Abstract: Disclosed is a novel process for preparing pure amorphous form of Atorvastatin employing a suitable solvent system selected from water, water miscible solvents or water immiscible solvents or mixture thereof.
PROCESS FOR THE PREPARATION OF AMORPHOUS ATORVASTATIN CALCIUM SALT

FIELD OF THE INVENTION

This invention, in general relates to the field of HMG Coenzyme A reductase inhibitors, in particular to Atorvastatin. More specifically the present invention provides novel and industrially feasible process to achieve a pure form of amorphous Atorvastatin calcium employing suitable solvent system.

BACKGROUND OF THE INVENTION

[R(R*,R*)]-2-(4-Fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid, commonly known as Atorvastatin is known to be therapeutically useful compound. Atorvastatin calcium, a synthetic HMG-CoA reductase inhibitor, is used for the treatment of hyperlipidemia and hypercholesterolemia, both of which are risk factors for arteriosclerosis and coronary heart disease. For use in the treatment of aforementioned diseases, open dihydroxy carboxylic acid, lactone and various salt forms of Atorvastatin have been synthesized.

US Patent No. 4,681,893 discloses certain trans-6-[2-(3- or 4-carboxamido substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones, which includes trans(+)5-(4-fluorophenyl)-2-(l-methylethyl)-N,4-diphenyl-1[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-IH-pyrrole-3-carboxamide, whereas US Patent No. 5,273,995 discloses that R-enantiomer of the ring-opened acid form of trans-5-(4-fluorophenyl)-2-(l-methylethyl)-N,4-diphenyl-1[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-IH-pyrrole-3-carboxamide has surprising inhibition of the biosynthesis of cholesterol. Atorvastatin in its calcium salt form, i.e. [R(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula I; is more suited for
developing formulations and has been recommended as a drug.

US Patent Nos. 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,342,952 and 5,397,792 disclose various processes and key intermediates for preparing Atorvastatin.

One of the disadvantage of processes described in above mentioned patents, is the preparation of (R-cis)-l,l-dimethylethyl-6-[2[2-(4-fluorophenyl)-5-(l-methylethyl)-3-phenyl-4-phenylcarbamoyl-lH-pyrrol-1-yl]ethyl]-2,2dimethyl-1,3-dioxane-4-acetate, where in binary or ternary solvent system is used in the condensation step. This makes the recovery of the solvent very difficult at plant scale and thus these processes are not commercially viable on industrial scale.

Another disadvantage of the processes discussed in these patents is the inconsistency in the polymorphic nature of the final product i.e. Atorvastatin calcium. The final product is in the form of mixture of crystalline and amorphous forms, which has unsuitable filtration and drying characteristics and are not suitable for large-scale production.

It is known that the amorphous forms in a number of pharmaceutical substances exhibit different dissolution characteristics and bioavailability patterns compared to crystalline forms (Konnq T., Chem. Phar. Bull. 1990, 38, 2003-2007). For some therapeutic indications the bioavailability is one of the key parameters determining the form of the substance to be used in a pharmaceutical formulation. There is a constant need for processes which enable the preparation of Atorvastatin in an amorphous form without
simultaneous formation of crystalline form, or which will enable the conversion of the crystalline forms into the amorphous form.

Atorvastatin calcium is very slightly water-soluble, and it has been found that in comparison to amorphous form, crystalline forms are less readily soluble and adversely affect the bioavailability of Atorvastatin in the body.

PCT application WO 97/03959, discloses novel crystalline forms of Atorvastatin calcium designated as form I, form II and form IV and process for their preparation. PCT application WO 97/03960 and US Patent No. 6,274,740 describe the processes for the preparation of amorphous form, by conversion of the crystalline form of Atorvastatin. Process disclosed therein comprises dissolving Atorvastatin crystalline form I in a non-hydroxylic solvent like tetrahydrofuran or mixtures of tetrahydrofuran and toluene. This process involves complete removal of the solvent under high temperature (about 90°C) and high vacuum (about 5 mm). The exposure of the material to high temperature for several days leads to degradation of the product. This makes the process very inconvenient to operate at a large scale. Slow removal of solvent at a manufacturing scale renders this process as less productive.

