Title: SALTS OF ROSUVASTATIN AND PROCESSES FOR THEIR PREPARATION

Abstract: Novel salts of rosuvastatin and processes for their preparation are disclosed. Pharmaceutical compositions comprising a therapeutically effective amount of one or more salts of rosuvastatin selected from the group consisting of a barium salt, strontium salt, zinc salt, cesium salt, cadmium salt and mixtures thereof are also disclosed.
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SALTS OF ROSUVASTATIN AND PROCESSES FOR THEIR PREPARATION

PRIORITY

[0001] This application claims the benefit under 35 U.S.C. §119 to Indian Provisional Application No. 1245/MUM/2006, filed on August 4, 2006, and to Indian Provisional Application No. 1267/MUM/2006, filed on August 10, 2006, and to Indian Provisional Application No. 1268/MUM/2006, filed on August 10, 2006, the contents of each of which are incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention generally relates to novel metal salts of rosuvastatin, processes for their preparation, pharmaceutical compositions containing the same, a process for their conversion into rosuvastatin calcium, and a method of treatment of hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type Ia and lib).

2. Description of the Related Art

[0003] Rosuvastatin, also known as [(E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methylsulfonyl) amino] pyrimidin-5-yl}(3R,5S)-3,5-dihydroxyhept-6-enoic acid), is represented by the structure of Formula I:

![Structure of Formula I](image)

(I).

[0004] Generally, rosuvastatin is a synthetic lipid-lowering agent that acts as an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMG-CoA Reductase inhibitor). This enzyme catalyzes the conversion of HMG-CoA to mevalonate,
an early and rate-limiting step in cholesterol biosynthesis. HMG-CoA reductase inhibitors are commonly referred to as "statins." Statins are therapeutically effective drugs used for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. Rosuvastatin is used in the treatment of hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb).

[0005] Rosuvastatin calcium (monocalcium bis(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidine)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoate) is an HMG-CoA reductase inhibitor for the once daily oral treatment of hyperlipidaemia. Rosuvastatin calcium is a superstatin, which can lower LDL-cholesterol and triglycerides more effectively than first generation drugs. Rosuvastatin calcium is sold under the brand name CRESTOR® for treatment of a mammal such as a human.

[0006] U.S. Patent No. 5,260,440 ("the '440 patent") discloses pyrimidine derivatives such as rosuvastatin, its calcium salt (2:1) and its lactone form. The '440 patent further discloses a process for the preparation of pyrimidine derivatives in a four step reaction scheme.

SUMMARY OF THE INVENTION

[0007] In accordance with one embodiment of the present invention, a novel salt of rosuvastatin are provided.

[0008] In accordance with a second embodiment of the present invention, a barium salt of rosuvastatin is provided.

[0009] In accordance with a third embodiment of the present invention, a strontium salt of rosuvastatin is provided.

[0010] In accordance with a fourth embodiment of the present invention, a zinc salt of rosuvastatin is provided.

[0011] In accordance with a fifth embodiment of the present invention, a cesium salt of rosuvastatin is provided.

[0012] In accordance with a sixth embodiment of the present invention, a cadmium salt of rosuvastatin is provided.
In accordance with a seventh embodiment of the present invention, a zinc salt of rosuvastatin characterized by an X-ray powder diffraction pattern (XPRD) substantially in accordance with Figure 1 is provided.

In accordance with an eighth embodiment of the present invention, a zinc salt of rosuvastatin characterized by a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 2 is provided.

In accordance with a ninth embodiment of the present invention, a strontium salt of rosuvastatin characterized by an XPRD substantially in accordance with Figure 3 is provided.

In accordance with a tenth embodiment of the present invention, a strontium salt of rosuvastatin characterized by a DSC thermogram substantially in accordance with Figure 4 is provided.

In accordance with an eleventh embodiment of the present invention, a barium salt of rosuvastatin characterized by an XPRD substantially in accordance with Figure 5 is provided.

In accordance with a twelfth embodiment of the present invention, a barium salt of rosuvastatin characterized by a DSC thermogram substantially in accordance with Figure 6 is provided.

In accordance with a thirteenth embodiment of the present invention, a process for the preparation of a metal salt of rosuvastatin selected from the group consisting of zinc, strontium, barium, cesium and cadmium salt is provided, the process comprising contacting a HMG-CoA reductase inhibitor rosuvastatin acid form or an ester or salt thereof with a source of metal in a suitable solvent to afford the desired salt of FIMG-CoA reductase inhibitor rosuvastatin.

In accordance with a fourteenth embodiment of the present invention, a process for converting a metal salt of rosuvastatin into rosuvastatin or a pharmaceutically active salts is provided.

In accordance with a fifteenth embodiment of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of a pharmaceutically active metal salt of rosuvastatin selected from the group consisting of
zinc, strontium, barium, cesium and cadmium salt and at least one pharmaceutically acceptable carrier.

[0022] In accordance with a sixteenth embodiment of the present invention, a method of treating hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson type Ha and lib) is provided, the method comprising administering to a subject in need of treatment thereof a pharmaceutical composition containing a therapeutically effective amount of a pharmaceutically active metal salt of rosvastatin selected from the group consisting of zinc, strontium, barium, cesium and cadmium salt and at least one pharmaceutically acceptable carrier.

