(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 January 2012 (26.01.2012)

PCT

(10) International Publication Number
WO 2012/011129 A2

(51) **International Patent Classification:**
C07D 239/42 (2006.01)

(21) **International Application Number:**
PCT/IN20 11/000485

(22) **International Filing Date:**
21 July 201 1 (21 .07.201 1)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
2088/CHE/2010 22 July 2010 (22.07.2010) IN

(71) **Applicant** *(for all designated States except US):* **MSN LABORATORIES LIMITED** [IN/IN]; Sy. No: 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad 502329 Andhra Pradesh (IN).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only):* **SATYANARAYANA REDDY, Manne** [IN/IN]; Sy. No: 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad 502329 Andhra Pradesh (IN). **THIRUMALAI RAJAN, Srinivasan** [IN/IN]; Sy. No: 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad 502329 Andhra Pradesh (IN). **SAHADEVA REDDY, Maramreddy** [IN/IN]; Sy. No: 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad 502329 Andhra Pradesh (IN). **SRINIVASA REDDY, Ningam** [IN/IN]; Sy. No: 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad 502329 Andhra Pradesh (IN).

(74) **Common Representative: THIRUMALAI RAJAN, Srinivasan;** Sy. No: 317 & 323, Rudraram (Vil), Patancheru (Mdl), Medak (Dist), Hyderabad 502329 Andhra Pradesh (IN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/011129 A2

(54) **Title:** NOVEL POLYMORPH OF BIS[(E)-7-[4-(4-FLUOROPHENYL)-6-ISO-PROPYL-2-[METHYL (METHYLSULFONYL)AMINO]PYRIMIDIN-5-YL](3R,5S)-3,5-DIHYDROXYHEPT-6-ENOIC ACID] CALCIUM SALT

(57) **Abstract:** The present invention is relates to novel polymorph of bis[(e)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3r,5s)-3,5-dihydroxyhept-6-enoic acid] calcium salt

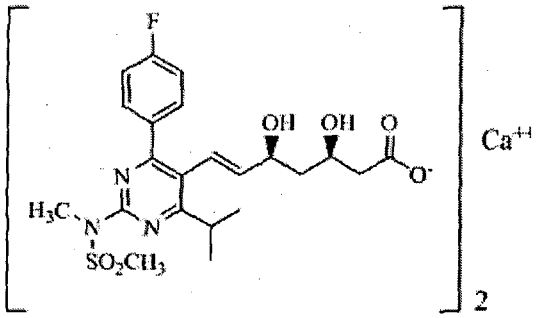
Novel polymorph of bisliEV7-f4-(4-fluorophenyr)-6-iso-propyl-2-fmethyl fmethylsulfonyl)aminolpyrimidin-5-yll(3R,5S)-3,5-dihydroxyhept-6-enoic acidl calcium salt

Related Application:

This application claims the benefit of priority of our Indian patent application number 2088/CHE/2010 filed on 22nd July 2010 which is incorporated herein by reference.

Field of the Invention:

The present invention relates to novel polymorphic forms of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl (methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium and its use in the preparation of pharmaceutical composition. Bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium is generically known as Rosuvastatin calcium and is represented by the following structural formula-1



Formula-1

Rosuvastatin calcium is commercially available under the brand name of Crestor® for the treatment of high cholesterol and related conditions, and to prevent cardiovascular disease, marketed by AstraZeneca.

Background of the Invention:

Rosuvastatin, its pharmaceutically acceptable salts, especially calcium salt and process for its preparation have been disclosed in US 5260440. The disclosed process involves the dissolution of rosuvastatin sodium salt in water, adding calcium chloride and

isolating the resultant precipitate by filtration then drying it to get calcium salt of rosuvastatin. Rosuvastatin calcium obtained as per this process is an amorphous powder.

