose range should be about 6, 8, 10, 12, or 14 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 2 mg to about 5 mg and increased up to about 8 mg or higher depending on the patient's global response.

In young and elderly patients, it may be advisable to administer a smaller dosage, e.g., 4 mg or 8 mg per day, divided into two equal doses taken at separate times during the day.
Quinapril

Quinapril is an antihypertensive that has the chemical name \([3S,2R,3R]-2\) [\(1-(\text{Ethoxycarbonyl})-3\)-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isouquinolinecarboxylic acid. Procedures for the preparation of quinapril are described in Eur. Pat. Appl. 49,605 and U.S. Patents 4,344,949 and 4,761,479. The pharmacological and antihypertensive properties of quinapril are described in H. R. Kaplan et al. *Fed. Proc.* 1984, 43, 1326 and P. Sayanvalammi et al. *J. Cardiovasc. Pharmacol.* 1988, 12, 88. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 900 mg. Preferably, a daily dose range should be between about 10 mg to about 200 mg. The chemical structure of quinapril is presented below.

![Chemical structure of Quinapril](image1)

Ramipril

Ramipril is a non-sulphydryl, long-acting, ACE inhibitor that is sold under the trade name Altace®. Its active metabolite is the free diacid ramiprilat, which is obtained in vivo upon administration of ramipril by hepatic cleavage of the ester group. Procedures for the preparation of ramipril are described in Eur. Pat. Appl. 79,022; U.S. Patent 4,587,258; and U.S. Patent 6,407,262. The pharmacology and antihypertensive properties of ramipril are described in *Arzneimittel-Forsch.* 1984, 34, 1402 and *Am. J. Cardiol.* 1987, 59, 1D-177D. The chemical name of ramipril is \((2S,3aS,6aS)-1[(S)-N-((S)-1-Carboxy-3-phenylpropyl)alanyl]-octahydrocyclopenta[b]pyrrole-2-carboxylic acid, 1-ethyl ester and the structure is presented below.

![Chemical structure of Ramipril](image2)

In hypertensive patients, administration of ramipril is known to cause a reduction in peripheral arterial resistance and thus a reduction of the blood pressure without a compensatory rise in heart rate. It is being used in the treatment of hypertension and congestive heart failure. Furthermore, ramipril has been shown to reduce mortality in
patients with clinical signs of congestive heart failure after surviving an acute myocardial infarction. Ramipril has been suggested to have an added advantage over many other ACE inhibitors due to its pronounced inhibition of ACE in tissues resulting in organ protective effects in e.g. the heart, lung, and kidney.

Ramipril is a white, crystalline solid that is soluble in water and polar organic solvents. Ramipril is sensitive to high temperature, moisture, or compression. Due to the sensitivity of ramipril, pharmaceutical formulations must be prepared with special attention in order to retain its stability (See U.S. Pat. No. 5,151,433).

The size of a prophylactic or therapeutic dose of ramipril in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 60 mg. Preferably, a daily dose range should be between about 2 mg to about 40 mg. Most preferably, a daily dose range should be between about 1 mg to about 20 mg. In certain embodiments, the daily dose range should be about 2, 5, 8, 10, or 15 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about 1 mg to about 3 mg and increased up to about 5 mg or higher depending on the patient's global response. In patients with renal impairment, it may be advisable to administer a smaller dosage, e.g., 1 mg or 2 mg per day.

Spirapril

Spirapril is an antihypertensive that has the chemical name [8S-[7[R*(R*)],*8R*]-7-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid. Procedures for the preparation of spirapril are described in E. M. Smith et al. J. Med. Chem. 1989, 32, 1600 and U.S. Patent 4,470,972. The pharmacological and antihypertensive properties of spirapril are described in B. J. Sybertz et al. Arch. Int. Pharmacodym. Ther. 1987, 286, 216 and G. P. Reams et al. J. Clin. Pharmacol. 1993, 33, 348. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 900 mg. Preferably, a daily dose range should be between about 10 mg to about 200 mg. The chemical structure of spirapril is presented below.
Temocapril

Temocapril is an antihypertensive that has the chemical name [2S-[2α,6β(R*)]-6-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5H)-acetic acid. Procedures for the preparation of temocapril are described in U.S. Patent 4,699,905 and J. Med. Chem. 1987, 30, 1984. The pharmacological and antihypertensive properties of temocapril are described in K. Oizumi et al. Hapan. J. Pharmacol. 1988, 48, 349 and M. Arita et al. Clin. Exp. Pharmacol. Physiol. 1994, 21, 195. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 900 mg. Preferably, a daily dose range should be between about 10 mg to about 200 mg. The chemical structure of temocapril is presented below.

Trandolapril

Trandolapril is a non-sulphhydryl compound approved for the treatment of hypertension that is sold under the trade name Mavik®. Procedures for the preparation of trandolapril are described in Eur. Pat. Appl. 84,164 and U.S. Patent 4,933,361. The pharmacological and antihypertensive properties of trandolapril are described in F. De Ponti et al. Cur. J. Clin. Pharmacol. 1991, 40, 149 and Am. J. Hypertension 1995, 8, 63S-74S. Trandolapril showed low incidence of side effects in clinical trials. Common side effects were headache, fatigue, dizziness, and cough. The chemical name of trandolapril is [2S-[[1[R*(R*)],2α,3α,7αβ]-1-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydro-1H-indole-2-carboxylic acid and the structure is presented below.
The size of a prophylactic or therapeutic dose of trandolapril in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 0.1 mg to about 30 mg. Preferably, a daily dose range should be between about .05 mg to about 10 mg. Most preferably, a daily dose range should be between about 0.5 mg to about 5 mg. In certain embodiments, the daily dose range should be about 1, 2, 3, or 4 mg. In managing the patient, the therapy may be initiated at a lower dose, perhaps about .05 mg to about 1 mg and increased up to about 4 mg or higher depending-on the patient's global response. In many instances, it is advisable to administer trandolapril 1-2 hours before meals because food reduces the amount of trandolapril that is absorbed. In addition, patients with compromised renal function often require smaller dosages of trandolapril.

Zofenopril

Zofenopril is an antihypertensive that has the chemical name [(4S)-(2S)-3-(benzoylthio)-2-methylpropionyl-4 (phenylthio)-L-proline. Procedures for the preparation of zofenopril are described in U.S. Patent 4,316,906. In some instances, the preferred form of zofenopril is the calcium salt which can exist in two polymorphic forms. See U.S. Patent 6,515,012. The pharmacological and antihypertensive properties of zofenopril are described in C. Borghi et al. *Am. J. Hypertens.* **1999**, *12*, 665-72. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose ranges, for the conditions described herein, is from about 1 mg to about 900 mg. Preferably, a daily dose range should be between about 10 mg to about 200 mg. The chemical structure of zofenopril is presented below.

![Chemical structure of zofenopril](image)

Other ACE inhibitors include captopril, ceronapril, enalapril, fentiapril, libenzapril, moveltipril, pentopril, and pivopril. ACE inhibitors are also described in "Pharmacology of Antihypertensive Therapeutics" (Eds. D. Ganten, P. J. Mutrow) Springer Verlag, Berlin 1990, pp. 377-480.
5. Combination Therapy

One aspect of the present invention relates to combination therapy. This type of therapy is advantageous because the co-administration of active ingredients achieves a therapeutic effect that is greater than the therapeutic effect achieved by administration of only a single therapeutic agent. In a preferred embodiment, the co-administration of two or more therapeutic agents achieves a synergistic effect, i.e., a therapeutic effect that is greater than the sum of the therapeutic effects of the individual components of the combination.

The active ingredients that comprise a combination therapy may be administered together via a single dosage form or by separate administration of each active agent. In certain embodiments, the first and second therapeutic agents are administered in a single dosage form. The agents may be formulated into a single tablet, pill, capsule, or solution for parenteral administration and the like.

Alternatively, the first therapeutic agent and the second therapeutic agents may be administered as separate compositions, e.g., as separate tablets or solutions. The first active agent may be administered at the same time as the second active agent or the first active agent may be administered intermittently with the second active agent. The length of time between administration of the first and second therapeutic agent may be adjusted to achieve the desired therapeutic effect. In certain instances, the second therapeutic agent may be administered only a few minutes (e.g., 1, 2, 5, 10, 30, or 60 min) after administration of the first therapeutic agent. Alternatively, the second therapeutic agent may be administered several hours (e.g., 2, 4, 6, 10, 12, 24, or 36 hr) after administration of the first therapeutic agent. In certain embodiments, it may be advantageous to administer more than one dosage of the second therapeutic agent between administrations of the first therapeutic agent. For example, the second therapeutic agent may be administered at 2 hours and then again at 10 hours following administration of the first therapeutic agent. Alternatively, it may be advantageous to administer more than one dosage of the first therapeutic agent between administrations of the second therapeutic agent. Importantly, it is preferred that the therapeutic effects of each active ingredient overlap for at least a portion of the duration of each therapeutic agent so that the overall therapeutic effect of the combination therapy is attributable in part to the combined or synergistic effects of the combination therapy.

