Title: NAPARTICULATE FORMULATIONS COMPRISING HMG COA REDUCTASE INHIBITOR DERIVATIVES ("STATINS"), NOVEL COMBINATIONS THEREOF AS WELL AS MANUFACTURING OF THESE PHARMACEUTICAL COMPOSITIONS

Abstract: The present invention is directed to nanoparticulate compositions comprising statin such as lovastatin or simvastatin including surface stabilizer. The statin particles of the composition have an effective average particle size of less than about 2000 nm. In another aspect of this invention, novel combinations of statins and other cholesterol lowering agents are described and methods of using same are taught.
FIELD OF THE INVENTION

The present invention relates to nanoparticulate compositions comprising statin, preferably lovastatin or simvastatin, and novel statin combinations. The nanoparticulate statin particles preferably have an effective average particle size of less than about 2000 nm. In another aspect, this invention includes novel combinations of statins and other cholesterol lowering agents and methods of using the same.

BACKGROUND OF THE INVENTION

I. Background Regarding Nanoparticulate Active Agent Compositions

Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto, or associated with, the surface thereof a non-crosslinked surface stabilizer. Many factors can affect bioavailability including the dosage form and various properties, e.g., dissolution rate of the drug. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. By decreasing the particle size of an active agent, the surface area of the composition is increased, thereby generally resulting in an increased bioavailability. The '684 patent does not teach nanoparticulate compositions of statins.

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


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

Recently, a number of new drugs collectively known as statins or vastatins have been introduced to reduce serum LDL cholesterol levels (representative examples of these drugs are detailed in *The Merck Index*). High LDL cholesterol levels have been shown to be an important risk factor in the development of arteriosclerosis and ischaemic heart disease. Statins have been found to lower serum LDL cholesterol levels in a dose dependent manner. Additionally, these drugs lower serum triglyceride levels, which is another risk factor for heart disease.

Statins lower serum LDL cholesterol levels by competitive inhibition of 3-hydroxyl-3-methylglutaryl-Coenzyme A reductase (HMG-COA reductase), an enzyme involved in the biosynthesis of cholesterol. By binding tightly to the active site of the enzyme, statins block the reduction of HMG-CoA, a step necessary in the biosynthesis of cholesterol. This inhibition of cholesterol biosynthesis by a statin results in a decrease in the production and secretion of LDL cholesterol. In addition, the upregulation of LDL receptors, especially in the liver, leads to the removal of LDLs from the serum. Thus, by reducing the production of LDL cholesterol and by causing LDL cholesterol to be removed from the serum, statins effectively reduce overall serum LDL cholesterol levels.

Two-thirds of the total cholesterol found in the body is of endogenous origin. The major site of cholesterol biosynthesis is in the liver. Such liver-derived cholesterol is the main cause of the development of hyper-cholesterolaemia. In contrast, cholesterol production in non-hepatic cells is needed for normal cell function. Therefore, selective inhibition of HMG-CoA reductase in the liver is an important requirement for HMG-COA reductase inhibitors. In this regard, statins typically have high oral availability and high hepatic extraction during their first pass through the liver. Statins have been associated with significant liver toxicity.

Even though the current HMG-CoA reductase inhibitors are quite potent, a need exists for safer, and higher potency HMG-CoA reductase inhibitors. The present
invention satisfies these needs.

**SUMMARY OF THE INVENTION**

The present invention relates to nanoparticulate active agent compositions comprising at least one statin, such as lovastatin or simvastatin, and novel statin combinations. The compositions preferably comprise at least one statin and at least one surface stabilizer adsorbed on or associated with the surface of the one or more statin particles. The nanoparticulate statin particles preferably have an effective average particle size of less than about 2000 nm.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate statin composition of the invention. The pharmaceutical compositions preferably comprise at least one statin, at least one surface stabilizer, and at least one pharmaceutically acceptable carrier, as well as any desired excipients known to those in the art and formulated into the dosage form desired.

In another aspect of this invention, novel combinations of statins and at least one other cholesterol lowering agent are described and methods of using the same are taught.

Another aspect of the invention is directed to a nanoparticulate statin composition having improved pharmacokinetic profiles as compared to conventional microcrystalline statin formulations, such as improved $T_{\text{max}}$, $C_{\text{max}}$, and AUC parameters.

One embodiment of the invention encompasses a statin composition, wherein the pharmacokinetic profile of the statin is not substantially affected by the fed or fasted state of a subject ingesting the composition, preferably as defined by $C_{\text{max}}$ and AUC guidelines given by the U.S. Food and Drug Administration and/or the corresponding European regulatory agency (EMEA).

In yet another embodiment, the invention encompasses a statin composition of the invention, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular
as defined by $C_{\text{max}}$ and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMEA).

Other embodiments of the invention include, but are not limited to, nanoparticulate statin compositions which, as compared to conventional non-nanoparticulate formulations of the same statin, preferably have one or more of the following properties: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) an increased rate of dissolution for the nanoparticulate statin compositions; and (6) bioadhesive statin compositions.

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

The present invention is also directed to methods of treatment using the nanoparticulate statin compositions of the invention for conditions such as hypercholesterolemia, hypertriglyceridemia, coronary heart disease, and peripheral vascular disease (including symptomatic carotid artery disease). In one aspect, the compositions of the invention can be used as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). In another aspect, the compositions can be used as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Markedly elevated levels of serum triglycerides (e.g., >2000 mg/dL) may increase the risk of developing pancreatitis. Other diseases that may be directly or indirectly associated with elevated, uncontrolled cholesterol metabolism, e.g., restenosis and Alzheimer's disease, may also be treated with the compositions of this invention. Other methods of treatment using the nanoparticulate statin compositions of the present invention are known to those of skill in the art.
Such methods comprise administering to a subject a therapeutically effective amount of a nanoparticulate statin pharmaceutical composition according to the invention.

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

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to nanoparticulate active agent compositions comprising at least one statin, such as lovastatin or simvastatin, and novel statin combinations. The compositions preferably comprise at least one statin and at least one surface stabilizer adsorbed on or associated with the surface of the statin particles. The nanoparticulate statin particles preferably have an effective average particle size of less than about 2000 nm.

As taught in the ‘684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable nanoparticulate statin formulations can be made.

Even though the current HMG-CoA reductase inhibitors are quite potent, a need exists for safer and higher potency HMG-CoA reductase inhibitors. Compositions of nanoparticulate statins decrease the amount of drug needed and the amount that escapes from the liver and this, in turn, decreases adverse side effects while providing maximum dose response. Additionally, a longer plasma half-life is believed to be associated with nanoparticulate statin compositions of the invention. Moreover, increasing the duration of effect of the HMG-CoA reductase inhibitor is expected to result in even lower serum cholesterol levels, with a further reduction in dose expected.