**BRIEF DESCRIPTION OF THE DRAWINGS**

[0023] Figure 1 is a characteristic XRPD of a zinc salt of rosvastatin.
[0024] Figure 2 is a characteristic DSC thermogram of a zinc salt of rosvastatin.
[0025] Figure 3 is a characteristic XRPD of a strontium salt of rosvastatin.
[0026] Figure 4 is a characteristic DSC thermogram of a strontium salt of rosvastatin.
[0027] Figure 5 is a characteristic XRPD of a barium salt of rosvastatin.
[0028] Figure 6 is a characteristic DSC thermogram of a barium salt of rosvastatin.
[0029] Figure 7 is a characteristic XRPD of a calcium salt of rosvastatin.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

[0030] The present invention provides novel metal salts of rosvastatin. In one embodiment, a barium salt of rosvastatin is provided. In another embodiment, a strontium salt of rosvastatin is provided. In another embodiment, a zinc salt of rosvastatin is provided. In another embodiment, a cadmium salt of rosvastatin is provided. In another embodiment, a cesium salt of rosvastatin provided.

[0031] It has been found that different metal salts of pharmaceuticals can have different characteristics and uses. For example, a specific salt may exhibit better compressibility or dissolution characteristics and therefore, it would be advantageous to use this salt rather than other salts. Additionally, a specific metal salt may provide
protection during the manufacturing process and, therefore, be used more efficiently as an intermediate. Accordingly, the inventors determined to identify and characterize novel metal salts of rosuvastatin and processes for their manufacture.

[0032] In one embodiment, a barium salt of rosuvastatin can be prepared by contacting a rosuvastatin ester, rosuvastatin acid or salt thereof with a barium salt of an acid in a suitable solvent to form rosuvastatin barium.

[0033] In one embodiment, a strontium salt of rosuvastatin can be prepared by contacting a rosuvastatin ester, rosuvastatin acid or salt thereof with a strontium salt of an acid in a suitable solvent to form rosuvastatin strontium.

[0034] In one embodiment, a zinc salt of rosuvastatin can be prepared by contacting a rosuvastatin ester, rosuvastatin acid or salt thereof with a zinc salt of an acid in a suitable solvent to form rosuvastatin zinc.

[0035] In one embodiment, a cesium salt of rosuvastatin can be prepared by contacting a rosuvastatin ester, rosuvastatin acid or salt thereof with a cesium salt of an acid in a suitable solvent to form rosuvastatin cesium.

[0036] In one embodiment, a cadmium salt of rosuvastatin can be prepared by contacting a rosuvastatin ester, rosuvastatin acid or salt thereof with a cadmium salt of an acid in a suitable solvent to form rosuvastatin cadmium.

[0037] The barium salt of an acid for use herein can be a salt of any inorganic or organic acid. Representative examples of such salts include barium chloride, barium bromide, barium nitrate, barium sulphate, barium phosphate, barium carbonate, barium oxalate, barium acetate, barium lactate, barium succinate, barium citrate, barium tartrate and the like.

[0038] The strontium salt of an acid for use herein can be a salt of any inorganic or organic acid. Representative examples of such salts include strontium chloride, strontium bromide, strontium nitrate, strontium sulphate, strontium phosphate, strontium carbonate, strontium oxalate, strontium acetate, strontium lactate, strontium succinate, strontium citrate, strontium tartrate and the like.

[0039] The zinc salt of an acid for use herein can be a salt of any inorganic or organic acid. Representative examples of such salts include zinc chloride, zinc bromide,
zinc nitrate, zinc sulphate, zinc phosphate, zinc carbonate, zinc oxalate, zinc acetate, zinc lactate, zinc succinate, zinc citrate, zinc tartrate and the like.

[0040] The cesium salt of an acid for use herein can be a salt of any inorganic or organic acid. Representative examples of such salts include cesium chloride, cesium bromide, cesium nitrate, cesium sulphate, cesium phosphate, cesium carbonate, cesium oxalate, cesium acetate, cesium lactate, cesium succinate, cesium citrate, cesium tartrate, cesium fumarate, cesium malate and the like.

[0041] The cadmium salt of an acid for use herein can be a salt of any inorganic or organic acid. Representative examples of such salts include cadmium chloride, cadmium bromide, cadmium nitrate, cadmium sulphate, cadmium phosphate, cadmium carbonate, cadmium oxalate, cadmium acetate, cadmium lactate, cadmium succinate, cadmium citrate, cadmium tartrate, cadmium fumarate, cadmium malate and the like.

[0042] Useful solvents for carrying out the processes of the present invention include, but are not limited to, water, ketones such as acetone, methylethylketone, methyl isobutyl ketone, 2-butane and the like; esters such as methyl acetate, ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, carbon tetrahydrochloride and the like; ethers such as 1,4-dioxane, tetrahydrofuran (THF), dimethylether, diethyl ether, methylethylether, diisopropylether, methyltertiarybutyl ether and the like; alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutyl alcohol, tertiary butyl alcohol and the like; hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane, benzene, toluene and the like; nitriles such as acetonitrile, propionitrile and the like; dipolar aprotic solvents such as dimethylsulfoxide (DMSO), dimethyl acetamide (DMAc), N,N-dimethylformamide (DMF) and the like; and mixtures thereof.

[0043] The solvent from the solution can either be removed or saturated using such techniques as, for example, distillation under vacuum, precipitation by using antisolvents, spray drying, or agitated thin film drying. The solvent can also be removed from the solution using other techniques known in art including, for example, distillation, evaporation, oven drying, tray drying, rotational drying (such as with the Buchi Rotavapor), freeze-drying, fluidized bed drying, flash drying, spin flash drying, and the like.
Any form of a rosuvastatin ester, e.g., tertiary butyl ester, or rosuvastatin acid or a salt thereof, e.g., tertiary butyl amine salt, can be used as a starting material in the processes of making the metal salts of rosuvastatin of the present invention.

