Title: STABLE NON-CRYSTALLINE FORMULATION COMPRISING HMG-CoA REDUCTASE INHIBITOR

Abstract: One or more embodiments of the present invention relate to a formulation comprising an HMG-CoA reductase inhibitor, to co-formulations of HMG-CoA reductase inhibitors with excipients, to methods for preparing the formulations, pharmaceutical compositions comprising the formulations and to their use in medical treatment. Also provided are stable oral pharmaceutical formulations comprising HMG-CoA reductase inhibitors such as atorvastatin, an associated methods for their preparation and use of (administering) the stable oral pharmaceutical formulations and co-formulations. The formulations which result in desired, especially improved or enhanced, solubility or dissolution characteristics, resulting in desired, especially improved or enhanced, bioavailability and/or pharmacokinetics.
Background of The Invention

[0001] One or more embodiments of the present invention relate to a formulation comprising an HMG-CoA reductase inhibitor, to co-formulations of HMG-CoA reductase inhibitors with excipients, to methods for preparing the formulations, pharmaceutical compositions comprising the formulations and to their use in medical treatment. One or more embodiments of the present invention relates more particularly to co-formulations of HMG-CoA reductase inhibitors, such as atorvastatin with one or more oligomeric and/or polymeric excipients, and to methods of making and methods of delivering, which result in desired, especially improved or enhanced, solubility or dissolution characteristics, resulting in desired, especially improved or enhanced, bioavailability and/or pharmacokinetics. Also provided are stable oral pharmaceutical formulations comprising HMG-CoA reductase inhibitors such as atorvastatin, an associated methods for their preparation and use of (administering) the stable oral pharmaceutical formulations and co-formulations.

Description of Related Art

[0002] HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase) inhibitors such as atorvastatin have been widely used for treating hyperlipidemia and/or hypercholesterolemia. HMG-CoA reductase is an enzyme that is believed to catalyse the intracellular synthesis of cholesterol. By administering effective amounts of an HMG-CoA reductase inhibitor to a patient, the synthesis of cholesterol is inhibited and levels of cholesterol in the patient’s blood stream is reduced. Various statins have been found to be effective HMG-CoA reductase inhibitors. Statins that are currently available for treating hyperlipidemia and/or hypercholesterolemia include atorvastatin (Lipitor® from Pfizer), simvastatin (Zocor® from Merck), pravastatin (Pravachol® from Bristol Myers Squibb), fluvastatin (Lescol® from Novartis), lovastatin (Mevacor® from Merck), and rosuvastatin (Crestor® from AstraZeneca).
Atorvastatin has proven to be a particularly safe and effective HMG-CoA reductase inhibitor. Atorvastatin, chemically (R, R-2-(4-fluorophenyl)-beta, delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, has been described in various forms. For example, certain trans-6-[2-(3 or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and corresponding pyran ring-opened hydroxy acids derived therefrom are described in U.S. Patent 4,681,893. A stereo-specific isomer of atorvastatin calcium salt is described in U.S. Patent 5,273,995. Crystalline Forms I, II, and IV of atorvastatin calcium and hydrates thereof, are described in U.S. Patent 5,969,156 which is incorporated herein by reference in its entirety. All of the above patents are incorporated herein by reference in their entireties.

An oral dosage form of crystalline atorvastatin calcium is commercially available under the proprietary name Lipitor® from Pfizer. The crystalline atorvastatin calcium is available as an orally delivered tablet in 10 mg, 20 mg, 40 mg, and 80 mg strengths. The tablet is made by compressing crystalline atorvastatin powder and various excipients, as described in U.S. Patents 5,686,104 and 6,126,971, both of which are incorporated herein by reference in their entireties.

According to the Pfizer product description, LIPITOR® is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. The empirical formula of atorvastatin calcium in LIPITOR® is \((\text{C}_{33}\text{H}_{34}\text{FN}_{2}\text{Os})_{2}\text{Ca}\cdot\text{3H}_2\text{O}\) and its molecular weight is 1209.42. Atorvastatin calcium has the structural formula:

![Structural formula of atorvastatin calcium](attachment:image.png)
[0006] The atorvastatin calcium in LIPITOR® is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. The atorvastatin calcium in LIPITOR® is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol. According to product literature, LIPITOR® tablets are also said to contain the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalHne cellulose, NF; Opadry White YS-17040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion. It has proven difficult to provide atorvastatin containing products with sufficient stability to withstand normal drug storage periods and conditions while maintaining acceptable pharmaceutical efficacy. Atorvastatin calcium has a tendency to change its physical form and/or to undergo degradation, such as by forming the corresponding lactone, under normal drug storage conditions. This adversely affects its pharmaceutical efficacy and hence the useful shelf-life of the product.

[0007] As described for example in U.S. 6,126,971, the crystalline atorvastatin calcium compound as formulated for the LIPITOR® tablet product is unstable in that it is susceptible to heat, moisture, low pH, and light. To provide stability to the LIPITOR® tablet formulation, calcium carbonate is added to the tablet formulation in an amount of about 22%. The calcium carbonate prevents degradation of the atorvastatin due to lactone formation. Without calcium carbonate, the atorvastatin calcium powder described in the ’971 patent experienced 2.45% degradation during a four week stability study at 45°C. However, the ’971 patent teaches that with the addition of calcium carbonate, the atorvastatin calcium powder experienced only 0.25% degradation. Also according to the ’971 patent, a tablet formulation which included calcium carbonate limited degradation of the atorvastatin calcium to 0.53% under the same study conditions. Solid formulations of HMG-CoA reductase inhibitors, such as atorvastatin, stabilized with buffering agents such as sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium carbonate, sodium or potassium hydrogen carbonate or lauryl sulphate, among others, are described in WO 00/35425, which is incorporated herein by reference in its entirety.
[0008] The addition of the stabilizing amount of an anti-degradant, such as calcium carbonate during the tablet formulation process has certain disadvantages. For example, under certain conditions, calcium carbonate can break down into calcium oxide and carbon dioxide. If this occurs, the stabilizing effect of the calcium carbonate might be compromised. Furthermore, any significant time interval between the preparation of the atorvastatin powder and the formulation of the tablet may exacerbate degradation and/or oxidation of the powder. In addition, the atorvastatin tablet may contain excipients such as one or more binders, diluents, disintegrants, lubricants, surfactants, etc. The addition of substantial amounts of the calcium carbonate and/or other anti-degradant(s) can complicate the formulation and increase the likelihood of interactions with and/or between the excipients. Additionally, when the atorvastatin is in a form that is more susceptible to degradation, for example a non-crystalline form, the addition of an anti-degradant, such as calcium carbonate, in the manner described in the prior art may not be sufficient to prevent significant degradation of the atorvastatin.

[0009] For pharmaceutical use, it is often desirable to produce an HMG-CoA reductase inhibitor, especially atorvastatin, in a non-crystalline form, such as an amorphous form. The existing crystalline forms of atorvastatin may have disadvantages. While the crystalline polymorphic forms are relatively physically stable in that they do not easily convert to another form during storage or processing, the crystalline forms may be less bioactive than non-crystalline forms, such as amorphous forms. Non-crystalline forms of active agents may have increased dissolution rates over crystalline forms. Accordingly, the non-crystalline forms may have increased bioavailability when administered to a user because of their ability to dissolve faster in the GI tract, as recognized in the art. This increased bioavailability can allow for the active agent to be taken up faster for systemic delivery. Also, the increased bioactivity can allow for a reduction in the amount of the active agent that needs to be administered to the user. There is, however, a tendency for amorphous drugs to revert to the crystalline form over extended storage periods, with attendant adverse affects on the dissolution profile. In addition, amorphous drug powders often have a larger active surface area than crystalline drug powders, making the amorphous drug powders more susceptible to degradation and/or oxidation during processing and storage.
[0010] Prior art attempts to formulate a non-crystalline HMG-CoA reductase inhibitor, especially atorvastatin have met with limited success. Amorphous HMG-CoA reductase inhibitors, such as atorvastatin, of the prior art may have limited physical and/or chemical stability, and/or less than desirable micromeritic properties, such as flowability and handling properties. Pure amorphous forms are thermodynamically less favored, thus under normal storage conditions, they tend to alter their form and convert to one or more crystalline forms. Because the degree of crystalline conversion at a particular time during storage is often unknown, it is difficult to assure that dosages are administered in a consistent solid form. As a result, the atorvastatin must either be administered immediately after formulation or a sufficient amount of storage time must pass so that full conversion to a crystalline form takes place, in which case the advantages of having the atorvastatin in amorphous form are lost. In addition, non-crystalline forms of active agents such as atorvastatin may be difficult to process into stable pharmaceutical compositions, such as tablets.

[0011] Moreover, the noted disadvantages of prior art formulations of HMG-CoA reductase inhibitors, especially atorvastatin, have made it difficult to provide an oral formulation, especially a tablet formulation. In particular, the prior art has met with only limited success in making an oral formulation comprising an HMG-CoA reductase inhibitor with an improved (or at least parity to a commercial crystalline formulation) dissolution rate and/or stability in terms of its resistance to solid state transformation and/or its resistance to degradation and/or its resistance to oxidation.

[0012] Therefore, in view of the foregoing, there is a need to solve one or more of these disadvantages of prior art forms of HMG-CoA reductase inhibitors such as atorvastatin.

Summary of the Invention

[0013] One or more embodiments of the present invention satisfies one or more of these needs.

[0014] In one aspect of the invention, a solid, non-crystalline formulation comprises an HMG-CoA reductase inhibitor such as atorvastatin wherein the formulation is physically stable.
[0015] In another aspect of the invention, a solid, non-crystalline formulation comprises an HMG-CoA reductase inhibitor such as atorvastatin wherein the formulation maintains its non-crystalline form when stored at 25°C and 60% relative humidity for a period of at least 1 week, more preferably at least 1 month, more preferably at least one year.

[0016] In another aspect of the invention, a solid, non-crystalline formulation comprises an HMG-CoA reductase inhibitor such as atorvastatin wherein the formulation maintains its non-crystalline form when stored at 40°C and 75% relative humidity for a period of at least 1 week, more preferably at least 1 month, more preferably at least three months.

[0017] In one aspect of the invention, a solid non-crystalline formulation comprises an HMG-CoA reductase inhibitor such as atorvastatin calcium wherein the formulation exhibits at least one of the characteristics of acceptable, or parity dissolution, solubility, stability, shelf life or bioavailability, when compared to a commercially-available formulation.

[0018] In one aspect of the invention, a solid, non-crystalline formulation comprises an HMG-CoA reductase inhibitor such as atorvastatin and an excipient, wherein the formulation exhibits at least one of the characteristics of enhanced dissolution, solubility, stability, shelf life, bioavailability, or tableting ease or manufacturing cost-effectiveness.

[0019] In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise an HMG-CoA reductase inhibitor such as atorvastatin and an excipient.

[0020] In another aspect of the invention, a solid formulation comprises a tablet dosage form, wherein the tablet comprises non-crystalline an HMG-CoA reductase inhibitor such as atorvastatin and a stabilizing excipient and wherein the tablet contains no binder.

[0021] In one aspect of the invention, a stable oral HMG-CoA reductase inhibitor formulation, comprises an HMG-CoA reductase inhibitor such as atorvastatin with a reduced level of tablet excipients.

[0022] In another aspect of the invention, a solid formulation comprises a tablet dosage form, wherein the tablet comprises non-crystalline an HMG-CoA reductase inhibitor such as
atorvastatin and a stabilizing excipient and wherein the tablet contains no binder and which provides bioavailability at least parity with that of a commercially-available product.

[0023] In one aspect of the invention, a stable oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor, one or more fillers, optionally one or more disintegrants, optionally one or more compressibility enhancers, optionally one or more diluents, optionally one or more lubricants, and optionally one or more anti-degradants, wherein the formulation is substantially absent the addition any one or all of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

[0024] In one aspect of the invention, a stable oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor and one or more fillers, wherein the formulation is substantially absent the addition any one or all of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxides, and wherein the formulation when stored for one month at 40°C is degraded by less than 2% relative to the amount present initially.

[0025] In one aspect of the invention, a stable oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor and one or more fillers, wherein the formulation is substantially absent the addition any one or all of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxides, and wherein oral formulation when stored for one month at 40°C experiences less than 2%, preferably less than 1%, lactone formation.

[0026] In one aspect of the invention, a stable oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor and one or more fillers, wherein the formulation is substantially absent the addition any one or all of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium
hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxides.

[0027] In another aspect of the invention, a stable oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor in non-crystalline form, one or more fillers, optionally one or more disintegrants, optionally one or more compressibility enhancers, optionally one or more diluents, optionally one or more lubricants, and optionally one or more anti-degradants, wherein the formulation is substantially absent the addition of any one or all of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

[0028] In another aspect of the invention, a stable oral pharmaceutical formulation comprises a solid solution comprising an HMG-CoA reductase inhibitor and an excipient, one or more fillers, optionally one or more disintegrants, optionally one or more compressibility enhancers, optionally one or more diluents, optionally one or more lubricants, and optionally one or more anti-degradants, wherein the formulation is substantially absent the addition of any one or all of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

[0029] In another aspect of the invention, a stable oral pharmaceutical formulation comprises a non-crystalline or amorphous solid solution comprising an HMG-CoA reductase inhibitor and an excipient, one or more fillers, optionally one or more disintegrants, optionally one or more compressibility enhancers, optionally one or more diluents, optionally one or more lubricants, and optionally one or more anti-degradants, wherein the formulation is substantially absent the addition of any one or all of the additive selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

[0030] In another aspect, the stable oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor, one or more fillers, optionally one or more disintegrants, optionally one
or more compressibility enhancers, optionally one or more diluents, optionally one or more lubricants, and optionally one or more anti-degradants, wherein the formulation further comprises one or more additives from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

[0031] In another aspect of the invention, a stable oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor, one or more fillers, and an anti-degradant. In specific aspects according to this aspect of the invention, the HMG-CoA reductase inhibitor may be crystalline, non-crystalline, amorphous, in the form of a solid solution, and/or in the form of a non-crystalline solid solution. In one particular aspect the oral formulation comprises particles comprising the HMG-CoA reductase inhibitor and anti-degradant.

[0032] In another aspect of the invention, a pharmaceutical formulation comprises a powder for subsequent formulation into an oral dosage form, the powder consisting essentially of first particles and second particles, wherein the first particles comprise an HMG-CoA reductase inhibitor and the second particles comprise an anti-degradant. In a particular aspect, the first particles comprise non-crystalline or amorphous HMG-CoA reductase inhibitor and an anti-degradant. In another particular aspect, the first particles comprise a solid solution comprising an HMG-CoA reductase inhibitor. In another particular aspect, the first particles comprise a non-crystalline solid solution comprising HMG-CoA reductase inhibitor.

[0033] In another aspect, any of the formulations, such as the oral formulations, have at least one of the following stability characteristics when stored for one month at 40°C: (a) is degraded by less than 2%, and/or (b) experiences less than 2%, preferably less than 1%, lactone formation, and/or (c) experiences less than 1.5 times, less than two times, less than three times, or less than four times the lactone formation as compared to the same formulation with the addition of calcium carbonate, such as about 22% calcium carbonate.

[0034] In another aspect of the invention, a method of treating hyperlipidemia and/or hypercholesterolemia comprises administering to a user a non-crystalline formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin.
In another aspect of the invention, a method of treating hyperlipidemia and/or hypercholesterolemia comprises administering to a user a non-crystalline formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin following storage of the non-crystalline formulation.

In another aspect of the invention, a method of treating hyperlipidemia and/or hypercholesterolemia comprises administering to a user a particulate formulation wherein the particles comprise a non-crystalline HMG-CoA reductase inhibitor such as atorvastatin and an excipient.

In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing an aqueous liquid containing an HMG-CoA reductase inhibitor such as atorvastatin and removing the aqueous liquid to produce particles comprising an HMG-CoA reductase inhibitor such as atorvastatin.

In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing a liquid containing an HMG-CoA reductase inhibitor such as atorvastatin and spray drying the liquid under conditions appropriate to produce particles comprising non-crystalline HMG-CoA reductase inhibitor such as atorvastatin.

In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing a liquid containing an HMG-CoA reductase inhibitor such as atorvastatin and lyophilizing the liquid under conditions appropriate to produce particles comprising non-crystalline HMG-CoA reductase inhibitor such as atorvastatin.
In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing a liquid comprising an HMG-CoA reductase inhibitor such as atorvastatin and contacting liquid with a supercritical or near critical fluid to remove the solvent form the liquid to produce particles comprising non-crystalline HMG-CoA reductase inhibitor such as atorvastatin.

In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing an aqueous liquid containing an HMG-CoA reductase inhibitor such as atorvastatin and an excipient and removing the aqueous liquid to produce particles comprising an HMG-CoA reductase inhibitor such as atorvastatin and the excipient.

In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise an HMG-CoA reductase inhibitor such as atorvastatin and a stabilizing excipient, wherein the formulation has a higher glass transition temperature than a formulation without the stabilizing excipient.

In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise an HMG-CoA reductase inhibitor such as atorvastatin and a stabilizing excipient, wherein the formulation has a glass transition temperature of above about 40°C.

In another aspect of the invention, a solid, non-crystalline formulation comprises particles, wherein the particles comprise an HMG-CoA reductase inhibitor such as atorvastatin and a stabilizing excipient or a surface modifying agent, or both, wherein the formulation has a lower hygroscopicity than a formulation without the stabilizing excipient, or the surface modifying agent, or both.

In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing an aqueous liquid containing an HMG-CoA reductase inhibitor such as atorvastatin and optionally, an excipient, and removing the aqueous liquid to produce particles comprising non-crystalline HMG-CoA reductase inhibitor such as atorvastatin and optional excipient wherein the
particles exhibit at least one of the characteristics of parity or enhanced dissolution, solubility, stability, shelf life, or bioavailability when compared to a commercially-available product, or tableting ease or manufacturing cost-effectiveness.

[0047] In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing an organic solvent containing an HMG-CoA reductase inhibitor such as atorvastatin and removing the organic solvent to produce particles comprising an HMG-CoA reductase inhibitor such as atorvastatin.

[0048] In another aspect of the invention, a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing an organic solvent containing an HMG-CoA reductase inhibitor such as atorvastatin and an excipient and removing the organic solvent to produce particles comprising an HMG-CoA reductase inhibitor such as atorvastatin and the excipient.

[0049] In another aspect of the invention a method of making a formulation comprising an HMG-CoA reductase inhibitor such as atorvastatin comprises providing a liquid containing atorvastatin free acid and adding a base, preferably calcium hydroxide. The liquid is then removed to form a non-crystalline atorvastatin salt.

[0050] In another aspect of the invention a method of making a formulation comprising atorvastatin calcium comprises providing a liquid containing atorvastatin sodium and exchanging the sodium ion for a calcium ion, resulting in the atorvastatin calcium salt. The liquid may then be then removed to form a non-crystalline atorvastatin calcium salt.

[0051] In another aspect of the invention, a method of making an oral pharmaceutical formulation comprises (i) compressing any of the above formulations into a tablet and optionally coating the tablet; (ii) filling any of the above formulations into a capsule; (iii) adding any of the above formulations to a liquid oral carrier; or (iv) otherwise converting any of the above formulations into an oral dosage form.
In any of the aspects of the invention, the HMG-CoA reductase inhibitor may comprise one or more statins, such as atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, rosuvastatin, and the like, including pharmaceutically effective salts of the above listed statins and including combinations of all of the above.

In another aspect of the invention, an HMG-CoA reductase inhibitor in any foregoing aspect comprises atorvastatin.

In another aspect of the invention, any two or more of the foregoing aspects are combined.