The dosage of the active agents will generally be dependent upon a number of factors including pharmacodynamic characteristics of each agent of the combination, mode and route of administration of active agent(s), the health of the patient being treated, the
extent of treatment desired, the nature and kind of concurrent therapy, if any, and the
frequency of treatment and the nature of the effect desired. In general, dosage ranges of the
active agents often range from about 0.001 to about 250 mg/kg body weight per day. For a
normal adult having a body weight of about 70 kg, a dosage in the range of from about 0.1
to about 25 mg/kg body weight is typically preferred. However, some variability in this
general dosage range may be required depending upon the age and weight of the subject
being treated, the intended route of administration, the particular agent being administered
and the like. Since two or more different active agents are being used together in a
combination therapy, the potency of each agent and the interactive effects achieved using
them together must be considered. Importantly, the determination of dosage ranges and
optimal dosages for a particular mammal is also well within the ability of one of ordinary
skill in the art having the benefit of the instant disclosure.

In certain embodiments, it may be advantageous for the pharmaceutical combination
to have a relatively large amount of the first component compared to the second
component. In certain instances, the ratio of the first active agent to second active agent is
30:1, 20:1, 15:1, 10:1, 9:1, 8:1, 7:1, 6:1, or 5:1. In certain embodiments, it may be
preferable to have a more equal distribution of pharmaceutical agents. In certain instances,
the ratio of the first active agent to the second active agent is 4:1, 3:1, 2:1, 1:1, 1:2, 1:3, or
1:4. In certain embodiments, it may be advantageous for the pharmaceutical combination
to have a relatively large amount of the second component compared to the first
component. In certain instances, the ratio of the second active agent to the first active agent
is 30:1, 20:1, 15:1, 10:1, 9:1, 8:1, 7:1, 6:1, or 5:1. Importantly, a composition comprising
any of the above-identified combinations of first therapeutic agent and second therapeutic
agent may be administered in divided doses 1, 2, 3, 4, 5, 6, or more times per day or in a
form that will provide a rate of release effective to attain the desired results. In a preferred
embodiment, the dosage form contains both the first and second active agents. In a more
preferred embodiment, the dosage form only has to be administered one time per day and
the dosage form contains both the first and second active agents.

For example, a formulation intended for oral administration to humans may contain
from 0.1 mg to 5 g of the first therapeutic agent and 0.1 mg to 5 g of the second therapeutic
agent, both of which are compounded with an appropriate and convenient amount of carrier
material varying from about 5 to about 95 percent of the total composition. Unit dosages
will generally contain between from about 0.5 mg to about 1500 mg of the first therapeutic
agent and 0.5 mg to about 1500 mg of the second therapeutic agent. In a preferred embodiment, the dosage comprises 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg, etc., up to 1500 mg of the first therapeutic agent. In a preferred embodiment, the dosage comprises 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg, etc., up to 1500 mg of the second therapeutic agent.

The optimal ratios of the first and second therapeutic agent can be determined by standard assays known in the art. For example, the phenyl-p-benzoquinone test may be used to establish analgesic effectiveness. The phenyl-p-benzoquinone induced writhing test in mice (Blumberg, H. et al. Proc. Soc. Exp. Med. 1965, 118, 763-766) and known modifications thereof is a standard procedure which may be used for detecting and comparing the analgesic activity of different classes of analgesic drugs with a good correlation with human analgesic activity. Data for the mouse, as presented in an isobologram, can be translated to other species where the orally effective analgesic dose of the individual compounds are known or can be estimated. The method consists of reading the percent ED$_{50}$ dose for each dose ratio on the best fit regression analysis curve from the mouse isobologram, multiplying each component by its effective species dose, and then forming the ratio of the amount of COX-2 inhibitor and opioid analgesic. This basic correlation for analgesic properties enables estimation of the range of human effectiveness (Pelikan, E. W. The Pharmacologist 1959, 1, 73). Thus, application of an equieffective dose substitution model and a curvilinear regression analysis utilizing all the data for the individual compounds and various dose ratios for the combinations can be used to establish the existence of unexpectedly enhanced analgesic activity of combinations of active agents, i.e., the resulting activity is greater than the activity expected from the sum of the activities of the individual components.

The toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD$_{50}$ (the dose lethal to 50% of the population) and the ED$_{50}$ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD$_{50}$/ED$_{50}$. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating
concentrations that include the ED$_{50}$ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC$_{50}$ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of RT production from infected cells compared to untreated control as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography (HPLC).

6. Synergism

The term “synergistic” refers to a combination which is more effective than the additive effects of any two or more single agents. A synergistic effect permits the effective treatment of a disease using lower amounts (doses) of either individual therapy. The lower doses result in lower toxicity without reduced efficacy. In addition, a synergistic effect can result in improved efficacy, e.g., improved antiviral activity. Finally, synergy may result in an improved avoidance or reduction of disease as compared to any single therapy.

Combination therapy often allows for the use of lower doses of the first therapeutic or the second therapeutic agent (referred to as “apparent one-way synergy” herein), or lower doses of both therapeutic agents (referred to as “two-way synergy” herein) than would normally be required when either drug is used alone. By using lower amounts of either or both drugs, the side effects associated with them are reduced.

In certain embodiments, the synergism exhibited between the second therapeutic agent and the first therapeutic agent is such that the dosage of the first therapeutic agent would be sub-therapeutic if administered without the dosage of the second therapeutic agent. In other embodiments, the present invention relates to a pharmaceutical composition comprising an therapeutically effective dose of a first therapeutic agent together with a dose of a second therapeutic agent effective to augment the therapeutic effect of the first therapeutic agent. Alternatively, the synergism exhibited between the second therapeutic agent and the first therapeutic agent is such that the dosage of the second therapeutic agent would be sub-therapeutic if administered without the dosage of the first therapeutic agent. In other embodiments, the present invention relates to a pharmaceutical composition comprising an therapeutically effective dose of a second therapeutic agent together with a
dose of a first therapeutic agent effective to augment the therapeutic effect of the second therapeutic agent.

In certain preferred embodiments, the invention is directed in part to synergistic combinations of the first therapeutic agent in an amount sufficient to render a therapeutic effect together with a second therapeutic agent. For example, in certain embodiments a therapeutic effect is attained which is at least about 2 (or at least about 4, 6, 8, or 10) times greater than that obtained with the dose of the first therapeutic agent alone. In certain embodiments, the synergistic combination provides a therapeutic effect which is up to about 20, 30 or 40 times greater than that obtained with the dose of first therapeutic agent alone. In such embodiments, the synergistic combinations display what is referred to herein as an "apparent one-way synergy", meaning that the dose of second therapeutic agent synergistically potentiates the effect of the first therapeutic agent, but the dose of first therapeutic agent does not appear to significantly potentiate the effect of the second therapeutic agent.

In certain embodiments, the combination of active agents exhibit two-way synergism, meaning that the second therapeutic agent potentiates the effect of the first therapeutic agent, and the first therapeutic agent potentiates the effect of the second therapeutic agent. Thus, other embodiments of the invention relate to combinations of a second therapeutic agent and a first therapeutic agent where the dose of each drug is reduced due to the synergism between the drugs, and the therapeutic effect derived from the combination of drugs in reduced doses is enhanced. The two-way synergism is not always readily apparent in actual dosages due to the potency ratio of the first therapeutic agent to the second therapeutic agent. For instance, two-way synergism can be difficult to detect when one therapeutic agent displays much greater therapeutic potency relative to the other therapeutic agent.

The synergistic effects of combination therapy may be evaluated by biological activity assays. For example, the therapeutic agents are be mixed at molar ratios designed to give approximately equipotent therapeutic effects based on the EC_{50} values. Then, three different molar ratios are used for each combination to allow for variability in the estimates of relative potency. These molar ratios are maintained throughout the dilution series. The corresponding monotherapies are also evaluated in parallel to the combination treatments using the standard primary assay format. A comparison of the therapeutic effect of the combination treatment to the therapeutic effect of the monotherapy gives a measure of the
synergistic effect. Further details on the design of combination analyses can be found in Korba, B. E. Antiviral Res. 1996, 29, 49. Analysis of synergism, additivity, or antagonism can be determined by analysis of the aforementioned data using the CalcuSyn™ program (Biosoft, Inc.). This program evaluates drug interactions by use of the widely accepted method of Chou and Talalay combined with a statistically evaluation using the Monte Carlo statistical package. The data are displayed in several different formats including median-effect and dose-effects plots, isobolograms, and combination index [CI] plots with standard deviations. For the latter analysis, a CI greater than 1.0 indicates antagonism and a CI less than 1.0 indicates synergism.

