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Preparation of stable new polymorphic form of atorvastatin calcium

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ABSTRACT

*An efficient, simple, consistent and economic process for stable new polymorphic form of atorvastatin calcium **(1)** is described. The new polymorphic form of atorvastatin calcium **(1)** is characterizated by PXRD.*

Key words: atorvastatin calcium, polymorphism, PXRD.

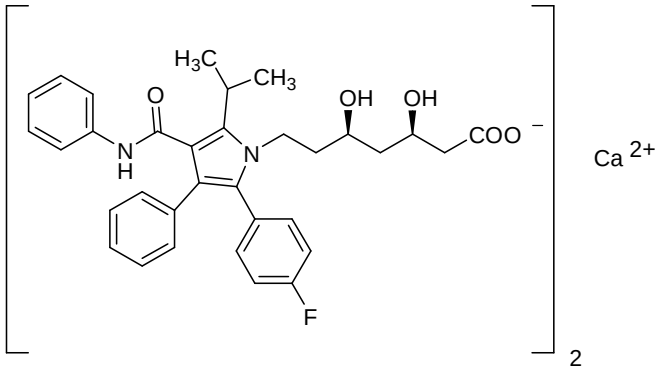
INTRODUCTION

Atorvastatin calcium **(1)** is a member of the class of drugs called statins. Statin drugs are currently the most therapeutically effective drugs available for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. A high level of LDL in the blood stream has been linked to the formation of coronary lesions which obstruct the flow of blood and can rupture and promote thrombosis.[1-3] Atorvastatin calcium **(1)** is chemically known as [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). Atorvastatin calcium **(1)** is marketed as the hemi calcium salt trihydrate under the trade name LIPITOR® by Pfizer. [4]

Crystalline and amorphous forms (polymorphic) have different properties due to the unique arrangement of molecules in the crystal lattice varying density of packing, and/or by varying hydrogen-bond network. Accordingly, individual crystalline and amorphous form may be thought of as distinct solids having distinct advantageous and/or disadvantageous and/or physical properties compared to other polymorphic form. A single molecule, like the atorvastatin calcium **(1)** may give rise to a variety of solids having distinct physical properties like melting point, X-ray diffraction pattern, and IR spectrum. The differences in the physical properties of

polymorphs result from the orientation and intermolecular interaction of adjacent molecules in the bulk solid. One of the most important physical properties of pharmaceutical polymorphs is their solubility in aqueous solution, particularly their solubility in the gastric juices of a patient. On the other hand, where the effectiveness of a drug correlates with peak blood stream levels of the drug, a more rapidly dissolving form is likely to exhibit increased effectiveness over a comparable amount of a more slowly dissolving form.

(**1**)



Atoravastatin calcium **(1)** exhibits several polymorphic forms reported in the literature.[5-13] The discovery of new polymorphic forms of a pharmaceutically useful compound provide a new opportunity to improve the performance characteristics of a pharmaceutical product. We have now found a new polymorphic form of atorvastatin calcium **(1)**, which is stable, reproducible and suitable for preparing pharmaceutical dosage forms.

MATERIALS AND METHODS

Experimental

The X-ray powder diffractogram is obtained using a Seifert, XRD 3003 TT system. The X-ray generator was operated at 40 kv and 30 mA, using the Kα line of copper at 1.540598 A° as the radiation source. It is scanned in the diffraction range of 2.4° to 40° 2θ at a scan rate of 0.03° 2θ.

Preparation of new polymorphic form of atorvastatin calcium (1): *Tert*-Butyl (4R,6R)-2-[[6-[2-4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrol-1–yl]ethyl-2-dimethyl-1,3-dioxan-4-yl]acetate **(2)** (150 g) was suspended in a mixture of 10% w/w aqueous ethanol (3000 ml). Catalytic amount of 2,6-bis(1,1-dimethylethyl)-4-methylphenol (0.45 g) was added to the above suspension. Then, 10% w/w aqueous hydrochloric acid (91.88 g) was added and stirred for 4h at 40-45°C. The reaction mass was cooled to 18-20°C. 10% w/w aqueous sodium hydroxide (241.67 g) was added and stirred for 2h at 18-20°C. After completion of reaction, the reaction mixture was treated with activated carbon (40.15 g) for 30 min at 20-30°C and filtered through hyflo bed. The clear filtrated pH was adjusted to 12.0-12.5 with 10% w/w aqueous hydrochloric acid and concentrated at < 35°C under reduced pressure. The obtained concentrated mass was dissolved in a mixture of ethanol and DM water (1:5 v/v, 1800 mL), washed with methyl tert-butyl ether (2 x 600 mL), adjusted the pH to 9.0-9.5 with 10% w/w aqueous hydrochloric acid and obtained aqueous reaction mass of atorvastatin sodium. 4.15 % w/w aqueous calcium acetate solution (626 g, 0.65 m.eq) was added to the reaction mass of atorvastatin sodium at 55-60°C.