The term "contacting" includes the known techniques for the preparation of the salts from substances with acid properties and substances with alkaline properties. Crystallization is carried out at a temperature ranging from about -10°C to about 30°C.

In another embodiment of the present invention, the foregoing metal salts are suitably used as a processing aid, a starting substance or as an intermediate in a process for preparing rosuvastatin in a purified form, in a modified form, in a pharmaceutically active salt form or in a lactone form. For example, the modified form is obtained by chemical modification, which modifications are known to those skilled in the art. The purified form is obtained by any known method, for example, crystallization. The pharmaceutically active salt is preferably a metal salt, such as the sodium salt or the calcium salt.

Optionally, the foregoing metal salts of rosuvastatin of the present invention can be further purified by recrystallization or slurrying in a suitable solvent(s).

Suitable solvents in which the metal salt of HMG-CoA reductase inhibitor rosuvastatin can be dissolved for purification include, but are not limited to, CpC₅ ketones such as acetone, ethyl methyl ketone, 2-butanone and the like; alcohols such as ethanol, methanol, and isopropanol and the like; ethers such as tetrahydrofuran, 1,4-dioxane and the like, esters such as ethyl acetate and the like; water; and mixtures thereof.

The concentration of the metal salt of the HMG-CoA reductase inhibitor rosuvastatin in the solvent can range from about 40 to about 80% or more. The solution can be prepared at an elevated temperature if desired to achieve a desired concentration. However, any temperature is acceptable for the dissolution as long as a clear solution of the rosuvastatin is obtained and not detrimental to the drug substance chemically or physically. The temperature of the solution may be decreased to a lower temperature for further processing if required or an elevated temperature may be used. A higher temperature will allow the precipitation from solutions with higher concentrations of rosuvastatin resulting in better economics of manufacture.
The product may optionally be further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at a temperature ranging from about 35°C to about 90°C. The drying can be carried out for any desired time until the required product purity is achieved, for example, a time period ranging from about 1 to about 20 hours.

Apart from the metal salts of rosuvastatin of the present invention, analogous metals of the periodic table including HA and HB groups can form salts of rosuvastatin by following the process described above resulting in respective crystalline or noncrystalline metal salts of rosuvastatin.

In another embodiment of the present invention, the foregoing metal salts of rosuvastatin can also advantageously be used as intermediates in the manufacture of the crystalline or non-crystalline rosuvastatin calcium salt, to isolate a crystalline or non-crystalline rosuvastatin calcium salt with a relatively high purity level and uniformly suitable for formulation to meet desired pharmaceutical requirements and specifications.

In yet another embodiment of the present invention, a process for the conversion of a metal salt of rosuvastatin into its pharmaceutically active salts is provided. The term "a process for the conversion of the metal salts of rosuvastatin into its pharmaceutically active salts " includes processes for the preparation of rosuvastatin by one of the known methods wherein the foregoing metal salts of HMG-CoA reductase inhibitor rosuvastatin are used as the starting substance. For example, any one of the foregoing metal salts of rosuvastatin of the present invention are hydrolysed with an acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid and the like and mixtures thereof and in one or more organic solvents such as water, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutyl alcohol, tertiary butyl alcohol and the like, ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanol and the like; esters selected from methyl acetate, ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like, ethers selected from 1,4-dioxane, tetrahydrofuran (THF), dimethylether, diethyl ether, methyl ethylether, diisopropylether, methyl tertiary butyl ether and the like and mixtures thereof. It is also contemplated that other acids known in the art can be used. Optionally, the resulting rosuvastatin acid in an
alkali metal salt form, such as sodium salt, can be isolated and further converted to rosuvastatin in a pharmaceutically active salt form such as calcium salt by treating the rosuvastatin acid in an alkali metal salt form with a calcium source such as calcium hydroxide, calcium chloride, calcium acetate, and the like in one or more organic solvents such as water, alcohols, esters, ethers and the like and mixtures thereof to obtain rosuvastatin calcium salt.

[0054] The resultant product may optionally be further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at a temperature ranging from about 35°C to about 90°C. The drying can be carried out for any desired time until the required product purity is achieved, e.g., a time period ranging from about 1 to about 20 hours.

[0055] When using the metal salts of rosuvastatin according to the present invention as a starting material or as an intermediate, the yield and the purity of the resulting rosuvastatin calcium salt can be equal to or greater than about 99.8% as determined by HPLC when using the rosuvastatin calcium from methods known in the art.

[0056] The metal salts of rosuvastatin of the present invention are further characterized by X-ray powder diffraction patterns:

[0057] The rosuvastatin zinc salt has an XRPD substantially in accordance with the Figure 1.

[0058] The rosuvastatin strontium salt has an XRPD substantially in accordance with the Figure 3.

[0059] The rosuvastatin barium salt has an XRPD substantially in accordance with the Figure 5.

[0060] Powder x-ray diffraction patterns were obtained by methods known in the art. For example, the X-Ray powder diffraction can be measured by an X-ray powder diffractometer equipped with a Cu-anode (λ=1.54 Angstrom), X-ray source operated at 45kV, 40 mA and a Ni filter is used to strip K-beta radiation. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=2-50° 20; step width=0.017°; and measuring time per step=5 sec.
The metal salts of rosuvastatin of the present invention are further characterized by a DSC thermogram:

- The rosuvastatin zinc salt has a characteristic DSC thermogram substantially in accordance with Figure 2.
- The rosuvastatin strontium salt has a characteristic DSC thermogram substantially in accordance with Figure 4.
- The rosuvastatin barium salt has a characteristic DSC thermogram substantially in accordance with Figure 6.