In general, the rate of dissolution of a particulate drug can increase with increasing surface area, *e.g.*, decreasing particle size. Consequently, methods of making finely
divided drugs have been studied and efforts have been made to control the size and size range of drug particles in pharmaceutical compositions. However, nanoparticulate active agent formulations suitable for administration as a pharmaceutical require formulation of the active ingredient into a colloidal dispersion exhibiting the acceptable nanoparticle size range and the stability to maintain such size range and not agglomerate. Merely increasing surface area by decreasing particle size does not assure success. Further challenges include forming solid dose forms redispersible into the nanoparticle form upon administration to the patient to maintain the benefit of the nanoparticle statin over the traditional dosage form.

Advantages of the nanoparticulate statin formulations of the invention as compared to conventional non-nanoparticulate formulations of the same statin preferably include, but are not limited to: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) increased bioavailability; (4) substantially similar pharmacokinetic profiles of the nanoparticulate statin compositions when administered in the fed versus the fasted state; (5) improved pharmacokinetic profiles; (6) bioequivalency of the nanoparticulate statin compositions when administered in the fed versus the fasted state; (7) an increased rate of dissolution for the nanoparticulate statin compositions; (8) bioadhesive statin compositions; and (9) the nanoparticulate statin compositions can be used in conjunction with other active agents.

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

A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or
granules. The solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

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

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

"Conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2 microns.

"Poorly water soluble drugs" as used herein means those having a solubility of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml. Such drugs tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. Moreover, poorly water soluble drugs tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water soluble drug substances.

As used herein with reference to stable statin particles, "stable" includes, but is not limited to, one or more of the following parameters: (1) that the statin particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the statin particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the statin particles are chemically stable; and/or (4) where the statin has not been subject to a heating step at or above the melting point of the statin in the preparation of the nanoparticles of the invention.
“Therapeutically effective amount” as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that “therapeutically effective amount,” administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a ‘therapeutically effective amount’ by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

I. Preferred Characteristics of the Statin Compositions of the Invention

A. Increased Bioavailability and Lower Dosages

The statin compositions of the invention preferably exhibit increased bioavailability, at the same dose of the same statin, require smaller doses, and show longer plasma half-life as compared to prior conventional statin formulations.

In one aspect of the invention, pharmaceutical statin compositions have enhanced bioavailability such that the statin dosage can be reduced, resulting in a decrease in toxicity associated with such statins. It has been surprisingly found in the present invention that stable compositions of nanoparticulate statins can be formed that permit therapeutic levels at desirably lower dosage.

Greater bioavailability of the statin compositions of the invention can enable a smaller solid dosage size. This is particularly significant for patient populations such as the elderly, juvenile, and infant.

B. Improved Pharmacokinetic Profiles

The invention also preferably provides statin compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the statin compositions preferably includes, but is not limited to: (1) that the $T_{\text{max}}$ of a statin when assayed in the plasma of a mammalian subject following administration is preferably less than the $T_{\text{max}}$ for a conventional, non-
nanoparticulate form of the same statin, administered at the same dosage; (2) that the $C_{\text{max}}$ of a statin when assayed in the plasma of a mammalian subject following administration is preferably greater than the $C_{\text{max}}$ for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage; and/or (3) that the AUC of a statin when assayed in the plasma of a mammalian subject following administration, is preferably greater than the AUC for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage.

The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of a statin. The compositions can be formulated in any way as described below and as known to those of skill in the art.

A preferred statin composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same statin, administered at the same dosage, a $T_{\text{max}}$ not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, or not greater than about 10% of the $T_{\text{max}}$, exhibited by the non-nanoparticulate formulation of the same statin.

A preferred statin composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same statin, administered at the same dosage, a $C_{\text{max}}$ which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 100% greater than the $C_{\text{max}}$ exhibited by the non-nanoparticulate formulation of the same statin.

A preferred statin composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same statin, administered at the same dosage, an AUC which is at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 100% greater than the AUC exhibited by the non-nanoparticulate formulation of the same statin.
Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions, gels, aerosols, ointments, creams, solid dose forms, etc. of a nanoparticulate statin.

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

The invention encompasses a statin composition wherein the pharmacokinetic profile of the statin is preferably not substantially affected by the fed or fasted state of a subject ingesting the composition, when administered to a human. This means that there is no substantial difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate statin compositions are administered in the fed versus the fasted state.

The invention also encompasses a statin composition in which administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state. “Bioequivalency” is preferably established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both $C_{\text{max}}$ and AUC under U.S. Food and Drug Administration regulatory guidelines, or a 90% CI for AUC of between 0.80 to 1.25 and a 90% CI for $C_{\text{max}}$ of between 0.70 to 1.43 under the European EMEA regulatory guidelines ($T_{\text{max}}$ is not relevant for bioequivalency determinations under USFDA and EMEA regulatory guidelines).

In the prior art, lovastatin given under fasting conditions, has been shown to result in plasma concentrations of total inhibitors that were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal. This significant difference of about 33% in absorption observed with conventional statin formulations is undesirable. The nanoparticulate statin formulations of the invention alleviate this problem, as the nanoparticulate statin formulations of the invention reduce differences in or preferably do not produce significantly different, absorption levels when administered under fed as compared to fasting conditions.
Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed.

The difference in absorption of the statin compositions of the invention, when administered in the fed versus the fasted state, preferably is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

D. Dissolution Profiles of the Statin Compositions of the Invention

The statin compositions of the invention preferably have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. To improve the dissolution profile and bioavailability of statins it would be useful to increase the drug’s dissolution so that it could attain a level close to 100%.

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

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

E. Redispersibility Profiles of the Statin Compositions of the Invention

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

This is because nanoparticulate active agent compositions benefit from the small particle size of the active agent; if the active agent does not redisperse into the small particle sizes upon administration, then “clumps” or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall well below that observed with the liquid dispersion form of the nanoparticulate active agent.

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

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

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

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

Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.
Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

In other embodiments of the invention, the redispersed statin particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By “an effective average particle size of less than about 2000 nm” it is meant that at least 50% of the statin particles have a particle size less than the effective average, by weight, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, when measured by the above-noted techniques. Preferably, at least about 70%, about 90%, about 95%, or about 99% of the statin particles have a particle size less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, *etc*.

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

Bioadhesive statin compositions of the invention comprise at least one cationic surface stabilizer, which are described in more detail below. Bioadhesive formulations of statins exhibit exceptional bioadhesion to biological surfaces, such as mucous. The term bioadhesion refers to any attractive interaction between two biological surfaces or between a biological and a synthetic surface. In the case of bioadhesive nanoparticulate statin compositions, the term bioadhesion is used to describe the adhesion between the nanoparticulate statin compositions and a biological substrate (i.e. gastrointestinal mucin, lung tissue, nasal mucosa, etc.). See e.g., U.S. Patent No. 6,428,814 for “Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers,” which is specifically incorporated by reference.