DRAWINGS

These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of a particular example or drawing, and the invention includes any combination of these features, where:

Figure 1 is a schematic diagram of one embodiment of an apparatus for carrying out a particle precipitation process according to the present invention;

Figure 2 is a schematic block diagram of one embodiment of a spray-drying process according to the present invention;

Figure 3 is a schematic diagram of one embodiment of an apparatus for carrying out a spray-drying process according to the present invention;

Figure 4 is a graph showing an X-ray diffraction (XRD) profile for non-crystalline atorvastatin prepared using a Nektar™ supercritical fluid particle precipitation process in accordance with one or more aspects of the present invention;

Figure 5 is a graph showing two X-ray powder diffraction (XRPD) profiles for (i) particles comprising pure non-crystalline atorvastatin; and (ii) particles comprising non-
crystalline atorvastatin plus a stabilizing excipient, both formulations produced by removing an aqueous solvent from a solution containing the atorvastatin, in accordance with one or more aspects of the present invention;

[0061] Figures 6-8 are XRD profiles for co-formulations of atorvastatin with HPMC, prepared in accordance with one or more embodiments of the Nektar™ SEDS™ particle precipitation process of the present invention, after two months storage at 40°C and 75% RH;

[0062] Figure 9 is a dynamic vapor sorption (DVS) isotherm plot for various atorvastatin formulations, and co-formulations of atorvastatin with excipient, prepared in accordance with one or more embodiments of the present invention, as well as for a polymer excipient alone; and

[0063] Figure 10 is a drug concentration in human plasma time plot showing three atorvastatin tablet formulations made in accordance with one or more methods of the present invention, compared with a commercially-available prior art formulation (as LIPTOR®). Drug concentration (in ng/mL) is plotted against post dose time (in hours).

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

[0064] One or more embodiments of the present invention relate to a formulation comprising an HMG-CoA reductase inhibitor, to co-formulations of HMG-CoA reductase inhibitors with excipients, to methods for preparing the formulations, pharmaceutical compositions comprising the formulations and to their use in medical treatment. One or more embodiments of the present invention relates more particularly to co-formulations of HMG-CoA reductase inhibitors, such as atorvastatin with one or more oligomeric and/or polymeric excipients, and to methods of making and methods of delivering, which result in desired, especially improved or enhanced, solubility or dissolution characteristics, resulting in desired, especially improved or enhanced, bioavailability and/or pharmacokinetics. One or more embodiments of the present invention further relate to a stable oral pharmaceutical formulation comprising a hypolipidemic and/or hypcholesterolemic agent, such as an HMG-CoA reductase inhibitor, and to an associated method for the preparation and use of the stable oral pharmaceutical formulation. Although the invention is illustrated in the
context of a tablet formulation comprising one or more statins, the present invention can be used in other forms and for purposes other than for those specifically disclosed, and the invention should not be limited to the examples provided herein.

[0065] Before describing the present invention in detail, it is to be understood that the invention is not limited to the particularly exemplified apparatus, systems, methods, or processes disclosed herein, which may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to limit the scope of the invention in any manner.

Definitions

[0066] All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference.

[0067] It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include the plural unless the context clearly dictates otherwise.

[0068] Reference herein to "one embodiment", "one version" or "one aspect" shall include one or more such embodiments, versions or aspects, unless otherwise clear from the context.

[0069] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. A number of methods and materials similar or equivalent to those described herein can be used in the practice of the present invention.

[0070] Amount of ingredients, materials or substances are listed as the ranges or levels of ingredients in the descriptions, which follow hereto.

[0071] The use of the term "about" or "approximately" to modify a numerical range or series means that all numerals in the range or series are so modified, unless otherwise clear from the context that only certain numerals are to be modified.
Anti-degradant means any material which acts to slow, mitigate, reduce or eliminate any degradation of the target material (e.g. the drug) by any degradation pathway.

"Therapeutically ly-effective amount" means that amount of active present in the composition that is needed to provide the desired level of drug in the subject to be treated to yield the expected physiological response.

"Drug" means any compound or composition which induces a desired pharmacologic and/or physiologic effect, when administered appropriately to the target organism (human or animal). Atorvastatin is one example of a drug.

The term "vehicle" means a fluid which dissolves a solid or solids, to form a solution, or which forms a suspension of a solid or solids which do not dissolve or have a low solubility in the fluid. The vehicle can be composed of one or more fluids.

As used herein, a 'co-formulation' refers to two or more substances formulated at substantially the same time and/or formulated so that a particle comprising a co-formulation contains the two or more substances. For example, a co-formulation may comprise a solid dispersion of a first substance and a second substance, such as an intimate mixture of an active substance and an excipient. In some versions, the intimate mixture may comprise an active agent, especially a pharmaceutically-active agent, such as atorvastatin, dispersed in a "matrix" of a carrier material, especially an excipient, such as an oligomeric and/or polymeric excipient. In some versions, a co-formulation may result in, for example, discrete particles of the separate substances or in particles containing a mixture of the separate substances, such as a mixture of discrete substances or in a solid solution of the substances. The co-formulations of one or more embodiments of the present invention with an excipient may advantageously modify the solubility and/or dissolution characteristics of the active substance. Unless otherwise clear from the context, a formulation includes a co-formulation.

"HMG-CoA reductase inhibitor" as used herein means any active agent that is effective in inhibiting the HMG-CoA reductase catalysis of the intracellular synthesis of cholesterol. Examples of HMG-CoA reductase inhibitors include various statins.
[0078] "Statins" as used herein any one or more of atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, rosuvastatin, and equivalents thereof. The term also includes any pharmaceutically acceptable salts, such as a metal salt, of any of the above listed statins. The term "pharmacetically acceptable salts" therefore includes, but is not limited to, alkali metal or alkaline earth metal salts such as sodium, potassium, calcium, lithium, magnesium, zinc or the like.

[0079] "Atorvastatin" as used herein means either the compound as the free compound or as any pharmaceutically acceptable salt, such as a metal salt, as described in any of U.S. Patents 4,681,893; 5,273,995; 5,686,104; 5,969,156; and 6,126,971, all of which are incorporated herein by reference in their entireties. In some embodiments, the atorvastatin is in the form of its calcium salt. "Atorvastatatin" it is meant the compound (βR,δR)-2-(4-fluorophenyl)-beta,di-hydroxy-5-(l-methylethyl)-3-phenyl-4-[((phenylamino)carbonyl]-lH-pyrrole-l-heptanoic acid and includes all compounds comprising the following chemical formula:
wherein

X is -CH

R1 is

1-naphthyl;
2-naphthyl;
cyclohexyl;
norbornenyl;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;
either of R2 or R3 is CONR5R6 where R5 and R6 are independently
hydrogen;
alkyl of from one to six carbon atoms;
phenyl;
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
cyano,
trifluoromethyl, or
carboalkoxy of from three to eight carbon atoms;
and the other of R2 or R3 is
hydrogen;
alkyl of from one to six carbon atoms;
cyclopropyl;
cyclobutyl;
cyclopentyl;
cyclohexyl;
phenyl; or
phenyl substituted with
fluorine,
chlorine,
bromine,
hydroxyl,
trifluoromethyl,
alkyl of from one to four carbon atoms,
alkoxy of from one to four carbon atoms, or
alkanoyloxy of from two to eight carbon atoms;
\(R_4\) is
- alkyl of from one to six carbon atoms;
- cydopropyl;
- cyclobutyl;
- cyclopentyl;
- cyclohexyl; or
- trifluoromethyl;
- or a hydroxy acid or pharmaceutically acceptable salts thereof, corresponding to the opened lactone

ring of the compounds of structural formula I above.

[0081] "Simvastatin" as used herein means either the compound as the free acid or as any pharmaceutically acceptable salt, such as a metal salt, as described in any of U.S. Patents 4,444,784; RE36481; and RE36520, all of which are incorporated herein by reference in their entireties.

[0082] "Pravastatin" as used herein means either the compound as the free acid or as any pharmaceutically acceptable salt, such as a metal salt, as described in any of U.S. Patents 4,346,227; 5,030,447; 5,180,589; and 5,622,985; all of which are incorporated herein by reference in their entireties. Preferably, pravastatin is in the form of its sodium salt.

[0083] "Fluvastatin" as used herein means either the compound as the free acid or as any pharmaceutically acceptable salt, such as a metal salt, as described in any of U.S. Patents 5,354,772; and 5,356,896. Preferably, fluvastatin is in the form of its sodium salt.

[0084] "Lovastatin" as used herein means either the compound as the free acid or as any pharmaceutically acceptable salt, such as a metal salt, as described in U.S. Patent 4,23 1,938.

[0085] "Rosuvastatin" as used herein means either the compound as the free acid or as any pharmaceutically acceptable salt, such as a metal salt, as described in any of U.S. Patents 6,316,460; 6,589,959; and RE 37,314, all of which are incorporated herein by reference in their entireties. Preferably, rosuvastatin is in the form of its calcium salt.

[0086] By "crystalline" it is meant any solid which gives a wide angle x-ray diffraction pattern showing one or more characteristic peaks due to its three dimensional structure, including pure compounds and mixtures which show such peaks. The x-ray powder diffraction may be
performed by any suitable instrument, such as a D5000 XRD (Siemens, Germany) between 2
and 40° 2Θ at a scan rate of 0.02 degrees per second.

[0087] By "non-crystalline" it is meant any solid which does not give rise to one or more
characteristic peaks in wide angle x-ray powder diffraction indicative of crystallinity as
defined above. This includes amorphous materials, which are disordered at the molecular
level, and liquid crystals, such as frozen thermotropic liquid crystals, which can be
distinguished from amorphous materials because they exhibit birefringence under polarized
light, and microcrystalline forms which do not give rise to one or more characteristic-peaks in
wide angle x-ray diffraction. "Non-crystalline" also includes pure amorphous materials and
amorphous mixtures of materials. In the case of a mixture, this includes molecular solid
dispersions, which are comparable to liquid solutions in that there is a single phase which is
disordered at the molecular level, non-molecular solid dispersions, which have one or more
distinct amorphous phases, and to other homogeneous or non-homogeneous mixtures,
provided there is no crystallinity as defined above.

[0088] One or more embodiments of the present invention provide an improved formulation
comprising an HMG-CoA reductase inhibitor, such as atorvastatin. Among other
improvements, the atorvastatin-containing formulations described herein offer improvements
over prior art formulations containing crystalline atorvastatin in that the present formulation
provides non-crystalline atorvastatin in a stable form, and where it has a dissolution rate
which provides a desired, especially a commercially-desired, bioavailability. Additionally or
alternatively, one or more embodiments of the present formulation is advantageous over
known amorphous forms of atorvastatin in that the one or more embodiments have improved
mechanical stability and/or processability and/or improved physical stability and/or improved
chemical stability, allowing the present formulation to be stored over longer periods of time
and/or allowing the formulation more time for being processed into a solid dosage form, such
as a tablet. One or more embodiments of the present invention are also effective in
maintaining the chemical stability of the atorvastatin, such as by preventing degradation of
the particulate or powdered atorvastatin by preventing or minimizing lactone formation
during storage.
[0089] As discussed above, the crystalline form of atorvastatin has proven to be stable and effective. However, a non-crystalline form with good stability and a desired dissolution rate (e.g. comparable to a commercially-available crystalline form) is commercially desirable. Accordingly, in one or more versions of the present invention, a formulation comprising HMG-CoA reductase inhibitor such as atorvastatin is provided in non-crystalline form. By providing non-crystalline atorvastatin, the efficacy of the atorvastatin is maintained while the desired dissolution rate is attained, thereby providing an improved form of the pharmaceutical agent. In one or more embodiments, the desired dissolution rate and/or profile is substantially equal to, or parity with a commercially-available product, such as LIPITOR® 80 mg tablets. In other embodiments, the desired dissolution rate and/or profile is better than a commercially-available product, such as LIPITOR® 80 mg tablets. In other embodiments of the non-crystalline atorvastatin, and process for making herein, the result is a particulate material with desirable micromeritic properties, such as a free-flowing and/or non-sticky powder with good handling qualities enabling easy post processing, such as tablet processing.

[0090] One or more embodiments of the present invention further provide a stable oral pharmaceutical formulation comprising an HMG-CoA reductase inhibitor, such as a statin, especially atorvastatin. The oral pharmaceutical formulation may be processed into an oral dosage form, such as a tablet, capsule, elixir, or the like, so that the oral pharmaceutical formulation may be administered to a patient in need thereof. For example, the oral pharmaceutical formulation may be administered to treat and/or prevent high cholesterol levels in a patient.

[0091] In one or more versions, the oral pharmaceutical formulation comprises an HMG-CoA reductase inhibitor (such as atorvastatin) formed into a tablet for oral administration. In such version(s), a powder comprising the HMG-CoA reductase inhibitor is mixed with one or more fillers and optionally with one or more additional excipients. The mixed components are then compressed using a standard compression machine to form oral dosage tablets. The one or more additional excipients may include, for example, disintegrants, compressibility enhancers or binders, diluents, lubricants, or other additives known in the art of tablet formation. In some embodiments, the powder is densified to optimize compaction into a
tablet. In such embodiments, an intermediate granulation process may be applied. In a dry granulation process, the powder comprising the HMG-CoA reductase inhibitor is combined with a dry binder and optionally with a disintegrant and a filler. The mixture is then compacted, such as by roller compaction, and may then be milled to form dry granules. The dry granules are then mixed with one or more fillers and optionally with one or more additional excipients of the type described above. The granules, fillers, and optional additives are then compressed into tablets. In one or more alternative granulation processes, the HMG-CoA reductase inhibitor powder made into a wet mass by mixing it and a wet binder with a liquid, such as water and/or alcohol. This forms wet granules that are then passed through a screen to form uniformly sized wet granules. The wet granules are then dried, and the dried granules are then mixed with one or more fillers and optionally with one or more additional excipients of the type described above. The granules, fillers, and optional additives are then compressed into tablets. Examples of the additional excipients are provided in U.S. Patent 6,126,971 which is incorporated herein by reference in its entirety.

[0092] Statin HMG-CoA reductase inhibitors, especially atorvastatin, are generally susceptible to degradation. In particular, in the presence of heat, moisture, light, and/or low pH, lactone formation occurs. When a prior art HMG-CoA reductase inhibitor is formulated as a tablet, the fillers and/or excipients used in the tablet formulation often create a sufficiently acidic environment to facilitate lactone formation, thereby decreasing the stability of the formulation. Accordingly, in these conventional tablets, stabilizers such as calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide, and in particular calcium carbonate, have been taught to be used as stabilizing excipients in the tablet. However, it has been unexpectedly discovered that when the HMG-CoA reductase inhibitor, such as atorvastatin, is properly formulated, sufficient degradation prevention can be provided even in the absence of any or all of heretofore believed to be necessary stabilizers including calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

[0093] Accordingly, in one or more versions, an oral pharmaceutical formulation of the present invention comprises an HMG-CoA reductase inhibitor, such as atorvastatin, one or more
fillers, optionally one or more disintegrants, optionally one or more compressibility enhancers, optionally one or more diluents, optionally one or more lubricants, and optionally one or more antioxidants, wherein the formulation is substantially absent the addition any one or all of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide. In some versions, the oral pharmaceutical formulation undergoes less than about 3% or less than about 2% degradation during a one-month stability study at about 40°C. Additionally, during the same study less than about 2%, or less than about 1%, of the oral pharmaceutical formulation converts to lactone. Furthermore, the oral formulation according to an aspect of the present invention, when stored for one month at 40°C experiences less than 1.5 times, less than two times, less than three times, or less than four times lactone formation as compared to the same formulation with the addition of 22% calcium carbonate in the formulation, i.e. lactone formation is only no more than 25% or 33% or 50% or 75% of lactone formation absent the calcium carbonate.

[0094] In one or more embodiments the HMG-CoA reductase inhibitor, such as atorvastatin, may be formulated in a manner which provides desired, adequate, or optimal protection against degradation, such as by lactone formation. In one or more versions, the formulation may comprise a pure HMG-CoA reductase inhibitor, such as atorvastatin, i.e. absent any stabilizing excipients. In one or more versions, the HMG-CoA reductase inhibitor, such as atorvastatin, is formulated as particles, each of which comprise the HMG-CoA reductase inhibitor and a stabilizing excipient. In other versions, the particles are in the form of a solid solution, the solid solution comprising the HMG-CoA reductase inhibitor and the stabilizing excipient. The intimate contact afforded by the co-habitation of the components in the particles protects the HMG-CoA reductase inhibitor even in the presence of an acidic environment, and mitigates or prevents lactone formation that would otherwise occur in the acidic environment. In one or more embodiments, therefore, there is little or no need for a basic excipient within the tablet for the purpose of creating a basic environment within the tablet. As such, a stable oral pharmaceutical formulation comprising HMG-CoA reductase inhibitor can be provided even in the absence of one or more of calcium carbonate, calcium
hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminolate, and aluminum magnesium hydroxide.

[0095] In one or more versions, a stable non-crystalline formulation comprising a pure HMG-CoA reductase inhibitor (i.e. absent any stabilizing excipient), especially atorvastatin, is produced by forming a solution or dispersion of the material and removing the solvent therefrom, to yield a physically stable, non-crystalline form. In one or more versions, the solvent removal process comprises a supercritical fluid particle precipitation process in accordance with one or more embodiments of the present invention. In one or more versions, a physically stable formulation comprising non-crystalline HMG-CoA reductase inhibitor, especially atorvastatin, is produced by a spray-drying process in accordance with one or more embodiments of the present invention.

[0096] In one or more embodiments, the stable non-crystalline formulation comprising an HMG-CoA reductase inhibitor, especially atorvastatin is physically stable with respect to reversion to crystalline form, for at least one month, preferably three months, more preferably at least six months, and most preferably for at least one year after its preparation. By "stable" is meant that over the specified time period, there is no significant change in the X-ray diffraction (XRD) pattern of the atorvastatin and, where measurable, in its differential scanning calorimetry (DSC) profile. Preferably there is no significant change in the dissolution profile of the atorvastatin. Preferably there is little or no (for example less than 10%, preferably less than 5%, more preferably less than 1%) change in degree of crystallinity of the atorvastatin within the formulation with respect to the initial amount. Particularly preferably, there is no detectable crystalline atorvastatin present in the formulation either before or after storage. Stability may suitably be assessed by storing the formulation according to the invention at ambient temperature (eg, from about 18 to 25 °C, or from about 20 to 23 °C, such as about 22 °C, or at the accepted industrial standard temperature of 25 °C), and at up to about 20 % or 30 % or 40 % or 60 % or even 75 % relative humidity (RH). Higher storage temperatures and/or humidities may be used, in conventional manner, to mimic longer term storage periods, as may conventional thermal cycling procedures such as freeze/thaw cycling. The formulation according to the invention is preferably stable, for the periods mentioned above, when stored at about 25°C and up to about 60% RH. Even more
preferably, it is stable when stored at about 40°C, most preferably at about 40°C and up to about 75% RH. The degree of crystal Unity of the formulation may be assessed by conventional techniques, for example using X-ray diffraction (XRD) techniques, particularly high resolution X-ray powder diffraction (XRPD) using a synchrotron radiation source. Levels of amorphous phase may also be assessed by reference to its moisture uptake at any given temperature and humidity.

[0097] In one or more versions, the HMG-CoA reductase inhibitor, such as atorvastatin, is provided in the form of a solid solution comprising the HMG-CoA reductase inhibitor and a solid state stabilizing excipient. By being in the non-crystalline or amorphous state, the HMG-CoA reductase inhibitor has improved solubility and/or bioavailability properties. The solid state stabilizing excipient contributes to maintaining the non-crystalline or amorphous HMG-CoA reductase inhibitor in the non-crystalline form.

[0098] Accordingly, in one or more versions of the present invention, a non-crystalline formulation comprising atorvastatin is formulated so as to improve its physical stability. For example, the improved stability may be provided by combining the non-crystalline atorvastatin with a stabilizing excipient. The stabilizing excipient is provided in a sufficient quantity to reduce the tendency of the non-crystalline atorvastatin to convert to a crystalline form. Preferably, the stabilizing excipient is in intimate contact with the non-crystalline atorvastatin. The stabilizing excipient may be either non-crystalline or crystalline, as long as it serves to maintain the atorvastatin in a non-crystalline form. Formulation or co-formulation of the non-crystalline atorvastatin with one or more excipients and/or surface modifying agents as described in the one or more embodiments, versions or aspects herein may permit manipulation of the surface composition and/or topology to provide desired, especially improved, pharmaceutical and/or micromeritic properties.