PCT application WO 00/71116 describes the process for the preparation of amorphous Atorvastatin, which involves dissolving crystalline form in non-hydroxylated solvent followed by precipitation of amorphous Atorvastatin by adding non-polar hydrocarbon solvent, in this case high levels of hydrocarbon are necessary to obtain the desired product. A similar approach is described in PCT application WO 01/42209, which describes conversion of the crystalline form of Atorvastatin to the amorphous form by dissolving in a variety of solvents including both non-hydroxylated solvents and lower alcohols, followed by precipitation with solvents in which Atorvastatin is insoluble like non-polar hydrocarbons or aliphatic ethers. This process also is not recommended for commercial production of amorphous Atorvastatin calcium due to the use of large excess of diethyl ether, which is not safe on commercial scale. PCT application WO 2005/092852 describes the preparation of amorphous Atorvastatin starting from diol protected ester derivative of Atorvastatin, which is converted first to crude Atorvastatin.
calcium, purify it to crystalline Atorvastatin calcium and then treated with tetrahydrofuran and cyclohexane to get the desired product.

Whereas, PCT application WO 01/28999 describes the purification of crude amorphous Atorvastatin calcium by dissolving crude amorphous material in a large excess of boiling ethanol or 2-propanol and filtering the hot solution and recovering the material at low temperature. The hot solution is difficult to filter at the industrial scale.

The present invention provides a novel and industrially viable process for preparing Atorvastatin in pure amorphous form to avoid the drawback associated with the prior arts.

**SUMMARY OF THE INVENTION**

It is a principal aspect of the present invention to provide a novel process for preparation of pure amorphous form of Atorvastatin calcium employing suitable solvent system.

The aspects of the present invention is further described hereinafter in different preferred embodiments in accordance with the best mode of the invention, however it is not restricted to the described embodiments.

In accordance with one preferred embodiment of the present invention, there is provided a novel process for preparation of pure amorphous form of Atorvastatin calcium, wherein process comprises the steps of:

(a) treating a solution of 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy heptanoic acid tert-butyl ester of formula (II) in water or water miscible solvent with a base;

(b) adding aqueous solution of calcium salt to solution of step (a) to prepare Atorvastatin calcium;

(c) adding organic solvent;
(d) separating the organic layer and evaporating to afford crude amorphous Atorvastatin calcium as a foamy solid;

(e) adding anti solvents to step (d) in which Atorvastatin calcium is insoluble;

(f) separating the resultant precipitate to obtain pure amorphous Atorvastatin calcium.

In accordance with further embodiment of present invention, there is provided a novel process for preparation of pure amorphous form of Atorvastatin calcium, wherein the foamy solid obtained according to step (d) is optionally stirred by using tetrahydrofurane followed by adding anti solvent to obtain the amorphous form of Atorvastatin calcium.

In accordance with another embodiment of the present invention, said process comprises treating a solution of 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy heptanoic acid \(\tau\)-butyl ester of formula (II) in a water miscible solvent with a base, wherein said water miscible solvent is selected from methanol, isopropyl alcohol and ethanol.

In accordance with another embodiment of the present invention, said process comprises treating a solution of 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy heptanoic acid \(\tau\)-butyl ester of formula (II) in a water immiscible solvent with aqueous base, wherein said water immiscible solvent is selected from methyl ethyl ketone or methyl isobutyl ketone.

In accordance with one other embodiment of the present invention, there is provided a process for preparing amorphous form of Atorvastatin, wherein said calcium salt used to prepare a salt of Atorvastatin is selected from calcium chloride, calcium hydroxide, calcium acetate or calcium 2-ethyl hexanoate, more preferred is calcium 2-ethyl hexanoate.
In accordance with yet another embodiment of the present invention, there is provided a process to prepare pure form of amorphous Atorvastatin, wherein said compound 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-l-yl]-3,5-dihydroxy heptanoic acid t-butyl ester of formula (II) is prepared by reacting 1,1-dimethylethyl 6-(2-aminoethyl)-2-phenyl-1,3-dioxane-4-acetate (IV) with 4-fluoro-α-[2-methyl-l-oxopropyl]-γ-oxo-N,β-diphenylbenzenebutaneamide (V) in presence of pivalic acid and solvent selected from cyclic or acyclic hydrocarbon to afford t-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrrol-l-yl]ethyl}-2,2-dimethyl [1,3]dioxan-4-yl)acetate (III), treating compound of formula III with mineral acid to get the compound of formula II, which is further used in the process for preparing Amorphous form of Atorvastatin as described in above mentioned embodiments.