International publication WO 00/42024 disclosed a crystalline form A of rosuvastatin calcium, which is prepared by dissolving the amorphous rosuvastatin calcium in a mixture of water and an organic solvent such as acetonitrile under heating then cooling the obtained reaction mixture to get the crystalline form A of rosuvastatin calcium.

International publication WO 05/023779 disclosed hydrated crystalline form-B and anhydrous crystalline form-B1 of rosuvastatin calcium. Form B is prepared by dissolving the amorphous form in water and where as form-B1 is prepared by removing water from the crystal lattice of form-B.

International publication WO 06/079611 disclosed crystalline form-B and form-C rosuvastatin calcium. The said crystalline forms are prepared by dissolving the amorphous rosuvastatin in a mixture of water and an anionic surfactant such as alkyl sulphates or dissolving the amorphous form in a mixture of water and organic solvent under heating and then cooling the obtained solution to precipitate crystalline form B or form C.

Crystalline forms often show different physical and/or biological characteristics which may assist in the manufacture or formulation of the active compound, with the purity levels and uniformity required for regulatory approval. Crystalline forms of such active compounds may also possess improved pharmacological characteristics, for example, improved bioavailability, and therefore, novel crystalline forms offer enhanced possibilities to modulate and design improved drug products. Therefore there exists a need for crystal forms other than those prior reported forms of rosuvastatin calcium which have the desired and the required biological qualities which would be helpful in optimizing, manufacturing and formulating an effective pharmaceutical composition.

Brief Description the Invention:

The first aspect of the present invention provides a novel crystalline form-M of rosuvastatin calcium and hydrates thereof.

The second aspect of the present invention is to provide a process for the preparation of novel crystalline form-M of rosuvastatin calcium and hydrates thereof.

The third aspect of the present invention is to provide a process for the preparation of novel crystalline form-M of rosuvastatin calcium and hydrates thereof.

The fourth aspect of the present invention is to provide a process for the preparation of novel crystalline form-M of rosuvastatin calcium.

Brief description of the Figures:

Figure-1: Illustrates PXRD of crystalline form-M of bis[(E)-7-[4-(4-fluorpphenyl)-6-iso-propyl-2-[methyl (methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

Figure-II: Illustrates DSC of crystalline form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyI (methyl suIfonyI)amino]pyrimidin-5-yI](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt.

Detailed Description of the Invention:

As used herein the present invention, the term "suitable solvent" refers to the solvent selected from "polar solvents" such as water;- "polar aprotic solvents" such as dimethylsulfoxide, dimethylacetamide, dimethyl formamide and the like; "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like; "ether solvents" such as di-tert-butylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran and dimethoxyethane; "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol and n-butanol and the like; "chloro solvents" such as methylene chloride, ethylene dichloride, carbon tetra chloride, chloroform and the like; "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane; "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like;

"esters solvents" such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like; and their mixtures thereof.

As used herein the present invention the term "suitable base" refers to the bases selected from "alkali metal hydroxides" such as sodium hydroxide, .potassium hydroxide and the like; "alkali metal carbonates" such as sodium carbonate, potassium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate and the like; "alkali metal alkoxide" such as sodium methoxide, potassium methoxide, sodium tertiary butoxide and potassium tertiary butoxide and the like;

The amorphous rosuvastatin calcium and rosuvastatin tertiary butyl amine salts used in the present invention are obtained according to the processes reported in the patent publications WO2007125547 or WO2008044243.

The first aspect of the present invention provides a novel crystalline form of rosuvastatin calcium, which is characterized by its powder X-ray diffraction pattern showing characteristic peaks at 3.33, 5.30, 7.52 and 22.46 ±0.2 degrees 2Θ. This crystalline form of rosuvastatin calcium is hereinafter designated as crystalline form-M. The crystalline form-M of the present invention further characterized by its PXRD showing peaks at 10.37 and 20.45 ±0.2 degrees 2θ. The PXRD of crystalline form-M is substantially similar to the PXRD pattern depicted in figure-1.