[0099] In one or more versions, the solid solution may comprise an HMG-CoA reductase inhibitor, such as atorvastatin, and one or more excipients, such as oligomeric or polymeric excipients, to give products which exhibit acceptable dissolution characteristics and stability for pharmaceutical use. Particularly advantageously, non-crystalline or amorphous co-formulations of HMG-CoA reductase inhibitor with an oligomeric or polymeric excipient
may be prepared, affording the pharmaceutical formulation advantageous bioavailability and dissolution profiles. The oligomeric or polymeric excipient used in the formulation according to the invention may suitably be hydrophilic or hydrophobic and is preferably non-toxic and pharmaceutically acceptable.

[00100] The stabilizing excipient may be any excipient that serves to reduce the conversion of non-crystalline HMG-CoA reductase inhibitor for example, atorvastatin, to crystalline atorvastatin when compared to non-crystalline atovastatin in the absence of the stabilizing excipient and/or which serves to reduce the amount of lactone formation and/or degradation products or any impurities, when compared to atorvastatin in the absence of the stabilizing excipient. For example, the excipient may comprise one or more polymeric or oligomeric excipients, such as polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), vinylpyrrolidone/vinyl acetate copolymer (PVP-VA), vinylpyrrolidone/vinyl acetate (40:60) copolymer in a VA:VP of 60:40 (PVP-VA 64), polyethylene oxide (PEO), cellulose, starch, polyethylene glycol (PEG), hydroxypropyl cellulose (HPC), hydroxyl propyl methyl cellulose (HPMC), and their copolymers and derivatives; carbohydrates; polyols; sugars; oligo saccharides such as cyclodextrins; proteins, peptides and amino acids; lipids and modified lipids such as lipid-PEG and lipid-sugar esters; salts; citric acid; citrates; known glass formers; or the like. Some stabilizing excipients are described in U.S. Patent 6,582,728, and in PCT WO 01/15664, all of which are incorporated herein by reference in their entireties.

[00101] In one or more embodiments, the excipient is selected to be non-hygroscopic, such as being hydrophobic, and wherein the resultant formulation or co-formulation with atorvastatin is relatively non-hygroscopic. In one or more embodiments, the selection of excipient is based, at least in part, on the hydrophobicity or hydrophilicity of the excipient, considering the solvent removal process and type of solvent used therein. Thus, in one or more embodiments, for example, the excipient is selected to be non or minimally hygroscopic, and also to be sufficiently soluble in the solvent or solvent mixture from which the formulation or co-formulation is precipitated. Additionally, it is preferred that the excipient's solubility be compatible with, and especially optimal for processing by, the particular solvent removal process employed. In one or more embodiments, the excipient is
selected such that at any given environmental condition(s), such as relative humidity, the excipient will absorb less moisture than the atorvastatin absent the excipient.

[00102] In other embodiments of the present invention, the excipient alternatively or additionally comprises a surface modifying agent, such that when formulated or co-formulated with the atorvastatin and produced as a particle or powder, the surface of the particle, in particular, is hydrophobic. This may provide desired or advantageous micromeritic and/or mechanical properties, such as desired and/or improved, flowability, dispersibility or dispensibility, or combinations thereof. In one or more embodiment, lipid and lipid derivatives, including lipid carbohydrate esters are suitable to provide such advantageous micromeritic and/or mechanical properties. Such lipid and lipid derivatives often tend to remain on the surface of the particle produced therewith, thus can be used to impart surface hydrophobicity. In one or more embodiments, the surface modification agents alternatively or additionally permit desired surface topologies to be attained. In particular, a surface modification agent may improve flowability by reducing the particles’ surface hydrophilicity.

[00103] Further examples of suitable polymeric excipients for formulation with the HMG-CoA reductase inhibitor according to the invention comprise celluloses and cellulose derivatives, such as alkyl (for example, methyl or ethyl) cellulose, hydroxyalkyl celluloses (such as hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, hydroxyethyl cellulose, hydroxypropyl cellulose), carboxymethylcellulose, sodium carboxymethyl cellulose, microcrystalline cellulose, microfine cellulose) or mixtures thereof; traditional "natural" source materials, their derivatives and their synthetic analogues, such as acacia, tragacanth, alginates (for instance calcium alginate), alginic acid, starch, agar, carrageenan, xanthan gum, chitosan, gelatin, guar gum, pectin, amylase or lecithin; homo- and co-polymers of hydroxy acids such as lactic and glycolic acids; hydrated silicas, such as bentonite or magnesium aluminium silicate; polymeric surfactants, such as polyoxyethylene or polyoxypropylene, or polyalkylene oxides such as polyethylene oxides; phospholipids, such as DMPC (dimyristoyl phosphatidyl choline), DMPG (dimyristoyl phosphatidyl glycerol) or DSPC (distearyl phosphatidyl choline); carbohydrates, such as lactose, dextrins, cyclodextrins or cyclodextrin derivatives; dendrimeric polymers, such as those based on 3,5
hydroxy benzyl alcohol; poly(ε-caprolactones), DL-lactide-co-caprolactones and their
derivatives; poly(orthoester)s and poly(orthoester)/poly(ethylene glycol) copolymers,
including block copolymers, such as are described in U.S. Patent 5,968,543 and U.S. Patent
5,939,453, both of which are incorporated herein by reference in their entireties, derivatives
of such polymers, such polymers with incorporated esters of short chain α-hydroxy acids or
glycolic-co-lactic acid copolymers; mixtures thereof, and combinations of any excipients.

[00104] In some versions, the excipient of the formulation comprises a cellulose or a
cellulose derivative, especially ethylcellulose (EC), hydroxypropylcellulose (HPC),
hydroxypropyl methyl cellulose (HPMCL), hydroxypropyl methyl cellulose phthalate
(HPMCP) or mixtures thereof.

[00105] In other versions, the HMG-CoA reductase inhibitor formulation according to the
invention may suitably comprise one or more amido- or amino-group containing polymers
such as vinyl polymers (such as polyvinyl chloride, polyvinyl alcohols, polyvinyl acetates,
polyvinyl pyrrolidones, cross-linked polyvinyl pyrrolidones or carboxy vinyl copolymers) or
acrylates and their derivatives, such as the "Eudragit™" polymers. In other versions, the
HMG-CoA reductase inhibitor formulation according to the invention may comprise one or
more amino acid, amino-acid containing or amino-acid derivative excipients. In some
versions, the amino acid excipients comprise those with aliphatic R groups, such as glycine,
alanine, valine, leucine and isoleucine.

[00106] The excipient may be present in an amount by weight sufficient to provide a
stable formulation. In some embodiments, the excipient is present at a concentration in the
range of from about 1 to about 99% w/w, or from about 5% to about 10%, or from about
10% to about 50% w/w of the formulation. In embodiments where the excipient is an
oligomeric or polymeric excipient, the excipient may be present in a range of about 0.1 to
about 10% w/w.

[00107] The HMG-CoA reductase inhibitor, such as atorvastatin, may be present in a
therapeutically effective amount in the formulation according to the invention, that is, in an
amount which is sufficient to treat a patient having a condition treatable thereby. In one or
more embodiments, the HMG-CoA reductase inhibitor may be present in a therapeutically effective amount as an antihyperlipoproteinemic agent. In one or more embodiments, the HMG-CoA reductase inhibitor comprises an atorvastatin, present in an amount which is effective beneficially to treat hypercholesterolemia and/or hyperlipidemia. For example, the HMG-CoA reductase inhibitor may be present in an amount of from 10% to 95%, preferably from 30% to 90%, especially from 50% to 90% w/w of the pharmaceutical formulation that will subsequently be formulated into an oral dosage form. In some embodiments, between 80 and 100% of the HMG-CoA reductase inhibitor is present in a non-crystalline or amorphous form. Preferably between 95% and 100% and more preferably greater than 97% or 98% or 99% of the HMG-CoA reductase inhibitor is present in a non-crystalline or amorphous form.

[00108] In one or more embodiments, the formulation may comprise additional excipients or may comprise the HMG-CoA reductase inhibitor and only a stabilizing excipient. In one or more versions, a formulation according to the invention contains no or only minor amounts (for example, less than about 5% w/w, or about 4% w/w, or about 3% w/w, and preferably less than about 2% w/w or 1% w/w) of additional ingredients, that is it consists essentially of the HMG-CoA reductase inhibitor and the oligomeric or polymeric excipient. The powder formulation may be in particulate form, especially in the form of fine particles having a volume mean diameter (VMD) of from preferably 10 µm or less, more preferably of from 5 µm or less, most preferably from 0.5 or 1 to 5 µm. Particle sizes may be measured for instance using a laser diffraction sensor such as the Helos™ system available from Sympatec GmbH, Germany (which provides a geometric projection equivalent (mass mean diameter, MMD)). Volume mean diameters may be obtained using commercially available software packages.

[00109] In one or more embodiments, following formulation with at least one excipient, such as an oligomeric or polymeric excipient, the powder formulation comprising the HMG-CoA reductase inhibitor is stable with respect to reversion to crystalline form, for at least one month, preferably three months, more preferably at least six months, and most preferably for at least one year after its preparation. By "stable" is meant that over the specified time period, there is no significant change in the X-ray diffraction (XRD) pattern of the
atorvastatin and, where measurable, in its differential scanning calorimetry (DSC) profile. Preferably there is no significant change in the dissolution profile of the atorvastatin. Preferably there is little or no (for example less than 10%, preferably less than 5%, more preferably less than 1%) change in degree of crystalinity of the atorvastatin within the formulation with respect to the initial amount. Particularly preferably, there is no detectable crystalline atorvastatin present in the formulation either before or after storage. Stability may suitably be assessed by storing the formulation according to the invention at ambient temperature (e.g., from about 18 to 25 °C, or from about 20 to 23 °C, such as about 22 °C, or at the accepted industrial standard temperature of about 25 °C), and at up to about 20 % or 30% or 40 % or 60 % or even 75 % relative humidity (RH). Higher storage temperatures and/or humidities may be used, in conventional manner, to mimic longer term storage periods, as may conventional thermal cycling procedures such as freeze/thaw cycling. The formulation according to the invention is preferably stable, for the periods mentioned above, when stored at about 25°C and up to about 60% RH. Even more preferably, it is stable when stored at about 40°C, most preferably at about 40°C and up to about 75% RH. The degree of crystallinity of the formulation may be assessed by conventional techniques, for example using X-ray diffraction (XRD) techniques, particularly high resolution X-ray powder diffraction using a synchrotron radiation source. Levels of amorphous phase may also be assessed by reference to its moisture uptake at any given temperature and humidity.

[00110] In one or more embodiments, a coformulation according to the invention may be prepared by removing solvent from a solution containing the HMG-CoA reductase inhibitor, such as atorvastatin, or by removing solvent from a solution containing the HMG-CoA reductase inhibitor, such as atorvastatin, and a solid state stabilizing excipient. Such a solvent removal process may comprise by co-precipitating the atorvastatin, or the atorvastatin and excipient(s) from a common solvent or solvent mixture, suitably using a compressed (typically supercritical or near-critical) fluid anti-solvent as in a GAS (Gas Anti-Solvent) particle precipitation method.

[00111] An example of a GAS particle precipitation method using a supercritical or near-critical fluid involves contacting a solution or suspension containing HMG-CoA reductase inhibitor, e.g. atorvastatin in a fluid (the "atorvastatin solution/suspension") with a
compressed fluid (generally a supercritical or near-critical fluid) anti-solvent under conditions which allow the anti-solvent to extract the fluid from the atorvastatin solution/suspension and to cause particles comprising atorvastatin to precipitate from the solution/suspension. The conditions are such that the fluid mixture formed between the anti-solvent and the extracted fluid is still in a compressed (generally supercritical or near-critical) state. The anti-solvent fluid should generally be a nonsolvent for the atorvastatin and be miscible with the fluid. In the context of this or any other solvent removal process, a solution may be construed to include a suspension or dispersion.

In one or more versions, the solvent removal process is a supercritical fluid particle formation process, such as the process known as the "SEDS™" (Solution Enhanced Dispersion by-Supercritical fluids) process of Nektar Therapeutics in San Carlos, California and in Bradford, United Kingdom. In one version, this process involves using the anti-solvent fluid substantially simultaneously both to extract the vehicle from, and to disperse, the atorvastatin solution/suspension. In this context, 'disperse' refers generally to the transfer of kinetic energy from one fluid to another, usually implying the formation of droplets, or of other analogous fluid elements, of the fluid to which the kinetic energy is transferred. Examples of Nektar Therapeutics' supercritical fluid processes are described in PCT Publications WO 95/01221, WO 96/00610, WO 98/36825, WO 99/44733, WO 99/59710, WO 01/03821, WO 01/15664, WO 02/38127 and WO 03/008082. Other suitable processes are described in PCT Publications WO 99/52507, WO 99/52550, WO 00/30612, WO 00/30613, WO 00/67892 and WO 02/058674. All of these publications (as well as any corresponding US publications) are incorporated herein by reference in their entireties, and with specific reference to supercritical fluid processing methods, materials and apparatus. The target solution/suspension and the anti-solvent are preferably contacted with one another in the manner described in WO 95/01221 and/or WO 96/00610, being co-introduced into a particle formation vessel using a fluid inlet which allows the mechanical energy (typically the shearing action) of the anti-solvent flow to facilitate intimate mixing and dispersion of the fluids at the point where they meet. The target solution/suspension and the anti-solvent preferably meet and enter the particle formation vessel at substantially the same point, for instance via separate passages of a multi-passage coaxial nozzle. Alternatively, or
additionally, the supercritical fluid process may be of the type described in WO 03/008082, which is incorporated herein by reference in its entirety, in which the target solution/suspension and the anti-solvent enter the vessel at separate, although close, locations.

Reference to an anti-solvent fluid being in a compressed state means that, at the relevant operating temperatures, it is above its vapor pressure, preferably above atmospheric pressure, more preferably from about 50 to 250 bar. The anti-solvent fluid is preferably a fluid which is a gas at atmospheric pressure and ambient temperature. Preferably, "compressed" means close to; at or more preferably above the critical pressure \( P_c \) for the fluid concerned. The anti-solvent is preferably a supercritical or near-critical fluid or may alternatively be a compressed liquid. A "supercritical fluid" is a fluid at or above its critical pressure \( P_c \) and its critical temperature \( T_c \) simultaneously. A "near-critical fluid" is either (a) above its \( T_c \) but slightly below its \( P_c \) or (b) above its \( P_c \) but slightly below its \( T_c \) or (c) slightly below both its \( P_c \) and \( T \). The terms "compressed fluid", "supercritical fluid" and "near-critical fluid" each encompass a mixture of fluid types, so long as the overall mixture is in the compressed, supercritical or near-critical state respectively.

Various anti-solvents, solvents, and process conditions may be used. The anti-solvent used is preferably supercritical, near-critical or liquid \( \text{CO}_2 \), especially supercritical \( \text{CO}_2 \). Preferred solvents include one or more of methanol, ethanol, isopropyl alcohol, acetone, tetrahydrofuran, ethylacetate, dimethylformamide, dichloromethane, MeCN (acetonitrile), N,N-dimethylacetamide (DMA). Hydroxylic solvents are preferred. The processing conditions are preferably chosen to produce particles of desired sizes and/or to reduce residual solvent levels. If atorvastatin is co-formulated with an excipient, and the SEDS™ particle precipitation process is used, the excipient is preferably soluble or miscible with the solvent. Excipients with varying degrees of hydrophilicity may thus be suitable depending upon the solvent employed in the SEDS™ process.

By "sonic velocity" and "supersonic velocity" is meant respectively that the velocity of the anti-solvent fluid as it enters the vessel is the same as or greater than the velocity of sound in that fluid at that point. By "near-sonic velocity" is meant that the anti-
solvent velocity on entry into the vessel is slightly lower than, but close to, the velocity of sound in that fluid at that point—for instance its "Mach number" M (the ratio of its actual speed to the speed of sound) is greater than about 0.8, preferably greater than about 0.9 or about 0.95. Generally speaking, in the method of the invention, the Mach number for the anti-solvent fluid on entering the particle formation vessel may be between about 0.8 and about 1.5, preferably between about 0.9 and about 1.3.

[00116] In one or more embodiments, the method of the present invention comprises a method for forming a substance, or co-forming two or more substances, in particulate form, the method comprising introducing into a particle formation vessel (a) a solution or suspension of the target substance in a fluid vehicle (the "target solution/suspension") and (b) a compressed fluid anti-solvent for the substance, and allowing the anti-solvent fluid to extract the vehicle from the target solution/suspension so as to form particles of the target substance, wherein (i) the pressure in the particle formation vessel is $P_i$ which is preferably greater than the critical pressure $P_c$ of the anti-solvent, (ii) the anti-solvent is introduced through a restricted inlet so as to have a back pressure $P_2$, where $P_2$ is greater than $P_i$, (iii) the temperature in the particle formation vessel is $T_i$ which is preferably greater than the critical temperature $T_c$ of the anti-solvent, (iv) the anti-solvent is introduced into the vessel at a temperature $T_2$, where $T_2$ is greater than $T_i$, (v) $T_i$ and $T_2$ are such that Joule-Thomson cooling of the anti-solvent as it enters the vessel does not reduce the anti-solvent temperature to below that required of it at the point of particle formation (and are preferably such that the anti-solvent temperature does not fall below $T_c$ within the vessel) and (vi) $T_1, P_2, T_i$ and $T_2$ are such that the anti-solvent fluid has a sonic, near-sonic or supersonic velocity as it enters the particle formation vessel.

[00117] Although not intending to be bound by theory, it is believed that in the method of the invention, a so-called "Mach disk" is generated in the anti-solvent flow downstream of the second fluid inlet means. In this region the fluid velocity will change abruptly to sub-sonic thus generating shock waves in the fluids present (in effect a continuous, low volume, supersonic boom). These shock waves are thought to aid mixing and dispersion of the target solution/suspension with the anti-solvent. Moreover they will propagate in the direction of the anti-solvent flow, rather than in a counter-current sense.
[00118] The arrangement of the first and second inlet means will preferably be such that
the Mach disk is generated upstream (in the direction of anti-solvent flow) of the point of
entry of the target solution/suspension into the particle formation vessel. It should occur in
line with the longitudinal axis of the second inlet means, i.e., in line with the direction of
anti-solvent flow.

[00119] The near-sonic, sonic or supersonic anti-solvent velocity is ideally achieved, in
one or more methods of the present invention, by the use of appropriate anti-solvent flow
rates, back pressures and/or operating temperatures, and preferably without the aid of
mechanical, electrical and/or magnetic input such as for example from impellers, impinging
surfaces especially within the anti-solvent introducing means, electrical transducers and the
like. Introducing the anti-solvent via a convergent nozzle, ideally as a single fluid stream,
may also help in the achievement of appropriate fluid velocities.

[00120] The use of near-sonic, sonic or supersonic anti-solvent velocities can allow
achievement of smaller particle sizes and narrower size distributions in a supercritical or
near-critical fluid-based particle formation processes. In particular it can allow the formation
of small micro- or even nano-particles, for instance of volume mean diameter less than about
5 microns, preferably less than 2 microns, more preferably less than about 1 micron. Such
particulate products preferably have narrow size distributions, such as with a standard
deviation of 2.5 or less, more preferably 2.0 or less, most preferably 1.9 or even 1.8 or less.

[00121] The use of near-sonic, sonic or supersonic anti-solvent velocities also appears to
lead to more efficient vehicle extraction, thus potentially yielding particles with lower
residual solvent levels, less agglomeration and generally improved handling properties.

[00122] Preferably the two fluids meet immediately downstream of the point of anti-
solvent entry. "Immediately" in this context implies a sufficiently small time interval
(between the anti-solvent entering the particle formation vessel and its contact with the target
solution/suspension) as preferably still to allow transfer of mechanical energy from the anti-
solvent to the solution/suspension so as to achieve dispersion. Nevertheless, there is still
preferably a short interval of time between anti-solvent entry and fluid contact so as to
eliminate, or substantially eliminate or at least reduce, the risk of apparatus blockage due to particle formation at the point of anti-solvent entry. The timing of the fluid contact will depend on the natures of the fluids, the target substance and the desired end product, as well as on the size and geometry of the particle formation vessel and the apparatus used to introduce the fluids and on the fluid flow rates. The contact may occur within about 0.0001 to about 50 milliseconds, or within about 0.001 to about 25 milliseconds. The contact preferably occurs within about 0.001 to about 20 milliseconds, such as within about 0.01 to about 10 milliseconds, of the anti-solvent entering the particle formation vessel.

