Title: Process for the preparation of amorphous atorvastatin calcium from crystalline atorvastatin calcium.

Abstract:
The present invention relates to the process for the preparation of amorphous form of Atorvastatin calcium which comprises the conversion of crystalline Atorvastatin calcium to amorphous Atorvastatin calcium.

Keywords:
Amorphous Atorvastatin calcium; Crystalline Atorvastatin calcium; lipid lowering agent; 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA); Non-hydroxylic solvents.

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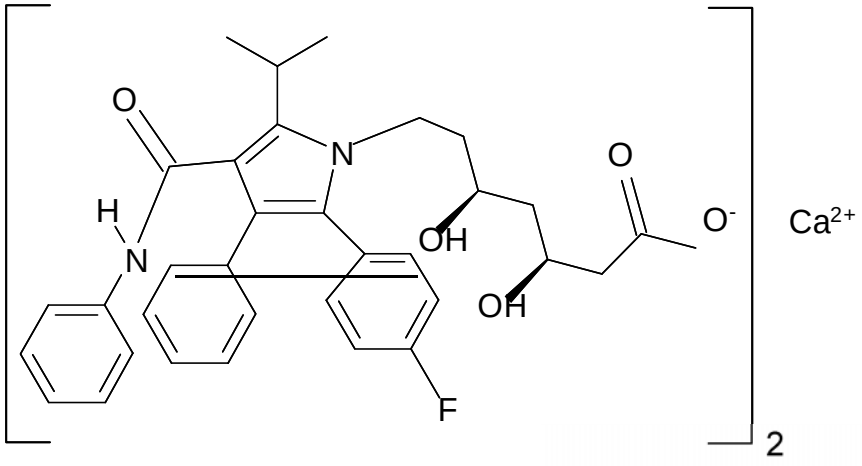
Introduction:

Atorvastatin calcium is a drug compound that is used as a lipid-lowering agent, for treating hypercholesterolemia. The compound has the chemical name[R-(R*,R*)]-2-(4-fluorophenyl)-3,ö-dihydroxy-5-(1-methylethyl)-3-phenyl-4-{(phenylamino)carbonyl}-1H-pyrolle-1-hepatonic acid, calcium salt (2:1) trihydrate. Pharmaceutical products containing crystalline atorvastatin calcium trihydrate are sold using the trademark LIPITOR.



Atorvastatin calcium exists in various crystalline and amorphous forms. The amorphous form is of interest, due to atleast in part to its enhanced solubility as compared to crystalline forms, a higher solubility thought to provide an improved bioavailability profile. It has been disclosed that the amorphous forms of a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability pattern compared to crystalline form (Konno T., Chem. Pharma. Bull., 1990;38:2003-2007).

The second aspect of the present invention is a method of using amorphous atorvastatin calcium to treat subjects suffering from hypercholesterolemia and/or hyperlipidemia, osteoporosis, benign prostatic hyperplasia (BPH) and Alzheimer's disease.

Brief Description:

The conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway. This step is catalyzed by the enzyme HMG-CoA reductase. Statins inhibit HMG-CoA reductase from catalyzing this conversion. As such, statins are collectively potent lipid lowering agents.

A number of patents have issued disclosing atorvastatin, formulations of atorvastatin, as well as processes and key intermediates for preparing atorvastatin. Additionally, a number of published International Patent Applications and patents have disclosed processes which doesnot produce Atorvastatin calcium in its amorphous form consistently. Often a mixture of crystalline and amorphous form is obtained which is not suitable for filtration and drying and therefore not desirable process for large scale production.

The present invention provides a novel process for the preparation of amorphous Atorvastatin calcium which comprises of following steps:

a) dissolving crystalline atorvastatin calcium in a non-hydroxylic solvent;
b) adding the dissolved atorvastatin calcium to the non-polar anti-solvent to precipitate out atorvastatin calcium; and
c) removing the solvent by filtration to afford amorphous atorvastatin calcium.