The differential scanning calorimetric (DSC) thermogram can be measured by a Differential Scanning Calorimeter (DSC 822, Mettler Toledo) at a scan rate of 10°C per minute with an Indium standard. In this regard, it should be understood that the endotherm measured by a particular differential scanning calorimeter is dependent upon a number of factors, including the rate of heating (i.e., scan rate), the calibration standard utilized, instrument calibration, relative humidity, and upon the chemical purity of the sample being tested. Thus, an endotherm as measured by DSC on the instrument identified above may vary by as much as ±1°C or even ±2°C.

Another embodiment of the present invention provides rosuvastatin zinc salt having a chemical purity greater than or equal to about 96% as measured by high performance liquid chromatography (HPLC), preferably about 99% or more, and more preferably about 99.5% or more.

Another embodiment of the present invention provides rosuvastatin strontium salt having a chemical purity greater than or equal to about 96% as measured by HPLC, preferably about 99% or more, and more preferably about 99.5% or more.

Another embodiment of the present invention provides rosuvastatin barium salt having a chemical purity greater than or equal to about 96% as measured by HPLC, preferably about 99% or more, and more preferably about 99.5% or more.

Another embodiment of the present invention provides rosuvastatin cesium salt having a chemical purity greater than or equal to about 96% as measured by HPLC, preferably about 99% or more, and more preferably about 99.5% or more.
Another embodiment of the present invention provides rosuvastatin cadmium salt having a chemical purity greater than or equal to about 96% as measured by HPLC, preferably about 99% or more, and more preferably about 99.5% or more.

In one embodiment, one or more of the zinc or barium or strontium or cesium or cadmium metal salts of rosuvastatin disclosed herein for use in the pharmaceutical compositions of the present invention can independently have a D$_{50}$ and D$_{90}$ particle size less than about 300 microns, preferably less than about 200 microns, more preferably less than about 150 microns, still more preferably less than about 50 microns and most preferably less than about 10 microns. It is noted the notation D$_x$ means that X% of the particles have a diameter less than a specified diameter D. Thus, a D$_{90}$ of about 300 microns means that 90% of the micronized particles in a composition have a diameter less than about 300 microns. Any milling, grinding micronizing or other particle size reduction method known in the art can be used to bring the solid state metal salts such as zinc, barium and strontium salts of the rosuvastatin into any desired particle size range set forth above.

The novel metal salts of rosuvastatin of the present invention are believed to be useful because they may be stable under conditions of high relative humidity and elevated temperatures.

Another embodiment of the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of one or more of the zinc or barium or strontium or cesium or cadmium metal salts of rosuvastatin disclosed herein which can be formulated with at least one or more pharmaceutically acceptable carriers, also known as excipients, which ordinarily lack pharmaceutical activity, but have various useful properties which may, for example, enhance the stability, sterility, bioavailability, and ease of formulation of a pharmaceutical composition. These carriers are pharmaceutically acceptable, meaning that they are not harmful to humans or animals when taken appropriately and are compatible with the other ingredients in a given formulation. The carriers may be solid, semi-solid, or liquid, and may be formulated with the compound in bulk. The resulting mixture may be manufactured in the form of a unit-dose formulation (i.e., a physically discrete unit containing a specific amount of active ingredient) such as a tablet or capsule. Generally, the pharmaceutical compositions of the
present invention may be prepared by uniformly admixing the active ingredient with liquid or solid carriers and then shaping the product into the desired form.

[0074] The pharmaceutical compositions may be in the form of suspensions, solutions, elixirs, aerosols, or solid dosage forms. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. A tablet may be prepared by, for example, direct compression, wet granulation, or molding, of the active ingredient(s) with a carrier and other excipients in a manner known to those skilled in the art. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made on a suitable machine. A mixture of the powdered compound moistened with an inert liquid diluent is suitable in the case of oral solid dosage forms (e.g., powders, capsules, and tablets). If desired, tablets may be coated by standard techniques. The compounds of this invention may be formulated into typical disintegrating tablets, or into controlled or extended release dosage forms. The amount of active ingredient included in a unit dosage form depends on the type of formulation that is formulated. A pharmaceutical composition of the invention will generally include about 0.1% by weight to about 99% by weight of active ingredient, preferably about 1% by weight to 50% by weight.

[0075] Suitable carriers include, but are not limited to, fillers, binders, lubricants, inert diluents, surface active/dispersing agents, flavorants, antioxidants, bulking and granulating agents, adsorbants, preservatives, emulsifiers, suspending and wetting agents, glidants, disintegrants, buffering agents and preadjusting agents, colorants and the like. Examples of carriers include celluloses, modified celluloses, cyclodextrins, starches, oils, polyols, sugar alcohols and sugars, and others. For liquid formulations sugar, sugar alcohols, ethanol, water, glycerol, and polyalkylene glycols are particularly suitable, and may also be used in solid formulations. Cyclodextrins may be particularly useful for increasing bioavailability. Formulations for oral administration may optionally include enteric coatings known in the art to prevent degradation of the formulation in the stomach and provide release of the drug in the small intestine. One example of a pharmaceutical tablet of the rosuvastatin strontium salt may include, as inactive ingredients, hypromellose
2910, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin and one or more of synthetic red and yellow iron oxides and talc.

The active ingredient of the invention may also be administered via fast dispersing or fast dissolving dosage forms or in the form of high energy dispersion or as coated particles. Suitable pharmaceutical composition of the invention may be in coated or uncoated form as desired.

Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, the compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such as calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Other excipients contemplated by the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants like magnesium and calcium stearate and sodium stearoyl fumarate; flavorings; sweetening agents; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

Capsule dosages will contain the solid composition within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be
employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric coating.