[00123] At the point where the target solution/suspension and the anti-solvent meet, the angle between their axes of flow may be from about 0 degrees (i.e., the two fluids are flowing in parallel directions) to about 180 degrees (i.e., oppositely-directed flows). In one embodiment of the present invention, they meet at a point where they are flowing in approximately perpendicular directions, i.e., the angle between their axes of flow is from about 70 to about 110 degrees, more preferably from about 80 to about 100 degrees, such as about 90 degrees. In another embodiment of the present invention, the flows of target solution/suspension and the anti-solvent meet at a point where they are flowing in approximately parallel directions, i.e., the angle between their axes of flow is from about 0 to about 70 degrees, more preferably from about 0 to about 30 degrees, such as about 0 degrees.

[00124] When carrying out one or more embodiments of the present invention, the particle formation vessel temperature and pressure may be controlled so as to allow particle formation to occur at or substantially at the point where the target solution/suspension meets the anti-solvent fluid. The conditions in the vessel must generally be such that the anti-solvent fluid, and the solution which is formed when it extracts the vehicle, both remain in the compressed (preferably supercritical or near-critical, more preferably supercritical) form whilst in the vessel. For the supercritical, near-critical or compressed solution, this means that at least one of its constituent fluids (usually the anti-solvent fluid, which in general will be the major constituent of the mixture) should be in a compressed state at the time of particle formation. There should at that time be a single-phase mixture of the vehicle and the anti-solvent fluid, otherwise the particulate product might be distributed between two or
more fluid phases, in some of which it might be able to redissolve. This is why the anti-solvent fluid is preferably miscible or substantially miscible with the vehicle.

[00125] The flow rate of the anti-solvent fluid relative to that of the target solution/suspension, and its pressure and temperature, should be sufficient to allow it to accommodate the vehicle, so that it can extract the vehicle and hence cause particle formation. The anti-solvent flow rate will generally be higher than that of the target solution/suspension - typically, the ratio of the target solution/suspension flow rate to the anti-solvent flow rate (both measured at or immediately prior to the two fluids coming into contact with one another) will be about 0.001 or greater, preferably from about 0.01 to about 0.2, more preferably from about 0.03 to about 0.1. The anti-solvent flow rate will also generally be chosen to ensure an excess of the anti-solvent over the vehicle when the fluids come into contact, to minimize the risk of the vehicle re-dissolving and/or agglomerating the particles formed.

[00126] Figure 1 shows one embodiment of an apparatus suitable for carrying out methods in accordance with the present invention. Reference numeral 100 denotes a particle formation vessel, within which the temperature and pressure can be controlled by means of a heating jacket 102 and back a pressure regulator 103. The vessel 100 contains a particle collection device (not shown) such as a filter, filter basket or filter bag. A fluid inlet assembly 104 allows introduction of a compressed (typically supercritical or near-critical) fluid anti-solvent from source 105 and one or more target solutions/suspensions from sources such as 106 and 107. The elements labeled 108 are pumps, and 109 is a cooler. A recycling system 110 allows solvent recovery.

[00127] The fluid inlet assembly 104 may for example take the forms shown in U.S. Patent 6,063,138 and/or U.S. Patent 5,851, 435, the disclosures of which are incorporated by reference in their entireties, and in particular with regard to apparatus, steps, methods and conditions. The fluid inlet assembly 104 includes a nozzle (not shown) for introduction of the anti-solvent fluid. The nozzle may comprise a single passage of circular cross section, with a circular outlet, or may alternatively comprise a multi-component nozzle, with anti-solvent introduced through one or more of its passages and the remaining passages either
closed off or else used to introduce additional reagents. (For example, a multi-passage nozzle of the type described in WO-95/01221 and/or corresponding U.S. Patent 5,851,453 or WO-96/00610 may be used). Such nozzles have two or more concentric (coaxial) passages, the outlets of which are typically separated by a short distance to allow a small degree of internal mixing to take place between fluids introduced through the respective passages before they exit the nozzle. The anti-solvent could for instance be introduced through the inner passage of such a nozzle, traversing a small "mixing" zone as it exits that inner passage and then passing through the main nozzle outlet into the particle formation vessel).

[00128] The opening at the outlet end (tip) of the nozzle may have a diameter in the range of about 0.05 to about 2 mm, preferably between about 0.1 and about 0.3 mm, typically about 0.2 mm. The outlet end of the nozzle may be tapered depending upon the desired velocity of the fluids introduced through the nozzle; an increase in the angle may be used, for instance, to increase the velocity of the supercritical fluid introduced through the nozzle and hence to increase the amount of physical contact between the supercritical fluid and the vehicle.

[00129] The anti-solvent used is preferably supercritical, near-critical or liquid CO2, especially supercritical CO2. Preferred solvents include one or more of methanol, ethanol, isopropylalcohol, acetone, tetrahydrofuran, ethylacetate, dimethylformamide, dichloromethane, MeCN (acetonitrile), N,N-dimethylacetamide (DMA). Hydroxylic solvents are particularly preferred. The processing conditions are preferably chosen to produce particles of desired sizes and/or to reduce residual solvent levels.

[00130] Alternatively or additionally, the particles comprising the HMG-CoA reductase inhibitor (such as atorvastatin), or the particles comprising the HMG-CoA reductase inhibitor (such as atorvastatin) and the excipient, such as an oligomeric or polymeric excipient, can be obtained by spray drying a liquid containing the HMG-CoA reductase inhibitor or the HMG-CoA reductase inhibitor and the excipient or low temperature sublimation of solvent via lyophilization process.

[00131] By "spray drying" it is meant the process of producing a particulate solid from a solution, slurry, emulsion, or suspension, or the like, of the atorvastatin in a liquid, such as an
aqueous or organic liquid, by atomizing the liquid to form droplets and drying the droplets to form a particulate solid. Generally, the particles have a moisture content of less than about 10% by weight water, preferably less than about 5% by weight water and sometimes less than about 3% by weight water, and may be from about 3% to about 5%. The drying conditions are suitably chosen to provide the desired moisture levels. The particle size (mass mean diameter) may be tailored to be a particular size as dictated by the end usage. For tableting, the size may be about 10 to about 500 µm, and in one or more versions is in the range of about 10 to about 200 µm, or about 20 to about 100 µm, or about 20 to about 50 µm. Smaller particle sizes, for example about 10 µm or less, or larger particle sizes, for example about 500 or greater, may have applications in additional or alternative dosage forms.

[00132] During the spray drying process, atomization of the liquid may be performed using a conventional atomizer such as a centrifugal, sonic, pressure and/or rotary atomizer. In one or more versions, a rotary atomizer is used in which the liquid flows over the wheel surface as a thin film, and is sheared away into discrete droplets. Other suitable atomizers include two-fluid atomizers, wherein liquid and atomization gas stream are delivered concurrently. Typically, the atomization gas is pressurized to high pressure for delivery through an atomization nozzle. Often the gas is air although other gases such as nitrogen may also be used. An example of a suitable spray drying method is a method as described in The Spray Drying Handbook, by Keith Masters, Longman Publishing, 5th Ed., September 1991, the contents of which is incorporated herein by reference in its entirety. Other spray-drying references include US 6,592,904 and/or WO 03/037303, the contents of which are incorporated herein by reference in their entireties.

[00133] In one or more embodiments of the present invention, and referring to Figure 2, a spray-drying process comprises an atomization operation 10 that produces droplets of a liquid medium, which are subsequently dried in a drying operation 20. The drying operation 20 may be a single drying chamber or a multi-stage operation. Drying of the liquid droplets results in formation of the discrete particles that form the dry powder compositions which are then collected in a separation operation 30. Each of these unit operations is described in greater detail below.
The atomization process 10 may utilize any one of several conventional forms of atomizers. The atomization process increases the surface area of the starting liquid. Due to atomization there is an increase in the surface energy of the liquid, the magnitude of which is directly proportional to the surface area increase. The source of this energy increase depends on the type of atomizer used. Any atomizer (rotary, centrifugal, sonic, pressure, two fluid) which is capable of producing droplets with a mass median diameter of less than about 100 microns, is suitable.

If a two fluid atomizer is used, the atomization gas may be nitrogen which has been filtered or otherwise cleaned to remove particulates and other contaminants. Nitrogen may be particularly advantageous in respect of atorvastatin, as it may help to mitigate degradation. Alternatively, other gases, such as air may be used. The atomization gas will be pressurized for delivery through the atomization nozzle, typically to a pressure above 5 psig, preferably being above 10 psig. The atomization conditions, including atomization gas flow rate, atomization gas pressure, liquid flow rate, and the like, are controlled to produce liquid droplets having a desired particle diameter as known to the art.

The feedstock for the process may be a solution, suspension, colloidal system, or other dispersion of an active agent in a suitable solvent, or co-solvent system, and is preferably a homogenous solution. The active agent comprises a drug, pharmaceutical, compound, formulation or co-formulation, which is desired to be spray-dried. In one embodiment, the active agent is present as a solution in water. Alcohol/water co-solvent systems according to this invention may also be employed. Other suitable solvents include, but are not limited to, alcohols such as methanol, ketones such as acetone, polar aprotic solvents, hydrogenated hydrocarbons such as methylene chloride, hydrocarbons such as cyclohexane, and mixtures thereof. The total dissolved solids, including the insoluble active agent and other carriers, excipients, etc., that may be present in the final dried particle, may be present at a wide range of concentrations, typically being present at from about 0.1% by weight to about 50% by weight, and often about 1% to about 25% by weight. It will thus be understood that the term "feedstock" as used herein is used broadly and encompasses mixtures such as solutions, slurries, suspensions, emulsions, microemulsions, multiple emulsions, and reverse emulsions.
The drying operation 20 is performed next to evaporate liquid from the droplets produced by the atomization operation 10. In some embodiments, the drying comprises introducing energy to the droplets, typically by mixing the droplets with a heated gas which causes evaporation of the water or other liquid medium. In some embodiments, the mixing is done in a spray dryer or equivalent chamber where a heated gas stream has been introduced. In some embodiments, the heated gas stream may flow concurrently with the atomized liquid; in other embodiments a counter-current flow, cross-current flow, or other flow pattern of the heated gas is employed. It is also possible to perform the drying operation in multiple stages as described, for example, in more detail in WO 01/00312 the disclosure of which is incorporated by reference in its entirety, and in particular with regard to drying apparatus, steps methods and conditions.

The drying rate may be controlled based on a number of variables, including the droplet size distribution, the inlet temperature of the gas stream, the outlet temperature of the gas stream, the inlet temperature of the liquid droplets, and the manner in which the atomized spray and hot drying gas are mixed. In one embodiment, the drying gas stream has an inlet temperature of at least about 70°C, and may be at least about 120°C, at least about 135°C, at least about 145°C, and may often be over about 175°C, or even as high as about 200°C, depending on the active agent being dried. At least in part, the inlet temperature of the heated gas drying stream depends on the lability of the active agent being treated. The outlet temperature is usually in the range of about 50-100°C. The drying gas may be moved through the system using conventional blowers or compressors.

The separation operation 30 is selected to achieve high efficiency collection of the particles produced by the drying operation 20. Any of several conventional separation operations may be used, although in some cases they could be modified to assure collection of a specified particle size range. In one or more embodiments, separation is achieved using a cyclone separator. Other separators, such as filters, for example, a membrane medium (bag filter), a sintered metal fiber filter, or the like may also be used. The separation operation should achieve collection of at least about 70% of all particles, and in some embodiments collects more than about 85%, more than about 90%, or even more than about 95% of such particles.
Referring now to Figure 3, one embodiment of a spray-dryer system is described. The system includes a spray dryer 50, which may be a commercial spray dryer such as those available from suppliers such as Buchi, Niro, APV, Yamato Chemical Company, Okawara Kakoki Company, and others. The spray dryer 50 is provided with a feedstock as described above through a supply pump 52, filter 54, and supply line 56. The supply line 56 is connected to an atomizer 57. Atomizing air is supplied from a compressor 58, a filter 60, and line 62 to the atomizer 57. Drying air is also provided to the spray dryer 50 through a heater 65 and a filter 66.

In this embodiment, dried particles from the spray dryer 50 are carried by the air flow through conduit 70 to a separator 72. In one embodiment, the separator 72 comprises a cyclone. Alternatively, the separator 72 may be a filter, with filter media such as bag filters, cloth filters, and cartridge filters. The dried particles comprising powder are collected in a particle collection canister 76, which may be periodically be removed and replaced. The dry powder in the canister 76 may be used for packaging in unit dosage or other forms. The carrier gas passes out from the top of the separator 72 through line 80 and an exhaust fan 84.

As alternatives to spray drying, the liquid may be removed from the solution, slurry, emulsion, or suspension by other known techniques. For example, the liquid may be removed by freeze drying (lyophilization), vacuum drying, spray freeze drying, evaporation, bubble drying, or the like. In one or more embodiments, spray drying is often advantageous in terms of its efficiency and reproducibility. In other embodiments, supercritical or near critical particle precipitation processes are often advantageous in terms of their efficiency and reproducibility. In another embodiment, non-aqueous lyophilization process is often advantageous in terms of efficiency, scalability and reproducibility.

Powder formulations comprising an HMG-CoA reductase inhibitor, having improved stability as compared to HMG-CoA reductase inhibitors alone such that they can better withstand normal drug storage conditions prior to tablet formulation, may be prepared from solutions using the solvent removal processes described herein. The dissolution profile of the stabilized formulations remains substantially unchanged during storage, leading to an improved shelf-life compared to the HMG-CoA reductase inhibitor alone. Particularly
advantageously, one or more embodiments of the present invention affords the possibility of obtaining stable formulations containing HMG-CoA reductase inhibitor in non-crystalline form which can be absorbed at an acceptable rate and to an acceptable extent in vivo for pharmaceutical use.

As described above, a particulate HMG-CoA reductase inhibitor formulation, prepared in accordance with one or more embodiments of a solvent removal process of the present invention, even in the absence of a stabilizing excipient, possesses advantageous stability and/or dissolution characteristics and/or bioavailability. In particular, a statin, such as atorvastatin, formulated as a powder by a spray drying or by a supercritical particle precipitation process as described in accordance with one or more embodiments of the present invention, possesses advantageous stability and/or dissolution characteristics, and/or bioavailability. In one or more embodiments, an excipient, such as an oligomeric or polymeric excipient, when incorporated as described herein, may provide solid state stability to the HMG-CoA reductase inhibitor (e.g. while in powder form), and may additionally or alternatively provide stability against HMG-CoA reductase degradation while in powder form, and after the powder formulation is formed into an oral dosage form, such as a tablet. In one or more embodiments of the present invention an amino acid containing, and/or amino acid derivative based excipient, when incorporated as described herein, further may provide solid state stability to the HMG-CoA reductase inhibitor, especially atorvastatin, but may also provide stability against atorvastatin degradation after the powder formulation is formed into an oral dosage form, such as a tablet. Accordingly, the formulated tablet does not need to include an additional degradation stabilizing excipient, such as calcium carbonate. The solid state stabilization and/or degradation stabilization is illustrated by the following examples.

It has also been unexpectedly discovered that versions of powder formulations comprising non-crystalline or amorphous forms of an HMG-CoA reductase inhibitor (e.g. atorvastatin) have better intrinsic compaction behavior than powders comprising crystalline forms of the HMG-CoA reductase inhibitor. Accordingly, when using the powder to formulate a tablet, the powder with the non-crystalline or amorphous HMG-CoA reductase inhibitor can be combined with additional compaction enhancers, such as calcium citrate.
and/or Avicel, to produce tablets with improved properties, such as micromeretic properties, over tablets made from powders having crystalline forms of the HMG-CoA reductase inhibitor. For example, by adding calcium citrate and/or Avicel to a powder comprising non-crystalline or amorphous atorvastatin calcium, acceptable hardness, disintegration times, and dissolution properties can be obtained with significantly less excipient than would be required for the crystalline form. These effects are illustrated in the examples which follow.

[00146] As described herein, the amorphous form of a drug substance is generally less stable than the crystalline form. The stability differences may be more pronounced as the drug undergoes degradation. Without intending to be bound by theory, it is believed that one mechanism of degradation, especially of the non-crystalline atorvastatin, involves rearrangement of a hydroxyl functional group, leading to ring opening of the pyrrole and subsequent loss of the aliphatic side chain. Since the degradation tends to be more pronounced in the amorphous state, the solid state stability of SEDSTM processed powders were conducted at various temperature and humidity conditions. Initial solid state stability studies on the processed drug suggest the presence of three major degradants, labeled, for discussion purposes only, as OXDn, i.e. OXD1, OXD2, and OXD3.

Powder Formulation Examples

[00147] Non-crystalline forms of atorvastatin are prepared by dissolving or dispersing the starting material, such as crystalline atorvastatin, and optionally, excipient, in a solvent or solvent solution, followed by a solvent removal process, performed under conditions selected to result in the formation of a desired form of atorvastatin, such as a non-crystalline form and/or a chemically stable form. Such conditions generally comprise those that result in the formation of at least a partially non-crystalline form of atorvastatin, and having at least one of the properties of a free-flowing powder, a non-sticky powder, a reduced hygroscopicity, a wet Tg of above about 40°C, or a dry Tg (without any residual solvents) of above about 90°C. Preferred is the formation of at least a partially non-crystalline form of atorvastatin having at two or more of the foregoing properties. Co-formulations comprising non-crystalline atorvastatin and excipient are prepared in the in a similar manner, i.e. by dissolving or dispersing the starting material, such as crystalline atorvastatin, and excipient, in a solvent or
solvent solution, followed by a solvent removal process, performed under conditions selected to result in the formation of a desired form of atorvastatin, such as a non-crystalline form and/or a chemically stable form.

[00148] In one or more embodiments, the solvent removal process comprises spray drying as described herein. The processing conditions, ranges, parameters and equipment may, however, be varied to achieve the desired result, such as the formation of a non-crystalline form and/or a chemically stable form. In one or more embodiments, the solvent removal process comprises supercritical particle precipitation process as described herein. The processing conditions, ranges, parameters and equipment may, however, be varied to achieve the desired result, such as the formation of a non-crystalline form and/or a chemically stable form.

[00149] In one or more embodiments, a supercritical particle precipitation method is essentially as the Nektar™ SCF particle precipitation process of the type described in WO 03/008082. In one or more embodiments of this method, the nozzles are arranged such that the direction of flow of the atorvastatin-containing solution is perpendicular to the flow of the anti-solvent. The anti-solvent is introduced at a near-sonic, sonic or supersonic velocity.

[00150] In another embodiment, the non-crystalline atorvastatin salt is obtained by

(A)(i) preparing a desired salt of atorvastatin in solution in a first solvent; and

(ii) optionally adding at least one initial stabilizer for said atorvastatin salt to the solution of step (A)(i) to yield a second solution; or

(B) (i) optionally preparing a solution of said initial stabilizer in a second solvent, which may be the same as said first solvent, to form a third solution; and

(ii) adding said atorvastatin salt to said third solution of step (B)(i) to yield a fourth solution; or

(C) (i) following step (A)(i);
(ii) following step (B)(i); and

(iii) combining the result of steps (C)(i) and (C)(U) to yield a fifth solution; and removing the respective first and second solvents from said second, fourth, and fifth solutions via a technique selected from the group consisting of one or more of lyophilization, spray drying, supercritical fluid solvent extraction, and near critical fluid extraction.