Compositions of the invention present the opportunity for obtaining relief from moderate to severe cases of disease. Due to the synergistic and/or additive effects provided by the inventive combination of the first and second therapeutic agent, it may be possible to use reduced dosages of each of therapeutic agent. By using lesser amounts of other or both drugs, the side effects associated with each may be reduced in number and degree.

Moreover, the inventive combination avoids side effects to which some patients are particularly sensitive.

7. Compositions & Methods of the Invention

One aspect of the present invention relates to a pharmaceutical composition, comprising optically pure (S)-amlodipine and an ACE inhibitor.

In certain embodiments, the present invention relates to the aforementioned pharmaceutical composition, wherein said ACE inhibitor is alacepril, benazepril, captopril, cerenalpril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentoipril, perindopril, pivoipril, quinapril, ramipril, spirapril, temocapril,trandolapril, zofenopril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

In certain embodiments, the present invention relates to the aforementioned pharmaceutical composition, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

Another aspect of the present invention relates to a pharmaceutical composition comprising optically pure (S)-amlodipine and an ACE inhibitor, wherein said ACE inhibitor is benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.
Another aspect of the present invention relates to a pharmaceutical composition comprising optically pure (S)-amlodipine and an ACE inhibitor, wherein said ACE inhibitor is ramipril or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

Another aspect of the present invention relates to a pharmaceutical composition consisting essentially of optically pure (S)-amlodipine, an ACE inhibitor, and at least one pharmaceutically acceptable carrier.

In certain embodiments, the present invention relates to the aforementioned pharmaceutical composition, wherein said ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, pivopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

In certain embodiments, the present invention relates to the aforementioned pharmaceutical composition, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

Another aspect of the present invention relates to a pharmaceutical composition consisting essentially of optically pure (S)-amlodipine, an ACE inhibitor, and at least one pharmaceutically acceptable carrier, wherein said ACE inhibitor is benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

Another aspect of the present invention relates to a pharmaceutical composition consisting essentially of optically pure (S)-amlodipine, an ACE inhibitor, and at least one pharmaceutically acceptable carrier, wherein said ACE inhibitor is ramipril or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In certain embodiments, the present invention relates to the aforementioned pharmaceutical composition, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

In certain embodiments, the present invention relates to the aforementioned pharmaceutical composition, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine L-malate, or a polymorph, pseudopolymorph or solvate thereof.
Another aspect of the present invention relates to a method of treating a patient suffering from a medical condition selected from the group consisting of hypertension, congestive heart failure, angina, myocardial infarction, atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache; comprising the step of co-administering to a patient in need thereof a therapeutically effective amount of optically pure (S)-amlodipine and an ACE inhibitor.

In certain embodiments, the present invention relates to the aforementioned method, wherein said ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, pivopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

In certain embodiments, the present invention relates to the aforementioned method, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

Another aspect of the present invention relates to a method of treating a patient suffering from a medical condition selected from the group consisting of hypertension, congestive heart failure, angina, myocardial infarction, atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache; comprising the step of co-administering to a patient in need thereof a therapeutically effective amount of optically pure (S)-amlodipine and an ACE inhibitor; wherein said ACE inhibitor is benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

Another aspect of the present invention relates to a method of treating a patient suffering from a medical condition selected from the group consisting of hypertension, congestive heart failure, angina, myocardial infarction, atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache; comprising the step of co-administering to a patient in need thereof a therapeutically effective amount of optically pure (S)-amlodipine and an ACE inhibitor; wherein said ACE inhibitor is ramipril.
In certain embodiments, the present invention relates to the aforementioned method, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

In certain embodiments, the present invention relates to the aforementioned method, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine L-malate, or a polymorph, pseudopolymorph or solvate thereof.

In certain embodiments, the present invention relates to the aforementioned method, wherein said medical condition is hypertension, congestive heart failure, angina, or myocardial infarction.

In certain embodiments, the present invention relates to the aforementioned method, wherein said medical condition is hypertension.

Another aspect of the present invention relates to products for containing a therapeutically effective amount of amount of optically pure (S)-amlodipine and a therapeutically effective amount of an ACE inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of hypertension, congestive heart failure, angina, myocardial infarction, atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, or headache.

In certain embodiments, the present invention relates to the aforementioned products, wherein said ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, pivopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril, or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

In certain embodiments, the present invention relates to the aforementioned products, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

Another aspect of the present invention relates to products for containing a therapeutically effective amount of amount of optically pure (S)-amlodipine and a therapeutically effective amount of an ACE inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of hypertension, congestive heart failure, angina, myocardial infarction, atherosclerosis, diabetic nephropathy, diabetic
cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, or headache; wherein said ACE inhibitor is benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

Another aspect of the present invention relates to products for containing a therapeutically effective amount of amount of optically pure (S)-amlodipine and a therapeutically effective amount of an ACE inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of hypertension, congestive heart failure, angina, myocardial infarction, atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, or headache; wherein said ACE inhibitor is ramipril or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In certain embodiments, the present invention relates to the aforementioned products wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

In certain embodiments, the present invention relates to the aforementioned products wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine L-malate, or a polymorph, pseudopolymorph or solvate thereof.

In certain embodiments, the present invention relates to the aforementioned products wherein said medical condition is hypertension, congestive heart failure, angina, or myocardial infarction.

In certain embodiments, the present invention relates to the aforementioned products wherein said medical condition is hypertension.

8. Immediate/Sustained Release Combination Therapy Dosage Forms

The combination therapy may be formulated in an immediate release dosage form or a sustained release dosage form. In certain embodiments, the present invention relates to immediate release dosage forms of the first and second therapeutic agents. An immediate release dosage form may be formulated as a tablet or multiparticulate which may be encapsulated. Other immediate release dosage forms known in the art can be employed. In certain embodiments, the combination of therapeutic agents may be formulated to provide for an increased duration (sustained release) of therapeutic action. These formulations, at comparable daily dosages of conventional immediate release drug, are often associated with a lower incidence or severity of adverse drug reactions; and they can also be administered
at a lower daily dose than conventional oral medication while maintaining therapeutic activity.

In certain embodiments, the combination therapy can be formulated to delivery the therapeutic agents at the same time or at separate times. In certain embodiments, the first and second therapeutic agents are administered via an oral solid dosage form that includes a sustained release carrier causing the sustained release of the first therapeutic agent, or both the first therapeutic agent and the second therapeutic agent when the dosage form contacts gastrointestinal fluid. The sustained release dosage form may comprise a plurality of substrates which include the drugs. The substrates may comprise matrix spheroids or may comprise inert pharmaceutically acceptable beads which are coated with the drugs. The coated beads are then preferably overcoated with a sustained release coating comprising the sustained release carrier. The matrix spheroid may include the sustained release carrier in the matrix itself; or the matrix may comprise a normal release matrix containing the drugs, the matrix having a coating applied thereon which comprises the sustained release carrier.

In other embodiments, the oral solid dosage form comprises a tablet core containing the drugs within a normal release matrix, with the tablet core being coated with a sustained release coating comprising the sustained release carrier. In further embodiments, the tablet contains the drugs within a sustained release matrix comprising the sustained release carrier. In additional embodiments, the tablet contains the first therapeutic agent within a sustained release matrix and the second therapeutic agent coated into the tablet as an immediate release layer.

The term “sustained release” is defined for purposes of the present invention as the release of the therapeutic agent from the formulation at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration or “MEAC”) but below toxic levels over a period of time of about 12 hours or longer.

The first and second therapeutic agents can be formulated as a controlled or sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may optionally include a sustained released carrier which is incorporated into a matrix along with the active agents, or which is applied as a sustained release coating.

The sustained release dosage form may include the first therapeutic agent in sustained release form and second therapeutic agent in the sustained release form or in
immediate release form. The first therapeutic agent may be incorporated into the sustained release matrix along with the second therapeutic agent; incorporated into the sustained release coating; incorporated as a separated sustained release layer or immediate release layer; or may be incorporated as a powder, granulation, etc., in a gelatin capsule with the substrates of the present invention. Alternatively, the sustained release dosage form may have the first therapeutic agent in the sustained release form and the second therapeutic agent in the sustained release form or immediate release form.

An oral dosage form according to the invention may be provided as, for example, granules, spheroids, beads, pellets (hereinafter collectively referred to as "multiparticulates") and/or particles. An amount of the multiparticulates which is effective to provide the desired dose of the therapeutic agents over time may be placed in a capsule or may be incorporated in any other suitable oral solid form. In one certain embodiments of the present invention, the sustained release dosage form comprises such particles containing or comprising the active ingredient, wherein the particles have diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm.

In certain embodiments, the particles comprise normal release matrixes containing the first therapeutic agent with the second therapeutic agent. These particles are then coated with the sustained release carrier in embodiments where the first therapeutic agent is immediately released, the first therapeutic agent may be included in separate normal release matrix particles, or may be co-administered in a different immediate release composition which is either enveloped within a gelatin capsule or is administered separately. In other embodiments, the particles comprise inert beads which are coated with the second therapeutic agent with the first therapeutic agents. Thereafter, a coating comprising the sustained release carrier is applied onto the beads as an overcoat.