In accordance with still another embodiment of the present invention, there is provided a process to prepare pure form of amorphous Atorvastatin, wherein said compound 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-l-yl]-3,5-dihydroxy heptanoic acid t-butyl ester of formula (II) is prepared by reacting 1,1-dimethylethyl 6-(2-aminoethyl)-2-phenyl-1,3-dioxane-4-acetate (IV) with 4-fluoro-α-[2-methyl-l-oxopropyl]-γ-oxo-N,β-diphenylbenzene butaneamide (V) in presence of pivalic acid and cyclohexane to afford t-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrrol-l-yl]ethyl}-2,2-dimethyl[1,3]dioxan-4-yl)acetate (III), treating t-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrrol-l-yl]ethyl}-2,2-dimethyl[1,3]dioxan-4-yl)acetate (III) with mineral acid to get the compound of formula II, which is further used in the process for preparing Amorphous form of Atorvastatin as described in above mentioned embodiments.

DETAILED DESCRIPTION OF THE INVENTION

While this specification concludes with claims particularly pointing out and distinctly claiming that which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and examples.
The disclosed embodiment of the present invention deals with a process for the preparation of pure amorphous Atorvastatin calcium employing suitable solvent systems.

The process for the preparation of the pure amorphous Atorvastatin using a compound of formula II is disclosed in the present invention, wherein the process comprises contacting a compound of formula II with water, solvent or mixture thereof at room temperature, adding an aqueous solution of base, wherein base is selected from the group consisting of but not limited to alkali or alkaline earth metal hydroxide, preferably sodium hydroxide, potassium hydroxide, lithium hydroxide or calcium hydroxide, more preferably sodium hydroxide. The solvent used in hydrolysis step is selected from the group consisting of but not limited to water miscible solvent such as alcoholic solvents like methanol, isopropyl alcohol and ethanol and water immiscible solvent such as methyl ethyl ketone and methyl isobutyl ketone. After the complete hydrolysis, reaction mixture is cooled and then aqueous solution of calcium salt is added, where in calcium salt is selected from the group consisting of but not limited to calcium acetate, calcium chloride, calcium hydroxide or calcium 2-ethyl hexanoate, preferably calcium acetate and calcium 2-ethylhexanoate. The addition of source of calcium ions is carried out at a temperature from 40-60°C. Atorvastatin calcium prepared is then extracted with the organic solvent, wherein organic solvent is selected from the group consisting of but not limited to ethyl acetate, xylene, toluene and methyl isobutyl ketone (MIBK), preferably ethyl acetate. This extracted organic layer is washed twice with water and then evaporated to dryness to get a foamy solid, which is in crude amorphous form of Atorvastatin calcium as characterized by powder X-ray diffraction pattern. The powder XRD of foamy solid is describing that the product is 100% amorphous. This foamy solid is then taken into anti solvent in which the product is less soluble or insoluble at room temperature or optionally first dissolved in tetrahydrofuran at room temperature and then added to anti solvents or vice versa. The anti solvents are selected from the group consisting of but not limited to methyl t-butyl ether (MTBE), cyclohexane, hexane, heptane, octane, isopropyl alcohol, diisopropyl
ether and diethyl ether or mixture thereof, preferably cyclohexane and methyl isobutyl ketone.

A compound of formula II is prepared by the process, which comprises the reaction of compound of formula IV with a compound of formula V in presence of pivalic acid and solvent to get an intermediate III, which is further treated with a mineral acid, wherein mineral acid is selected from the group consisting of, but not limited to hydrochloric acid and sulfuric acid, to afford a compound of formula II.