The solvent removal step utilizes at least a lyophilization step and is generally carried out in the ordinary lyophilization procedures or those set forth in copending US 11/282,507, filed 11/18/2005, incorporated herein in its entirety. In some embodiments, an anti-solvent is added prior to the lyophilization in the manner set forth in US 11/282,507. In these embodiments, the definition of solvent and anti-solvent follows the definitions in US 11/282,507 rather than that above. Furthermore, in these lyophilization procedures, the active agent and optionally one or more of the excipients and other non-active materials of the formulation is/are dissolved in one or more solvents and where more than one solvents are used they are miscible with each other and act as solvents or co-solvents for each of the components dissolved therein. This solution is then added to a lyophilization vial alone or together with an anti-solvent, which is a solvent type material which is not a solvent for the materials in the solution to which it is added but is miscible with the solvents in the solution to which it is added. This mixture is then lyophilized to obtain an amorphous, non-crystalline solid atorvastatin material which is then further formulated with the remainder of the formulation components. In a particularly preferred embodiment, atorvastatin (or the lactone variant thereof or a salt thereof) is dissolved in a suitable aqueous or non-aqueous solvent or mixture thereof. When solid atorvastatin Na is the starting point, a 50%-methanol/50%-water v/v mixture is preferred. If the atorvastatin is the free compound or the lactone thereof or a salt thereof other than the hemicalcium salt, it is converted to the hemicalcium salt in solution, generally with the addition of calcium chloride, tricalcium phosphate, or tricalcium citrate as preferred calcium donators (although other calcium salts including the sulfates, sulfites, and sulfides as well as other calcium phosphate and non-phosphate salts can be used). Tricalcium phosphate has the additional advantage of adjusting the pH to about 10, a most desired pH for the present lyophilization process for atorvastatin, and the concurrently formed sodium phosphates can themselves act as stabilizers for the
atorvastatin calcium. A stabilizer, generally an antioxidant, may be added in amounts of up to 10%, generally 1-7.5%, more preferably about 2-about 5% w/v may be added at this point. Where desired, other additional formulation components can be added to the lyophilization solution before lyophilization takes place, however, it is preferable that no other components are added and most preferably the only components of the lyophilization solution are the solvents, atorvastatin and optionally the calcium providing salt. The solution is then lyophilized (typically at about -40°C, but other temperatures known to those of ordinary skill in the art will work as well) to result in solid amorphous atorvastatin hemicalcium salt suitable for use in the formulations of the present invention. In the lyophilization process of obtaining the amorphous atorvastatin hemicalcium salt, it should be noted that the material also contains the sodium ion (from the original atorvastatin sodium) and the counterion of whatever calcium salt was used. Thus, in the use of the amorphous material obtained from this lyophilization, appropriate adjustments of weight must be made to account for the sodium and the non-atorvastatin anion that is present.

[00152] The additional formulation components that are potentially present in the material being lyophilized can be any of stabilizer excipients, diluents, disintegrants, surfactants, binders, and lubricants. Preferably, when such a formulation component is present in the lyophilizate, it is a formulation stabilizer and selected at least from the oligomeric and/or polymeric excipients described hereinbefore. Other formulation stabilizers include salts of organic acids such as di-, tri- or tetra- sodium EDTA, sodium salts of citric acid, especially trisodium citrate, and sodium salts of dicarboxylic acids, such as malic acid, maleic acid, etc., as well as others well known in the art. Formulation diluents include for example cellulose, mono-, di, and poly saccharides, trisodium citrate, di- and tri-calcium phosphate, as well as others well known in the art. Formulation disintegrants are suitably chosen from crosipovidone, Ac-Di-Sol, and Explotab, among a host of others well known in the art. Suitable formulation surfactants include polysorbates and the like. Formulation lubricants include fatty acids such as stearic acid, and behenic acid, their sodium or potassium or magnesium salts, and their glycerin mono-, di-, and tri-esters. Other lubricants such as talc and the like known in the art are also suitable. Formulation binders may be typically selected from polyvinylpyrrolidones, starches, pregelatinized starch, carboxy cellulose and other
known in the art. Preferably, the material subjected to lyophilization has as few components in addition to the solvents, optional antisolvent, and active agent as possible but often will include the excipient oligomeric or polymeric stabilizer.

Supercritical Particle Precipitation Examples

[00153] Examples 1 and 2 are pure non-crystalline formulations of atorvastatin (absent any stabilizing excipient), prepared by SEDS™ processing. Additional Examples of non-crystalline formulations of Atorvastatin and stabilizing excipient(s) were prepared by SEDS™ processing, and as further described below.

EXAMPLE 1

[00154] Non-crystalline atorvastatin, in the form of its calcium salt, was prepared using the Nektar™ SCF particle precipitation process as described herein. Additionally, processing conditions comprised a reactor vessel pressure of about 125 bar. Methanol was used as the drug solvent. The anti-solvent and solution nozzles were arranged such that the direction of flow of the atorvastatin-containing solution was perpendicular to the flow of the anti-solvent.

[00155] The product was in the form of a finely dispersed particulate powder which was non-cohesive and easy-flowing with good handling properties. Figure 4 is an XRPD, showing that the product was non-crystalline. Additionally, the glass transition temperature (Tg onset) was determined by DSC to be 136°C, further indicating that the amorphous powder is likely to remain stable, when stored at pharmaceutically relevant temperatures, with respect to reversion of the amorphous phase drug to crystalline form(s).

[00156] Samples of powder made per Example 1 were stored (in the form of the as-prepared powder) at 25°C and 60% relative humidity (RH) and at 40°C and 75% relative humidity. The samples were stored in capped and uncapped HDPE containers. Smaller samples were removed at intervals and their crystallinity assessed using XRPD. All samples were found to be stable (that is remained 100% amorphous) after storage for two months under these conditions. The 'loss on drying' of the product on drying at 100°C, determined by thermogravimetric analysis, was found to show little change (3.2%) from the initial loss
on drying levels. This shows an absence of significant hygroscopicity, indicating that the product is less likely to revert from amorphous phase to crystalline form on storage.

EXAMPLE 2

Example 2 is another example of a pure non-crystalline atorvastatin powder, produced by the Nektar SEDSTM supercritical particle precipitation process. The following steps were carried out under ambient conditions:

800 g atorvastatin calcium was added to 3.2 L of methanol, and dissolved by stirring at about 60 RPM.

The resultant solution was processed into a powder using a SEDSTM process as described herein. Additionally, processing was conducted using a BExMiN-2 nozzle with a 400 µm tip for the CO2 line and a 250 µm tip for the solution line. The conditions used were a reactor vessel pressure of about 125 bar, a reactor vessel temperature of about 40°C, a CO2 inlet temperature of about 48°C, a CO2 flow (the anti-solvent) of about 50 kg-hr⁻¹ and a solution flow of about 0.8 kg-hr⁻¹. The operating conditions may be varied, as known to the art, for commercial scale production.

The powder was analyzed and found to be non-crystalline. Figure 5 is an XRPD showing the pure non-crystalline powder (lower curve). The upper curve depicts atorvastatin co-formulated with HPC, to result in a non-crystalline powder, according to Example 3 below. The powder of this Example remained flowable after exposure to ambient conditions. In other words the formulation has an improved handlability for down stream processing such as tableting.

EXAMPLE 3

This Example illustrates a co-formulation of atorvastatin calcium with an excipient, specifically hydroxypropylcellulose (HPC).

The following steps were carried out under ambient conditions:
80 g hydroxy propyl cellulose (HPC) was added slowly to 3.2 L of methanol. The HPC was dissolved by stirring at about 60 RPM.

720 g atorvastatin calcium was added to the solution made from step 1, and dissolved by stirring at about 60 RPM. The orders of step 1 and 2 are not critical and can be reversed.

The resultant solution was processed into a powder using a SEDS™ process as described herein. Additionally, processing was conducted using a BExMiN-2 nozzle with a 400 µm tip for the CO₂ line and a 250 µm tip for the solution line. The conditions used were a reactor vessel pressure of about 125 bar, a reactor vessel temperature of about 40°C, a CO₂ inlet temperature of about 48°C, a CO₂ flow (the anti-solvent) of about 50 kg-hr⁻¹ and a solution flow of about 0.8 kg-hr⁻¹. The operating conditions may be varied, as known to the art, for commercial scale production.

The solution of this, and the other examples, can alternatively be removed by other solvent removal processes, such as by lyophilization or freeze-drying, spray-freeze drying, vacuum drying, evaporation, bubble drying or extraction. This process can be performed in other solvents, such as organic solvents.

The bulk powders of Example 2 (pure non-crystalline atorvastatin) and Example 3 (co-formulated atorvastatin:HPC) were analyzed for purity by HPLC shortly after production. Tables 1 and 2 below show percentages of various components in the pure non-crystalline atorvastatin calcium powder, for two different samples of each (G06A and G06B). Tables 3 and 4 show percentages of various components in the non-crystalline atorvastatin calcium/HPC co-formulation powder, for two different samples of each (G12A and G06B). It can be seen that atorvastatin purity is high, and lactone and oxidation product (designated OX2) formation is desirably low.

| Table 1 |
| Pure non-crystalline atorvastatin |
| Sample G06A |
Table 4
Atorvastatin : HPC (9:1)
Sample G12B

<table>
<thead>
<tr>
<th>Retention Time (mins)</th>
<th>Relative Retention Time</th>
<th>Component Information</th>
<th>% Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.98</td>
<td>0.57</td>
<td>Amide</td>
<td>0.083</td>
</tr>
<tr>
<td>7.98</td>
<td>0.91</td>
<td>Desfluoro</td>
<td>0.094</td>
</tr>
<tr>
<td>8.35</td>
<td>0.96</td>
<td>Diastereoisomer</td>
<td>0.018</td>
</tr>
<tr>
<td>8.72</td>
<td>1.00</td>
<td>Atorvastatin</td>
<td>99.633</td>
</tr>
<tr>
<td>13.67</td>
<td>1.57</td>
<td>Unknown</td>
<td>0.032</td>
</tr>
<tr>
<td>16.29</td>
<td>1.87</td>
<td>Lactone</td>
<td>0.121</td>
</tr>
<tr>
<td>23.55</td>
<td>2.70</td>
<td>OX 2</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Table 2
Pure non-crystalline atorvastatin
Sample G06B

<table>
<thead>
<tr>
<th>Retention Time (mins)</th>
<th>Relative Retention Time</th>
<th>Component Information</th>
<th>% Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.95</td>
<td>0.57</td>
<td>Amide</td>
<td>0.078</td>
</tr>
<tr>
<td>7.05</td>
<td>0.81</td>
<td>Unknown</td>
<td>0.023</td>
</tr>
<tr>
<td>7.96</td>
<td>0.91</td>
<td>Desfluoro</td>
<td>0.095</td>
</tr>
<tr>
<td>8.33</td>
<td>0.96</td>
<td>Diastereoisomer</td>
<td>0.024</td>
</tr>
<tr>
<td>8.71</td>
<td>1.00</td>
<td>Atorvastatin</td>
<td>99.535</td>
</tr>
<tr>
<td>13.80</td>
<td>1.58</td>
<td>Unknown</td>
<td>0.033</td>
</tr>
<tr>
<td>16.27</td>
<td>1.87</td>
<td>Lactone</td>
<td>0.174</td>
</tr>
<tr>
<td>23.54</td>
<td>2.70</td>
<td>OX 2</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Table 3
Atorvastatin: HPC (9:1)
Sample G12A

<table>
<thead>
<tr>
<th>Retention Time (mins)</th>
<th>Relative Retention Time</th>
<th>Component Information</th>
<th>% Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.04</td>
<td>0.57</td>
<td>Amide</td>
<td>0.081</td>
</tr>
<tr>
<td>8.02</td>
<td>0.91</td>
<td>Desfluoro</td>
<td>0.096</td>
</tr>
<tr>
<td>8.45</td>
<td>0.96</td>
<td>Diastereoisomer</td>
<td>0.058</td>
</tr>
<tr>
<td>8.79</td>
<td>1.00</td>
<td>Atorvastatin</td>
<td>99.494</td>
</tr>
<tr>
<td>12.59</td>
<td>1.43</td>
<td>Unknown</td>
<td>0.013</td>
</tr>
<tr>
<td>13.10</td>
<td>1.49</td>
<td>O-Methyl</td>
<td>0.018</td>
</tr>
<tr>
<td>16.18</td>
<td>1.84</td>
<td>Lactone</td>
<td>0.142</td>
</tr>
<tr>
<td>16.98</td>
<td>1.93</td>
<td>Imp X</td>
<td>0.047</td>
</tr>
<tr>
<td>23.29</td>
<td>2.65</td>
<td>OX 2</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Table 4
Atorvastatin : HPC (9:1)
Sample G12B
Examples 4 and 5 illustrate the production of non-crystalline atorvastatin co-formulations comprising an amino acid. In the Examples below, the atorvastatin was co-formulated with glycine or alanine, using the Nektar SEDSTM supercritical fluid particle precipitation process.

**EXAMPLE 4**

This Example illustrates a co-formulation of atorvastatin calcium with an amino-acid excipient, specifically glycine.

The following steps were carried out under ambient conditions:

7 g glycine was added slowly to a solution containing 4.2g of sodium methoxide. The glycine was dissolved by stirring at about 60 RPM.

70 g atorvastatin calcium was added to the solution made from step 1, and dissolved by stirring at about 60 RPM. The orders of step 1 and 2 are not critical and can be reversed. The resultant solution contained atorvastatin:sodium methoxide:glycine in the ratio of 82:8:10.

The resultant solution was processed into a powder using a SEDSTM process as described herein. Additionally, processing was conducted using a BexMiN-2 nozzle with a 400 µm tip for the CO₂ (the anti-solvent) line and a 250 µm tip for the solution line. The conditions used (at pilot plant scale) were a reactor vessel pressure of about 125 bar, a reactor vessel temperature of about 40°C, a CO₂ inlet temperature of about 48°C, a CO₂ flow of
about 12 kg-hr\(^{-1}\) and a solution flow of about 0.2 kg-hr\(^{-1}\). The operating conditions may be varied, as known to the art, for commercial scale production.

**EXAMPLE 5**

[00174] This Example illustrates a co-formulation of atorvastatin calcium with another amino-acid excipient, specifically alanine.

[00175] The following steps were carried out under ambient conditions:

[00176] 1.5 g alanine was added slowly to a solution containing 1.2 g of sodium methoxide. The alanine was dissolved by stirring at about 60 RPM.

[00177] 15 g atorvastatin calcium was added to the solution made from step 1, and dissolved by stirring at about 60 RPM. The orders of step 1 and 2 are not critical and can be reversed. The resultant solution contained atorvastatin:sodium methoxide:alanine in the ratio of 82:8:10.

[00178] The resultant solution was processed into a powder using a SEDST\(^{TM}\) process, using conditions and parameters as described for Example 4. The solution of this, and the prior examples, can alternatively be removed by other solvent removal processes, such as by freeze-drying, spray-freeze drying, vacuum drying, evaporation, bubble drying or extraction. This process can be performed in other solvents, such as organic solvents.

[00179] Tables 5 and 6 are show stability data for a co-formulation of atorvastatin with glycine according to Example 4 and for a co-formulation of atorvastatin with alanine according to Example 5. Samples of the products were stored (in the form of the as-prepared powder, in capped and uncapped HDPE containers) under refrigerated conditions (at about 2-8\(^{\circ}\)C). Smaller samples were removed at indicated intervals of one, two and three months, and their stability was assessed using HPLC.

| Table 5 |
| Atorvastatin:sodium methoxide:glycine (82:8:10) |
Atorvastatin, in the form of its calcium salt, was co-formulated with various polymers in accordance with the present invention using the Nektar™ SEDS™ supercritical particle precipitation process as described herein. The process resulted in a particulate solid solution with each particle comprising a solid solution of non-crystalline (amorphous) atorvastatin calcium (the "drug") and polymer. Different drug:polymer concentration ratios were used as outlined in Table 7 below.

Methanol was used as the drug/polymer solvent (or 1:1 methanol:acetone in the case of the co-formulation with hydroxypropylcellulose (HPC) as polymer at a drug:polymer ratio of 9:1). This gave dispersions of suitably low viscosity, which contributes to processing without significant nozzle blockage. The glass transition temperatures of the various co-formulations were determined (by DSC) and their 'loss on drying' at 100°C was determined. Additionally, XRPD results showed all of the products as non-crystalline.

### Table 6

<table>
<thead>
<tr>
<th>Peak Identity</th>
<th>Amide</th>
<th>Desfluoro</th>
<th>Diastere</th>
<th>Atorvastatin calcium</th>
<th>O-methyl</th>
<th>Lactone</th>
<th>Impurity X</th>
<th>Methyl Ester</th>
<th>OX1</th>
<th>OX2</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRT:</td>
<td>0.57</td>
<td>0.91</td>
<td>0.95</td>
<td>1.00</td>
<td>1.48</td>
<td>1.82</td>
<td>1.94</td>
<td>2.10</td>
<td>2.17</td>
<td>2.66</td>
</tr>
<tr>
<td>T = 0m</td>
<td>0.08</td>
<td>0.128</td>
<td>0.103</td>
<td>99.631</td>
<td>0.058</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T = 1m</td>
<td>0.055</td>
<td>0.128</td>
<td>0.053</td>
<td>99.535</td>
<td>0.068</td>
<td>0.032</td>
<td></td>
<td></td>
<td>0.027</td>
<td>0.04</td>
</tr>
<tr>
<td>T = 2m</td>
<td>0.077</td>
<td>0.125</td>
<td>0.046</td>
<td>99.433</td>
<td>0.056</td>
<td>0.039</td>
<td>0.022</td>
<td>0.018</td>
<td>0.040</td>
<td>0.08</td>
</tr>
<tr>
<td>T = 3m</td>
<td>0.059</td>
<td>0.126</td>
<td>0.049</td>
<td>99.351</td>
<td>0.071</td>
<td>0.030</td>
<td>0.027</td>
<td>0.026</td>
<td>0.077</td>
<td>0.07</td>
</tr>
</tbody>
</table>

For Table 6, the atorvastatin:sodium methoxide:alanine ratio is 82:8:10.
As can be seen from the results presented in Table 7 in all cases the glass transition temperature (Tg) remains high, indicating that the amorphous atorvastatin/polymer co-formulation is likely to remain stable with respect to reversion of the amorphous phase drug to crystalline form(s).

Studies to investigate the storage stability of the products of Table 7 above confirmed that the co-formulations remained stable. Samples of the products were stored (in the form of the as-prepared powder, in capped and uncapped HDPE containers) at 25°C and 60% relative humidity (RH) and at 40°C and 75% relative humidity. Smaller samples were removed at intervals and their crystallinity assessed using XRD. All samples were found to be stable (that is remained 100% non-crystalline) after storage for two months under these conditions. Their "loss on drying" (an indication of the increase in water content on storage) was also determined by thermogravimetric analysis and the samples were found to show little change in their initial loss on drying levels. Table 8 below compares loss on drying (weight percent water) of a pure non-crystalline atorvastatin produced by SEDSTM processing (Example 2) and the SEDSTM processed atorvastatin:HPC formulation of Example 3.
Figures 6-8 are XRPD profiles of some of the HPMC co-formulations of Table 8, taken after two months storage (at 25°C and 60% RH) show that the samples are still 100% amorphous in form. Figure 6 shows Sample 3 (atorvastatin calcium/HPMC 1:1); Figure 7 shows Sample 2 (atorvastatin calcium/HPMC 3:1); and Figure 8 shows Sample 1 (atorvastatin calcium/HPMC (9:1)).

Figure 9 is a moisture sorption isotherm, measured by DVS, for the HPC polymer excipient alone and for certain of the non-crystalline formulations comprising atorvastatin. From these DVS data showed that pure atorvastatin, prepared by the Nektar™ SEDS™ particle precipitation process, sorbed the least amount of water, with the atorvastatin:HPC (9:1) formulation being virtually identical. This represents a significant advantage for formulations and/or co-formulations comprising atorvastatin, prepared using the Nektar™ SEDS™ particle precipitation process, as the less water taken up by the product, the less likely it is to revert from non-crystalline phase to crystalline form on storage.

Additional DVS data demonstrate that the cellulose based excipients alone, and/or a particulate co-formulation of the cellulose-based excipient with atorvastatin, are desirably low in hygroscopicity. Ethyl Cellulose, HPMC and HPC all exhibit low hygroscopicity. Non-crystalline co-formulations of atorvastatin with cellulose excipients according to one or more embodiments of the present invention would be expected to show particularly advantageous stability, with respect to the crystalline form of atorvastatin.