There are basically two mechanisms which may be responsible for this bioadhesion phenomena: mechanical or physical interactions and chemical interactions. The first of these, mechanical or physical mechanisms, involves the physical interlocking or interpenetration between a bioadhesive entity and the receptor tissue, resulting from a good wetting of the bioadhesive surface, swelling of the bioadhesive polymer, penetration of the bioadhesive entity into a crevice of the tissue surface, or interpenetration of bioadhesive composition chains with those of the mucous or other such related tissues. The second possible mechanism of bioadhesion incorporates forces such as ionic attraction, dipolar forces, van der Waals interactions, and hydrogen bonds. It is this form of bioadhesion which is primarily responsible for the bioadhesive properties of the nanoparticulate statin compositions of the invention. However, physical and mechanical interactions may also play a secondary role in the bioadhesion of such nanoparticulate compositions.

The bioadhesive statin compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive statin compositions coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.
A bioadhesive statin composition slows the transit of the composition, and some statin particles would also most likely adhere to tissue other than the mucous cells and therefore give a prolonged exposure to the statin, thereby increasing absorption and the bioavailability of the administered dosage.

G. Statin Compositions Used in Conjunction with Other Active Agents

The statin compositions of the invention can additionally comprise one or more compounds useful: (1) in treating conditions such as dyslipidemia, hyperlipidemia, hypercholesterolemia, cardiovascular disorders, hypertriglyceridemia, coronary heart disease, and peripheral vascular disease (including symptomatic carotid artery disease), or related conditions; (2) as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb); (3) as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia); (4) in treating pancreatitis; (5) in treating restenosis; and/or (6) in treating Alzheimer's disease.

Exemplary non-statin compositions useful in the claimed invention include, but are not limited to, cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, sterols and/or stanols.

Useful cholesterol lowering agents are well known to those of skill in the art and include, but are not limited to, ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives such as fish oil, long chain plant extract alcohols such as policosanol, ezetimibe, and cellulosics.

Useful polycosanols include, but are not limited to, triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, tetacontanol, or natural products or extracts from natural products containing such compounds.

Useful alkanoyl L-carnitines include, but are not limited to, acetyl L-carnitine, propionyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine, and isovaleryl L-carnitine, or a pharmacologically acceptable salt thereof.
Examples of antihypertensives include, but are not limited to diuretics ("water pills"), beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin receptor blockers (formal medical name angiotensin-2-receptor antagonists, known as "sartans" for short).

Examples of sterols and stanols include, but are not limited to plant sterols, plant sterol esters, fish oil, sitosterol, sitostanol, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, beta-sitosterol, and the like.

Such additional compounds can have a conventional non-nanoparticulate particle size, i.e., an effective average particle size greater than about 2 microns, or such additional compounds can be formulated into a nanoparticulate particle size, i.e., an effective average particle size of less than about 2 microns. If such one or more non-statin compounds have a nanoparticulate particle size, then preferably such non-statin compounds are poorly soluble in at least one liquid media (poorly soluble as defined in the “Definitions” section, above), and have at least one surface stabilizer adsorbed on or associated with the surface of the non-statin compound. The one or more surface stabilizers utilized in the composition of the non-statin compound can be the same as or different from the one or more surface stabilizers utilized in the statin composition. A description of surface stabilizers useful in the invention is provided below.

II. Compositions

The present invention is directed to nanoparticulate active agent compositions comprising at least one statin, such as lovastatin or simvastatin, and novel statin combinations. The compositions preferably comprise at least one statin and at least one surface stabilizer adsorbed on, or associated with, the surface of the statin. The nanoparticulate statin particles preferably have an effective average particle size of less than about 2000 nm. In another aspect of this invention, novel combinations of statins and other cholesterol lowering agents are described and methods of using the same are taught.
The present invention also includes nanoparticulate statin compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for various routes of administration including but not limited to, oral, rectal, ocular, and parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid (the preferred route), liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (e.g., in powder, ointment or drop form), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

A. Statin Particles

As used herein “statin” means any HMG-CoA Reductase Inhibitor (including their analogs), or a salt thereof, having preferably the solubility in water of lovastatin or simvastatin, or a solubility in water of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, or more preferably less than about 1 mg/ml.

The one or more statin particles, or salt thereof, can be in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

Such statin compounds include, but are not limited to, atorvastatin (Lipitor®) (U.S. Patent No. 4,681,893) and other 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives as disclosed in U.S. Patent No. 4,647,576; fluvastatin (Lescol®) (U.S. Patent No. 5,354,772); lovastatin (U.S. Patent No. 4,231,938); pravastatin (U.S. Patent No. 4,346,227); simvastatin (U.S. Patent No. 4,444,784); velostatin; fluvastatin; fluindostatin (Sandoz XU-62-320); pyrazole analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488; rivastatin and other pyridyldihydroxyheptenoic acids, as disclosed in European Patent 491226A; Searle’s SC-45355 (a 3-substituted pentanedioic acid derivative); dichloroacetate; imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393; 2,3-di-substituted pyrrole, furan, and thiophene derivatives, as disclosed in European Patent Application No. 0221025; naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237;
octahydnaphthalenes, such as those disclosed in U.S. Patent No. 4,499,289; keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No. 0,142,146 A2; phosphinic acid compounds; as well as other HMG CoA reductase inhibitors.

Lovastatin is one of the most important known cholesterol lowering agents. Lovastatin as used herein (CAS Registry No. 75330-75-5) is also known as mevinolin or monacolin K and is chemically known as beta,beta-dihydroxy-7-[1,2,6,7,8,8a-hexahydro-2,6-dimethyl-8-(2-methyl -butyroloxy)-1-naphthalen-1-yl]-heptanoic acid beta-lactone. Lovastatin is one member of a class of compounds which are referred to generally as statins and which are known to exist in open ring hydroxy acid and in lactone form.

Lovastatin and its analogs inhibit HMG-CoA reductase. Lovastatin is specifically advantageous because, as a result of its application, biosynthetic intermediates that have a toxic steroid skeleton formed at a later stage of biosynthesis fail to accumulate. Lovastatin also increases the number of LDL-receptors at the surface of the cell membrane, which remove the LDL cholesterol circulating in the blood, thereby inducing the lowering of blood plasma cholesterol level.

Lovastatin is routinely produced via fermentation and is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile.

Lovastatin tablets are commercially supplied as 10 mg, 20 mg, and 40 mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains cellulose, lactose, magnesium stearate, and starch. Butylated hydroxyanisole (BHA) is added as a preservative.

Lovastatin is well known in the art and is readily recognized by one of ordinary skill. High LDL cholesterol is usually first treated with exercise, weight loss in obese individuals, and a diet low in cholesterol and saturated fats. When these measures fail, cholesterol-lowering medications such as lovastatin can be added. The National Cholesterol Education Program (NCEP) has published treatment guidelines for use of statins such as lovastatin. These treatment guidelines take into account the level of LDL
cholesterol as well as the presence of other risk factors such as diabetes, hypertension, cigarette smoking, low HDL cholesterol level, and family history of early coronary heart disease. The effectiveness of the statin medications in lowering cholesterol is dose-related. Blood cholesterol determinations are performed in regular intervals during treatment so that dosage adjustments can be made. A reduction in LDL cholesterol level can be seen two weeks after starting therapy with a statin.