The solvent used herein is selected from the group consisting of, but not limited to cyclic hydrocarbon such as cyclohexane etc. and acyclic hydrocarbon such as hexane, pentane, heptane etc. In the preparation of an intermediate III single solvent is used, whereas in prior art binary or ternary system is used. The advantages of the use of single solvent system are the recovery and reuse of the solvent in the process and the separation of the final product III is much easier than the binary or ternary systems. In latter cases the workup is much tedious, time consuming, environmentally and economically not feasible at industrial scale, which is eliminated in this process.

Having thus described the various methods for the preparation of amorphous form of Atorvastatin calcium of the present invention, the following examples are provided to
illustrate specific embodiments of the present invention. They are, however, not intended to be limiting the scope of present invention in any way.

**Example 1**

Dihydroxy ester (II) (5 g) was taken in water (50 ml) and sodium hydroxide (0.35 g) was added. Temperature was raised to 75-80°C and reaction mass was stirred and then cooled. Calcium acetate (1.00 g) was added and stirred for 1 hr and pH was adjusted to 8. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. The foamy solid residue was taken in diisopropyl ether or cyclohexane or t-butyl methyl ether or isopropyl alcohol (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin calcium.

**Example 2**

Dihydroxy ester (II) (5 g) was taken in water (50 ml) and sodium hydroxide (0.35 g) was added. Temperature was raised to 75-80°C and reaction mass was stirred and then cooled. Calcium acetate solution (1.00 g) was added and stirred for 1 hr and pH was adjusted to 8. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. The foamy solid residue was taken in mixture of cyclohexane and t-butyl methyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin calcium.

**Example 3**

Dihydroxy ester (II) (5 g) was taken in water (50 ml) and sodium hydroxide (0.35 g) was added. Temperature was raised to 75-80°C and reaction mass was stirred for 12 hrs and then cooled. Calcium 2-ethyl hexanoate solution (2.20 g) was added and stirred for 1 hr. The pH was adjusted to 8. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. The foamy
solid residue was taken in diisopropyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin calcium.

**Example 4**

Dihydroxy ester (II) (5 g) was taken in water (25 ml) and methyl ethyl ketone (25 ml). Sodium hydroxide (0.35 g) was then added. Temperature was raised to 60°C and reaction mass was stirred for 2 hrs. After the completion of reaction, calcium acetate (1.00 g in 5 ml water) was added and stirred, followed by the cooling of the reaction mixture to room temperature. Methyl ethyl ketone (25 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. The foamy solid residue was taken in diisopropyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin.

**Example 5**

Dihydroxy ester (II) (5 g) was taken in water (25 ml) and methyl ethyl ketone (25 ml) followed by the addition of sodium hydroxide (0.35 g). Temperature of the reaction mixture was raised to 60°C and stirred for 2 hrs. After the completion of the reaction, calcium acetate (1.00 g in 5 ml water) was added and stirred for 2 hrs. Reaction mixture was cooled to room temperature. The pH was adjusted to 8. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. The foamy solid residue was taken in diisopropyl ether or cyclohexane or t-butyl methyl ether or isopropyl alcohol or mixture of cyclohexane and t-butyl methyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin.

**Example 6**

Dihydroxy ester (II) (5 g) was taken in water (25 ml) and methyl ethyl ketone (25 ml) followed by the addition of sodium hydroxide (0.35 g). Temperature of the reaction
mixture was raised to 60°C and stirred for 2 hrs. After the completion of the reaction, Calcium 2-ethyl hexanoate (2.20 g in 5 ml water) was added and stirred for 2 hrs. Reaction mixture was cooled to room temperature. The pH was adjusted to 8. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy residue. The foamy solid residue was taken in diisopropyl ether or cyclohexane or t-butyl methyl ether or isopropyl alcohol or mixture of cyclohexane and t-butyl methyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin.