The particles are preferably film coated with a material that permits release of the active agents at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, a desired in vitro release rate. The sustained release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Coatings

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation.
In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the first active agent, second active agent, or both in the desired areas of the gastro-intestinal (GI) tract, e.g., the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about twelve hours and preferably up to twenty-four hours of therapeutic benefit to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine. In certain embodiments, the first therapeutic agent is released in one area of the GI tract and the second therapeutic agent is released in a second area of the GI tract. In certain embodiments, the first and second therapeutic agents are released in nearly equal amounts at the same location in the GI tract.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like. Thus, one aspect of the present invention relates to a formulation wherein the first therapeutic agent is coated over the enteric coat and released into the stomach while the second therapeutic agent is protected by the enteric coating and is released further down the GI tract. Alternatively, one aspect of the present invention relates to a formulation wherein the second therapeutic agent is coated over the enteric coat and released into the stomach while the first therapeutic agent is protected by the enteric coating and is released further down the GI tract.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the first therapeutic agent (with or without the second therapeutic agent) is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight
gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Alternatively, the invention relates to instances wherein the substrate (e.g., tablet core bead, matrix particle) containing the second therapeutic agent (with or without the first therapeutic agent) is coated with a hydrophobic material. Such formulations are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493. Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the formulations according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating.

One commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Acrylic Polymers

In other preferred embodiments of the present invention, the hydrophobic material comprising the controlled release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl
methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminooalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a desirable dissolution profile, it may be necessary to incorporate in a coating two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Rohm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit® S does not swell at about pH<6.5 and is soluble at about pH>7.

Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.
The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.
It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent. 

*Processes for Preparing Coated Beads*

When the aqueous dispersion of hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, *e.g.*, gastric fluid or dissolution media.

The stabilized controlled release bead formulations of the present invention slowly release the therapeutically active agent, *e.g.*, when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with a therapeutically active agent are prepared, *e.g.*, by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the active agents to the beads, and/or to color the solution, *etc.* For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (*e.g.*, Opadry, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (*e.g.*, for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an
effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit® can be used.

5 The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color be added to Aquacoat® via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat®. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

10 The plasticized aqueous dispersion of hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined controlled release of said therapeutically active agent when said coated substrate is exposed to aqueous solutions, e.g., gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

15 The release of the therapeutically active agent from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble
material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain. The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864. The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

Matrix Bead Formulations

In other embodiments of the present invention, the controlled release formulation is achieved via a matrix having a controlled release coating as set forth above. The present invention may also utilize a controlled release matrix that affords in-vitro dissolution rates of the active agent within the preferred ranges and that releases the active agent in a pH-dependent or pH-independent manner. The materials suitable for inclusion in a controlled release matrix will depend on the method used to form the matrix.

For example, a matrix in addition to the first active agent and (optionally) the second active agent may include: (1) Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials; the list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting controlled release of the active agent and which
melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention. (2) Digestible, long chain (C₈-C₅₀, especially C₁₂-C₄₀), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols.

The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxycapryl methacrylates, cynoethyl methacrylate, aminoalkyl methacrylate copolymers, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 30 to about 200 °C, preferably from about 45 to about 90 °C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point from about 30 to about 100°C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C₈-C₅₀, especially C₁₂-C₄₀), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting
point of between 25 and 90 C. are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

In certain instances, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it may be selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12} -C_{36}, preferably C_{14} -C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_{1} to C_{6}) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of release desired for the therapeutic agent. The at least one aliphatic alcohol may be, for example, lauril alcohol, myristyl alcohol or stearyl alcohol. In certain embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of release desired for the therapeutic agent. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the active agent from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.
The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1,000 and 15,000 especially between 1,500 and 12,000. Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C<sub>12</sub> to C<sub>36</sub> aliphatic alcohol and, optionally, a polyalkylene glycol. In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials. In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

9. Pharmaceutical Compositions

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and
animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate,
naphtylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. "Pharmaceutical Salts", J. Pharm. Sci. 1977, 66, 1-19.)

The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., supra)

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin,
propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.
In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trowches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginites, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g.,
freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.
Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Pouders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.
Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and 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 coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

The therapeutic agent alone or on combination with other therapeutic agents can be employed in admixtures with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, intravenous, subcutaneous, enteral, or any other suitable mode of administration, known to the art. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. They can also be combined where desired with other active agents, e.g., other analgesic agents. For parenteral application, particularly suitable are oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. Ampoules are convenient unit dosages. For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gels.
one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

Aqueous suspensions contain the above-identified combination of drugs and that mixture has one or more excipients suitable as suspending agents, for example pharmaceutically acceptable synthetic gums such as hydroxypropylmethylcellulose or natural gums. Oily suspensions may be formulated by suspending the above-identified combination of drugs in a vegetable oil or mineral oil. The oily suspensions may contain a thickening agent such as beeswax or cetetyl alcohol. A syrup, elixir, or the like can be used wherein a sweetened vehicle is employed. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. It is also possible to freeze-dry the active compounds and use the obtained lyophilized compounds, for example, for the preparation of products for injection.

One aspect of combination therapy pertains to a method for providing effective therapeutic treatment in humans, comprising administering an effective or sub-therapeutic amount of a first therapeutic agent; and administering an effective amount of a second therapeutic agent in an amount effective to augment the therapeutic effect provided by said first therapeutic agent. The second therapeutic agent can be administered before, simultaneously with, or after administration of the first therapeutic agent, as long as the dosing interval of the second therapeutic agent overlaps with the dosing interval of the first therapeutic agent (or its therapeutic effect). In other words, according to the method of the present invention, in certain preferred embodiments the second therapeutic agent need not be administered in the same dosage form or even by the same route of administration as the first therapeutic agent. Rather, the method is directed to the surprising synergistic and/or additive benefits obtained in humans, when therapeutically effective levels of a first therapeutic agent have been administered to a human, and, prior to or during the dosage interval for the second therapeutic agent or while the human is experiencing the therapeutic effect, an effective amount of a second therapeutic agent to augment the therapeutic effect.
of the first therapeutic agent is administered. If the second therapeutic agent is administered prior to the administration of the first therapeutic agent, it is preferred that the dosage intervals for the two drugs overlap, i.e., such that the therapeutic effect over at least a portion of the dosage interval of the first therapeutic agent is at least partly attributable to the second therapeutic agent.

In an additional method of the invention, the surprising synergistic and/or additive benefits obtained in the patient are achieved when therapeutically effective levels of the second therapeutic agent have been administered to the patient, and, during the dosage interval for the second therapeutic agent or while the patient is experiencing the therapeutic effect by virtue of the administration of a second therapeutic agent, an effective amount of a first therapeutic agent to augment the therapeutic effect of the second therapeutic agent is administered.

Another aspect of combination therapy relates to an oral solid dosage form comprising an therapeutically effective amount of a first therapeutic agent together with an amount of a second therapeutic agent or pharmaceutically acceptable salt thereof which augments the effect of the first therapeutic agent.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.
The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of
absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, oral, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

The compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other pharmaceuticals.

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the subject compounds, as described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous
solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin, lungs, or mucous membranes; or (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually or buccally; (6) ocularly; (7) transdermally; or (8) nasally.

The term "treatment" is intended to encompass also prophylaxis, therapy and cure.

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

The compound of the invention can be administered as such or in admixtures with pharmaceutically acceptable carriers and can also be administered in conjunction with antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy, thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutical effects of the first administered one is not entirely disappeared when the subsequent is administered.

*Micelles*

Recently, the pharmaceutical industry introduced microemulsionification technology to improve bioavailability of some lipophilic (water insoluble) pharmaceutical agents.

Examples include Trimetrine (Dorduno, S. K. *et al. Drug Development and Industrial Pharmacy 1991, 17(12), 1685-1713*) and REV 5901 (Sheen, P. C. *et al. J. Pharm. Sci. 1991, 80(7), 712-714*). Among other things, microemulsionification provides enhanced bioavailability by preferentially directing absorption to the lymphatic system instead of the circulatory system, which thereby bypasses the liver, and prevents destruction of the compounds in the hepatobiliary circulation.

In one aspect of invention, the formulations contain micelles formed from a compound of the present invention and at least one amphiphilic carrier, in which the micelles have an average diameter of less than about 100 nm. More preferred embodiments provide micelles having an average diameter less than about 50 nm, and even more preferred embodiments provide micelles having an average diameter less than about 30 nm, or even less than about 20 nm.