B. Surface Stabilizers

Surface stabilizers especially useful herein physically adhere on or associate with the surface of the nanoparticulate statin but do not chemically react with the statin particles or itself. Preferably, individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The choice of a surface stabilizer for a statin is non-trivial and required extensive experimentation to realize a desirable formulation for the active ingredient’s therapeutic effect desired. For example, the effectiveness of using of a particular stabilizer with an active ingredient is unpredictable because the stabilizer among other factors, will effect dissolution and pharmacokinetic profiles for a statin. Accordingly, the present invention is directed to the surprising discovery that stable, therapeutically useful, nanoparticulate statin compositions can be made.

Combinations of more than one surface stabilizer can preferably be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Preferred surface stabilizers include nonionic, anionic, cationic, and zwitterionic surfactants.

Representative examples of surface stabilizers include hydroxypropylmethylcellulose (anionic), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate (anionic), gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium
chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol
emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such
as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan
fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and
Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (e.g., Carbowaxs 3550® and
934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates,
carboxymethylcellulose calcium, carboxymethylcellulose sodium, methyl cellulose,
hydroxyethylcellulose, hydroxypropylmethylcellulose phthlate, noncrystalline cellulose,
magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-
tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as
tyloxapol, superione, and triton), poloxamers (e.g., Pluronics F68® and F108®, which are
block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic
908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer
derived from sequential addition of propylene oxide and ethylene oxide to
ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-
1508) (BASF Wyandotte Corporation), Triton X-200®, which is an alkyl aryl polyether
sulfonate (Dow Chemical); Crodesta F-110®, which is a mixture of sucrose stearate and
sucrose distearate (Croda Inc.); p-isonyonlphenoxypoly-(glycidol), also known as Olin-
LOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda,
Inc.); and SA9OHCO, which is C₁₈H₃₇CH₂(CON(CH₃)-CH₂(CHOH)₄(CH₂OH)₂
(Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-
deetyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside;
heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-
thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β-D-
glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-
thioglucopyranoside; PEG-derivatized phospholipid, PEG- derivatized cholesterol, PEG-
derivatized cholesterol derivative, PEG- derivatized vitamin A, PEG- derivatized vitamin
E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like such
as Plasdone® S630 in a 60:40 ratio of the pyrrolidone and vinyl acetate.
More examples of useful surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, cationic phospholipids, chitosan, polylezine, polyvinylimidazole, polybrene, polymethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexadecyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauril dimethyl (ethenoxy)_{4} ammonium chloride or bromide, N-alkyl (C_{12-18}) dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18}) dimethyl-benzyl ammonium chloride, N-tetradecylidimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauril trimethyl ammonium chloride, ethoxylated alkylamidoalkyl/dialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecylidimethyl ammonium chloride, N-tetradecylidimethyl benzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecylidimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides,
alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALQUIAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkyldiaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

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

Nonpolymeric surface stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula NR₁R₂R₃R₄⁺. For compounds of the formula NR₁R₂R₃R₄⁺:

(i) none of R₁-R₄ are CH₃;
(ii) one of R₁-R₄ is CH₃;
(iii) three of R₁-R₄ are CH₃;
(iv) all of R₁-R₄ are CH₃;
(v) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ is an alkyl chain of seven carbon atoms or less;
(vi) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ is an alkyl chain of nineteen carbon atoms or more;
(vii) two of R₁-R₄ are CH₃ and one of R₁-R₄ is the group C₆H₅(CH₂)ₙ, where n>1;
(viii) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ comprises at least one heteroatom;
(ix) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ comprises at least one halogen;
(x) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ comprises at least one cyclic fragment;
(xi) two of R₁-R₄ are CH₃ and one of R₁-R₄ is a phenyl ring; or
(xii) two of R₁-R₄ are CH₃ and two of R₁-R₄ are purely aliphatic fragments.

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

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

**C. Other Pharmaceutical Excipients**

Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients depending upon the route of administration and the dosage form desired. Such excipients are known in the art.

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

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

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.
Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

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

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

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

**D. Nanoparticulate Statin Particle Size**

The compositions of the invention contain statin nanoparticles, such as lovastatin or simvastatin nanoparticles, which have an effective average particle size of less than about 2000 nm (i.e., 2 microns). In a preferred embodiment of the invention, the statin nanoparticles have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about...
400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less
than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50
nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By “an effective average particle size of less than about 2000 nm” it is meant that
at least 50% of the statin particles have a particle size less than the effective average, by
weight, i.e., less than about 2000 nm, about 1900 nm, about 1800 nm, etc., when
measured by the above-noted techniques. Preferably, at least about 70%, about 90%,
about 95%, or about 99% of the statin particles have a particle size of less than the
effective average, i.e., less than about 2000 nm, about 1900 nm, about 1800 nm, etc..

In the present invention, the value for D50 of a nanoparticulate statin composition
is the particle size below which 50% of the statin particles fall, by weight. Similarly, D90
is the particle size below which 90% of the statin particles fall, by weight.

E. Concentration of Nanoparticulate Statin and Surface Stabilizers

The relative amounts of at least one statin and one or more surface stabilizers can
vary widely. The optimal amount of the individual components depends, for example,
upon one or more of the physical and chemical attributes of the particular statin selected
and surface stabilizer(s) selected, such as the hydrophilic lipophilic balance (HLB),
melting point, and the surface tension of water solutions of the stabilizer, etc.

Preferably, the concentration of the at least one statin can vary from about 99.5%
to about 0.001%, preferably from about 95% to about 0.1%, preferably from about 90% to
about 0.5%, by weight, based on the total combined weight of the statin and at least one
surface stabilizer, not including other excipients. Higher concentrations of the active
ingredient are generally preferred from a dose and cost efficiency standpoint.

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

Exemplary useful ratios of active ingredient to stabilizers herein are preferably
about 1:1, preferably about 2:1, preferably about 3:1, preferably about 4:1, preferably
about 5:1, preferably about 6:1, preferably about 7:1, preferably about 8:1, and preferably
about 10:1, by weight, based on the total combined dry weight of the statin and at least
one surface stabilizer, not including other excipients.

III. Methods of Making Nanoparticulate Statin Compositions

The nanoparticulate statin compositions can be made using any suitable method
known in the art such as, for example, milling, homogenization, or precipitation
techniques. Exemplary methods of making nanoparticulate compositions are described in
the '684 patent. Methods of making nanoparticulate compositions are also described in
Patent No. 5,718,388 for “Continuous Method of Grinding Pharmaceutical Substances;”
U.S. Patent No. 5,862,999 for “Method of Grinding Pharmaceutical Substances;” U.S.
Patent No. 5,665,331 for “Co-Microprecipitation of Nanoparticulate Pharmaceutical
Agents with Crystal Growth Modifiers;” U.S. Patent No. 5,662,883 for “Co-
Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth
Modifiers;” U.S. Patent No. 5,560,932 for “Microprecipitation of Nanoparticulate
Contrast Compositions Containing Nanoparticles;” U.S. Patent No. 5,534,270 for
“Method of Preparing Stable Drug Nanoparticles;” U.S. Patent No. 5,510,118 for
“Process of Preparing Therapeutic Compositions Containing Nanoparticles;” and U.S.
Patent No. 5,470,583 for “Method of Preparing Nanoparticle Compositions Containing
Charged Phospholipids to Reduce Aggregation,” all of which are specifically incorporated
by reference.