The aqueous solubilities of the commercially-available crystalline atorvastatin, and SEDS™-processed atorvastatin:excipient co-formulations were investigated, as were the dissolution characteristics in different pH conditions. Instantaneous solubility studies of the drug powder were carried out in various media covering the range of physiological pH to...
compare with solubility of pure non-crystalline atorvastatin powder, prepared by the Nektar™ SEDS™ particle precipitation process. Sample preparation included dissolving the drug in a fixed volume of the buffer solution by shaking and/or sonicating for 10 minutes. The solution was supersaturated until undissolved drug was visible even after shaking and sonication. The solution was filtered and the absorption was immediately measured by UV at 246 nm. Results are shown in Table 9:

<table>
<thead>
<tr>
<th>Buffer</th>
<th>Atorvastatin Instantaneous solubility (μg/ml)</th>
<th>Commercial crystalline powder (prior art) Instantaneous Solubility (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 N HCl</td>
<td>41.70</td>
<td>17.44</td>
</tr>
<tr>
<td>pH 4.5 Acetate buffer</td>
<td>107.27</td>
<td>25.05</td>
</tr>
<tr>
<td>pH 6.8 Phosphate buffer</td>
<td>646.31</td>
<td>275.34</td>
</tr>
</tbody>
</table>

As shown by the data in the Table, the instantaneous solubility of supercritical fluid processed pure non-crystalline atorvastatin is significantly higher than that of the prior art crystalline material alone.

Spray Dried Examples

EXAMPLE 7

In this Example, pure, non-crystalline atorvastatin (absent any excipient), in the form of its calcium salt, was prepared using the spray drying method as described herein, and spray-drying conditions were selected to obtain a free-flowing powder with good handling qualities. In general such conditions may comprise result in the formation of a non-crystalline form of atorvastatin comprising a free-flowing, non-sticky powder and/or having a T <sub>g</sub> above about 40°C, or a dry T <sub>g</sub> of the particles (without any residual solvents) of above about 70°C, or both. Spray drying was performed on a Büchi 190 laboratory spray dryer under a nitrogen atmosphere under the following conditions: Feed rate was 5.0 ml/min; inlet temperature was 75°C; outlet temperature was 57°C; atomization pressure was 40 psi. These
conditions may be varied, as known to the art, for other models of dryers, and/or for other production scales, such as commercial scale production.

[00190] A dry powder of neat atorvastatin calcium was prepared from a 50% ethanol 50% water solution of atorvastatin calcium at approximately 1% solids content. From XRPD, the resulting product was found to be non-crystalline. The resulting powder was found to be free flowing, with good micromeritic properties, such as tableting. The glass transition temperature ($T_g$, onset), as determined by DSC, of the product was found to remain high (133°C) indicating that the amorphous material is likely to remain stable with respect to reversion of the amorphous phase drug to crystalline form(s).

[00191] Samples of the product of Example 7 were stored in the form of the as-prepared powder in uncapped HDPE containers under two different storage conditions (at 25°C and 60% relative humidity (RH) and at 40°C and 75% relative humidity) and were found to be stable (that is 100% amorphous) when assessed by XRD after storage for one month under these conditions. The "loss on drying" (an indication of the increase in water content on storage) of the product on drying at 100°C was determined by thermogravimetric analysis and was found to show little change in the initial loss on drying levels.

EXAMPLE 8

[00192] A dry powder comprised of 90% atorvastatin calcium and 10% hydroxypropyl cellulose was prepared from an ethanol in water solution: 5.4 g of atorvastatin calcium and 0.6 g of hydroxypropyl cellulose were added into a mixture of 450 ml ethanol and 150 ml of water at room temperature. The mixture was warmed up to about 60 °C with stirring until a clear solution was attained. Spray drying was performed as described with respect to Example 7 above. A white dry powder was obtained at approximately 60% yield.

EXAMPLE 9

[00193] In any of the foregoing Examples, the solvent can additionally or alternatively be removed by other aqueous solvent removal processes, such as freeze drying, spray freeze drying, evaporation, vacuum drying, bubble drying, supercritical particle precipitation, or combinations thereof. The solvent of one or more examples herein may alternatively or
additionally comprise solvents other than those indicated, such as water, or organic solvents. For example, the solvent may comprise ethanol, iso-propanol, methanol, other short chain alcohols, esters, ethers, other low boiling point solvents, and mixtures thereof.

EXAMPLE 10

[00194] In any of the above examples, the free compound (i.e. acid) of atorvastatin may be used as the starting material instead of the crystalline atorvastatin calcium salt. The free compound may be obtained as such from a commercial source, or as an intermediate in a synthetic process, or may be produced from atorvastatin, as known to the art. To the free compound, a molar equivalent of a base, such as an alkali metal, alkali earth metal, or alkaline earth metal, and counterion may be added to form the salt.

[00195] In some embodiments of the present invention, it may be desirable to uses as the starting material the sodium salt, rather than the calcium salt. The following Examples describe methods for preparation of the calcium salt from the sodium salt.

EXAMPLE 11

[00196] A starting solution of atorvastatin calcium for use in any suitable particle formation process can be prepared by a process comprising the steps of:

<table>
<thead>
<tr>
<th>Table X</th>
<th>dissolving a known amount of the sodium salt of atorvastatin in a suitable solvent or mixture of solvents,</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ii)</td>
<td>dissolving at least one equivalent of calcium chloride in a suitable solvent or mixture of solvents,</td>
</tr>
<tr>
<td>(iii)</td>
<td>reacting the solution of step (i) with the solution of step (ii), to produce atorvastatin calcium in solution and sodium chloride, which substantially precipitates from the solution, and</td>
</tr>
<tr>
<td>(iv)</td>
<td>removing the sodium chloride from the mixture of step (iii), leaving a solution of atorvastatin calcium.</td>
</tr>
</tbody>
</table>
The sodium salt of atorvastatin is a known compound and its preparation is described in US Patent 4,681,893 in either a crystalline or non-crystalline form. Since atorvastatin calcium is the hemicalcium salt of atorvastatin, one equivalent of calcium chloride, as used in step (ii) of this process, means one half of the number of moles of atorvastatin sodium used in step (i). The solvents employed in this process, and the conditions of mixing in step (iii), are chosen so that sodium chloride is precipitated from the solution in step (iii) but little or no precipitation of atorvastatin calcium occurs.

In one or more versions, the solvent chosen for step (i) may be any solvent, or mixture of solvents, in which the sodium salt of atorvastatin can be dissolved leaving no solid remaining. Typically, the solvent chosen may be a polar solvent such as a low molecular weight alcohol, for example methanol or ethanol, or a combination thereof, optionally mixed with water. In one or more versions, the solvent comprises methanol and water in a volume ratio in the region of 2:1. In one or more versions, the concentration of atorvastatin sodium salt in solvent is in the order of 0.01 to 0.1 moles per liter.

The solvent or mixture of solvents used in step (ii) of the process may be the same as that used in step (i) of the process or it may be different, provided that the solvent or mixture of solvents chosen is one in which calcium chloride is soluble. Typically the solvent is a polar solvent such as water, a low molecular weight alcohol such as methanol or ethanol, or a mixture thereof. Preferably, the solvent is water. The concentration of calcium chloride in the solution is suitably in the order of 0.01 to 0.1 moles per liter. Where it is intended to use the atorvastatin calcium resulting from step (iii) directly in a solvent removal process, such as a GAS particle precipitation process (e.g. the Nektar™ SEDS™ process), it will be appreciated that solvent or solvent mixtures suitable for use in this process should be employed in steps (i) and (ii) above.

The total number of moles of calcium chloride added to the atorvastatin sodium in step (iii) is typically in the region of 1.0 to 1.5 times the number of moles of atorvastatin sodium.
Reaction of the solution of the sodium salt of atorvastatin and the solution of calcium chloride according to step (iii) may be accomplished by adding the solution of step (i) to the solution of step (ii). Precipitation of the resulting atorvastatin calcium may be prevented by maintaining a sufficiently high temperature, suitably in a range of from about 30°C to about 70°C, preferably about 60°C, and by stirring or otherwise agitating the mixture during addition. Where a mixture of solvents is used, the ratio of solvents will preferably be chosen such that precipitation does not occur during mixing. Removal of the sodium chloride may be achieved by filtering the mixture of step (iii).

EXAMPLE 12

In this Example, a solution of atorvastatin calcium is prepared by a process comprising the steps of:

1. **dissolving a known amount of the sodium salt of atorvastatin in a suitable solvent or mixture of solvents,**
2. **dissolving at least one equivalent of calcium chloride in a suitable solvent or mixture of solvents,**
3. **reacting the solution of step (i) with the solution of step (ii), to produce atorvastatin calcium and sodium chloride in solution,**
4. **spray drying the solution of step (iii) to produce solid particles comprising non-crystalline atorvastatin calcium (optionally with one or more excipients as defined above),**
5. **removing sodium chloride from the solid particles produced in step (iv), and**
6. **dissolving the solid particles comprising atorvastatin calcium, from step (v), in a suitable solvent.**

The solution prepared by this method may be used to produce non-crystalline atorvastatin by means of a solvent removal process, such as a GAS particle precipitation process (e.g. theNektar™ SEDS™ process), by spray drying or by any other suitable particle...
formation process. Alternatively, the method may be ended after step (iv), resulting in solid particles of atorvastatin calcium.

[00204] The solvents used in steps (i) and (ii) and the relative quantities of atorvastatin sodium and calcium chloride used, are selected on the same basis as in the method described for Example 11 above. The solvent mixture that results in step (iii), and the temperature and agitation conditions of the mixing process, must be such that no precipitation occurs at this stage. The solution from step (iii) may suitably be kept warm to avoid precipitation until the spray drying step (iv) is carried out. In the spray drying step, a method as described above may be used.

[00205] Removal of the sodium chloride according to step (v) may be effected by washing the solid particles produced in step (iv) with a suitable solvent. The solvent used to wash the solid particles in step (v) should be one in which atorvastatin calcium does not dissolve but in which sodium chloride is freely soluble. Preferably the solvent is water. The washing may be carried out at a temperature between about 0°C and about 25°C.

EXAMPLE 13

[00206] 100 g of atorvastatin sodium was obtained from Sai Life Sciences Limited of Hyderabad, India. Slurrying the atorvastatin sodium in MeOH/a water mixtures (as described for atorvastatin calcium to induce the formation of a crystalline form) did not enhance its crystallinity significantly. The atorvastatin sodium dissolved freely in MeOH resulting in a pink/purple solution.

[00207] The solubility of the actives was measured in pure MeOH and in a mixture of MeOH/Acetone (1:1) at room temperature (about 25°C) and at elevated (about 50°C) temperature. Both solvents (mixture) were previously used to process either pure atorvastatin calcium or co-formulated with hydroxypropyl cellulose. Solubilities are given in the Table below.

<table>
<thead>
<tr>
<th>Table 10</th>
<th>MeOH / mg·ml⁻¹</th>
<th>MeOH/Acetone (1:1) / mg·ml⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The solubility experiments show that the atorvastatin sodium salt is significantly less soluble than both the atorvastatin calcium salt and the CaCl₂·2H₂O. On average, solubility is very high. It can be seen that only processing at elevated temperatures allows to reach concentrations in excess of 225 mg·mL⁻¹ in MeOH/Acetone (1:1) or 450 mg·mL⁻¹ in MeOH to obtain the feed stock for processing. Despite the theoretically high concentrations it was difficult to dissolve the material fully to achieve a clear solution.

The reaction of atorvastatin sodium to the calcium salt in solution obeys the following reaction scheme (ATV = atorvastatin):

$$2 \text{ATV-Na} + \text{CaCl}_2·2\text{H}_2\text{O} \rightarrow (\text{ATV})_2\text{Ca} + 2\text{NaCl} + 2\text{H}_2\text{O}$$

Five separate experiments were carried out varying the reaction temperature, solvent system and batch size. An excess of 5 %w/w of CaCl₂·2H₂O was used in all experiments.

**EXAMPLE 14**

Atorvastatin calcium is made from atorvastatin sodium, in steps comprising

- Dissolve 2322 mg of ATV-Na in 10 mL of MeOH at about 25°C.
- Dissolve 310 mg of CaCl₂·2H₂O in 1.6 mL of MeOH at about 25°C.
- Slowly add CaCl₂·2H₂O solution to the ATV-Na solution under stirring while keeping the temperature at about 25°C.
- Filter solution after 15 minutes through a Büchner funnel.
Dry the residue in an oven at 70°C for 2 hours.

Rotary evaporate the solution to recover the ATV-Ca.

94 mg was recovered in the Büchner funnel and the residue consisted only of NaCl (40% theoretical).

From the rotary evaporator 2323 mg of ATV-Ca (100.5% theoretical) was recovered. Excellent recovery of ATV-Ca but low NaCl recovery is probably due to residual solubility in MeOH. Recovery in excess of 100% for ATV-Ca is probably due to some of the NaCl or unreacted ATV-Na co-precipitating during recovery.

**EXAMPLE 15**

Atorvastatin calcium is made from atorvastatin sodium, in steps comprising:

Dissolve 2322 mg of ATV-Na in 15 ml of MeOH/Acetone (1:1).

Dissolve 310 mg of CaCl₂·2H₂O in 2 ml of MeOH/Acetone (1:1).

Slowly add CaCl₂·2H₂O solution to the ATV-Na solution at room temperature.

Stir overnight for 15 hours.

Filter solution with a Büchner funnel.

Evaporate the solution on a rotary evaporator to obtain first crop.

Wash filter on Büchner funnel with MeOH/Acetone (1:1) and rotary evaporate the filtrate to get second crop.

Dry residue on filter in an oven at about 70°C for 2 hours.

250 mg of residue was recovered from the Büchner funnel. The residue was confirmed by XRPD to be NaCl (107% theoretical). The residue after rotary evaporation was determined to be amorphous. 2316 mg were recovered (100% theoretical). 1000 mg were slurried in MeOH/water (3:17) overnight to transform the amorphous powder into a
known polymorph of ATV-Ca. After 15 h of slurrying the powder was filtered on a Büchner funnel and evaporated to dryness in a rotary evaporator. The XRPD of the powder showed peaks of Form I ATV-Ca in a diffractogram, but a high percentage of amorphicity is still present, in contrast to that obtained using Form I generated from amorphous ATV-Ca. Additionally, a peak at approximately 8.5 2θ looks like ATV-Na starting material.

The reaction at room temperature in MeOH/Acetone (1:1) yielded an excellent recovery of NaCl and ATV-Ca. The low concentration of atorvastatin in solution (150 mg·ml⁻¹) may suggest an additional evaporation step to increase the concentration.

Example 16 is similar to Example 15, but at a higher concentration.

Dissolve the CaCl₂·2H₂O in 9 ml MeOH/Acetone (1:1).

Add the ATV-Na slowly as a solid.

Stir the mixture for 20 hours at about 25°C.

Other experimental steps are identical to those of Example 15.

92.3 mg of NaCl (39.4 % theoretical) and 783 mg of ATV-Ca (33.9 % theoretical) were recovered. The reaction mixture is a slurry in which the ATV-Na dissolves, reacting with the CaCl₂·2H₂O to produce ATV-Ca in solution. The high concentration initially leads to a slurry of ATV-Na which should dissolve during the reaction. Less desirable recoveries were observed in this experiment, probably due to high solution viscosity and incomplete reaction. It also appeared as if solid ATV-Ca was trapped in the slurry which had to be washed off the NaCl filter cake.

Example 17 is similar to Example 16, but at higher concentration and at elevated temperature with half the batch size.

Dissolve 1161 mg of ATV-Na in 4.5 ml of MeOH/Acetone (1:1) at about 30°C.
Add 155 mg of CaCl2·2H2O while stirring at about 300°C.

Stir the mixture for 1 hour at about 300°C.

Other experimental steps are identical to those of Example 14.

101.2 mg of NaCl (86.6 % theoretical) and 650 mg of ATV-Ca (56.3 % theoretical) were recovered.

Example 18 represents a four-fold scale-up to the previous Examples.

Dissolve 9290 mg of ATV-Na in 40 ml of MeOH/Acetone (1:1) at about 300°C.

Dissolve 1240 mg of CaCl2·2H2O in 6.4 ml of MeOH/Acetone (1:1) at about 300°C.

Slowly add CaCl2·2H2O solution to the ATV-Na solution under stirring while keeping the temperature at about 300°C.

Other experimental steps identical to those of Example 14.

1240 mg of NaCl (133 % theoretical) and 7900 mg of ATV-Ca (86 % theoretical) were recovered.

The recovered ATV-Ca was slurried in water/methanol to induce crystallization into a known polymorph. The XRPD of the powder showed the expected peaks of Form I ATV-Ca in the diffractogram, but again a high percentage of amorphicity is present in the recovered powder. Additionally, again a peak at approximately 8.5 2Θ looks like ATV-Na starting material.

In some embodiments, attempting to dissolve 225 mg·ml⁻¹ of ATV-Na in the solvent mixture lead to a gelatinous slurry, and more solvent had to be added to lower the concentration to 150 mg·ml⁻¹ before the CaCl2·2H2O was added. The reaction appears to
work well with good recovery of ATV-Ca. An excess of NaCl is recovered probably due to a co-precipitation of ATV-Ca or unreacted ATV-Na.

EXAMPLE 19

[00252] 1 mole of atorvastatin sodium salt is dissolved, with gentle warming, in 30 liters methanol (solution 1). 0.5 moles of calcium chloride are dissolved, with gentle warming, in 20 liters methanol (solution 2). Both solutions are brought to a temperature of about 60°C, until a clear solution was attained. Solution 2 is then added slowly to solution 1 while agitating vigorously. When addition is complete, the temperature is lowered to room temperature and then filtered to remove precipitated sodium chloride.

EXAMPLE 20

[00253] 1 mole of atorvastatin sodium salt is dissolved, with gentle warming, in 30 liters methanol (solution 1). 0.5 moles of calcium chloride are dissolved, with gentle warming, in 20 liters water (solution 2). Both solutions are brought to a temperature of about 60°C, then solution 2 is added slowly to solution 1 while agitating vigorously and maintaining the temperature. When addition is complete, the solution is spray-dried and the solid particles collected. The particles are then washed with water at about 15°C to remove sodium chloride. The washed, solid particles comprising non-crystalline atorvastatin calcium may then be dissolved in a suitable solvent for further processing.

STABLE ORAL FORMULATION EXAMPLES

[00254] Two formulations, designated Examples A and B, were manufactured with the SCF processed atorvastatin calcium, without excipient (pure). One formulation, designated Example C was manufactured using the SEDS™ processed atorvastatin calcium:HPC (9:1)(w/w). The powder for this tablet Example is as described in Table 7, sample 4.

EXAMPLE A

[00255] In step (i), polysorbate 80 was dissolved in water under stirring and heating at 50°C to form a clear solution. HPC (as Klucel® LF) was added to the solution with stirring, then additional water was added. The HPC was allowed to hydrate for 4 hours. Isopropyl
Alcohol (IPA) was added just before use. (ii) Calcium carbonate, Croscarmellose sodium, Lactose monohydrate, MCC PH101 were sifted through a 40 mesh sieve and collected in a stainless steel container.

(ii) The sifted ingredients of step (ii) and SEDSTM processed pure atorvastatin calcium were loaded into a Braun mixer and mixed for 5 minutes at a speed of 7. (iv) The mixture of step (iii) and solution of step (i) was granulated over a period of about 2-4 minutes to form a wet mass. (v) The wet mass was sieved through 12 mesh sieve and dried using fluid bed processor at about 50-60°C for about 30 minutes to achieve the desired loss on drying (LOD) of 2-5% w/w, followed by sifting using a 20 mesh sieve. (vi) Croscarmellose sodium, and pigment blend yellow were sifted through 40 and 80 mesh sieves respectively, mixed in a stainless steel bowl, and added to the sized granules of step (v) in a drum blender with mixing for 10 minutes at about 22 rpm. (vii) Mg-stearate was sifted through a 60 mesh sieve and added to blend of step (vi) in the drum blender and mixed for 2 minutes at about 22 rpm. (viii) The blend of step (vii) was compressed into tablets using 21 X 9 mm capsule shaped standard concave punches.