Further the crystalline form-M of the rosuvastatin calcium is characterized by its DSC thermo gram. The DSC having an endotherm at about 103.3°C and another endotherm at about 175.7°C. The DSC of crystalline form-M of rosuvastatin calcium is depicted in Figure-II.

The second aspect of the present invention provides a process for the preparation of crystalline form-M of rosuvastatin calcium, which comprises of

a) Taking the amorphous rosuvastatin calcium in mixture of ketone solvent and water,
b) warming the mixture to obtain a clear solution,
c) cooling the reaction mixture to ambient temperature and stirring for 15-20 hours,

d) filtering the precipitated solid,

e) drying the solid compound under aerial conditions to provide the crystalline form.

Wherein in step a) the ketone solvent used is selected from acetone or methyl isobutyl ketone; the ratio of water is in amount of about 2 volumes to about 15 volumes preferably 10 volumes to the weight of the compound. The amount of ketone solvent taken is about 2 volumes to about 15 volumes, preferably 10 volumes to the weight of the compound taken. In step b) the temperature to which the mixture is heated is in the range of 25°C to 50°C, preferably 41°C and in step c) ambient temperature refers to the temperature in the range of 25°C to 28°C.

The third aspect of the present invention provides a process for the preparation of crystalline form-M of rosuvastatin calcium, which comprises of,

a) Taking the amorphous rosuvastatin calcium in a suitable solvent,

b) heating the mixture up to the suitable temperature,

c) stirring the reaction mixture,

d) cooling the reaction mixture to ambient temperature,

e) filtering the precipitated solid,

f) drying the solid compound to provide the crystalline form-M.

Wherein in step a) the suitable solvent is selected from polar solvents like water, ketone solvents and alcohol solvents, preferably water;

in step b) the suitable temperature is 35°C to reflux temperature of the solvent used in the reaction;

in step d) ambient temperature refers to the temperature in the range of 25°C to 28°C.

The preferred embodiment of the present invention provides a process for the preparation of crystalline form-M of rosuvastatin calcium, which comprises of,

a) Taking the amorphous rosuvastatin calcium in water,

b) heating the reaction mixture to 90-95°C,

c) stirring the reaction mixture for 10 hours at 90-95 °C,

d) cooling the reaction mixture to ambient temperature,

e) filtering the precipitated solid,

f) drying the solid compound under aerial conditions for 22 hours, further drying the compound at 35-40°C for 6 hours to provide the crystalline form-M.

The fourth aspect of the present invention provides a novel process for the preparation of crystalline form-M of rosuvastatin calcium, which comprises of,

a) Taking the rosuvastatin tertiary butyl amine salt in a suitable solvent,

b) adding aqueous base solution to the above reaction mixture,

c) stirring the reaction mixture,

d) expelling the tertiary butyl amine from the reaction mixture using nitrogen gas,

e) adding suitable solvent to the reaction mixture,

f) adjusting the pH of the reaction mixture to 9.0 to 9.3 using aqueous acid,

g) filtering the reaction mixture,

h) adding suitable calcium source to the filtrate obtained in step g),

i) heating the reaction mixture up to suitable temperature,

j) stirring the reaction mixture at same temperature,

k) cooling the reaction mixture to ambient temperature,

I) filtering the precipitated solid and washing with suitable solvent,

m) drying the solid compound to provide the crystalline form-M.