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

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Solid dose forms of the dispersions of novel statin formulations according to the present invention can be made as described in U.S. Patent No. 6,375,986.

A. Milling to Obtain Nanoparticulate Statin Dispersions

Milling a statin to obtain a nanoparticulate statin dispersion comprises dispersing statin particles in a liquid dispersion medium in which the statin is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the statin to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

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

B. Precipitation to Obtain Nanoparticulate Statin Compositions

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

Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for “Process of Preparing Therapeutic Compositions Containing Nanoparticles.” Such a method comprises dispersing statin particles in a liquid dispersion media in which the statin is poorly soluble, followed by subjecting the dispersion to homogenization to reduce the particle size of the statin to the desired effective average particle size. The statin particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the statin particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the statin/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

IV. Methods of Using Statin Formulations of the Current Invention

The statin compositions of the present invention can be administered to a subject via any conventional means including, but not limited to, preferably orally, rectally, ocularly, parenterally (e.g., intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (e.g., powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term “subject” is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

The present invention provides a method of prolonging plasma levels of statin in a subject while achieving the desired therapeutic effect. In one aspect, such a method comprises orally administering to a subject an effective amount of a composition of this invention comprising statin.

In one aspect, the compositions of the invention are useful in treating conditions that may be directly or indirectly associated with elevated and/or uncontrolled cholesterol metabolism as described herein and known to those in the art.
Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

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

Solid dosage forms for oral administration are preferred and include, but are not limited to, capsules, tablets, pills, powders, caplets, and granules. In such solid dosage forms, the active agent (i.e. the composition of this invention) is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium
stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

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

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

The effective amounts of the statin composition of this invention can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of statin in the nanoparticulate compositions of the invention may be varied to obtain an amount of statin that is effective to obtain a desired therapeutic response for a particular composition and method of administration and the condition to be treated. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered statin, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment;
drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

V. **Statin Combinations**

Statin compositions of the present invention are also particularly useful when given pursuant to the method of this invention in combination with a therapeutically effective amount of at least one other active agent useful: (1) in treating conditions such as dyslipidemia, hyperlipidemia, hypercholesterolemia, cardiovascular disorders, hypertriglyceridemia, coronary heart disease, and peripheral vascular disease (including symptomatic carotid artery disease), or related conditions; (2) as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb); (3) as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia); (4) in treating pancreatitis; (5) in treating restenosis; and/or (6) in treating Alzheimer’s disease.

Exemplary non-statin compositions useful in the claimed invention include, but are not limited to, cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, sterols and/or stanols.

Useful cholesterol lowering agents are well known to those of skill in the art and include, but are not limited to, ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives such as fish oil, long chain plant extract alcohols such as policosinol, ezetimibe, and celluloses.

Useful polycosanols include, but are not limited to, triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, tetracontanol, or natural products or extracts from natural products containing such compounds.

Useful alkanoyl L-carnitines include, but are not limited to, acetyl L-carnitine, propionyl L-carnitine, butyryl L-carnitine, valeryl L-carnitine, and isovaleryl L-carnitine, or a pharmacologically acceptable salt thereof.
Examples of antihypertensives include, but are not limited to diuretics ("water pills"), beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin receptor blockers (formal medical name angiotensin-2-receptor antagonists, known as "sartans" for short).

Examples of sterols and stanols include, but are not limited to plant sterols, plant sterol esters, fish oil, sitosterol, sitostanol, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, beta-sitosterol, and the like.

"Stanols" as used herein mean plant stanol esters, a food ingredient that can help reduce LDL cholesterol. Plant stanols are derived from naturally occurring substances in plants by techniques known to those in the art. The stanols are frequently combined with a small amount of canola oil to form stanol esters, producing an ingredient that can be used in a wide variety of foods and in combination with the compositions of this invention.

* * * * *

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

In the examples that follow, the particle sizes were measured using a Horiba LA-910 Laser Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, CA). The particle mean and D_{90} (which is the size below which 90% of the distribution is located) are obtained from a weight distribution. Furthermore, all formulations are given in weight % (w/w).

Several of the formulations in the examples that follow were also investigated using a light microscope.
Example 1

The purpose of this example was to prepare nanoparticulate dispersions of lovastatin, and to test the prepared compositions for stability at varying temperatures.

Four formulations of lovastatin were milled, as described in Table 1, by milling the components of the compositions under high energy milling conditions in a DYNO®-Mill KDL (Willy A. Bachofen AG, Maschinenfabrik, Basle, Switzerland) for 2 to 3 hours until the desired particle size was achieved.

Formulation 1 comprised 5% (w/w) lovastatin, 1.25% (w/w) hydroxypropylcellulose, super-low viscosity grade (HPC-SL), and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS).

Formulation 2 comprised 5% (w/w) lovastatin, 1.25% (w/w) hydroxypropylmethylcellulose (HPMC), and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS).

Formulation 3 comprised 5% (w/w) lovastatin, 1.25% (w/w) Povidone USP, Plasdone® K29/32 (PVPK29/32), and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS).

Formulation 4 comprised 5% (w/w) lovastatin, 1.25% (w/w) Plasdone S630 (S630), and 0.05% (w/w) dioctyl sodium sulfosuccinate (DOSS).

The particle size of the resultant compositions was measured using a Horiba LA-910 Laser Scattering Particle Size Distribution Analyzer ((Horiba Instruments, Irvine, CA)).
Table I

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Post-Milling Particle Size (nm)</th>
<th>Stability Particle Size @ 5C (nm)</th>
<th>Stability Particle Size @ 25C (nm)</th>
<th>Stability Particle Size @ 40C (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Mean: 165 D90: 218</td>
<td>Mean: 184 4 weeks</td>
<td>Mean: 188 D90: 247 4 weeks</td>
<td>Mean: 205 D90: 264 4 weeks</td>
</tr>
<tr>
<td>#2</td>
<td>Mean: 174 D90: 227</td>
<td>Mean: 183 D90: 241 4 weeks</td>
<td>Mean: 191 D90: 253 4 weeks</td>
<td>Mean: 213 D90: 280 4 weeks</td>
</tr>
</tbody>
</table>

The results of this experiment show that all formulations or compositions were stable.

Example 2

As described in the literature (Pharmazie, Volume 56, September 2001, p 738-740), lovastatin has a potential for oxidative degradation. To determine which of the formulations exhibited the least amount of degradants an HPLC analysis was performed on the compositions prepared in Example 1.

The method was a reversed phase HPLC method based on an existing assay method found in the literature (Pharmazie, Volume 56, September 2001, p 738-740). The results of these sample runs were compared to an active pharmaceutical ingredient (API), commercially available lovastatin, standard to determine which milled sample was least oxidized.