EXAMPLES B and C

(iii) The mixture of step (ii) and solution of step (i) was granulated with stirring over a period of about 2-5 minutes to form a wet mass. (iv) The wet mass was sieved through a 12 mesh sieve and dried using a tray drier at about 60°C for between about 2-7 hours to achieve the desired LOD of 2-5% w/w, followed by sizing the dried granules using a 20 mesh sieve. (v) Lactose DCL 15, MCC Avicel® PH 102 and sodium starch glycolate was sifted through a 40 mesh sieve, added to sized granules of step (iv) in the drum blender and mixed for 10 minutes at 22 rpm. For Example C, pigment blend yellow was sized through a 60 mesh screen and added to the mixture. (vi) Mg-stearate was sifted through a 60 mesh sieve and added to blend of step (v) in the drum blender and mixed for 2 minutes at about
22 rpm. (vii) The blend of step (vi) was compressed into tablets using either 18.5 x 8 mm oval shaped standard concave punches with score-lines on both sides, or one side embossed and other side plain, using a rotary compression machine.

[00259] The weight percentage of ingredients of each of the formulations is disclosed in the Table 11 below:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity mg/tab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example A</td>
</tr>
<tr>
<td><strong>Intra-granular</strong></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (100)%</td>
<td>82.87</td>
</tr>
<tr>
<td>Atorvastatin:HPC (90%:10%)</td>
<td>-</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>5.01</td>
</tr>
<tr>
<td>Croscarmellose Sodium (AC-DI-SOL from Signet)</td>
<td>60.45</td>
</tr>
<tr>
<td>Hydroxy propyl cellulose (HPC Klucel LF from Signet)</td>
<td>25.1</td>
</tr>
<tr>
<td>Lactose Monohydrate (Pharmatose 200M from DMV)</td>
<td>268.54</td>
</tr>
<tr>
<td>Microcrystalline cellulose (MCC Avicel PH 101 from Signet)</td>
<td>491.75</td>
</tr>
<tr>
<td>Calcium carbonate (From Jaimurthy)</td>
<td>275.7</td>
</tr>
<tr>
<td><strong>Extra-granular</strong></td>
<td></td>
</tr>
<tr>
<td>Croscarmellose Sodium (AC-DI-SOL from Signet)</td>
<td>37.6</td>
</tr>
<tr>
<td>Pigment blend yellow (From Colorcon)</td>
<td>4.00</td>
</tr>
<tr>
<td>Lactose Monohydrate (Pharmatose DCL 15)</td>
<td>-</td>
</tr>
<tr>
<td>Microcrystalline cellulose (MCC Avicel pH 102)</td>
<td>-</td>
</tr>
<tr>
<td>Sodium starch glycollate (Primogel from Avebe)</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium stearate (From Brooks)</td>
<td>6.98</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1258</td>
</tr>
</tbody>
</table>
Dissolution studies:

[00260] The three tablet dosage of Examples A, B and C were tested for drug release in pH 6.8 buffer medium and degassed water using the USP II dissolution apparatus at 50 RPM. The release profile is compared with that of the commercially available LIPITOR® tablets. The results of the dissolution profiles of the LIPITOR® tablets are shown in Tables 12 (pH 6.8) and 13 (degassed water). The dissolution profiles of the Nektar tablet dosage formulations of Example A are shown below in Tables 14 (pH 6.8) and 15 (degassed water). The dissolution profiles of the Nektar tablet dosage formulations of Example B are shown below in Tables 16 (pH 6.8) and 17 (degassed water). The dissolution profiles of the Nektar tablet dosage formulations of Example C are shown below in Tables 18 (pH 6.8) and 19 (degassed water).

[00261] The data in the tables is an average of multiple individual tablet runs. Thus tables 12 and 13 represent an average of eighteen runs. Table 14 represent an average of twelve runs, while Table 15 represents six runs. Tables 16, 17, and 18 represent an average of twelve runs, and Table 19 represents an average of six runs.

<table>
<thead>
<tr>
<th>Time (Mins.)</th>
<th>Average</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>62.6</td>
<td>52.9</td>
<td>73.2</td>
<td>6.9</td>
<td>11.0</td>
</tr>
<tr>
<td>15</td>
<td>78.8</td>
<td>68.3</td>
<td>89.4</td>
<td>5.4</td>
<td>6.9</td>
</tr>
<tr>
<td>30</td>
<td>83.8</td>
<td>70.1</td>
<td>94.5</td>
<td>5.2</td>
<td>6.2</td>
</tr>
<tr>
<td>45</td>
<td>87.1</td>
<td>75.7</td>
<td>97.2</td>
<td>5.1</td>
<td>5.8</td>
</tr>
<tr>
<td>60</td>
<td>89.5</td>
<td>76.6</td>
<td>98.0</td>
<td>4.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Recovery</td>
<td>100.7</td>
<td>93.5</td>
<td>109.3</td>
<td>4.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Table 12 – Lipitor® pH 6.8 Phosphate

<table>
<thead>
<tr>
<th>Time (Mins.)</th>
<th>Average</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>62.6</td>
<td>52.9</td>
<td>73.2</td>
<td>6.9</td>
<td>11.0</td>
</tr>
<tr>
<td>15</td>
<td>78.8</td>
<td>68.3</td>
<td>89.4</td>
<td>5.4</td>
<td>6.9</td>
</tr>
<tr>
<td>30</td>
<td>83.8</td>
<td>70.1</td>
<td>94.5</td>
<td>5.2</td>
<td>6.2</td>
</tr>
<tr>
<td>45</td>
<td>87.1</td>
<td>75.7</td>
<td>97.2</td>
<td>5.1</td>
<td>5.8</td>
</tr>
<tr>
<td>60</td>
<td>89.5</td>
<td>76.6</td>
<td>98.0</td>
<td>4.6</td>
<td>5.1</td>
</tr>
<tr>
<td>Recovery</td>
<td>100.7</td>
<td>93.5</td>
<td>109.3</td>
<td>4.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Table 13 – Lipitor® Degassed water
### Table 1 - Example B
in degassed water

<table>
<thead>
<tr>
<th>Time (Mins.)</th>
<th>Average</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>52.8</td>
<td>30.1</td>
<td>75.4</td>
<td>12.3</td>
<td>23.3</td>
</tr>
<tr>
<td>15</td>
<td>87.5</td>
<td>81.2</td>
<td>95.3</td>
<td>4.8</td>
<td>5.5</td>
</tr>
<tr>
<td>30</td>
<td>90.9</td>
<td>83.6</td>
<td>99.2</td>
<td>4.3</td>
<td>4.7</td>
</tr>
<tr>
<td>45</td>
<td>92.4</td>
<td>85.9</td>
<td>99.7</td>
<td>3.8</td>
<td>4.1</td>
</tr>
<tr>
<td>60</td>
<td>93.7</td>
<td>85.4</td>
<td>99.1</td>
<td>3.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Recovery</td>
<td>103.5</td>
<td>97.6</td>
<td>108.2</td>
<td>3.9</td>
<td>3.7</td>
</tr>
</tbody>
</table>

### Table 14 - Example A
pH 6.8 phosphate

<table>
<thead>
<tr>
<th>Time (Mins.)</th>
<th>Average</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>54.5</td>
<td>48.6</td>
<td>63.1</td>
<td>4.8</td>
<td>8.7</td>
</tr>
<tr>
<td>15</td>
<td>73.8</td>
<td>65.3</td>
<td>78.0</td>
<td>4.7</td>
<td>6.4</td>
</tr>
<tr>
<td>30</td>
<td>81.4</td>
<td>74.7</td>
<td>86.0</td>
<td>3.7</td>
<td>4.6</td>
</tr>
<tr>
<td>45</td>
<td>85.7</td>
<td>81.1</td>
<td>92.9</td>
<td>3.4</td>
<td>4.0</td>
</tr>
<tr>
<td>60</td>
<td>88.0</td>
<td>81.4</td>
<td>93.3</td>
<td>5.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Recovery</td>
<td>99.7</td>
<td>97.0</td>
<td>101.6</td>
<td>4.9</td>
<td>4.9</td>
</tr>
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</table>

### Table 15 - Example A
degassed H2O

<table>
<thead>
<tr>
<th>Time (Mins.)</th>
<th>Average</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>65.0</td>
<td>55.1</td>
<td>68.9</td>
<td>5.1</td>
<td>7.8</td>
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<tr>
<td>15</td>
<td>81.4</td>
<td>79.3</td>
<td>84.5</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>30</td>
<td>86.0</td>
<td>83.1</td>
<td>90.7</td>
<td>3.2</td>
<td>3.7</td>
</tr>
<tr>
<td>45</td>
<td>90.9</td>
<td>87.7</td>
<td>95.0</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>60</td>
<td>94.6</td>
<td>92.7</td>
<td>96.4</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Recovery</td>
<td>100.2</td>
<td>96.8</td>
<td>102.4</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

### Table 16 - Example B
pH 6.8 phosphate

<table>
<thead>
<tr>
<th>Time (Mins.)</th>
<th>Average</th>
<th>Min.</th>
<th>Max.</th>
<th>SD</th>
<th>RSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>61.2</td>
<td>47.0</td>
<td>73.7</td>
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<td>15</td>
<td>78.2</td>
<td>61.9</td>
<td>92.4</td>
<td>8.7</td>
<td>11.1</td>
</tr>
<tr>
<td>30</td>
<td>83.0</td>
<td>67.0</td>
<td>92.7</td>
<td>7.4</td>
<td>9.0</td>
</tr>
<tr>
<td>45</td>
<td>87.2</td>
<td>77.5</td>
<td>94.0</td>
<td>5.2</td>
<td>5.9</td>
</tr>
<tr>
<td>60</td>
<td>88.9</td>
<td>77.3</td>
<td>96.9</td>
<td>6.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Recovery</td>
<td>97.0</td>
<td>93.0</td>
<td>103.5</td>
<td>3.6</td>
<td>3.8</td>
</tr>
</tbody>
</table>

### Table 17 - Example B
in degassed water
Tables 20-22 present various standard tablet parameters, and acceptance criteria. Tablets made in accordance with Examples A-C herein, in an 80 mg dosage, were tested immediately after preparation, and again after one month’s storage at the indicated conditions. The tablets were stored in sealed HDPE containers with a silica gel desiccant.

Table 20 presents results for tablets made in accordance with Example A, and stored at about 25°C and 60% RH. Table 21 presents results for tablets made in accordance with Example B, and Table 22 presents results for tablets made in accordance with Example C. The storage conditions for the tablets of Examples B and C were about 10°C and 60% RH. The results
show that the dissolution times of the formulations in accordance with one or more embodiments of the present invention are as good as, or better than, the comparable Lipitor® tablets, on a dose per dose basis.

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Acceptance criteria</th>
<th>Initial-Results</th>
<th>1 month-Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Yellow colored, biconvex capsule shaped, uncoated tablet plain on both the sides.</td>
<td>Yellow colored, biconvex capsule shaped, uncoated tablet plain on both the sides.</td>
<td>Yellow colored, biconvex capsule shaped, uncoated tablet plain on both the sides.</td>
</tr>
<tr>
<td>Average weight</td>
<td>1280 mg ± 3.0%</td>
<td>1276.7 mg</td>
<td>1273.1 mg</td>
</tr>
<tr>
<td>Content Uniformity</td>
<td>Each dosage unit should be between 85% - 115% of the label claim and RSD is less than or equal to 6.0%</td>
<td>Completes</td>
<td>Completes</td>
</tr>
<tr>
<td>Disintegration Time (minutes)</td>
<td>NMT 15 minutes</td>
<td>37 seconds to 49 seconds</td>
<td>40 seconds to 48 seconds</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>Read and Record</td>
<td>100 N to 112 N</td>
<td>102 N to 119 N</td>
</tr>
<tr>
<td>Loss on Drying (% w/w)</td>
<td>For information purpose</td>
<td>-</td>
<td>1.19% w/w</td>
</tr>
<tr>
<td>Dissolution of Atorvastatin in Degassed water at 30 mins</td>
<td>NLT Q=65%</td>
<td>86.0%</td>
<td>83.0%</td>
</tr>
<tr>
<td>Dissolution of Atorvastatin in pH 6.8 Buffer at 30 mins</td>
<td>For information purpose</td>
<td>81.4%</td>
<td>87.8%</td>
</tr>
<tr>
<td>Assay (% Label claim)</td>
<td>90%-110% of Labeled amount</td>
<td>100.1%</td>
<td>100.2%</td>
</tr>
<tr>
<td>Related substances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Max</td>
<td>NMT 2.0%</td>
<td>0.23%</td>
<td>0.16%</td>
</tr>
<tr>
<td>Total Imp</td>
<td>NMT 4.0%</td>
<td>0.77%</td>
<td>0.75%</td>
</tr>
<tr>
<td>Lactone (RRT 1.88)</td>
<td>NMT 2.0%</td>
<td>0.33%</td>
<td>0.10%</td>
</tr>
<tr>
<td>Oxd1 (RRT 2.28)</td>
<td>NMT 2.0%</td>
<td>0.23%</td>
<td>0.18%</td>
</tr>
<tr>
<td>Oxd2 (RRT 2.75)</td>
<td>NMT 2.0%</td>
<td>0.09%</td>
<td>0.16%</td>
</tr>
<tr>
<td>Oxd3 (RRT 4.3 - 4.7)</td>
<td>NMT 2.0%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NMT = Not More Than  
NLT = Not Less Than
Table 21
Tablet Example B

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Acceptance criteria</th>
<th>Initial-Results</th>
<th>1 month-Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>White to off white, biconvex, oval shaped, uncoated tablet having a score line on both the sides.</td>
<td>White to off white, biconvex, oval shaped, uncoated tablet having a score line on both the sides.</td>
<td>White to off white, biconvex, oval shaped, uncoated tablet having a score line on both the sides.</td>
</tr>
<tr>
<td>Average weight</td>
<td>818.35 ± 3.0%</td>
<td>812.7 mg</td>
<td>818.39 mg</td>
</tr>
<tr>
<td>Content Uniformity</td>
<td>Each dosage unit should be between 85% - 115% of the label claim and RSD is less than or equal to 6.0%</td>
<td>Complies</td>
<td>Complies</td>
</tr>
<tr>
<td>Disintegration time (minutes)</td>
<td>NMT 15 minutes</td>
<td>41 seconds-49 seconds</td>
<td>50 seconds-59 seconds</td>
</tr>
<tr>
<td>Hardness (N)</td>
<td>Read &amp; Record</td>
<td>72.92N</td>
<td>73.87N</td>
</tr>
<tr>
<td>Loss on Drying (% w/w)</td>
<td>For information purpose</td>
<td>-</td>
<td>1.0% w/w</td>
</tr>
<tr>
<td>Dissolution of Atorvastatin in Al 30 mins</td>
<td>NLT Q=65%</td>
<td>75.2%</td>
<td>80.3%</td>
</tr>
<tr>
<td>Dissolution of Atorvastatin in Al 30 mins</td>
<td>For information purpose</td>
<td>83.0%</td>
<td>88.3%</td>
</tr>
<tr>
<td>Assay (% Label claim)</td>
<td>90%-110% of Labeled amount</td>
<td>101.1 %</td>
<td>100.3%</td>
</tr>
<tr>
<td>Related substances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Max</td>
<td>NMT 2.0%</td>
<td>0.21%</td>
<td>0.45%</td>
</tr>
<tr>
<td>Total Imp</td>
<td>NMT 4.0%</td>
<td>0.56%</td>
<td>1.03%</td>
</tr>
<tr>
<td>Lactone (RRT 1.88)</td>
<td>NMT 2.0%</td>
<td>0.11%</td>
<td>0.45%</td>
</tr>
<tr>
<td>Oxd1 (RRT 2.28)</td>
<td>NMT 2.0%</td>
<td>0.21%</td>
<td>0.45%</td>
</tr>
<tr>
<td>Oxd2 (RRT 2.75)</td>
<td>NMT 2.0%</td>
<td>0.10%</td>
<td>0.14%</td>
</tr>
<tr>
<td>Oxd 3 (RRT 4.3 – 4.7)</td>
<td>NMT 2.0%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Pharmacokinetic Trials

[00263] The tablets made in accordance with Examples A-C were tested against a commercially available LIPITOR® tablet in a randomized, open-label, four-treatment, four-period, single-dose crossover comparative pharmacokinetics trial. Healthy human adult male subjects were administered the atorvastatin tablet (80 mg) of the present invention and the LIPITOR® tablet (80 mg).

[00264] After a supervised overnight fast, subjects received a single oral dose of the assigned formulation, with 240 mL of water. At least 7 days between doses were required for washout. Thirty-six subjects completed all 4 arms. The subjects completing all 4 arms were used in the pharmacokinetic assessment. Blood samples were collected pre-dose and at
0.25 (15 min), 0.5 (30 min), 0.75 (45 min), 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hour post dose to define the plasma atorvastatin concentration-time profiles. Differences between least square means (LSM; obtained from ANOVA) were calculated for log-transformed AUCo-t, AUCo-∞ and Cmax values and visually compared between treatments. Ratios of means are expressed in percentage by taking the anti-log value of difference of LSM. Results are presented in Table 23 below.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Parameter</th>
<th>Mean</th>
<th>Relative Bioavailability</th>
<th>Cl 90 Lower</th>
<th>Cl 90 Lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet Example A</td>
<td>Cmax</td>
<td>65.2</td>
<td>86.1</td>
<td>69.26</td>
<td>106.89</td>
</tr>
<tr>
<td></td>
<td>AUCo-∞</td>
<td>393.4</td>
<td>119.1</td>
<td>105.59</td>
<td>134.25</td>
</tr>
<tr>
<td>Tablet Example B</td>
<td>Cmax</td>
<td>86.2</td>
<td>113.8</td>
<td>91.73</td>
<td>141.22</td>
</tr>
<tr>
<td></td>
<td>AUCo-∞</td>
<td>409.9</td>
<td>124.1</td>
<td>110.08</td>
<td>139.81</td>
</tr>
<tr>
<td>Tablet Example C</td>
<td>Cmax</td>
<td>84.6</td>
<td>111.7</td>
<td>89.93</td>
<td>138.78</td>
</tr>
<tr>
<td></td>
<td>AUCo-∞</td>
<td>399.8</td>
<td>121.0</td>
<td>107.32</td>
<td>136.44</td>
</tr>
<tr>
<td>LIPITOR®</td>
<td>Cmax</td>
<td>75.8</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>AUCo-∞</td>
<td>330.4</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

The mean plasma atorvastatin concentration-time profiles for the three tablet formulation comprising non-crystalline atorvastatin calcium, made in accordance with Examples A-C herein are shown in Figure 10 and are compared to those of a commercially-available LIPITOR® tablet. In the Figures, the curves labeled with circle symbols represent the LIPITOR® reference formulation. The curves labeled with the square symbols represent the formulation of the present invention designated X1 (Example A). The curves labeled with the diamond symbols represent the formulation of the present invention designated Y (Example B), and the curves labeled with the triangle symbols represent the formulation of the present invention designated Z1 (Example C). It can be seen that the concentration-time profiles closely match between formulations.
EXAMPLE D

Tablet Dosage forms using non-crystalline atorvastatin co-fomulated with a glycine amino acid excipient were prepared by a supercritical particle precipitation process as described herein and, with particular reference to Example 4. The resulting bulk powder was granulated using a wet granulation process, under substantially identical conditions and using substantially identical materials as described for tablet Example C. However, a non-crystalline powder comprising atorvastatin:sodium methoxide:glycine (82:8:10) made by the SEDS™ particle precipitation process was substituted for the atorvastatin: HPC shown in Table 11. A first portion of the granulated formulation was retained in granule form and comprised the intra-granular material, and a second portion compressed into tablets, including the intra- and extra-granular material. The tablets were packaged, in a dry box, in amber vials containing 2 tablets and a desiccant, in turn packaged inside a sealed foil pouch. The samples were then stored at about 25°C and about 60%RH. Samples were pulled after one and two months, and analyzed for chemical stability by HPLC. Results are shown in Tables 24 and 25 below. Table 24 shows the stability data for the granules comprising atorvastatin:sodium methoxide:glycine (82-8:10), polysorbate 80 and croscarmellose sodium, before tabletting. Table 25 shows the stability data for the entire tabletted formulation, including both intra-granular and extra-granular materials.