Amorphous atorvastatin calcium is formed by precipitation by a process in which a solution of atorvastatin calcium is added to a non-solvent mixture comprising a non-polar solvent and a hydroxylic co-solvent. Solvents suitable for dissolving atorvastatin calcium include, for example, polar organic solvents in which atorvastatin calcium is soluble.

Non-solvents suitable for use in the present process include alkanes and other non-polar anti-solvents and low polarity solvents, such as, for example, hexane, heptane fraction, n-heptane and cycloalkanes, such as, cyclohexane, and the like, as well as other non-polar and low-polar solvents, such as, for example, toluene, isopropyl ether. The non-hydroxylic solvent used in the preferred embodiment of this invention include organic solvents containing one or more hydroxyl groups like 1, 4-Dioxane. Solvents used for dissolution can be any solvent in which atorvastatin is soluble. Preferably atorvastatin has solubility of atleast 1 wt% and mo re preferably at least 5 wt% in the

dissolving solvent. Preferably, the solvent is also volatile with the boiling point of 150°C or less.

In addition the solvent should have relatively low toxicity and be able to be removed from the amorphous atorvastatin to a level that is acceptable according to The International Committee on Harmonization (ICH) guidelines.

Generally, crystalline atorvastatin calcium is dissolved in a non-hydroxylic solvent, e.g. 1, 4-Dioxane, at an ambient temperature and a non-polar hydrocarbon, is added at 0°C to 5°C preferably at 25 -30°C. The product is recovered by filtration at ambient temperature. Filtered material, a semi-dry powder, is further dried to remove the surface solvents in a vacuum tray drier, tray drier, fluid bed drier or a rotary vacuum drier at about 20°C to about 80°C for 6 to 48 hours to afford amorphous material.

Amorphous atorvastatin calcium prepared according to the process of the present invention may be characterized by its x-ray powder diffraction pattern as shown in the accompanied drawings. X-ray powder diffraction patterns show no peaks which demonstrate the amorphous nature of the product.

Brief Description of the Figures:

The given figure 1 shows a powder X-ray diffraction diffractogram of amorphous atorvastatin calcium.

Detailed Description of the Invention:

Preparation of amorphous Atorvastatin calcium:

Example 1:

Crystalline atorvastatin calcium (0.5gm) was dissolved in 1, 4-Dioxane (50ml) at 40-45°C in 15-20 min to obtain a clear solution. This solution was added in drop wise manner to cyclohexane (500ml) at 25-30°C for 20-25min.The material precipitated during the addition. The contents were stirred for 2 hours at 25-30°C, filtered and dried for 48 hours at 45-50°C in oven under vacuum. Amorphous atorvastatin calcium thus obtained was 4.2 gm (84 %).

Relative Purity (HPLC)	99.5%
Assay (OAB, HPLC)	98.9%
FTIR (KBr)	3407, 2964, 2930, 1665, 1595, 1562, 1527, 1506, 1435, 1321, 1223, 1156, 1109, 842, 752 cm^{-1}
Residual Solvent:	
1, 4-Dioxane	20 ppm
Cyclohexane	2000ppm

Example 2:

Crystalline atorvastatin calcium (1.0gm) was dissolved in ,4- Dioxane (10ml) at 45-50°C in 15-20 mins to obtain a clear solution. This was then added dropwise to n-heptane (100ml) at 25-30°C for 15-20 min. The material precipitates during the addition. The contents were stirred for 2 hours at 25-30°C. Then it was filtered and dried for 15 hours at 45-50°C in oven under vacuum. This resulted in the formation of 0.85 gm (85%) amorphous atorvastatin calcium.