Analysis took place after 4-5 weeks of storage. The four different samples were compared to an API standard. For this comparison three factors were used to determine which formulation was optimal: (1) the percent lovastatin, (2) overall appearance of impurity profile, and (3) the percent area of the peak at RRT 0.87. This peak was selected
was because it had the largest area of all the impurity peaks and seemed to increase as the area of the lovastatin peak decreased.

Formulation #2 containing HPMC compared the best with the API standard. Both had similar amount of impurities, percent lovastain, and comparable peak areas at RRT 0.87. The sample containing PVP K29/32 had the highest amount of impurities, lowest percent lovastatin, and the largest peak area at RRT 0.87.

The results of this experiment showed that the formulation containing HPMC yielded the best impurity profile. No significant differences from the lovastatin API profile were observed, indicating minimal oxidative degradation occurred during milling or subsequent storage.

**Example 3**

The purpose of this example was to evaluate the efficacy of nanoparticulate lovastatin compositions.

New Zealand White rabbits were fed a diet enriched with 1% cholesterol for four weeks. At the four week time point the animals were maintained on a high cholesterol diet but were dosed (in the fed state) each day for a additional four week period with 6 mg/kg dose of either suspensions of Formulation #2 (Example 1) or commercially available lovastatin (Mevacor®) tablets mortarized into a crude suspension comprising the same quantities of HPMC and DOSS as Formulation #2. Placebo also comprised the same quantities of HPMC and DOSS as formulation #2.

Blood samples for total cholesterol analysis were taken at -2, 0, 2, & 4 weeks after dosing. Total change in cholesterol for each group was as follows:

1. Mevacor® mortarized tablets dosed as a liquid suspension: -17.8% (N=6)
2. Formulation #2 dosed as a liquid suspension: -23.2% (N=8)
3. Placebo dosed as a liquid suspension: -12.3 (N=4)
4. Diet enriched with 1% cholesterol (not dosed): +0.10 (N=4)

Blood samples for liver activity (37.8 U of ALAT liver enzyme activity) showed the following percentage of rabbits above 3X normal levels as follows:
1. Mevacor® mortarized tablets dosed as a liquid: 20% (N=6)
2. Formulation #2 dosed as a liquid suspension: 7.6% (N=8)
3. Placebo dosed as a liquid: 0 (N=4)

The results indicate that Formulation #2 shows greater efficacy and lower liver toxicity trends than the other two groups measured.

* * * *

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

1. A statin composition comprising:
   (a) particles of at least one statin or a salt thereof, wherein the particles have
       an effective average particle size of less than about 2000 nm; and
   (b) at least one surface stabilizer.

2. The composition of claim 1, wherein the statin is selected from the group consisting of
   atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and
derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than
lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of
mevalonolactone derivatives; rivastatin; a pyridyldihydroxyheptenoic acid other than
rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-
2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives;
2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl
analogs of mevalonolactone; octahydropyrenalenes; phosphinic acid compounds.

3. The composition of claim 1 or claim 2, wherein the statin is lovastatin or
   simvastatin.

4. The composition of any one of claims 1-3, wherein the statin is selected
   from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline
   phase, a semi-amorphous phase, and mixtures thereof.

5. The composition of any one of claims 1-4, wherein the effective average
   particle size of the statin particles is selected from the group consisting of less than about
   1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm,
   less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than
   about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900
nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

6. The composition of any one of claims 1-5, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, opthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

7. The composition of any one of claims 1-6 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

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

9. The composition of any one of claims 1-8, wherein the at least one statin or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the statin or a salt thereof and at least one surface stabilizer, not including other excipients.

10. The composition of any one of claims 1-9, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5%
to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the statin or a salt thereof and at least one surface stabilizer, not including other excipients.

11. The composition of any one of claims 1-10, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

12. The composition of any one of claims 1-11, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

13. The composition of claim 12, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecyl sulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thiogluco side; n-hexyl β-D-glucopyranoside;
nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

14. The composition of claim 12, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

15. The composition of claim 12, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂-₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂-₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂-₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄-₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂-₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium
salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyl dimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkylidimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradeccyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

16. The composition of any of claims 12, 14, or 15, wherein the composition is bioadhesive.

17. The composition of any one of claims 1-16, comprising hydroxypropylmethylcellulose (HPMC) and dioctyl sodium sulfosuccinate (DOSS) as surface stabilizers.

18. The composition of any one of claims 1-17, wherein the $T_{\text{max}}$ of the statin, when assayed in the plasma of a mammalian subject following administration, is less than the $T_{\text{max}}$ for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage.
19. The composition of claim 18, wherein the $T_{\text{max}}$ is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the $T_{\text{max}}$, exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage.

20. The composition of any one of claims 1-19, wherein the $C_{\text{max}}$ of the statin, when assayed in the plasma of a mammalian subject following administration, is greater than the $C_{\text{max}}$ for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage.

21. The composition of claim 20, wherein the $C_{\text{max}}$ is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the $C_{\text{max}}$ exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage.

22. The composition of any one of claims 1-21, wherein the AUC of the statin, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage.

23. The composition of claim 22, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage.
24. The composition of any one of claims 1-23 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

25. The composition of claim 24, wherein the difference in absorption of the statin composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

26. The composition of any one of claims 1-25, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

27. The composition of claim 26, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for both $C_{\text{max}}$ and AUC, when administered to a human.

28. The composition of claim 26, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for $C_{\text{max}}$, when administered to a human.

29. The composition of any one of claims 1-28, wherein within about 5 minutes at least about 20% of the composition is dissolved, wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution.
30. The composition of claim 29, in which at least about 30% or at least about 40% of the composition is dissolved within about 5 minutes.

31. The composition of claim 29, wherein upon redispersion the statin particles have an effective average particle size of less than about 2 microns.

32. The composition of any one of claims 1-31, wherein within about 10 minutes at least about 40% of the composition is dissolved, wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution.

33. The composition of claim 32, wherein at least about 50%, about 60%, about 70%, or about 80% of the composition is dissolved within about 10 minutes.

34. The composition of claim 32, wherein upon redispersion the statin particles have an effective average particle size of less than about 2 microns.

35. The composition of any one of claims 1-34, wherein within about 20 minutes at least about 70% of the composition is dissolved, wherein dissolution is measured in a media which is discriminating and wherein the rotating blade method (European Pharmacopoeia) is used to measure dissolution.

36. The composition of claim 35, wherein at least about 80%, about 90%, or about 100% of the composition is dissolved within about 20 minutes.

37. The composition of claim 35, wherein upon redispersion the statin particles have an effective average particle size of less than about 2 microns.

38. The composition of any one of claims 1-37, additionally comprising one or more non-statin active agents selected from the group consisting of:
(a) an active agent useful in treating dyslipidemia;
(b) an active agent useful in treating hyperlipidemia;
(c) an active agent useful in treating hypercholesterolemia;
(d) an active agent useful in treating cardiovascular disorders;
(e) an active agent useful in treating hypertriglyceridemia;
(f) an active agent useful in treating coronary heart disease;
(g) an active agent useful in treating peripheral vascular disease;
(h) an active agent useful as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb);
(i) an active agent useful as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia);
(j) an active agent useful in treating pancreatitis;
(k) an active agent useful in treating restenosis; and
(l) an active agent useful in treating Alzheimer’s disease.