While all suitable amphiphilic carriers are contemplated, the presently preferred carriers are generally those that have Generally-Recognized-as-Safe (GRAS) status, and
that can both solubilize the compound of the present invention and microemulsify it at a later stage when the solution comes into a contact with a complex water phase (such as one found in human gastro-intestinal tract). Usually, amphiphilic ingredients that satisfy these requirements have HLB (hydrophilic to lipophilic balance) values of 2-20, and their structures contain straight chain aliphatic radicals in the range of C-6 to C-20. Examples are polyethylene-glycolized fatty glycerides and polyethylene glycols.

Particularly preferred amphiphilic carriers are saturated and monounsaturated polyethyleneglycolyzed fatty acid glycerides, such as those obtained from fully or partially hydrogenated various vegetable oils. Such oils may advantageously consist of tri-, di- and mono-fatty acid glycerides and di- and mono-polyethyleneglycol esters of the corresponding fatty acids, with a particularly preferred fatty acid composition including capric acid 4-10, capric acid 3-9, lauric acid 40-50, myristic acid 14-24, palmitic acid 4-14 and stearic acid 5-15%. Another useful class of amphiphilic carriers includes partially esterified sorbitan and/or sorbitol, with saturated or mono-unsaturated fatty acids (SPAN-series) or corresponding ethoxylated analogs (TWEEN-series).

Commercially available amphiphilic carriers are particularly contemplated, including Gelucire-series, Labrafil, Labrasol, or Lauroglycol (all manufactured and distributed by Gattefosse Corporation, Saint Priest, France), PEG-mono-oleate, PEG-di-oleate, PEG-mono-laurate and di-laurate, Lecithin, Polysorbate 80, etc (produced and distributed by a number of companies in USA and worldwide).

Polymers

Hydrophilic polymers suitable for use in the present invention are those which are readily water-soluble, can be covalently attached to a vesicle-forming lipid, and which are tolerated in vivo without toxic effects (i.e., are biocompatible). Suitable polymers include polyethylene glycol (PEG), polylactic (also termed polylactide), polyglycolic acid (also termed polyglycolide), a polylactic-polyglycolic acid copolymer, and polyvinyl alcohol. Preferred polymers are those having a molecular weight of from about 100 or 120 daltons up to about 5,000 or 10,000 daltons, and more preferably from about 300 daltons to about 5,000 daltons. In a particularly preferred embodiment, the polymer is polyethylene glycol having a molecular weight of from about 100 to about 5,000 daltons, and more preferably having a molecular weight of from about 300 to about 5,000 daltons. In a particularly preferred embodiment, the polymer is polyethylene glycol of 750 daltons (PEG(750)). Polymers may also be defined by the number of monomers therein; a preferred embodiment
of the present invention utilizes polymers of at least about three monomers, such PEG polymers consisting of three monomers (approximately 150 daltons).

Other hydrophilic polymers which may be suitable for use in the present invention include polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses such as hydroxymethylcellulose or hydroxyethylcellulose.

In certain embodiments, a formulation of the present invention comprises a biocompatible polymer selected from the group consisting of polyamides, polycarbonates, polyalkylenes, polymers of acrylic and methacrylic esters, polyvinyl polymers, polyglycolides, polysiloxanes, polyurethanes and co-polymers thereof, celluloses, polypropylene, polyethylenes, polystyrene, polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho)esters, poly(butic acid), poly(valeric acid), poly(lactide-cocaprolactone), polysaccharides, proteins, polyhyaluronic acids, polycyanoacrylates, and blends, mixtures, or copolymers thereof.

Cyclodextrins

Cyclodextrins are cyclic oligosaccharides, consisting of 6, 7 or 8 glucose units, designated by the Greek letter α, β or γ, respectively. Cyclodextrins with fewer than six glucose units are not known to exist. The glucose units are linked by alpha-1,4-glucosidic bonds. As a consequence of the chair conformation of the sugar units, all secondary hydroxyl groups (at C-2, C-3) are located on one side of the ring, while all the primary hydroxyl groups at C-6 are situated on the other side. As a result, the external faces are hydrophilic, making the cyclodextrins water-soluble. In contrast, the cavities of the cyclodextrins are hydrophobic, since they are lined by the hydrogen of atoms C-3 and C-5, and by ether-like oxygens. These matrices allow complexation with a variety of relatively hydrophobic compounds, including, for instance, steroid compounds such as 17β-estradiol (see, e.g., van Uden et al. Plant Cell Tiss. Org. Cult. 1994, 38, 1-113). The complexation takes place by Van der Waals interactions and by hydrogen bond formation. For a general review of the chemistry of cyclodextrins, see Agnew. Chem. Int. Ed. Engl. 1994 33, 803-822.

The physico-chemical properties of the cyclodextrin derivatives depend strongly on the kind and the degree of substitution. For example, their solubility in water ranges from insoluble (e.g., triacetyl-beta-cyclodextrin) to 147% soluble (w/v) (G-2-beta-cyclodextrin). In addition, they are soluble in many organic solvents. The properties of the cyclodextrins
enable the control over solubility of various formulation components by increasing or decreasing their solubility.

Numerous cyclodextrins and methods for their preparation have been described. For example, Parmeter (I), et al. (U.S. Pat. No. 3,453,259) and Gramera, et al. (U.S. Pat. No. 3,459,731) described electroneutral cyclodextrins. Other derivatives include cyclodextrins with cationic properties (Parmeter (II), U.S. Pat. No. 3,453,257), insoluble crosslinked cyclodextrins (Solms, U.S. Pat. No. 3,420,788), and cyclodextrins with anionic properties (Parmeter (III), U.S. Pat. No. 3,426,011). Among the cyclodextrin derivatives with anionic properties, carboxylic acids, phosphorous acids, phosphinous acids, phosphonic acids, phosphoric acids, thiophosphonic acids, thiosulphinic acids, and sulfonic acids have been appended to the parent cyclodextrin (see, Parmeter (III), supra). Furthermore, sulfoalkyl ether cyclodextrin derivatives have been described by Stella, et al. (U.S. Pat. No. 5,134,127).

**Liposomes**

Liposomes consist of at least one lipid bilayer membrane enclosing an aqueous internal compartment. Liposomes may be characterized by membrane type and by size. Small unilamellar vesicles (SUVs) have a single membrane and typically range between 0.02 and 0.05 μm in diameter; large unilamellar vesicles (LUVs) are typically larger than 0.05 μm. Oligolamellar large vesicles and multilamellar vesicles have multiple, usually concentric, membrane layers and are typically larger than 0.1 μm. Liposomes with several nonconcentric membranes, i.e., several smaller vesicles contained within a larger vesicle, are termed multivesicular vesicles.

One aspect of the present invention relates to formulations comprising liposomes containing a compound of the present invention, where the liposome membrane is formulated to provide a liposome with increased carrying capacity. Alternatively or in addition, the compound of the present invention may be contained within, or adsorbed onto, the liposome bilayer of the liposome. The compound of the present invention may be aggregated with a lipid surfactant and carried within the liposome's internal space; in these cases, the liposome membrane is formulated to resist the disruptive effects of the active agent-surfactant aggregate.

According to one embodiment of the present invention, the lipid bilayer of a liposome contains lipids derivatized with polyethylene glycol (PEG), such that the PEG chains extend from the inner surface of the lipid bilayer into the interior space encapsulated...
by the liposome, and extend from the exterior of the lipid bilayer into the surrounding environment.

Active agents contained within liposomes of the present invention are in solubilized form. Aggregates of surfactant and active agent (such as emulsions or micelles containing the active agent of interest) may be entrapped within the interior space of liposomes according to the present invention. A surfactant acts to disperse and solubilize the active agent, and may be selected from any suitable aliphatic, cycloaliphatic or aromatic surfactant, including but not limited to biocompatible lysophosphatidylcholines (LPCs) of varying chain lengths (for example, from about C14 to about C20). Polymer-derivatized lipids such as PEG-lipids may also be utilized for micelle formation as they will act to inhibit micelle/membrane fusion, and as the addition of a polymer to surfactant molecules decreases the CMC of the surfactant and aids in micelle formation. Preferred are surfactants with CMCs in the micromolar range; higher CMC surfactants may be utilized to prepare micelles entrapped within liposomes of the present invention, however, micelle surfactant monomers could affect liposome bilayer stability and would be a factor in designing a liposome of a desired stability.

Liposomes according to the present invention may be prepared by any of a variety of techniques that are known in the art. See, e.g., U.S. Pat. No. 4,235,871; Published PCT applications WO 96/14057; New RRC, Liposomes: A practical approach, IRL Press, Oxford (1990), pages 33-104; Lasic DD, Liposomes from physics to applications, Elsevier Science Publishers BV, Amsterdam, 1993.

For example, liposomes of the present invention may be prepared by diffusing a lipid derivatized with a hydrophilic polymer into preformed liposomes, such as by exposing preformed liposomes to micelles composed of lipid-grafted polymers, at lipid concentrations corresponding to the final mole percent of derivatized lipid which is desired in the liposome. Liposomes containing a hydrophilic polymer can also be formed by homogenization, lipid-field hydration, or extrusion techniques, as are known in the art.