Wherein in step a) The suitable solvent is selected from polar solvents, ketone solvents and alcohol solvents, preferably water;

in step b) the suitable base is selected from alkali metal hydroxides* preferably sodium hydroxide;

in step e) the suitable solvent is selected from polar solvents, ketone solvents and alcohol solvents, preferably water;

in step f) the suitable acid is selected from inorganic acids such as hydrochloric acid, hydro bromic acid and hydro iodic acid; preferably hydrochloric acid;

in step h) the suitable calcium source is selected from calcium chloride, calcium hydroxide and calcium acetate; preferably calcium acetate;

in step i) the suitable temperature is 35°C to reflux temperature of the solvent used in the reaction;

in step k) ambient temperature refers to the temperature in the range of 25°C to 28°C.

in step l) the suitable solvent is selected from polar solvents, ketone solvents and alcohol solvents, preferably water;

The preferred embodiment of the present invention provides a novel process for the preparation of crystalline form-M of rosuvastatin calcium, which comprises of,

a) Taking the rosuvastatin tertiary butyl amine salt in water,
b) adding aqueous sodium hydroxide solution to the above reaction mixture,
c) *stirring the* reaction mixture for 1.5 hours at *20-25°C,*
d) expelling the tertiary butyl amine from the reaction mixture using nitrogen gas,
e) adding water to the reaction mixture,
f) adjusting the pH of the reaction mixture to 9.0-9.3 using aqueous HCl solution,
g) filtering the reaction mixture through micron filter paper,
h) adding aqueous calcium acetate solution to the filtrate obtained in step g),
i) heating the reaction mixture to 90-95°C,
j) stirring the reaction mixture for 4 hours at same temperature,
k) cooling the reaction mixture to ambient temperature,
l) filtering the precipitated solid and washed with water,
m) drying the solid compound under aerial conditions for 14 hours, further drying the compound at 35-40°C for 6 hours to provide the crystalline form-M.

According to the present invention crystalline rosuvastatin calcium is stable even at higher temperatures like 90-95 °C in water in terms of purity by HPLC and in terms of polymorph, there is no change in polymorph even after slurring the crystalline rosuvastatin calcium in water at higher temperatures. The crystalline form-M is free flow solid and easy to handle during formulation.

In accordance with the present invention, there is provided a pharmaceutical composition comprising a polymorphic form of rosuvastatin calcium and pharmaceutically acceptable carrier or diluent. The polymorphic form includes form M of rosuvastatin calcium.

PXRD analysis of rosuvastatin calcium were carried out using BRUKER/AXS X-Ray diffractometer using Cu, Ka radiation of wavelength 1.54 A° and continuous scan speed of 0.045°/min. The thermal analysis of rosuvastatin calcium was carried out on Waters DSC Q-10 model differential scanning calorimeter.

Rosuvastatin calcium was analyzed by HPLC using the following conditions: A liquid chromatograph is equipped with variable wavelength UV detector or PDA detector; Column: Phenomenex, CI8, 250 x 4.6 mm, 5.0 µm or equivalent; wavelength: 248 nm; Temperature: 25°C; Load: 20 µl; Run time: 70 min; and using a mixture of acetonitrile and water in the ration of 1:1 as a diluent and mixture of water: acetonitirle: methanol: triethylamine as a mobile phase.

The present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Example-1: Preparation of crystalline Form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyI-2-[methyI(methyIsuIfonyI)aminoIpyrimidin-5-yI](3R,5S)-3,5-dihydroxy hept-6-enoic acid] calcium:

To 50 grams of amorphous rosuvastatin calcium salt added a mixture of water (550 ml) and acetone (550 ml) at 27°C. The reaction mixture was heated to 40°C and then slowly cooled to 27°C. Stirred the reaction mixture for 20 hrs at the same temperature. Filtered the precipitated product and dried under aerial conditions to get the crystalline form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl(methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium.
Yield: 31 grams

Example-2: Preparation of crystalline Form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxy hept-6-enoic acid] calcium:

To 50 grams of amorphous rosuvastatin calcium salt added a mixture of water (500 ml) and methylisobutylketone (500 ml) at 27°C. The reaction mixture was heated to 40°C and then slowly cooled to 27°C. Stirred the reaction mixture for 20 hrs at the same temperature. Filtered the precipitated product and dried under aerial conditions to get the crystalline form-M of bis[(E)-7-(4-(4-fluorophenyl)-6-iso-propyl-2-[methyl(methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium.
Yield: 32.6 grams