[0080] The process of present invention is simple, efficient, cost effective, ecofriendly, reproducible, scalable and robust to produce the desired metal salts of rosuvastatin as intermediates which are stable, free flowing and directly converted into desired pure form of rosuvastatin calcium which can be compressible into stable pharmaceutical formulations.

[0081] Yet another embodiment of the present invention provides a method for treating hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson type Ha and lib), which the method which involves administering to a subject in need of treatment thereof a pharmaceutical composition comprising a therapeutically effective amount of one or more of zinc or barium or strontium or cesium or cadmium metal salts of rosuvastatin of the present invention and at least a pharmaceutically acceptable carrier.

[0082] 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 this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described. For purposes of the present invention, the following terms are defined below.

[0083] The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.
The term "composition" as used herein is intended to include, but is not limited to, a powder, a suspension, an emulsion and/or mixtures thereof. The term composition is intended to encompass a product containing the specified ingredients in the specified amounts, as well as any product, which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. A "composition" may contain a single compound or a mixture of compounds.

The term 'pharmaceutical composition' is intended to encompass a product comprising the active ingredient(s), pharmaceutically acceptable excipients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing the active ingredient, additional active ingredient(s), and pharmaceutically acceptable excipients.

The term "isolating" as used herein is intended to mean separation of the compound being isolated regardless of the purity of the isolated compound from any unwanted substance which presents with the compound as a mixture. Thus, the degree of purity of the isolated or separated compound does not affect the status of isolating.

The term "therapeutically effective amount" as used herein is intended to mean an amount of the product of the present invention that is effective when administered alone or in combination to treat a state, disorder or condition, of a mammal and is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

The term "delivering" as used herein is intended to mean providing a therapeutically effective amount of an active ingredient to a particular location within a host means causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by topical, local or by systemic administration of the active ingredient to the host.

The term "excipient" as used herein is intended to mean a component of a pharmaceutical product that is not the active ingredient, such as filler, diluent, carrier, and
so on. The excipients that are useful in preparing a pharmaceutical composition are preferably generally safe, non-toxic and neither biologically nor otherwise undesirable, and are acceptable for veterinary use as; well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0090] The term "buffering agent" as used herein is intended to mean a compound used to resist a change in pH upon dilution or addition of acid of alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate 'and other such material known to those of ordinary skill in the art.

[0091] The term "sweetening agent" as used herein is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

[0092] The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in tablet granulations. Such compounds include, by way of example and without limitation, acacia alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch, combinations thereof and other material known to those of ordinary skill in the art.

[0093] When needed, other binders may also be included in the present invention. Exemplary binders include starch, poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC™ F68, PLURONIC™ F127), collagen, albumin, celluloses in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone), combinations thereof and other such materials known to those of ordinary skill in the art.
The term "diluent" or "filler" as used herein is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules. Such compounds include, by way of example and without limitation, kaolin, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "glidant" as used herein is intended to mean agents used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "lubricant" as used herein is intended to mean substances used in tablet formulations to reduce friction during tablet compression. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "disintegrant" as used herein is intended to mean a compound used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pregelatinized and modified starched thereof, sweeteners, clays, such as bentonite, microcrystalline cellulose (e.g. Avicel™), carrageenan (e.g. Amberlite™), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof and other such materials known to those of ordinary skill in the art.

The term "wetting agent" as used herein is intended to mean a compound used to aid in attaining intimate contact between solid particles and liquids. Exemplary wetting agents include, by way of example and without limitation, gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as...
cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, (e.g., TWEEN™s), polyethylene glycols, polyoxyethylene stearates colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxyl propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone (PVP), tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton), combinations thereof and other such materials known to those of ordinary skill in the art.

Most of these excipients are described in detail in, e.g., Howard C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, (7th Ed. 1999); Alfonso R. Gennaro et al., Remington: The Science and Practice of Pharmacy, (20th Ed. 2000); and A. Kibbe, Handbook of Pharmaceutical Excipients, (3rd Ed. 2000), which are incorporated by reference herein.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

**EXAMPLE 1**

Process for the preparation of rosuvastatin zinc salt from the rosuvastatin tertiary butyl ester. This reaction is generally shown below in Scheme 1.

**SCHEME 1**

Rosuvastatin tertiary butyl ester (30.0 g) was dissolved in ethanol (300 ml) followed by addition of aqueous sodium hydroxide (2.25 g) dissolved in water (225.0 ml). The reaction mass was stirred for 60 minutes at 25 to 30°C. Ethanol was removed by
distillation from the reaction mass under vacuum at 35 to 40°C. The resulting residue was dissolved in purified water (500.0 ml) and filtered through a hyflo bed. A 10% prefiltered aqueous zinc bromide solution (80.0 ml) was added drop wise to the clear filtrate at 20 to 25°C and stirred at 20 to 25°C for 2 hours. The resulting solid was filtered and washed with purified water. The wet product was dried at 40 to 45°C under reduced pressure to provide the rosuvastatin zinc salt (22.0 g).

[00103] H'-NMR [DMSO-d$_6$, $\delta$ (ppm)]: 7.71 (2H, t), 7.29 (2H, t), 6.47 (1H, d), 5.5 (1H, dd), 4.90 - 4.72 (2H, m), 4.2 (1H, m), 3.8 (1H, m), 3.55 (3H, s), 3.44 (3H, s), 3.38 (1H, m), 2.19 (2H, m), 1.42-1.48 (2H, m), 1.21 (6H, d).