In another exemplary formulation procedure, the active agent is first dispersed by sonication in a lysophosphatidylcholine or other low CMC surfactant (including polymer grafted lipids) that readily solubilizes hydrophobic molecules. The resultingmicellar suspension of active agent is then used to rehydrate a dried lipid sample that contains a suitable mole percent of polymer-grafted lipid, or cholesterol. The lipid and active agent suspension is then formed into liposomes using extrusion techniques as are known in the
art, and the resulting liposomes separated from the unencapsulated solution by standard column separation.

In one aspect of the present invention, the liposomes are prepared to have substantially homogeneous sizes in a selected size range. One effective sizing method involves extruding an aqueous suspension of the liposomes through a series of polycarbonate membranes having a selected uniform pore size; the pore size of the membrane will correspond roughly with the largest sizes of liposomes produced by extrusion through that membrane. See, e.g., U.S. Pat. No. 4,737,323 (Apr. 12, 1988).

Release Modifiers

The release characteristics of a formulation of the present invention depend on the encapsulating material, the concentration of encapsulated drug, and the presence of release modifiers. For example, release can be manipulated to be pH dependent, for example, using a pH sensitive coating that releases only at a low pH, as in the stomach, or a higher pH, as in the intestine. An enteric coating can be used to prevent release from occurring until after passage through the stomach. Multiple coatings or mixtures of cyanamide encapsulated in different materials can be used to obtain an initial release in the stomach, followed by later release in the intestine. Release can also be manipulated by inclusion of salts or pore forming agents, which can increase water uptake or release of drug by diffusion from the capsule. Excipients which modify the solubility of the drug can also be used to control the release rate. Agents which enhance degradation of the matrix or release from the matrix can also be incorporated. They can be added to the drug, added as a separate phase (i.e., as particulates), or can be co-dissolved in the polymer phase depending on the compound. In all cases the amount should be between 0.1 and thirty percent (w/w polymer). Types of degradation enhancers include inorganic salts such as ammonium sulfate and ammonium chloride, organic acids such as citric acid, benzoic acid, and ascorbic acid, inorganic bases such as sodium carbonate, potassium carbonate, calcium carbonate, zinc carbonate, and zinc hydroxide, and organic bases such as protamine sulfate, spermine, choline, ethanolamine, diethanolamine, and triethanolamine and surfactants such as Tween and Pluronic. Pore forming agents which add microstructure to the matrices (i.e., water soluble compounds such as inorganic salts and sugars) are added as particulates. The range should be between one and thirty percent (w/w polymer).

Uptake can also be manipulated by altering residence time of the particles in the gut. This can be achieved, for example, by coating the particle with, or selecting as the
encapsulating material, a mucosal adhesive polymer. Examples include most polymers with
free carboxyl groups, such as chitosan, celluloses, and especially polyacrylates (as used
herein, polyacrylates refers to polymers including acrylate groups and modified acrylate
groups such as cyanoacrylates and methacrylates).

Processes for Preparing Matrix-Based Beads

In order to facilitate the preparation of a solid, controlled release, oral dosage form
according to this invention, any method of preparing a matrix formulation known to those
skilled in the art may be used. For example incorporation in the matrix may be effected, for
example, by (a) forming granules comprising at least one water soluble hydroxyalkyl

10 cellulose and the active agent; (b) mixing the hydroxyalkyl cellulose containing granules
with at least one C 12 -C 36 aliphatic alcohol; and (c) optionally, compressing and shaping
the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl
cellulose/active agent with water. In a particularly preferred embodiment of this process,
the amount of water added during the wet granulation step is preferably between 1.5 and 5
times, especially between 1.75 and 3.5 times, the dry weight of the active agent.

15 In yet other alternative embodiments, a spherizing agent, together with the active
ingredient can be spherized to form spheroids. Microcrystalline cellulose is preferred. A
suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101
(Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient
and spherizing agent, the spheroids may also contain a binder. Suitable binders, such as
low viscosity, water soluble polymers, will be well known to those skilled in the
pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as
hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may
contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer,
such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such
20 embodiments, the sustained release coating will generally include a hydrophobic material
such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrix

Sustained release matrices can also be prepared via melt-granulation or melt-
extrusion techniques. Generally, melt-granulation techniques involve melting a normally
solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To
obtain a sustained release dosage form, it may be necessary to incorporate an additional
hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the
molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Pat. No. 4,861,598.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation. In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

Melt Extrusion Multiparticulates

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the active agent, together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours.
An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, a therapeutically active agent, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).
In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681 (Klimesch, et. al.).

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2 to about 30 percent, although the overcoat may be greater depending upon the physical properties of the particular active agent utilized and the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded multiparticulates containing one or more of the therapeutically active agents disclosed above before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release therapeutically active agent for prompt therapeutic effect. The immediate release therapeutically active agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., controlled release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of controlled release beads and matrix multiparticulates to achieve a desired effect.

The sustained release formulations of the present invention preferably slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the therapeutically active agent, which is added thereafter to the extrudate. Such formulations typically will have the therapeutically active agent blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/ or the retardant material.
Exemplification

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1

Formation of (S)-Amlodipine-hemi-D-Tartrate DMAC solvate from (RS)-Amlodipine free base.

A solution of D-Tartaric acid (9.48 kg, 63.15 moles) in DMAC (104.2 kg) is added to a slurry of (RS)-Amlodipine free base (24.9 kg, 60.9 moles) in N,N-Dimethylacetamide (DMAC, 104.3 kg). The reaction mixture is agitated and heated to about 70 °C. The reaction mass is held for one hour with agitation at about 70 °C. The resulting slurry is then cooled with agitation to about 22 °C over 2.5 to 3 hours with a linear cooling profile at about 0.30 °C/min. The slurry is held with agitation at about 22 °C for about 0.5 h. The solid is isolated by filtration, washed by re-slurrying with DMAC followed by a displacement wash with MTBE. The wet cake is dried at about 45 °C in vacuo to produce (S)-Amlodipine-hemi-D-Tartrate-DMAC solvate (13.92 kg, 24.37 moles, 40.0 % yield).

Example 2

Formation of (S)-Amlodipine-L-Malate from (S)-Amlodipine free base.

A slurry of (S)-Amlodipine free base (19.5 kg, 47.69 moles) in isopropanol-MTBE (141.9 kg IPA, 14.9 kg MTBE, 9.5 / 1, wt/wt) is agitated and heated to about 50 °C to form a solution. A solution of L-Malic acid (6.68 kg, 49.82 moles) in isopropanol-water (25.45 kg IPA, 5.73 kg water 4.44/1, wt/wt) is then added, and the reaction mixture is held with agitation for about one hour at about 50 °C to form a slurry. The resulting slurry is then cooled with agitation to about 0 °C over 2.5 to 3 hours, with a linear cooling profile at about 0.25 °C/min. The slurry is held with agitation at about 0 °C for about one hour. The solid product is isolated by filtration at about 0 °C, washed by re-slurrying with cold isopropanol followed by two displacement washes with MTBE. The wet cake is dried at about 60 °C in vacuo to provide (S)-Amlodipine-L-Malate (25.41 kg, 46.79 moles, 98.1 % yield).

Example 3

Detailed Process Description for (S)-Amlodipine Hemi-D-Tartrate DMAC solvate:
The following is a typical batch description for the process using the racemic besylate salt as an input.
1. \(N,N\)-Dimethylacetamide (DMAC) (152.7 kg) was charged to a 100 gal reactor (T-110A).

2. D-Tartaric acid (13.88 kg) was charged slowly to T-110A.

3. The solution in T-110A was mixed and held for use later in the batch.

4. \((RS)\)-Amlodipine besylate (49.81 kg) was charged to a 200 gal reactor (R-120), followed by methyl \(t\)-butyl ether (MTBE) (239.3 kg).

5. Aqueous sodium hydroxide (1N) (137.2kg) was added to R-120.

6. The contents of R-120 were agitated for 20-30 minutes and then the layers were allowed to separate for a minimum of 15 minutes.

7. The bottom aqueous layer was removed and USP water (66.0 kg) was charged to R-120.

8. The contents of R-120 were agitated for a minimum of 20 minutes and then the layers were allowed to separate for a minimum of 15 minutes.

9. The bottom aqueous layer was removed and USP water (66.0 kg) was charged to R-120.

10. The contents of R-120 were agitated for a minimum of 20 minutes and then the layers were allowed to separate for a minimum of 15 minutes.

11. The bottom aqueous layer was removed from R-120.

12. The contents of R-120 were polish filtered through a 3\(\mu\)m cartridge filter to R-110A, followed by a reactor and line rinse with MTBE (49.9 kg).

13. The contents of R-110A were concentrated under vacuum (maximum 50\(^\circ\)C) to a calculated volume (109 L).

14. DMAC (152.8 kg) was charged to the contents of R-110A.

15. The contents of R-110A were again concentrated under vacuum, this time until the batch temperature reached 45-55 \(^{\circ}\)C. The final volume was 208L.