<table>
<thead>
<tr>
<th>Time</th>
<th>Peak Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amide</td>
</tr>
<tr>
<td>T = 0m</td>
<td>0.076</td>
</tr>
<tr>
<td>T = 1m</td>
<td>0.088</td>
</tr>
<tr>
<td>T = 2m</td>
<td>0.087</td>
</tr>
</tbody>
</table>
### Table 25
**Atorvastatin:sodium methoxide:glycine (82:8:10)**

Wet granulated
Extra Granular (tablet)

<table>
<thead>
<tr>
<th>Time</th>
<th>Amide</th>
<th>Desfluoro</th>
<th>Diastereo</th>
<th>Atorvastatin</th>
<th>O-methyl</th>
<th>Lactone</th>
<th>Impurity X</th>
<th>OX1</th>
<th>OX2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T = 0m</td>
<td>0.083</td>
<td>0.102</td>
<td>0.024</td>
<td>99.570</td>
<td>0.018</td>
<td>0.027</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>T = 1m</td>
<td>0.078</td>
<td>0.092</td>
<td>0.025</td>
<td>99.683</td>
<td></td>
<td>0.022</td>
<td></td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>T = 2m</td>
<td>0.088</td>
<td>0.097</td>
<td>0.025</td>
<td>99.715</td>
<td></td>
<td>0.035</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**EXAMPLE E**

Additional tablet dosage forms using non-crystalline atorvastatin co-fomulated with the glycine amino acid excipient were prepared by a SEDSTM supercritical particle precipitation process as described herein and, with particular reference to powder formulation Example 4. The powder was formulated as a tablet, using the materials shown in the following Table 26. The resulting bulk powder was tabletted using a roller-compaction process. The tablets were prepared in a dry box, in amber vials containing 2 tablets and a desiccant, and then packaged inside a sealed foil pouch. The samples were stored at about 25°C and about 60% RH. Samples were pulled after one and two months, and analyzed for chemical stability by HPLC.
A first portion of the granulated formulation was retained in granule form and comprised the intra-granular material, and a second portion compressed into tablets, including the intra- and extra-granular material. The tablets were packaged, in a dry box, in amber vials containing 2 tablets and a desiccant, in turn packaged inside a sealed foil pouch. The samples were then stored at about 25°C and about 60% RH. Samples were pulled after one and two months, and analyzed for chemical stability by HPLC. Results are shown in Tables 27 and 28 below. Table 27 shows the stability data for the granules comprising the intra-granular materials, and Table 28 shows the stability data for the entire tabletted formulation, including both intra-granular and extra-granular materials.
EXAMPLE F

Any of the above examples may be administered to a patient (human or animal), for a condition treatable thereby, and particularly to treat a patient having hyperlipidemia and/or hypercholesterolemia. For example, the formulations described herein may be formulated into a tablet containing 10, 20, 40, 80 or more mg or more of atorvastatin. This amount may be altered in order to achieve a desired therapeutic profile.

Some of the materials used in making the formulations herein were as follow:
Analytical techniques

The analytical techniques employed with respect to some of Examples were as follow:

Differential scanning calorimetry (DSC)

DSC was used to determine glass transition temperatures. This technique provides a measure of the glass transition characteristic of amorphous materials. In addition the absence of a melting point is indicative of the lack of three dimensional order characteristic of crystalline materials. A Perkin-Elmer™ DSC 7 (Perkin-Elmer Ltd, UK) was used. 1-5 mg samples were examined in sealed, crimped aluminium pans, under an atmosphere of nitrogen.

X-ray (powder) diffraction (XRD/XRPD)

The amorphous nature of the sample was characterized by XRPD. The amorphous nature of the sample is indicated by the lack of diffraction peaks in the diffraction pattern which is characteristic of crystalline materials. Samples were analysed on a D5000 XRD (Siemens, Germany) between 2 and 40° 2Θ at a scan rate of 0.02 degrees per second.
Dynamic Vapor Sorption (DVS)

[00274] This method was used to measure moisture sorption isotherms, that is the equilibrium uptake of moisture as a function of the relative humidity. The moisture sorption isotherm of each powder at 25°C was measured using a dynamic vapor sorption (DVS) instrument made by Surface Measurement Systems, UK. This instrument gravimetrically measures uptake and loss of water vapor on a substrate by means of a recording microbalance with a resolution of ±0.1 µg and a daily drift of approximately ± 1 µg. In the first step of the experimental run, the sample was dried at 25°C and 0%RH for at least 300 minutes, in an attempt to bring the sample to near zero wt% H2O. Then, the instrument was programmed to increase in RH from 0%, 2%, then 5% to 90% RH in steps of 5% RH and decrease the RH in steps of 5%RH from 90% to 0% RH. A criterion of dm/dt =0.005%/min was chosen for the system to hold at each RH step before proceeding to the next RH step. Sample mass ranged between approximately 15 mg.

Thermogravimetric analysis

[00275] This method was used to assess changes in water content of the product during storage by measuring the loss of mass on heating. The sample weight loss at elevated temperatures was measured using TGA-2950 instrument made by TA Instruments. The sample was immediately heated, in order to minimize the initial dehydration by the dry nitrogen gas, from room temperature to 250°C at 2°C/min and or 0.2C/min. The % weight loss was calculated using the TA software.

UV spectrophotometry

[00276] The weight fraction of drug in samples was measured with an Ultrospec™ 4000 spectrophotometer (Pharmacia Biotech, Cambridge, England), from reconstituted solutions of the samples.

[00277] Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification. Furthermore, certain terminology has been used
for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.

LYOPHILIZATION EXAMPLE

[00278] Purified crystalline atorvastatin Na is obtained in the normal course and dissolved in a mixture of 50% methanol/50% water v/v. For each mole of atorvastatin present, two moles of tricalcium citrate are added to the solution to convert the atorvastatin Na to atorvastatin hemicalcium. The solution is then placed in lyophilization vials and cooled to about -40°C, after which, the solvents are removed under vacuum to yield an amorphous atorvastatin hemicalcium mixture with a sodium salt of citric acid.
We claim:

1. A method of preparing a non-crystalline atovastatin salt comprising
   (A) (i) preparing a desired salt of atorvastatin in solution in a first solvent; and
   (ii) optionally adding at least one initial stabilizer for said atorvastatin salt to the
   solution of step (A)(i) to yield a second solution; or
   (B) (i) optionally preparing a solution of said initial stabilizer in a second solvent,
   which may be the same as said first solvent, to form a third solution; and
   (ii) adding said atorvastatin salt to said third solution of step (B)(i) to yield a
   fourth solution; or
   (C) (i) following step (A)(i);
   (ii) following step (B)(i); and
   (iii) combining the result of steps (C)(i) and (C)(ii) to yield a fifth solution; and

   removing the respective first and second solvents from said second, fourth, and fifth
   solutions via a technique selected from the group consisting of one or more of
   lyophilization, spray drying, supercritical fluid solvent extraction, and near critical fluid
   extraction.

2. The method of claim 1 wherein said solvent removal step utilizes at least a lyophilization
   step.
3. The method of claim 2 further comprising adding an anti-solvent to said second, fourth, and fifth solutions prior to said lyophilization so that the solution subjected to lyophilization comprises the desired atorvastatin salt, said anti-solvent, and at least one of said first and second solvents, and optionally said stabilizer.

4. The method of claim 1 wherein said atorvastatin salt utilized in claim 1 step (A)(i) and claim 1 step (B)(ii) is an atorvastatin Ca salt.

5. The method of claim 4 wherein said atorvastatin Ca salt is atorvastatin hemicalcium.

6. The method of claim 1 wherein said atorvastatin salt is prepared from atorvastatin free acid, atorvastatin lactone, or another atorvastatin salt or mixtures thereof.

7. The method of claim 6 wherein said atorvastatin salt is a non-Na salt of atorvastatin and is prepared from atorvastatin Na.

8. The method of claim 7 wherein said non-Na atorvastatin salt is an atorvastatin Ca salt and is prepared by reacting atorvastatin Na with a calcium salt to result in said atorvastatin Ca salt and Na⁺ and said atorvastatin Ca salt is separated from said Na⁺ to result in an atorvastatin Ca solution that is used as is for said step (A)(i) either or both of said step (B)(U).

9. The method of claim 1 wherein said solvent in said step (A)(i) is an organic solvent and said addition of atorvastatin salt in said step (B)(U) is addition of atorvastatin salt in an organic solvent.

10. The method of claim 6 wherein said salt of atorvastatin salt is prepared by reacting said atorvastatin free acid, said atorvastatin lactone, or said another atorvastatin salt or
mixtures thereof with a basic salt of a cation selected from an alkali metal and alkaline earth metal, said cation being the desired cation of the atorvastatin salt being prepared.

11. The method of claim 10 wherein said basic salt of said cation is a hydroxide or an oxide or carbonate.

12. A non-crystalline solid atorvastatin salt prepared by the process of claim 1.

13. The non-crystalline solid atorvastatin salt of claim 12 which is an atorvastatin Ca salt.

14. The non-crystalline solid atorvastatin salt of claim 13 which is atorvastatin hemicalcium.

15. A non-crystalline solid atorvastatin salt having a bulk density of from about 0.05 to about 0.4 g/ml.

16. A non-crystalline solid atorvastatin salt having a mean particle size of about 0.5 microns to about 50 microns.

17. The salt of claim 16 wherein said mean particle size is about 15 to about 35 microns.

18. The salt of claim 16 wherein said mean particle size is about 20 microns to about 30 microns.

19. The salt of claim 16 wherein said mean particle size is about 25 microns.

20. A method of making a formulation of a non-crystalline solid atorvastatin salt comprising formulating the atorvastatin salt prepared by the process of claim 1 together with at least one excipient selected from group consisting of
   (a) one or more formulation stabilizers,
   (b) one or more diluents,
   (c) one or more disintegrants,
(d) one or more surfactants, and
(e) one or more lubricants,
to form a formulation mixture and preparing a dosage form from said formulation mixture.

21. A non-crystalline solid atorvastatin salt dosage form comprising
a non-crystalline solid atorvastatin salt and at least one pharmaceutical formulation excipient or carrier component

22. The non-crystalline solid atorvastatin salt dosage form of claim 21 wherein said at least one pharmaceutical formulation excipient or carrier component is selected from the group consisting of:
(a) one or more formulation stabilizers,
(b) one or more diluents,
(c) one or more disintegrants,
(d) one or more surfactants,
(e) one or more lubricants, and
(X) one or more binders.

23. The non-crystalline solid atorvastatin salt dosage form of claim 22 wherein said formulation stabilizers do not include stabilizers selected from the group consisting of calcium hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and magnesium aluminum hydroxides.

24. The non-crystalline solid atorvastatin salt dosage form of claim 22 wherein said formulation stabilizers do not include stabilizers selected from the group consisting of hydroxides and carbonates of alkali metals and alkaline earth metals and magnesium silicates and aluminates.

25. The non-crystalline solid atorvastatin salt dosage form of claim 22 wherein said formulation stabilizers do not include basifying stabilizers.
26. The dosage form of claim 22 wherein said stabilizers are selected from the group consisting of salts of organic acids.

27. The dosage form of claim 22 wherein said diluents are selected from the group consisting of cellulose, saccharides, disaccharides and polysaccharides, trisodium citrate, dicalcium phosphate, tricalcium phosphates and mixtures thereof.

28. The dosage form of claim 22 wherein said disintegrants are selected from the group consisting of crospovidone, Ac-Di-Sol, Explotab, and mixtures thereof.

29. The dosage form of claim 22 wherein said surfactants are selected from the group consisting of polysorbates.

30. The dosage form of claim 22 wherein said lubricants are selected from the group consisting of stearic acid, behenic acid, alkali metal salts of thereof, alkaline earth metal salts thereof, mono-, di- and tri- glycerides thereof, and other steryl and behenyl complexes, and mixtures thereof.

31. The dosage form of claim 22 wherein said binders are selected from the group consisting of polyvinyl pyrrolidones, starch, pregelatinized starch, carboxy cellulose, and mixtures thereof.

32. A process to density non-crystalline solid atorvastatin salt of claim 12 optionally in combination with one or more binders and optionally with one or more diluents comprising subjecting the non-crystalline solid atorvastatin salt of claim 12 optionally in admixture with one or more of (a) one or more binders and (b) one or more diluents to at least one procedure selected from (i) roller compaction, (ii) slugging, (iii) wet granulation, and (iv) fluidized bed granulation.
33. The process of claim 32 wherein said wet granulation is an aqueous granulation.

34. The process of claim 32 wherein said wet granulation is a non-aqueous granulation.

35. The process of claim 32 wherein said wet granulation is a high shear wet granulation.

36. The process of claim 32 wherein said wet granulation is a low shear wet granulation.

37. The process of claim 32 wherein said granulation is conducted using a C_{1-4} alcohol as a granulation solvent.

38. The process of claim 37 wherein said alcohol granulation solvent is about 50 to about 90% alcohol.

39. The dosage form of claim 21 which is selected from the group consisting of a tablet, a capsule, an oral disintegrating tablet, and a dispersible sachet, each of which a release rate which is selected from immediate release, sustained release, delayed release, and combinations thereof.

40. A composition comprising the atorvastatin of claim 12, an excipient, one or more fillers, optionally one or more disintegrants, optionally one or more compressibility enhancers, optionally one or more diluents, optionally one or more lubricants, and optionally one or more anti-degradants, wherein the formulation is substantially absent the addition of any of the additives selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

41. The composition of claim 40 wherein said excipient comprises at least one material selected from oligomeric and polymeric substances.
42. The composition of claim 40 wherein said excipient is selected from the group consisting of polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), vinylpyrrolidone/vinyl acetate copolymer (PVP-VA), vinylpyrrolidone/vinyl acetate (40:60) copolymer in a VArVP of 60:40 (PVP-VA 64), polyethylene oxide (PEO), cellulose, starch, polyethylene glycol (PEG), hydroxypropyl cellulose (HPC), hydroxyl propyl methyl cellulose (HPMC), and their copolymers and derivatives; carbohydrates; polyols; sugars; oligo saccharides, proteins, peptides, and amino acids; lipids and modified lipids, known glass formers; and mixtures thereof.

43. The composition of claim 40 wherein said excipient is selected from the group consisting of alkylcellulose, hydroxyalkyl celluloses, carboxymethylcellulose, sodium carboxymethyl cellulose, microcrystalline cellulose, microfine cellulose, acacia, tragacanth, alginates, alginic acid, starch, agar, carrageenan, xanthan gum, chitosan, gelatin, guar gum, pectin, amylase or lecithin; homo- and co-polymers of hydroxy acids; hydrated silicas, polyoxyethylene or polyoxypropylene, polyalkylene oxides, phospholipids, carbohydrates, dendrimeric polymers, DL-lactide-co-caprolactones, poly(orthoester)s and poly(orthoester)/poly(ethylene glycol) copolymers, such polymers with incorporated esters of short chain \( \alpha \)-hydroxy acids or glycolic-co-lactic acid copolymers and mixtures thereof.

44. The formulation of claim 40 having at least one of the following stability characteristics when stored for one month at 40°C: (a) is degraded by less than 2%, and/or (b) experiences less than 2% lactone formation, and/or (c) experiences less than four times the lactone formation as compared to the same formulation with the addition of calcium carbonate.

45. A non-crystalline solid compound salt of formula I below prepared by

(A) (i) preparing a desired salt of atorvastatin in solution in a first solvent; and

(ii) optionally adding at least one initial stabilizer for said atorvastatin salt to the solution of step (A)(i) to yield a second solution; or
(B) (i) optionally preparing a solution of said initial stabilizer in a second solvent, which may be the same as said first solvent, to form a third solution; and
(ii) adding said atorvastatin salt to said third solution of step (B)(i) to yield a fourth solution; or

(C) (i) following step (A)(i);
(ii) following step (B)(i); and
(iii) combining the result of steps (C)(i) and (C)(U) to yield a fifth solution; and

removing the respective first and second solvents from said second, fourth, and fifth solutions via a technique selected from the group consisting of one or more of lyophilization, spray drying, supercritical fluid solvent extraction, and near critical fluid extraction, said salt being a pharmaceutically acceptable salt of the compound of formula I
wherein

\[ X = \text{--CH}_2--\text{, --CH}_2\text{CH}_2--\text{, or --CH}_2\text{CH}_2\text{CH}_2--\text{, or} --\text{CH}_2\text{CH(CH}_3_\text{)--}; \]

\( R_1 \) is

- 1-naphthyl;
- 2-naphthyl;
- cyclohexyl;
- norbornenyl;
- phenyl;
- phenyl substituted with
  - fluorine,
  - chlorine,
  - bromine,
  - hydroxyl,
  - trifluoromethyl,
  - alkyloxy of from one to four carbon atoms,
  - alkoxy of from one to four carbon atoms, or
  - alkanoxy of from two to eight carbon atoms;

either of \( R_2 \) or \( R_3 \) is \(-\text{CONR}_5\text{R}_6\) where \( R_5 \) and \( R_6 \) are independent[iy]

- hydrogen;
- alkyl of from one to six carbon atoms;
- phenyl;
- phenyl substituted with
  - fluorine,
  - chlorine,
  - bromine,
  - cyano,
  - trifluoromethyl, or
  - carboalkoxy of from three to eight carbon atoms;

and the other of \( R_2 \) or \( R_3 \) is

- hydrogen;
- alkyl of from one to six carbon atoms;
- cyclopropyl;
- cyclobutyl;
- cyclopentyl;
- cyclohexyl;
- phenyl; or
- phenyl substituted with
  - fluorine,
  - chlorine,
  - bromine,
  - hydroxyl,
  - trifluoromethyl,
  - alkyloxy of from one to four carbon atoms,
  - alkoxy of from one to four carbon atoms, or
  - alkanoxy of from two to eight carbon atoms;
$R_4$ is:
- alkyl of from one to six carbon atoms;
- cyclopropyl;
- cyclobutyl;
- cyclopentyl;
- cyclohexyl; or
- trifluoromethyl;
- or a hydroxy acid or pharmaceutically acceptable salts thereof, corresponding to the opened lactone ring of the compounds of structural formula I above.

46. A method of preparing a solid non-crystalline atorvastatin salt (including an anhydrate, non-solvate thereof or a hydrate thereof) comprising

   (A) preparing a desired salt of atorvastatin in solution in a first solvent or solvent mixture;

   (B) optionally adjusting the pH with a salt (having the same cation as the desired salt of atorvastatin) to at least about 10; and

removing said first solvent or solvent mixture via a technique selected from the group consisting of one or more of lyophilization, spray drying, supercritical fluid solvent extraction, and near critical fluid extraction.

47. The method of claim 46 wherein said desired salt of atorvastatin is atorvastatin hemicalcium.

48. The method of claim 47 wherein said pH is adjusted in step (B) using tricalcium phosphate.
49. The method of claim 46 wherein said solid non-crystalline atorvastatin salt is solid non-crystalline atorvastatin hemicalcium (including an anhydrate, non-solvate thereof or hydrate thereof) comprising

(A) preparing a solution of atorvastatin Na in a solvent mixture of 50% methanol/50% water v/v;

(B) adding thereto at least about 2 moles of tricalcium phosphate for each mole of atorvastatin;

(C) optionally measuring the pH;

(D) optionally adding additional tricalcium phosphate to bring the pH to at least about 10; and

removing said methanol/water via a technique selected from the group consisting of one or more of lyophilization, spray drying, supercritical fluid solvent extraction, and near critical fluid extraction.

50. The method of claim 49 wherein said solvent removal technique is lyophilization.

51. The method of claim 50 wherein the lyophilization is carried out at about -40°C.
Mean Plasma Atorvastatin Concentration - Time Profiles Following Administration of Single 80mg doses of Nektar Atorvastatin Test Formulations X1, Y1, and Z1 and Lipitor Capsules (Ref) to 36 Healthy Subjects

FIG. 10