Example-3: Preparation of crystalline Form-M of bis[(E)-7-[4-(4-fliiorophenyl)-6-iso-propyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl] (3R,5S)-3,5-dihy droxy hept-6-enoic acid] calcium:

To 10 grams of amorphous rosuvastatin calcium salt added water (100 ml) at 25-30°C. The reaction mixture was heated to 94°C and stirred for 10 hrs at same temperature. Cooled the reaction mixture to 25-30°C. Filtered the precipitated product and washed with water. Dried the product to get the crystalline form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl (methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium.

Yield: 9 grams

Purity by HPLC: 99.80%

Example-4: Preparation of crystalline Form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yI](3R,5S)-3,5-dihydroxy hept-6-enoic acid] calcium:

To 25 grams of rosuvastatin tertiary butyl amine salt added water (126.5 ml) and aqueous sodium hydroxide solution(1.8 grams dissolved in 21.5 ml of water) at 25-30°C. Stirred the reaction mixture for 90 minutes. Tertiary butyl amine was expelled using nitrogen gas. Water was added to the reaction mixture and pH of the reaction mixture was adjusted to 9.0-9.3 using aqueous hydrochloric acid. Aqueous calcium acetate (4.3 grams dissolved in 25 ml of water) was added to the reaction mixture at 25 to 30°C and heated the reaction mixture to 90-95°C. Stirred the reaction mixture for 4 hours at 90-95°C. Cooled the reaction mixture to 25-30°C, filtered the precipitated compound and washed with water. Dried the compound to get crystalline form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl (methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium.

Yield: 19 grams

Purity by HPLC: 99.76%

We Claim:

1. A novel crystalline form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl (methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium characterized by its X-ray powder diffraction pattern shows peaks at 3.33, 5.30, 7.52 and 22.46 ± 0.2 degrees 2Θ
2. A novel crystalline form-M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl (methyl suifonyi)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium (Rosuvastatin calcium) of claim 1 is further characterized by its PXRD shown peaks at 10.37 and 20.45 ± 0.2 degrees 2Θ
3. A novel crystalline form M of bis[(E)-7-[4-(4-fluorophenyl)-6-iso-propyl-2-[methyl (methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium of claim 1 or 2 is further characterized by its DSC thermogram showing endotherm at about 103.3°C and another endotherm at about 175.7°C.
4. A process for the preparation of novel crystalline form-M of rosuvastatin calcium comprising of the following steps,
   a) Taking the amorphous rosuvastatin calcium in a mixture of ketone solvent and water,
   b) warming the mixture to obtain a clear solution,
   c) cooling the reaction mixture to ambient temperature and stirring for 15-20 hours,
   d) filtering the precipitated solid,
   e) drying the solid compound under aerial conditions to provide the crystalline form-M of rosuvastatin calcium.
5. A process for the preparation of novel crystalline form-M of rosuvastatin calcium comprising of the following steps,
   a) Taking the amorphous rosuvastatin calcium in a suitable solvent,
   b) heating the mixture up to the suitable temperature,
   c) stirring the reaction mixture,
   d) cooling the reaction mixture to ambient temperature,
   e) filtering the precipitated solid,
   f) drying the solid compound to provide the crystalline form-M of rosuvastatin calcium.

6. A process according to claim 4, wherein in step a) the ketone solvent is acetone.

7. A process according to claim-5, wherein

in step a) The suitable solvent is selected from polar solvents like water, ketone solvents and alcohol solvents, preferably water;

in step b) the suitable temperature is 35°C to reflux temperature of the solvent used in the reaction;

in step d) ambient temperature refers to the temperature in the range of 25°C to 28°C.