16. R-110A contents were cooled to 20 to 25 \(^{\circ}\)C, followed by the addition of the previously prepared D-tartaric acid solution (166.0kg) at 20-25 \(^{\circ}\)C over 20 to 30 minutes.

17. The mixture was heated to 68-72 \(^{\circ}\)C over 55 to 65 minutes, and held at this temperature for 55 to 65 minutes.

18. The reaction mixture was cooled to 21 to 23 \(^{\circ}\)C over 2 to 3 hours using a linear cooling profile and agitated at this temperature for 30 to 40 minutes.
19. The slurry was filtered on a centrifuge (CE-102) in one load and washed with DMAC (75.7 kg) and MTBE (59.9 kg).

20. The wet cake was discharged (20.33 kg) and dried in vacuum tray dryer (D-401) for a minimum of 6 hours at 45-50°C to yield 20.086 kg of (S)-Amlodipine Hemi–D-Tartrate DMAC solvate.

Example 4

Detailed Process Description for (S)-Amlodipine Free Base:

The following is a typical batch description for the process using the (S)-Amlodipine Hemi–D-Tartrate DMAC solvate salt as an input.

1. (S)-Amlodipine Hemi–D-Tartrate DMAC solvate (29.99 kg) was charged to a 200 gal reactor (R-120), followed by MTBE (245.4 kg).

2. The batch temperature was adjusted to 20-25°C, followed by the addition of 1N sodium hydroxide (85.6 kg) while maintaining a temperature of 20-25°C.

3. The contents of R-120 were agitated for 20-30 minutes and then the layers were allowed to separate for a minimum of 10 minutes.

4. The bottom aqueous layer was removed and USP water (81.8kg) was charged to R-120.

5. The contents of R-120 were agitated for 20-30 minutes and then the layers were allowed to separate for a minimum of 10 minutes.

6. The bottom aqueous layer was removed and USP water (82.5 kg) was charged to R-120.

7. The contents of R-120 were agitated for 20-30 minutes and then the layers were allowed to separate for a minimum of 10 minutes.

8. The bottom aqueous layer was removed.

9. The volume of R-120 was recorded and the solution was transferred to a 100 gal reactor (R-110A) through a 3 μm polishing filter, followed by a reactor and line rinse of MTBE (45.0 kg)

10. The solution was distilled to a calculated volume (87L) under vacuum at a maximum jacket temperature of 40 °C

11. The mixture in R-110A was cooled to 20-25 °C, and while maintaining this temperature, heptane (80.4 kg) was charged over 45-60 minutes.

12. The R-110A contents were agitated at 20 to 25 °C for 45-60 minutes.
13. The slurry was filtered on centrifuge CE-102 in one load and washed with heptane (131.4 kg).
14. The wet cake was discharged (21.22 kg) and dried in vacuum tray dryer D-404 at 40-50 °C to yield 19.72 kg of (S)-Amlodipine Free Base.

**Example 5**

**Detailed Process Description for (S)-Amlodipine L-Malate.**

The following is a typical batch description for the process using the (S)-Amlodipine free base as an input.

1. L-Malic acid (6.68kg), USP Water (5.73kg) and IPA (17.0kg) were charged to a suitable mixing vessel and mixed until a solution was obtained.
2. The L-Malic acid solution was drained through a 5μ polish filter into a HDPE drum, and TK-7 and the lines were rinsed forward to the drum with IPA (8.45kg). This solution was held for later use.
3. (S)-Amlodipine Free Base (Batch 283 0007, 19.5kg) was charged to R-110A, followed by IPA (141.9kg) and MTBE (14.9kg).
4. The temperature of R-110A was adjusted to 48-52°C over 20 to 30 minutes.
5. The previously prepared L-malic acid solution was charged to the contents of R-110A over 15 to 20 minutes while maintaining the temperature at 48-52 °C.
6. The contents of R-110A were held at 48-52 °C for 55 to 65 minutes.
7. The mixture was cooled to −2 to 2°C over 2 to 3 hours and held for a minimum of 1 hour.
8. The slurry was filtered in one load on centrifuge CE-102, followed by washes of IPA (43.6 kg) and MTBE (43.8 kg and 43.5 kg).
9. The material was discharged from the centrifuge to yield 28.88 kg wet cake, and dried under vacuum in vacuum tray dryer D-401 at 56-60 °C to an LOD of less than 1.0%.
10. The product was discharged from the dryer to yield 25.41 kg of (S)-amlodipine L-malate.

**Example 6**

**Polymorphs and Solvates of (S)-Amlodipine L-Malate.**

(S)-Amlodipine L-malate has several polymorphic and solvated forms. They were formed through crystallization and mechanical techniques. Characterization of crystal
forms were performed using X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetry (TG), hot stage microscopy, moisture balance, solution proton NMR spectroscopy, thermogravimetry-infrared spectroscopy (TG-IR), infrared (IR) and Raman spectroscopy.

1. (S)-Amlodipine-L-Malate (Form A)

Form A was found to lose approximately 0.1% up to 150 °C indicating an unsolvated material. The DSC curve for form A shows an endotherm at 164 °C. This was attributed to a melt based on hotstage data. Form A showed an increase in weight of 0.5% when equilibrated at 95% RH. The sample then lost this weight upon equilibrating back to 5% RH. XRPD data collected on the sample after the moisture balance experiment indicated that the sample form remained unchanged. Hygroscopicity studies shown that upon equilibrium at 31, 75, 84 and 95% relative humidity for approximately one week, form A remained unchanged. Solution \textsuperscript{1}H NMR data indicated that the (S)-amlodipine-L-malate molecule was intact. Based on these studies Form A is a crystalline, non-solvated material, which melts at 162 °C.

2. Amorphous (S)-Amlodipine L-Malate

An amorphous material was generated by both room temperature milling and cryogenic milling. At ambient temperature, amorphous material was produced by grinding in a mixer mill for a total of 40 or 50 minutes in 10 minutes intervals. (The sample was scraped from the walls of the canister every ten minutes). The 40 minute grind was performed at 30Hz. Ambient temperature grinding was also performed in an amalgamater for 30 and 45 minutes in 15 minute intervals. A cryogrinder was also used to make amorphous material. The sample was ground under liquid nitrogen for 6 cycles, where a cycle = 3 X 2-minute grinding times with two minutes of cooling between grinds.

Solution \textsuperscript{1}H NMR data indicated that the (S)-amlodipine-L-malate molecule was intact. The IR and Raman spectra of the amorphous form are virtually identical to those for form A. The DSC curve for the amorphous form shows an exotherm at 81°C and an endotherm at 162 °C. This may be due to the crystallization to form A followed by the form A melt. A glass transition was measured around 54 °C.

3. (S)-Amlodipine-L-Malate Hydrate (Form B)

Form B was obtained from water evaporation, slow evaporation from dioxane, fast and slow evaporations from EtOH, and a fast evaporation from IPA. Solution \textsuperscript{1}H NMR
indicated that the (S)-amlodipine molecule was intact. IR and Raman spectra were collected. Compared to form A, the IR and Raman for form B are virtually identical.

The DSC curve for form B shows endotherms at ~91, ~152, and ~190 °C. The endotherm at ~152 °C was attributed to the melt based on hotstage, while events correlated to thermal activity around 91 and 190 °C in the DSC curve were not observed during the hotstage investigation. Variable temperature XRPD experiments were performed on form B. The XRPD data suggests that around 100 °C, form B begins to undergo a conversion because the XRPD pattern is mostly amorphous. Furthermore, by 125 °C, the sample displayed an XRPD pattern indicative of form A.

Desolvation studies were performed on form B. When form B was heated at approximately 60 °C for approximately one week, it remained unchanged. When form B was placed in an approximately ~0% relative humidity chamber, the form remained unchanged. Moisture balance data showed an increase in weight of 17.2% when equilibrated at 95% RH. The sample then lost this weight upon equilibrating back to 5% RH.

Form B was found to lose 1.3% volatiles up to 150 °C. Identification of volatiles in form B was accomplished with Karl Fischer experiments. Karl Fischer water analysis resulted in 4.75% water. TG-IR analysis confirmed the Karl Fischer water analysis. Form B appears to be a hydrate because it is predominately crystallized from experiments involving water and the Karl Fischer data (1.5 moles of water) suggests more water than what can be attributed to just surface water. Form B was also crystallized from dioxane, IPA and EtOH without the presence of water, however these solvents may have contained water sorbed from the atmosphere. Form B appears to be a hydrate.

4. (S)-Amlodipine-Hemi-L-Malate (Form C)

Form C slurried from water, 1:4 EtOH:water, and 1:4 MeOH:water. The characterization of these samples via solution $^1$H NMR show that form C is the hemi-salt of (S)-amlodipine-L-malate (i.e., a salt consisting of 2 molecules of amlodipine for every molecule of L-malic acid). The hemi-malate could also be made from mixing two equivalents of (S)-amlodipine with one equivalent of L-malic acid in ethanol.