Relative Purity (HPLC)	99.6%
Assay (OAB, HPLC)	99.2%
Calcium content	3.09%
FTIR (KBr)	3407, 2964, 2931, 1665, 1595, 1563, 1525, 1506, 1435, 1321, 1225, 1156, 1109, 843, 752 cm^{-1}
Residual Solvent:	
1, 4-Dioxane	30 ppm
n-Heptane	1500 ppm

Example 3:

Crystalline atorvastatin calcium (1.0gm) was dissolved in 1, 4-Dioxane (10ml) at 45-50°C in 15-20 min. A clear solution was obtained. Then this solution was added to Methyl, t-butyl ether (100ml) dropwise at 25-30°C for 15-20 min. Precipitation reaction was observed. The reaction mass was stirred for 2 hours at 25-30°C, filtered and dried for 15 hours at 45-50°C in oven under vacuum. Amorphous atorvastatin thus obtained was about 0.7gm (70%).

Relative Purity (HPLC)	99.9%
Assay (OAB, HPLC)	99.5%
Calcium content	3.13%
FTIR (KBr)	3409, 2966, 2931, 1668, 1595, 1563, 1525, 1508, 1437, 1321, 1227, 1156, 1108, 843, 754 cm^{-1}
Residual Solvent:	
1, 4-Dioxane	25 ppm
Methyl, t-butyl ether	2200 ppm

Example 4:

Crystalline atorvastatin calcium (1.0gm) was dissolved in 1, 4-Dioxane (10ml) at 45-50°C in 15-20 min. This gave a clear solution. This clear solution was then added in dropwise manner to methyl, t-butyl ether (100ml) at 25-30°C for 15-20 min. The material was precipitated while addition of the above solution. The reaction mass was then stirred for 2 hours at 25-30°C, filtered and then dried for 12 hours at 50-55°C in oven under vacuum. 0.7 gm (70%) amorphous atorvastatin calcium was obtained.

Relative Purity (HPLC)	99.9%
Assay (OAB, HPLC)	99.6%
Calcium content	3.15%

FTIR (KBr)	3409, 2967, 2931, 1668, 1595, 1563, 1525, 1509, 1437, 1325, 1227, 1156, 1108, 843, 757 cm^{-1}
Residual Solvent:	
1, 4-Dioxane	22 ppm
Methyl, t-butyl ether	2300 ppm

Example 5:

(1.0gm) Crystalline atorvastatin calcium was dissolved in a mixture of t-butanol (150ml) and methanol (40ml) at 80-85°C in 1 hour. The clear solution thus obtained was stirred at 20-25°C for 2 hours. The recrystallized material was then filtered and dried or 15 hours at 50-55°C which gave 0.85 gm of amorphous atorvastatin calcium.

Relative Purity (HPLC)	99.7%
Assay (OAB, HPLC)	99.7%
Calcium content	3.20%
FTIR (KBr)	3409, 2967, 2931, 1663, 1595, 1566, 1525, 1509, 1437, 1324, 1229, 1156, 1108, 848, 755 cm^{-1}
Residual Solvent:	
t-butanol	20 ppm
Methanol	200 ppm

Example 6:

Crystalline atorvastatin calcium (1.0gm) was dissolved in a mixture of preheated acetonitrile (100ml) and toluene (200ml) at 70-75°C for 30-40 min. This clear solution was evaporated to about 1/10 th volume. This concentrated solution was added in dropwise to Methyl, t-butyl ether (250ml). The material precipitated during addition. The contents were stirred for 2 hours at 25-30°C, filtered and dried for 6 hours at 50-55°C in under vacuum that gave 0.65gm (65%) of amphours atrovastatin calcium.

Relative Purity (HPLC)	99.8%
Assay (OAB, HPLC)	99.9%
Calcium content	3.27%
FTIR (KBr)	3401, 2965, 2931, 1669, 1595, 1563, 1525, 1506, 1439, 1321, 1224, 1156, 1107, 843, 751 cm^{-1}
Residual Solvent:	
Acetonitrile	200 ppm
Toluene	200 ppm
Methyl, t-butyl ether	2100 ppm

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