8. A novel process for the preparation of crystalline form-M of rosuvastatin calcium, which comprising of,

a) Taking the rosuvastatin tertiary butyl amine salt in a suitable solvent,
b) adding aqueous base solution to the above reaction mixture,
c) stirring the reaction mixture,
d) expelling the tertiary butyl amine from the reaction mixture using nitrogen gas,
e) adding suitable solvent to the reaction mixture,
f) adjusting the pH of the reaction mixture to 9.0-9.3 using aqueous acid,
g) filtering the reaction mixture,
h) adding suitable calcium source to the filtrate obtained in step g),
i) heating the reaction mixture up to suitable temperature,
j) stirring the reaction mixture at same temperature,
k) cooling the reaction mixture to ambient temperature,
l) filtering the precipitated solid and washing with suitable solvent,
m) drying the solid compound to provide the crystalline form-M of Rosuvastatin calcium.

9. A process according to claim-8, wherein

in step a) The suitable solvent is selected from polar solvents like water, ketone solvents and alcohol solvents, preferably water;

in step b) the suitable base is selected from alkali metal hydroxides, preferably sodium hydroxide;

in step e) the suitable solvent is selected from polar solvents, ketone solvents and alcohol solvents, preferably water;

in step f) the suitable acid is selected from inorganic acids such as hydrochloric acid, hydro bromic acid and hydro iodic acid; preferably hydrochloric acid;

in step h) the suitable calcium source is selected from calcium chloride, calcium hydroxide and calcium acetate; preferably calcium acetate;

in step i) the suitable temperature is 35°C to reflux temperature of the solvent used in the reaction;

in step k) ambient temperature refers to the temperature in the range of 25°C to 28°C;

in step I) the suitable solvent is selected from polar solvents, ketone solvents and alcohol solvents, preferably water.

10. A process for the preparation of novel crystalline. form-M of rosuvastatin calcium comprising of the following steps,

a) Taking the amorphous rosuvastatin calcium in water,
b) heating the reaction mixture to 90-95°C,
c) stirring the reaction mixture for 10 hours at 90-95 °C,
d) cooling the reaction mixture to ambient temperature,
e) filtering the precipitated solid,
f) drying the solid compound under aerial conditions for 22 hours, further drying the compound at 35-40°C for 6 hours to provide the crystalline form-M of rosuvastatin calcium.

11. A process for the preparation of novel crystalline fo.rm-M of rosuvastatin calcium comprising of the following steps,

a) Taking the rosuvastatin tertiary butyl amine salt in water,
b) adding aqueous *sodium hydroxide solution to* the above reaction mixture,
c) stirring the reaction mixture for 1.5 hours at 20-25°C,
d) expelling the tertiary butyl amine from the reaction mixture using nitrogen gas,
e) adding water to the reaction mixture,
f) adjusting the pH of the reaction mixture to 9.0 using aqueous HC1 solution,
g) filtering the reaction mixture through micron filter paper,
h) adding aqueous calcium acetate solution to the filtrate obtained in step g),
i) heating the reaction mixture to 90-95°C,

j) stirring the reaction mixture for 4 hours at same temperature,

k) cooling the reaction mixture to ambient temperature, .

1) filtering the precipitated solid and washing with water,

m) drying the solid compound under aerial conditions for 14 hours, further drying the compound at 35-40°C for 6 hours to provide the crystalline form-M.

12. Crystalline rosuvastatin calcium obtained according to any one of the preceding claims having purity greater than 99.50%, preferably greater than 99.75%, more preferably 99.90% by HPLC.