39. The composition of any one of claims 1-38, additionally comprising one or more non-statin active agents selected from the group consisting of cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, and sterols and/or stanols.

40. The composition of claim 39, wherein the cholesterol lowering agent is selected from the group consisting of ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives, long chain plant extract alcohols, ezetimibe, and celluloses.

41. The composition of claim 39, wherein the polycosanol is selected from the group consisting of (1) triacontanol, (2) hexacontanol, (3) ecocosanol, (4) hexacosanol, (5) tetracosanol, (6) dotriacontanol, (7) tetracontanol, (8) natural products comprising
triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetacontanol; and (9) extracts of natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetacontanol.

42. The composition of claim 39, wherein the antihypertensive is selected from the group consisting of diuretics, beta blockers, alpha blockers, alpha-beta blockers, sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers.

43. The composition of claim 39, wherein the sterol is selected from the group consisting of plant sterols, plant sterol esters, sitosterol, sitostanol, fish oil, phytosterol, campestanol, stigmasterol, coprostanol, cholesterol, and beta-sitosterol.

44. The composition according to any one of claims 39-43, wherein at least one of the non-statin compounds has an effective average particle size of greater than about 2 microns.

45. The composition according to any one of claims 39-43, wherein at least one of the non-statin compounds has an effective average particle size of less than about 2 microns.

46. The composition of any one of claims 1-45, wherein upon administration the composition redisperses such that the statin particles have an effective average particle size selected from the group consisting of less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.
47. The composition of any one of claims 1-45, wherein the composition redisperses in a biorelevant media such that the statin particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

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

49. The method of claim 48, wherein said contacting comprises grinding.

50. The method of claim 49, wherein said grinding comprises wet grinding.

51. The method of claim 48, wherein said contacting comprises homogenizing.

52. The method of claim 48, wherein said contacting comprises:
(a) dissolving the particles of a statin or a salt thereof in a solvent;
(b) adding the resulting statin solution to a solution comprising at least one surface stabilizer; and
(c) precipitating the solubilized statin having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

53. The method of any one of claims 48-52, wherein the statin is selected from the group consisting of atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of mevalonolactone derivatives; rivastatin; a pyridyldihydroxyheptenoic acid other than rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives; 2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl analogs of mevalonolactone; octahydronaphthalenes; phosphinic acid compounds.

54. The method of any one of claims 48-53, wherein the statin is lovastatin or simvastatin.

55. The method of any one of claims 48-54, wherein the statin or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

56. The method of any one of claims 48-55, wherein the effective average particle size of the statin particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1000 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm,
less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

57. The method of any one of claims 48-56, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

58. The method of any one of claims 48-57, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

59. The method of any one of claims 48-58, wherein the statin or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the statin or a salt thereof and at least one surface stabilizer, not including other excipients.

60. The method of any one of claims 48-59, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the statin or a salt thereof and at least one surface stabilizer, not including other excipients.

61. The method of any one of claims 48-60, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.
62. The method of any one of claims 48-61, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

63. The method of claim 62, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetylmacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamid; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamid; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thiogluicoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamid; n-noyil β-D-glucopyranoside; octanoyl-N-methylglucamid; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.
64. The method of claim 62, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

65. The method of claim 62, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quaternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C12-15dimethyl hydroxyethyl ammonium chloride, C12-15dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)4 ammonium chloride, lauryl dimethyl (ethenoxy)4 ammonium bromide, N-alkyl (C12-18)dimethylbenzyl ammonium chloride, N-alkyl (C14-18)dimethylbenzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C12-14) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkydialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C12-14) dimethyl 1-naphthylmethyl ammonium chloride, dodecylmethylenbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl
ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyltrimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10\textsuperscript{TM}, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL\textsuperscript{TM}, ALKAQUAT\textsuperscript{TM}, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

66. The method of any of claims 62, 64, or 65, wherein the composition is bioadhesive.

67. The method of any one of claims 48-66, comprising hydroxypropylmethylcellulose (HPMC) and dioctyl sodium sulfosuccinate (DOSS) as surface stabilizers.

68. A method of treating a subject in need comprising administering to the subject an effective amount of a composition comprising:

(a) particles of a statin or a salt thereof, wherein the statin particles have an effective average particle size of less than about 2000 nm; and

(b) at least one surface stabilizer associated with the surface of the statin particles.

69. The method of claim 68, wherein the statin is selected from the group consisting of atorvastatin; a 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and
derivative other than atorvastatin; lovastatin; a keto analog of mevinolin other than
lovastatin; pravastatin; simvastatin; velostatin; fluindostatin; pyrazole analogs of
mevalonolactone derivatives; rivastatin; a pyridylidihydroxyheptenoic acid other than
rivastatin; SC-45355; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-
2-hydroxy-propane-phosphonic acid derivatives; 2,3-di-substituted pyrrole derivatives;
2,3-di-substituted furan derivatives; 2,3-di-substituted thiophene derivatives; naphthyl
anlogs of mevalonolactone; octahydronapthalenes; phosphinic acid compounds.

70. The method of claim 68 or claim 69, wherein the statin is lovastatin or
simvastatin.

71. The method of any one of claims 68-70, wherein the statin or a salt thereof
is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-
crystalline phase, a semi-amorphous phase, and mixtures thereof.

72. The method of any one of claims 68-71, wherein the effective average
particle size of the statin particles is selected from the group consisting of less than about
1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm,
less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than
about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900
nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than
about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm,
less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than
about 50 nm.

73. The method of any one of claims 68-72, wherein the composition is
formulated for administration selected from the group consisting of oral, pulmonary,
rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local,
buccal, nasal, and topical administration.
74. The method of any one of claims 68-73, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

75. The method of any one of claims 68-74, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

76. The method of any one of claims 68-75, wherein the statin or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the statin or a salt thereof and at least one surface stabilizer, not including other excipients.

77. The method of any one of claims 68-76, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the statin or a salt thereof and at least one surface stabilizer, not including other excipients.

78. The method of any one of claims 68-77, comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.
79. The method of any one of claims 68-78, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer.

80. The method of claim 79, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cетомакрогол emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecyl sulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucons; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglycoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.
81. The method of claim 79, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

82. The method of claim 79, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethoxy)_{4} ammonium chloride, lauryl dimethyl (ethoxy)_{4} ammonium bromide, N-alkyl (C_{12-15})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecylidmethyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecylidemethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl
benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkylidimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

83. The method of any of claims 79, 81, or 82, wherein the composition is bioadhesive.

84. The method of any one of claims 68–83, comprising hydroxypropylmethylcellulose (HPMC) and dioctyl sodium sulfosuccinate (DOSS) as surface stabilizers.

85. The method of any one of claims 68–84, wherein administration of the statin composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions, when administered to a human.