[00104] Mass m/z: 480.25 and 961.15 (- ion)

EXAMPLE 2

[00105] Process for the preparation of rosuvastatin zinc salt from the rosuvastatin tertiary butyl amine salt. This reaction is generally shown below in Scheme 2.

SCHEME 2

[00106] Rosuvastatin tert-butyl amine salt (25.0 g; 0.045 moles) was charged into purified water (250 ml) followed by the addition of a sodium hydroxide solution (1.90 g; 0.047 moles) dissolved in water (200.0 ml). The reaction mass was stirred for 60 minutes at room temperature. Water (100.0 ml) was distilled out from the reaction mass under vacuum at 35 to 40°C and filtered through a hyflo bed. A filtered aqueous zinc bromide solution (6.10 g; 0.027 moles into 75.0 ml purified water) was added drop wise to the clear filtrate at room temperature. The mixture was stirred for 120 minutes at room temperature, filtered and washed with purified water. The wet product was dried at 40 to 45°C to provide rosuvastatin zinc salt (22.50 g).
EXAMPLE 3

Process for the preparation of rosuvastatin strontium from the rosuvastatin tertiary butyl ester. This reaction is generally shown below in Scheme 3.

SCHEME 3

Rosuvastatin tertiary butyl ester (35.0 g) was dissolved in ethanol (350 ml) followed by addition of aqueous sodium hydroxide (2.60 g) dissolved in water (260.0 ml). The reaction mass was stirred for 60 minutes at 25 to 30°C. Ethanol was removed by distillation from the reaction mass under vacuum at 35 to 40°C. The resulting residue was dissolved in purified water (550.0 ml) and filtered through a hyflo bed. A 10% prefiltered aqueous strontium chloride solution (65.0 ml) was added drop wise to the clear filtrate at 20 to 25°C and stirred at 20 to 25°C for 120 minutes. The resulting solid was filtered and washed with purified water. The wet product was dried at 40 to 45°C under reduced pressure to provide rosuvastatin strontium salt (22.0 g).

H'-NMR [DMSO-d6, δ (ppm)]: 7.71 (2H,t), 7.26 (2H,t), 6.47 (lH,d), 5.48 (lH,dd), 5.07 (lH,m), 4.19 (lH,m), 3.69 (lH,m), 3.55 (3H,s), 3.44 (3H,s), 3.38 (lH,m), 1.88-2.01 (2H,m), 1.47 (lH,m), 1.31 (2H,m), 1.21 (6H,d).

Mass m/z: 480.25 and 961.09 (- ion)
EXAMPLE 4

[00115] Process for the preparation of rosuvastatin strontium from the rosuvastatin tertiary butyl amine salt. This reaction is generally shown below in Scheme 4.

SCHEME 4

[00116] Rosuvastatin tert-butyl amine salt (25.0 g; 0.045 moles) was charged into purified water (250 ml) followed by the addition of a sodium hydroxide solution (1.90 g; 0.047 moles) dissolved in water (200.0 ml). The reaction mass was stirred for 60 minutes at room temperature. Water (100.0 ml) was distilled out from the reaction mass under vacuum at 35 to 40°C and filtered through a hyflo bed. A filtered aqueous strontium chloride solution (6.60 g; 0.27 moles into 75.0 ml purified water) was added drop wise to the clear filtrate at room temperature. The mixture was stirred for 120 minutes at room temperature, filtered and washed with purified water. The wet product was dried at 40 to 45°C to provide rosuvastatin strontium salt (20.50 g).

[00117] H-NMR [DMSO-d_6, δ (ppm)]: 7.67 (2H,t), 7.23 (2H,t), 6.51-6.45 (IH,d), 5.52 (IH,dd), 5.12-5.04 (2H,m), 4.2 (IH,m), 3.79(IH,m), 3.52 (3H,s), 3.42 (3H,s), 3.36 (IH,m), 2.49 (2H,m), 1.47 (2H,m), 1.20-1.18 (6H,d).

[00118] IR (KBr) :2968.52 1546.31 1509.19 1437.53 1381.85 1229.55 1197.11 1155.03 965.03 844.32 810.70 776.09 576.02 566.72

[00119] Mass m/z: 480.27 and 961.22 (- ion).

[00120] Purity by HPLC: 99.72 %.
EXAMPLE 5

[00121] Process for the preparation of rosuvastatin barium salt from the rosuvastatin tertiary butyl ester. This reaction is generally shown below in Scheme 5.

SCHEME 5

[00122] Rosuvastatin tertiary butyl ester (35.0 g) was dissolved in ethanol (350 ml) followed by addition of aqueous sodium hydroxide (2.60 g) dissolved in water (260.0 ml). The reaction mass was stirred for 60 minutes at 25 to 30°C. Ethanol was removed by distillation from the reaction mass under vacuum at 35 to 40°C. The resulting residue was dissolved in purified water (550.0 ml) and filtered through a hyflo bed. A 10% prefiltered aqueous barium chloride solution (100.0 ml) was added drop wise to the clear filtrate at 20 to 25°C and stirred for 120 minutes. The resulting solid was filtered and washed with purified water. The wet product was dried at 40 to 45°C under reduced pressure to provide of rosuvastatin barium salt (23.5 g).

[00123] H1-NMR [DMSO-d6, δ (ppm)]: 7.69 (2H,t), 7.27 (2H,t), 6.46 (lH,d), 5.48 (lH,dd), 5.1 (lH,bs), 4.19 (lH,m), 3.7 (lH,m), 3.54 (3H,s), 3.43 (3H,s), 3.16 (lH,m), 1.9-2.04 (2H,dd), 1.47 (lH,m), 1.31 (2H,m), 1.19 (6H,d).