The slurry was cooled to 40-42°C and stirred for 30 min, filtered, washed with 1:2 mixture of ethanol and DM water (1200 mL) followed by methyl tert-butyl ether (600 mL) and hot DM water (600 mL). The resulting wet solid was suspended in methyl tert-butyl ether (750 mL) and DM water (300 mL), and treated with 10% w/w aqueous hydrochloric acid (91.88 g) for 1h at 20-30°C. The organic layer was washed with DM water (2 x 600 mL) and concentrated at 35°C under reduced pressure. The concentrated reaction mass was dissolved in a mixture of 10% w/w aqueous ethanol (3000 mL). 2,6-bis(1,1-dimethylethyl)-4-methyl phenol (0.45 g) was added. Then, 10% w/w aqueous sodium hydroxide (241.67 g) was added and stirred for 2h at 18-20°C. After hydrolysis, the reaction mixture was treated with activated carbon (40.15 g) for 30 min and filtered through hyflo bed. The clear filtrate pH was adjusted to 12.0-12.5 with 10% w/w aqueous hydrochloric acid and concentrated at <35°C under reduced pressure. The resulting solid was dissolved in a mixture of ethanol and DM water (1:5 v/v, 1800 mL), washed with methyl tert-butyl ether (2 x 600 mL), adjusted the pH to 9.0-9.5 with 10% w/w aqueous hydrochloric acid and obtained aqueous reaction mass of atorvastatin sodium. Separately, calcium acetate (26.24 g) was dissolved in DM water (600 mL), and added to the reaction mass of atorvastatin sodium at 55-60°C. The slurry was cooled to 40-42°C and stirred for 30 min, filtered, washed with 1:2 mixture of ethanol and DM water (1200 mL) followed by methyl tert-butyl ether (600 mL) and hot DM water (600 mL). The product was dried at 50-60°C under reduced pressure for 8 hr to yield the atorvastatin calcium **(1)** (116.79 g, yield = 88.24%).

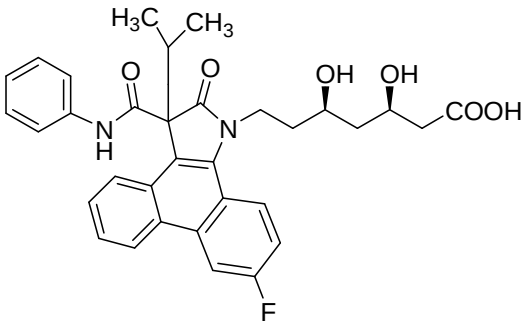
RESULT AND DISCUSSION

Stability studies of commercially available atorvastatin calcium amorphous were carried out at different temperature with different relative humidity (RH) and the reports are presented in table-1**.**

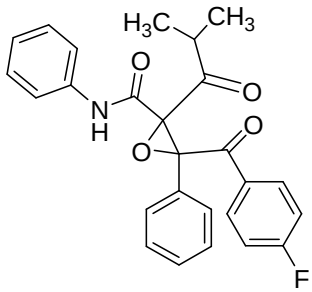
Table-1: Stability studies of atorvastatin calcium (1)

S.No.	Conditions Time /temperature/RH	Atorvastain calcium **(1)** purity (by HPLC)	Impurity-1	Impurity-2
01	Initial	99.56 [a]	0.04	0.03
02	1M/25°C/60%	99.50	0.10	0.06
03	2M/25°C/60%	99.43	0.11	0.06
04	3M/25°C/60%	99.41	0.10	0.08
05	6M/25°C/60%	99.35	0.11	0.09

[a]*rest of impurities of atorvastatin calcium is within the specification limit*