86. The method of claim 85, wherein the difference in absorption of the statin composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than
about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

87. The method of any one of claims 68-86, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

88. The method of claim 87, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both $C_{\text{max}}$ and AUC, when administered to a human.

89. The method of claim 87, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for $C_{\text{max}}$, when administered to a human.

90. The method of any one of claims 68-89, wherein the $T_{\text{max}}$ of the statin, when assayed in the plasma of a mammalian subject following administration, is less than the $T_{\text{max}}$ for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage.

91. The method of claim 90, wherein the $T_{\text{max}}$ is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the $T_{\text{max}}$, exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage.

92. The method of any one of claims 68-91, wherein the $C_{\text{max}}$ of the statin, when assayed in the plasma of a mammalian subject following administration, is greater
than the $C_{\text{max}}$ for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage.

93. The method of claim 92, wherein the $C_{\text{max}}$ is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the $C_{\text{max}}$ exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage.

94. The method of any one of claims 68-93, wherein the AUC of the statin, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same statin, administered at the same dosage.

95. The method of claim 94, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same statin, administered at the same dosage.

96. The method of any one of claims 68-95, additionally comprising administering one or more non-statin active agents selected from the group consisting of:

(a) an active agent useful in treating dyslipidemia;
(b) an active agent useful in treating hyperlipidemia;
(c) an active agent useful in treating hypercholesterolemia;
(d) an active agent useful in treating cardiovascular disorders;
(e) an active agent useful in treating hypertriglyceridemia;
(f) an active agent useful in treating coronary heart disease;
(g) an active agent useful in treating peripheral vascular disease;
(h) an active agent useful as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, and/or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb);

(i) an active agent useful as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia);

(j) an active agent useful in treating pancreatitis;

(k) an active agent useful in treating restenosis; and

(l) an active agent useful in treating Alzheimer’s disease.

97. The method of any one of claims 68-96, additionally comprising administering one or more non-sterol active agents selected from the group consisting of cholesterol lowering agents, polycosanols, alkanoyl L-carnitines, antihypertensives, and statins.

98. The method of claim 97, wherein the cholesterol lowering agent is selected from the group consisting of ACE inhibitors, nicotinic acid, niacin, bile acid sequestrants, fibrates, vitamins, fatty acid derivatives, long chain plant extract alcohols, ezetimibe, and celluloses.

99. The method of claim 97, wherein the polycosanol is selected from the group consisting of (1) triacontanol, (2) hexacontanol, (3) ecocosanol, (4) hexacosanol, (5) tetracosanol, (6) dotriacontanol, (7) tetracontanol, (8) natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol; and (9) extracts of natural products comprising triacontanol, hexacontanol, ecocosanol, hexacosanol, tetracosanol, dotriacontanol, or tetracontanol.

100. The method of claim 97, wherein the antihypertensive is selected from the group consisting of diuretics, beta blockers, alpha blockers, alpha-beta blockers,
sympathetic nerve inhibitors, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers.

101. The method of claim 97, wherein the sterol and/or stanol is selected from the group consisting of plant sterols, plant sterol esters, sitosterol, sitostanol, fish oil, phytosterol, campestanol, stigmasterol, coprostanol, cholestanol, and beta-sitosterol.

102. The method of any one of claims 68-101, wherein the subject is a human.

103. The method of any one of claims 68-102, wherein the method is used to treat a condition selected from the group consisting of hypercholesterolemia, hypertriglyceridemia, coronary heart disease, cardiovascular disorders, and peripheral vascular disease.

104. The method of any one of claims 68-102, wherein the method is used as adjunctive therapy to diet for the reduction of LDL-C, total-C, triglycerides, or Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia.

105. The method of any one of claims 68-102, wherein the method is used as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia.

106. The method of any one of claims 68-102, wherein the method is used to decrease the risk of pancreatitis.

107. The method of any one of claims 68-102, wherein the method is used to decrease the risk of or to treat Alzheimer's disease.

108. The method of any one of claims 68-102, wherein the method is used to treat indications where lipid regulating agents are typically used.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/44 A61K31/4025 A61K31/4164 A61K31/185 A61K31/216
A61P3/06 A61P9/10 A61P9/08 A61P9/00 A61P43/00

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
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Further documents are listed in the continuation of box C.

Date of the actual completion of the international search: 5 September 2003

Date of mailing of the international search report: 09/10/2003

Name and mailing address of the ISA
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Fax (+31-70) 340-3016

Authorized officer
Schifferer, H

Form PCT/ISA/2/10 (second sheet) (July 1992)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61F41/00

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP 0 499 299 A (STERLING WINTHROP INC) 19 August 1992 (1992-08-19)</td>
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X Further documents are listed in the continuation of box C. X Patent family members are listed in annex.

* Special categories of cited documents:
*"A" document defining the general state of the art which is not considered to be of particular relevance
*"E" earlier document not published on or after the international filing date
*"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another document or other special reason (see specification)
*"O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"A" document member of the same patent family

Date of the actual completion of the international search: 5 September 2003

Date of mailing of the international search report:

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 346-0340, Tx 31 551 epc nl, Fax (+31-70) 346-0316

Authorized officer
Schifferer, H
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Continuation of Box I.2

Claims Nos.: 1-12, 18-37, 48-62, 68-79, 85-95

1. Present claims 18-37 relate to a product, claims 85-95 to the use of this identical product defined by reference to a desirable characteristic or property, namely:
the Tmax of the statin in the nanoparticulate form being less than the Tmax for a conventional, non-nanoparticulate form of the same statin (claim 18, 90),
the Tmax of the statin in the nanoparticulate form not greater than defined percentages of the Tmax exhibited by a non-nanoparticulate formulation of the same statin (claim 19, 91),
the Cmax of the statin being greater than the Cmax for a conventional, non-particulate form of the same statin (claims 20, 21, 92, 93),
the AUC of the statin in the nanoparticulate form being greater than the AUC for a conventional, non-nanoparticulate form of the same statin (claims 22, 23, 94, 95),
comparable absorption levels under fed and fasting conditions (claims 24-28, 85-89),
a defined dissolution pattern under discriminating and rotating blade method conditions (claims 29-37).

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the product definition as it is expressed in claims 1-17.

2. Present claims 1, 48, 49, 68 relate to an extremely large number of possible compounds with the expression "statins". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the statin derivatives mentioned under claim 2 as well as the term "HMG CoA reductase inhibitor".

3. Present claims 1-12, 48-62, 68-79 (in complete) relate to an extremely large number of possible compounds with the expression "surface stabilizer".

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so
lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the statin derivatives mentioned under claims 13-17, 63-67, 80-84 as well as the terms "surface stabilizer"/"surface modifier" themselves.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
**INTERNATIONAL SEARCH REPORT**

**Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: 68–108
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - Although claims 68–108 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.

2. **X** Claims Nos.: 1–12, 18–37, 48–62, 68–79, 85–95
   - because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
     - see FURTHER INFORMATION sheet PCT/ISA/210

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
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