**Example 7**

Dihydroxy ester (II) (5 g) was taken in water (25 ml) and methyl ethyl ketone (25 ml) followed by the addition of sodium hydroxide (0.35 g). Temperature of the reaction mixture was raised to 60°C and stirred for 2 hrs. After the completion of the reaction, calcium acetate (1.00 g in 5 ml water) was added and stirred for 2 hrs. Reaction mixture was cooled to room temperature. The pH was adjusted to 8. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. The foamy solid residue was taken in diisopropyl ether or cyclohexane or t-butyl methyl ether or isopropyl alcohol or mixture of cyclohexane and t-butyl methyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin.

**Example 8**

Dihydroxy ester (II) (5 g) was taken in methyl ethyl ketone (40 ml) followed by the addition of sodium hydroxide (0.35 g). Temperature of the reaction mixture was raised to 60°C and stirred for 2 hrs. After the completion of the reaction, Calcium 2-ethyl hexanoate (2.20 g in 5 ml water) was added and stirred for 2 hrs. Reaction mixture was cooled to room temperature. The pH was adjusted to 8. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy...
solid residue. The foamy solid residue was taken in diisopropyl ether or cyclohexane or t-butyl methyl ether or isopropyl alcohol or mixture of cyclohexane and t-butyl methyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin.

Example 9

Dihydroxy ester (II) (5 g) was taken in water (25 ml) and methyl ethyl ketone (25 ml) followed by the addition of sodium hydroxide (0.35 g). Temperature of the reaction mixture was raised to 60°C and stirred for 2 hrs. After the completion of the reaction, Calcium acetate solution (1.00 g in 5 ml water) was added and stirred for 2 hrs. Reaction mixture was cooled to room temperature. The pH was adjusted to 8. Xylene (50 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. The foamy solid residue was taken in diisopropyl ether or cyclohexane or t-butyl methyl ether or isopropyl alcohol or mixture of cyclohexane and t-butyl methyl ether (50 ml) and stirred. Contents were filtered and dried to yield amorphous Atorvastatin.

Example 10

Dihydroxy ester (II) (5 g) was taken in water (50 ml) and methanol (5 ml). Sodium hydroxide (0.36g, 1.1 mole eq.) was then added. Temperature was raised to 80°C and reaction mass was stirred for 3 hrs at this temp. After reaction completion, reaction mixture was cooled. Calcium acetate solution (1.02 g in 5 ml water) was added at this temperature and then stirred for 1 hr. Ethyl acetate (40 ml) was added to extract the product from aqueous layer. Organic layer was washed with water and then dried over sodium sulfate. Solvent was removed under vacuum to give a foamy solid residue. To the residue tetrahydrofuran (15 ml) was added, stirred and stripped of the tetrahydrofuran under vacuum at 40-50°C to get the solid foam. Tetrahydrofuran (15 ml) was added and stirred for dissolution, followed by the addition of this solution to a cyclohexane : t-butyl methyl ether mixture (75 ml : 75 ml) at room temperature. After
the addition, the precipitated material was stirred for one hour. Contents were filtered and dried to yield amorphous Atorvastatin.

**Example 11**

**Preparation of compound II**

Diketo compound (V) (1.50 g) was taken in cyclohexane (10 ml) at room temperature. Amino ketal compound (FV) (1.00 g) in cyclohexane was added followed by the addition of pivalic acid (0.11 g). The reaction mixture was refluxed and after the completion of the reaction, reaction mixture was cooled and the precipitate filtered. Dried the material in vacuum oven at 50-55°C for 2 hr (moisture content is approx. 0.5%) to get crude compound III, which was recrystallized in isopropyl alcohol to give pure compound III as a solid. Compound III (1.40 gm) was then taken into methanol (20 ml) and stirred followed by the addition of dilute hydrochloric acid. Reaction mixture was warmed and stirred. After the completion of the reaction, reaction mixture was cooled and water was added. The precipitated material was filtered and dried under vacuum at 50-55°C for 12 hrs to afford the desired product II.

While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments. Rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modifications and variations would present themselves to those skilled in the art without departing from the scope and spirit of this invention.
We Claim:

1. The process for preparing pure amorphous form of Atorvastatin calcium comprising:
   (a) treating a solution of 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy heptanoic acid t-butyl ester of formula (II) in water or water miscible solvent with a base;
   (b) adding aqueous solution of calcium salt to a solution of step (a) to prepare Atorvastatin calcium;
   (c) adding organic solvent;
   (d) separating the organic layer and evaporating to afford crude amorphous Atorvastatin calcium as a foamy solid;
   (e) adding anti solvents in which Atorvastatin calcium is insoluble;
   (f) separating the resultant precipitate to obtain pure amorphous Atorvastatin calcium.