[00124] Mass m/z: 480.19 and 961.16 (- ion)

EXAMPLE 6

[00125] Process for the preparation of rosuvastatin barium salt from the rosuvastatin tertiary butyl amine ester. This reaction is generally shown below in Scheme 6.
Rosuvastatin tert-butyl amine salt, (25.0 g; 0.045 moles) was charged into purified water (250 ml) followed by the addition of a sodium hydroxide solution (1.90 g; 0.047 moles) dissolved in water (200.0 ml). The reaction mass was stirred for 60 minutes at room temperature. Water (100.0 ml) was distilled out from the reaction mass under vacuum at 35 to 40°C and filtered through a hyflo bed. A filtered aqueous barium chloride solution (6.60 g; 0.027 moles into 75.0 ml purified water) was added drop wise to the clear filtrate at room temperature. The mixture was stirred for 120 minutes at room temperature, filtered and washed with purified water. The wet product was dried at 40 to 45°C to provide rosuvastatin barium salt (21.0 g).

**H^1-NMR** [DMSO-d$_6$,$\delta$ (ppm)]: 7.66 (2H,t), 7.21 (2H,t), 6.50-6.45 (lH,d), 5.51 (lH,dd), 5.25 (lH,bs), 4.21 (lH,m), 3.85 (lH,m), 3.52 (3H,s), 3.42 (3H,s), 3.38 (lH,m), 2.19-2.01 (2H,dd), 1.50 (lH,m), 1.32 (2H,m), l. 18-1.16 (6H,d).

**IR** (KBr): 2968.25 2933.51 1549.16 1509.44 1229.56 1197.11 1154.93 965.29 844.33 810.78 776.20 575.99 566.77 544.33

**Mass m/z**: 480.33 and 961.14 (- ion)

**Purity by HPLC**: 99.81 %

**EXAMPLE 7**

Process for the preparation of rosuvastatin calcium salt from rosuvastatin barium salt. This reaction is generally shown below in Scheme 7.
Rosuvastatin barium salt obtained from Example 6 (5.0 g; 9.1 mmoles) was charged into purified water (50 ml) and ethyl acetate (50 ml) followed by the addition of dilute HCL solution (1.0 ml into 5 ml purified water). The reaction mass was stirred for 30 minutes at room temperature. The organic layer was separated and dried over sodium sulphate. Ethyl acetate was distilled out from the reaction mass under vacuum at 35 to 40°C. The resulting residue was dissolved into 40 ml ethanol and added aq. sodium hydroxide solution (0.38 g; 9.5 mmoles into 20 ml purified water). The reaction mass was stirred for 60 minutes at room temperature and solvents were distilled out from the reaction mass under vacuum at 35 to 40°C. The resulting residue was dissolved into 50 ml purified water and filtered through a hyflo bed. A filtered aqueous calcium chloride solution (0.80 g; 5.4 mmoles into 15.0 ml purified water) was added drop wise to the clear filtrate at room temperature. The mixture was stirred for 120 minutes at room temperature, filtered and washed with purified water. The wet product was dried at 40 to 45°C to provide rosuvastatin calcium salt (3.0 g).

H1-NMR [DMSO-d6, δ (ppm)]: 7.68 (2H,t), 7.24 (2H,t), 6.52-6.46 (1H,d), 5.54-5.47 (1H,dd), 5.06 (1H,bs), 4.19 (1H,m), 3.78 (1H,m), 3.53 (3H,s), 3.43 (3H,s), 3.39 (1H,m), 2.17-1.97 (2H,dd), 1.48 (1H,m), 1.32 (2H,m), 1.20-1.19 (6H, d).

IR (KBr): 2968.58 2933.51 1548.84 1510.21 1229.35 1197.29 1154.23 964.92 844.49 810.72 776.03 575.99 566.60.

Mass m/z: 480.25 and 960.98 (- ion).

Purity by HPLC: 99.64%.
EXAMPLE 8

The ingredients and amounts set forth below in Table 1 are illustrative of a pharmaceutical composition according to the present invention.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin zinc</td>
<td>13.86</td>
</tr>
<tr>
<td>Diluent</td>
<td>79.00</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>0.07</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>0.07</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>5.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>2.00</td>
</tr>
</tbody>
</table>

EXAMPLE 9

The ingredients and amounts set forth below in Table 2 are illustrative of a pharmaceutical composition according to the present invention.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin strontium</td>
<td>13.86</td>
</tr>
<tr>
<td>Diluent</td>
<td>79.00</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>0.07</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>0.07</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>5.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>2.00</td>
</tr>
</tbody>
</table>

EXAMPLE 10

The ingredients and amounts set forth below in Table 3 are illustrative of a pharmaceutical composition according to the present invention.
TABLE 3

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin barium</td>
<td>13.86</td>
</tr>
<tr>
<td>Diluent</td>
<td>79.00</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>0.07</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>0.07</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>5.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>2.00</td>
</tr>
</tbody>
</table>

EXAMPLE II

[00140] The ingredients and amounts set forth below in Table 4 are illustrative of a pharmaceutical composition according to the present invention.

TABLE 4

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin cesium</td>
<td>13.86</td>
</tr>
<tr>
<td>Diluent</td>
<td>79.00</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>0.07</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>0.07</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>5.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>2.00</td>
</tr>
</tbody>
</table>

EXAMPLE 12

[00141] The ingredients and amounts set forth below in Table 5 are illustrative of a pharmaceutical composition according to the present invention.
The ingredients and amounts set forth below in Table 6 are illustrative of a pharmaceutical composition according to the present invention.