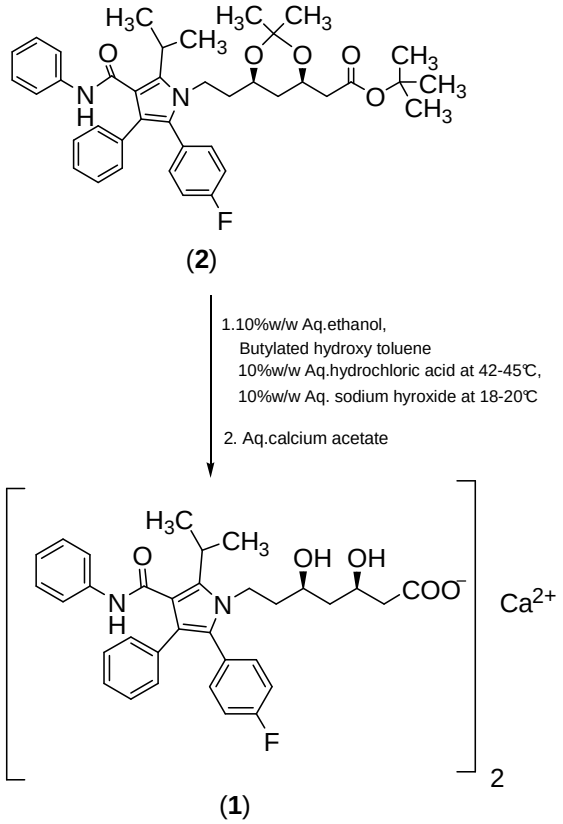
Impurity-1



Impurity-2

From the above stability studies, it was clearly understood that the atorvastatin calcium **(1)** was stable at 25°C at 60 % RH for two months. The purity of atorvastatin calcium **(1)** was decreased from 99.56 % to 99.35 %. Impurity-1 and impurity-2 were increased from 0.04%, 0.03% to 0.11%, 0.09% respectively. Surprisingly we found that, these impurities can be removed by making new polymorphic form of atorvastatin calcium **(1)**.

Scheme-1: Preparation of new polymorphic form of atorvastatin calcium (1)



Diprotected atorvastatin **(2)** was treated with aqueous hydrochloric acid in aqueous ethanol to remove acetyl group. The resulting reaction mass was hydrolysis with aqueous sodium hydroxide solution. After hydrolysis, the reaction mixture pH was adjusted to 9.0 with aqueous hydrochloric acid and evaporated to remove solvent. The residue obtained was dissolved in aqueous ethanol and washed with methyl tert-butyl ether. Further the aqueous layer was treated with aqueous calcium acetate. The precipitated solid was filtered. The wet solid was treated with aqueous hydrochloric acid in methyl tert-butyl ether. The organic layer was washed with DM water and concentrated under reduced pressure. The resulting concentrated mass was dissolved in aqueous ethanol and treated with aqueous sodium hydroxide solution. The reaction mixture pH was adjusted to 9.0 with aqueous hydrochloric acid, and concentrated under reduced pressure. The solid mass obtained was dissolved in aqueous ethanol and washed with methyl tert-butyl ether. Further the aqueous layer was treated with aqueous calcium acetate. The precipitated product was filtered and dried to yield new polymorphic from of atorvastatin calcium **(1)** (Fig. 1)

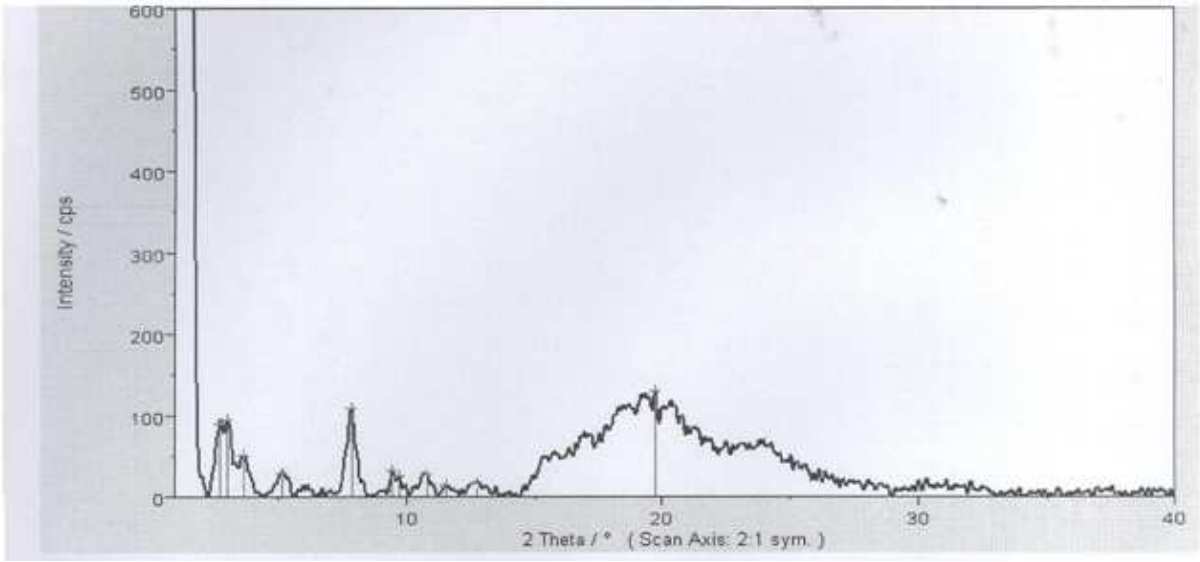


Fig-1: PXRD

CONCLUSION

We have developed an improved, simple and commercially scalable process for the atorvastatin calcium new polymorphic form, which is reproducible and suitable for preparing pharmaceutical dosage form the product having enhanced stability.

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