13. Use of rosuvastatin calcium crystalline form-M in the preparation of pharmaceutical composition.

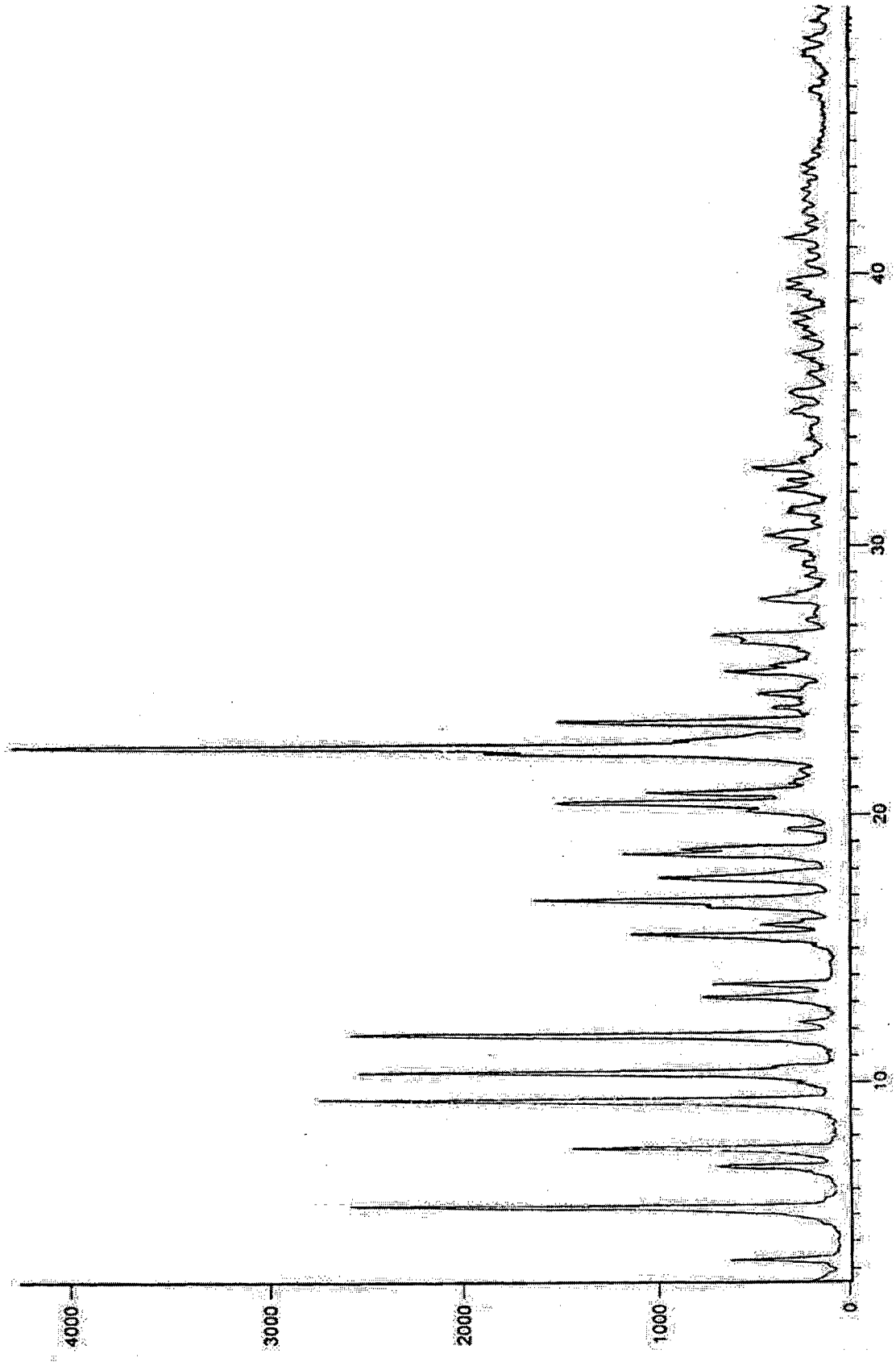


Figure-1

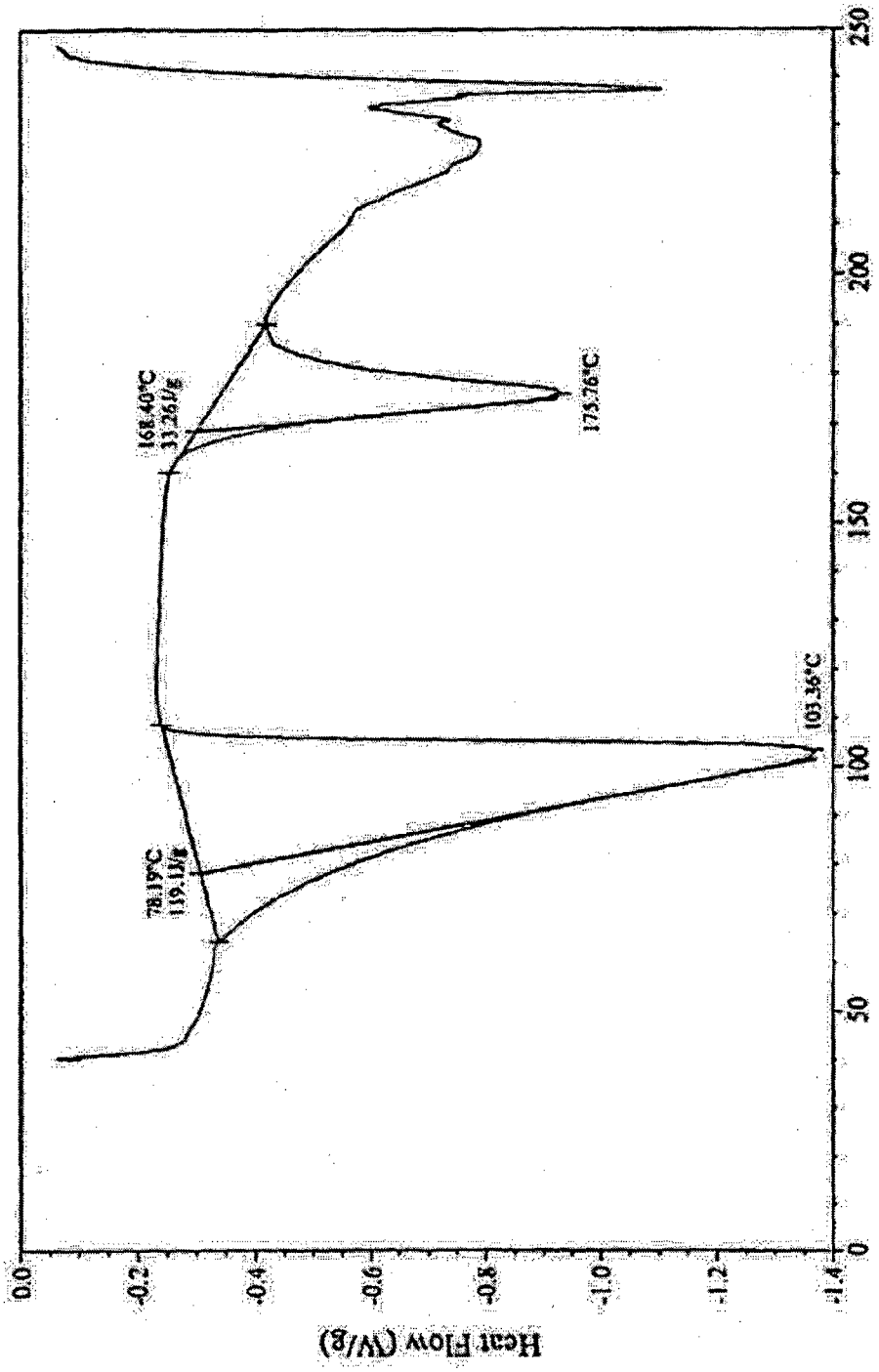

Heat Flow (W/g)
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
0
50
100
150
200
250
Temperature (°C)
78.19°C
119.1J/g
103.36°C
168.40°C
33.26J/g
175.76°C

Figure-2