2. The process according to claim 1, wherein the foamy solid obtained according to step (d) is optionally stirred by using tetrahydrofurane followed by adding anti solvent to obtain the amorphous form of Atorvastatin calcium.

3. The process according to claim 1, wherein said water miscible solvent is selected from methanol, isopropyl alcohol or ethanol.

4. The process according to claim 1, wherein said calcium salt is selected from calcium chloride, calcium hydroxide, calcium acetate or calcium 2-ethyl hexanoate.

5. The process according to claim 4, wherein said calcium salt is preferably calcium 2-ethyl hexanoate.

6. The process according to claim 1, wherein said organic solvent is selected from ethyl acetate, xylene, toluene or methyl isobutyl ketone.
7. The process according to claim 1, wherein said anti solvent is selected from methyl t-butyl ether (MTBE), cyclohexane, hexane, heptane, octane, isopropyl alcohol, diisopropyl ether or diethyl ether or mixture thereof.

8. A process for preparing pure amorphous form of Atorvastatin calcium, which comprises:
   (a) reacting a solution of 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-l-yl]-3,5-dihydroxy heptanoic acid t-butyl ester of formula (II) in water immiscible solvent with aqueous base;
   (b) adding aqueous solution of calcium salt to a solution of step (a) to prepare Atorvastatin calcium;
   (c) adding organic solvent;
   (d) separating the organic layer and evaporating to afford crude amorphous Atorvastatin calcium as a foamy solid;
   (e) adding anti solvents in which Atorvastatin calcium is insoluble;
   (f) separating the resultant precipitate to obtain pure amorphous Atorvastatin calcium.

9. The process according to claim 8, wherein said water immiscible solvent is selected from methyl ethyl ketone or methyl isobutyl ketone.

10. The process according to claim 8, wherein said calcium salt is selected from calcium chloride, calcium hydroxide, calcium acetate or calcium 2-ethyl hexanoate.

11. The process according to claim 10, wherein said calcium salt is preferably calcium 2-ethyl hexanoate.

12. The process according to claim 8, wherein said organic solvent is selected from ethyl acetate, xylene, toluene or methyl isobutyl ketone.
13. The process according to claim 8, wherein said anti solvent is selected from methyl t-butyl ether (MTBE), cyclohexane, hexane, heptane, octane, isopropyl alcohol, diisopropyl ether or diethyl ether or mixture thereof.

14. A process for preparing pure amorphous form of Atorvastatin calcium, wherein said process further comprising preparing 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy heptanoic acid t-butyl ester by reacting 1,1-dimethylethyl 6-(2-aminoethyl)-2-phenyl-1,3-dioxane-4-acetate (IV) with 4-fluoro-α-[2-methyl-1-oxopropyl]-γ-oxo-N,β-diphenylbenzenebutaneamide (V) in presence of pivalic acid and solvent to afford the t-butyl (6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoylpyrrol-1-yl]ethyl}-2,2-dimethyl[1,3]dioxan-4-yl) acetate (III) with mineral acid to get the compound of formula II, which is further used in the process for preparing pure amorphous form of Atorvastatin according to any of the preceding claims.

15. The process according to claim 14, wherein said solvent is selected from cyclic and acyclic hydrocarbon.

16. The process according to claim 15, wherein said cyclic hydrocarbon is selected from cyclohexane.

17. The process according to claim 15, wherein said acyclic hydrocarbon is selected from pentane, hexane, heptane or octane.

18. The process according to claim 14, wherein said mineral acid is selected from hydrochloric acid or sulfuric acid.
**A. CLASSIFICATION OF SUBJECT MATTER**
IPC(8):  C07D 207/00( 2006.01)
USPC:  548/537
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/537
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN CAS ON LINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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[ ] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search: 14 October 2006 (14.10.2006)
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