5. (S)-Amlodipine-L-Malate (Form D)

Form D was obtained from crystallization from ethanol: ethanol (2 mL) was added to (S)-amlodipine-L-malate (68.4 mg). The sample was sonicated and then placed on a 60 °C shaker block. All solids had dissolved after approximately one day at 60 °C. The sample
was then plunged into a dry ice/acetone bath and then placed in a freezer. After approximately five months, the solvent was decanted, and the solids were allowed to air dry.

The DSC curve for the D form shows an endotherm at 162 °C. The TGA spectra shows 0.2% weight loss at 125 °C. Moisture balance experiments showed a 1.5% weight increase from 5% to 95% RH and a return to initial weight upon desorption. Form D is a polymorph.

6. (S)-Amlodipine-L-Malate Solvate (Form E)

Form E was only formed in 1,2-propanediol with high cooling rates and it is a solvated form with 1,2-propanediol.

7. (S)-Amlodipine-L-Malate Solvate (Form F)

Form F was obtained as single phase and is strongly correlated with DMF as crystallization solvent, which indicate that it is a solvated form with DMF. The XRPD patterns of forms F and G are different, indicating that a different packing of the (S)-amlodipine molecules occurs in the two forms. It should be noticed that form F occurred in mixtures with form A also in other solvents, indicating that it is also a channel hydrate/solvate, but with a different crystal structure than form G. Form F can incorporate DMF, methanol and mixtures water:acetone (10:90), water:THF (80:20) and water:2-propanol (20:80). The TGA analysis of form F shows above 150 °C a high mass loss characteristic to a decomposition process occurred. The DSC shows a melting endothermic peak at 106.6 °C after which it recrystallizes and melts at 149.3 °C.

8. (S)-Amlodipine-L-Malate Solvate (Form G)

Form G is a solvated form that occurs with different solvents (pyridine, water, DMF). The XRPD patterns of form G obtained in these different solvents are the same, indicating that different solvent molecules can be incorporated in certain cavities present in the crystal structure (structures called channel hydrates/solvates) without leading to modifications in the XRPD patterns. Based on it properties we can conclude that form G is likely to be such a channel hydrate/solvate structure. We can conclude that form G can incorporate pyridine, water and DMF:water (wet DMF). The TGA analysis shows a 4.85 % mass loss in the 91-125 °C T interval after which a high mass loss characteristic to a decomposition process occurred. The DSC shows a melting endothermic peak at 150.9 °C and a wide decomposition endothermic peak at 192.2 °C.
**Incorporation by Reference**

All of the patents and publications cited herein are hereby incorporated by reference.

**Equivalents**

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.
We claim:

1. A pharmaceutical composition, comprising optically pure (S)-amlodipine and an ACE inhibitor.

2. The pharmaceutical composition of claim 1, wherein said ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, pivopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

3. The pharmaceutical composition of claim 1, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

4. A pharmaceutical composition comprising optically pure (S)-amlodipine and an ACE inhibitor, wherein said ACE inhibitor is benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

5. A pharmaceutical composition comprising optically pure (S)-amlodipine and an ACE inhibitor, wherein said ACE inhibitor is ramipril or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

6. A pharmaceutical composition consisting essentially of optically pure (S)-amlodipine, an ACE inhibitor, and at least one pharmaceutically acceptable carrier.

7. The pharmaceutical composition of claim 6, wherein said ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, pivopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

8. The pharmaceutical composition of claim 6, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

9. A pharmaceutical composition consisting essentially of optically pure (S)-amlodipine, an ACE inhibitor, and at least one pharmaceutically acceptable carrier,
wherein said ACE inhibitor is benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

10. A pharmaceutical composition consisting essentially of optically pure (S)-amlodipine, an ACE inhibitor, and at least one pharmaceutically acceptable carrier, wherein said ACE inhibitor is ramipril or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

11. The pharmaceutical composition of any one of claims 1-10, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

12. A method of treating a patient suffering from a medical condition selected from the group consisting of hypertension, congestive heart failure, angina, myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache; comprising the step of:

co-administering to a patient in need thereof a therapeutically effective amount of optically pure (S)-amlodipine and an ACE inhibitor.

13. The method of claim 12, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

14. The method of claim 12, wherein said ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, pivopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

15. The method of claim 14, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

16. The method of claim 12, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

17. The method of claim 16, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

18. A method of treating a patient suffering from a medical condition selected from the group consisting of hypertension, congestive heart failure, angina, myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal
insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive
dysfunction, stroke, and headache; comprising the step of:
co-administering to a patient in need thereof a therapeutically effective amount of
optically pure (S)-amlodipine and an ACE inhibitor; wherein said ACE inhibitor is
benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically
acceptable salt, solvate, or hydrate of any of them.

19. The method of claim 18, wherein said optically pure (S)-amlodipine is optically
pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

20. A method of treating a patient suffering from a medical condition selected from the
group consisting of hypertension, congestive heart failure, angina, myocardial
infarction, atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal
insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive
dysfunction, stroke, and headache; comprising the step of:
co-administering to a patient in need thereof a therapeutically effective amount of
optically pure (S)-amlodipine and an ACE inhibitor; wherein said ACE inhibitor is
ramipril.

21. The method of claim 20, wherein said optically pure (S)-amlodipine is optically
pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

22. The method of any one of claims 12-21, wherein said medical condition is
hypertension, congestive heart failure, angina, or myocardial infarction.

23. The method of any one of claims 12-21, wherein said medical condition is
hypertension.

24. Products for containing a therapeutically effective amount of amount of optically
pure (S)-amlodipine and a therapeutically effective amount of an ACE inhibitor as a
combined preparation for simultaneous, separate or sequential use in the treatment
of hypertension, congestive heart failure, angina, myocardial infarction,
atherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal
insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive
dysfunction, stroke, or headache.

25. The products of claim 24, wherein said ACE inhibitor is alacepril, benazepril,
captopril, ceronapril, cilazapril, delapril, enalapril, fentiapril, fosinopril, imidapril,
libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, pivopril,
quinapril, ramipril, spirapril, temocapril,trandolapril, zofenopril, or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

26. The products of claim 24, wherein said ACE inhibitor is benazepril, delapril, fosinopril, lisinopril, moexipril, perindopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

27. Products for containing a therapeutically effective amount of amount of optically pure (S)-amlodipine and a therapeutically effective amount of an ACE inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of hypertension, congestive heart failure, angina, myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, or headache; wherein said ACE inhibitor is benazepril, fosinopril, lisinopril, ramipril, trandolapril or a pharmaceutically acceptable salt, solvate, or hydrate of any of them.

28. Products for containing a therapeutically effective amount of amount of optically pure (S)-amlodipine and a therapeutically effective amount of an ACE inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment of hypertension, congestive heart failure, angina, myocardial infarction, artherosclerosis, diabetic nephropathy, diabetic cardiac myopathy, renal insufficiency, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, or headache; wherein said ACE inhibitor is ramipril or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

29. The products of any one of claims 24-28, wherein said optically pure (S)-amlodipine is optically pure (S)-amlodipine malate, or a polymorph, pseudopolymorph or solvate thereof.

30. The products of any one of claims 24-29, wherein said medical condition is hypertension, congestive heart failure, angina, or myocardial infarction.

31. The products of any one of claims 24-29, wherein said medical condition is hypertension.
Figure 1

Chemical reaction diagrams showing the synthesis process.
Figure 2

(±)-Amlodipine Besylate Salt methyl t-butyl ether 1 N Sodium Hydroxide

Mix

Phase separation

Phase separation

USP Water

Polish filtration

Vacuum distillation → Flammable waste

Vacuum distillation → Flammable waste

Dimethylacetamide

Cool

D-Tartaric acid

Dimethylacetamide

Resolution

Heat/Mix

Cool/Mix

Dimethylacetamide

Isolate/wash → Flammable waste

(5)-Amlodipine Hemi-D-Tartrate DMAC Solvate wet cake
Figure 3

(5)-Amlodipine-Hemi-D-Tartrate, DMAC Solvate methyl t-butyl ether
1 N Sodium Hydroxide

Mix

Phase separation

Basic Aqueous waste

Phase separations (2)

USP Water

USP Water

MTBE

Polish filtration

Vacuum distillation

Flammable waste

Cool

Mix

Heptane

Isolate/wash

Flammable waste

Vacuum Dry

(5)-Amlodipine
Figure 4

(5)-Amlodipine
Isopropanol
Methyl t-butyl ether

Mix

Heat/Dissolution

L-Malic acid
USP Water
Isopropanol

Charge solution
Salt Formation

5μ filtered

Cool

Mix

Filter

Motherliquors

Wash

WashLiquors

Vacuum Dry

(5)-Amlodipine-L-malate