**TABLE 5**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin cadmium</td>
<td>13.86</td>
</tr>
<tr>
<td>Diluent</td>
<td>79.00</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>0.07</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>0.07</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>5.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>2.00</td>
</tr>
</tbody>
</table>

**TABLE 6**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (wt. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin calcium</td>
<td>13.86</td>
</tr>
<tr>
<td>Diluent</td>
<td>79.00</td>
</tr>
<tr>
<td>Antioxidant</td>
<td>0.07</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>0.07</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>5.00</td>
</tr>
<tr>
<td>Lubricant</td>
<td>2.00</td>
</tr>
</tbody>
</table>

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.
WHAT IS CLAIMED IS:

1. A metal salt of rosuvastatin selected from the group consisting of strontium, barium, cesium zinc, and cadmium, characterized in that the salt is an intermediate or a starting substance in a process for preparing rosuvastatin or a pharmaceutically active salt thereof.

2. The metal salt of rosuvastatin according to claim 1, wherein the salt has a chemical purity greater than or equal to about 96% as determined by HPLC.

3. The metal salt of rosuvastatin according to claim 1, wherein the salt has a chemical purity greater than or equal to about 97% as determined by HPLC.

4. The metal salt of rosuvastatin according to claim 1, wherein the salt has a chemical purity greater than or equal to about 98% as determined by HPLC.

5. The metal salt of rosuvastatin according to claim 1, wherein the salt has a chemical purity greater than or equal to about 99.5% as determined by HPLC.

6. A process for preparing a metal salt of rosuvastatin, the process comprising adding a salt of a metal source selected from the group consisting of strontium, barium, cesium zinc, and cadmium to a crude medium of a rosuvastatin acid or an ester thereof.

7. The process according to claim 6, wherein the rosuvastatin in the crude medium is a tertiary butyl amine salt of rosuvastatin or a tertiary butyl ester of rosuvastatin.

8. The process according to claim 6, comprising (a) contacting the crude medium containing the rosuvastatin with the metal source; (b) crystallizing the crude medium; (c) filtering the crystals; (d) washing the crystals with an organic solvent; and (e) drying the crystals.
9. The process according to claim 8, wherein the step of crystallization is carried out at temperature of about 0 to about 30°C.

10. The use of a metal salt of rosuvastatin selected from the group consisting of strontium, barium, cesium zinc, and cadmium as a processing aid, a starting substance or an intermediate substance in a process for preparing rosuvastatin (i) in a purified form; or (ii) in a modified form; or (iii) in a pharmaceutically active salt form; or (iv) in a lactone form.

11. The use according to claim 10, wherein the purified form is prepared by crystallization.

12. The use according to claim 10, wherein the modified form is prepared by chemical modification.

13. The use according to claim 10, wherein the pharmaceutically active salt is calcium salt.

14. A process comprising converting a metal salt of rosuvastatin selected from the group consisting of strontium, barium, cesium zinc, and cadmium to rosuvastatin in a pharmaceutically active salt form.

15. The process according to claim 14, wherein the metal salt is a zinc salt of rosuvastatin.

16. The process according to claim 14, wherein the metal salt is a strontium salt of rosuvastatin.

17. The process according to claim 14, wherein the metal salt is a barium salt of rosuvastatin.
18. The process according to claim 14, wherein the metal salt is a cadmium salt of rosuvastatin.

19. The process according to claim 14, wherein the metal salt is a cesium salt of rosuvastatin.

20. The process according to claim 14, wherein the rosuvastatin in a pharmaceutically active salt form has a purity of greater than or equal to about 98% as determined by HPLC.

21. The process according to claim 14, wherein the rosuvastatin in a pharmaceutically active salt form has a purity of greater than or equal to about 99% as determined by HPLC.

22. The process according to claim 14, wherein the rosuvastatin in a pharmaceutically active salt form has a purity of greater than or equal to about 99.8% as determined by HPLC.

23. The process according to claim 14, wherein the rosuvastatin in a pharmaceutically active salt form is isolated in amorphous form.

24. A zinc salt of rosuvastatin characterized by an X-ray powder diffraction pattern (XPRD) substantially in accordance with Figure 1.

25. A zinc salt of rosuvastatin characterized by a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 2.

26. A strontium salt of rosuvastatin characterized by an XPRD pattern substantially in accordance with Figure 3.
27. A strontium salt of rosuvastatin characterized by a DSC thermogram substantially in accordance with Figure 4.

28. A barium salt of rosuvastatin characterized by an XPRD pattern substantially in accordance with Figure 5.

29. A barium salt of rosuvastatin characterized by a DSC thermogram substantially in accordance with Figure 6.

30. A pharmaceutical composition comprising a therapeutically effective amount of one or more of the metal salts of rosuvastatin according to claims 1-5 and 24-29.

31. The pharmaceutical composition of Claim 30, further comprising one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants.

32. The pharmaceutical composition of Claims 30 and 31, which is in a solid form.

33. The pharmaceutical composition of Claims 30-32, in a form of a tablet, caplet, capsule, suspension, troche or powder.

34. The use of one or more of the metal salts of rosuvastatin according to claims 1-5 and 24-29 in a pharmaceutical composition for treating hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson type Ha and lib).

35. A process for the preparation of an amorphous calcium salt of rosuvastatin, the process comprising (a) converting a metal salt of rosuvastatin selected from the group consisting of strontium, barium, cesium zinc, and cadmium to a sodium salt of rosuvastatin; and (b) reacting the sodium salt with a water soluble calcium salt under aqueous conditions to form the amorphous calcium salt of rosuvastatin.
FIGURE 2
FIGURE 6
FIGURE 7