Original Article

Detection of Impurities in a tablet of Atorvastatin

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Abstract

Identification of impurities and their amounts in the atorvastatin bulk drug and tablet DIVASTINTM (20 mg) were done using HPLC with diode array detector. The composition of mobile phase was acetonitril:phosphate buffer (45:55%; pH 4.0) with flow rate of 0.5 mL/min and detected at 248 ± 8 nm. Four impurities (desfluoro atorvastatin, distereoisomer, 3-o-methyl atorvastatin and lactone atorvastatin) were detected in the bulk drug whereas five impurities were detected in the tablet DIVASTINTM (20 mg). The total amounts of impurities in atorvastatin bulk drug and tablet were 0.804 and 0.983% respectively. In conclusion, the total amount of impurities was less than 1% which is acceptable.

Introduction

Atorvastatin is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor that has been demonstrated to be efficacious in reducing both cholesterol and triglyceride (Bakker-Arkema et al., 1996). It is administered as the calcium salt of the active hydroxy acid and is used between 10 and 80 mg per day to reduce the raised lipid levels in patients with primary hyperlipidemia.

The presence of impurities in the tablets reflects the quality of the manufacturing process for the bulk drug, so that high manufacturing standards and practices should translate to reduced impurity levels). The presence of impurities even in small amounts may influence the efficacy and safety of the pharmaceutical products. There are 2 types of impurities in medicines: (1) impurities associated with active pharmaceutical ingredients and (2) impurities that are created during formulation and or with aging or that are related to the formulated forms (Roy, 2002).

At least 20 impurities are identified of which four important impurities are atorvastatin diol methyl ester, lactone atorvastatin, diastereo-isomer atorvastatin, desfluoro-atorvastatin and 3-0-methyl atorvastatin. Atorvastatin lactam impurity is the photodegradation product.

The purpose of this study is to examine the presence of impurities in tablet DIVASTINTM.

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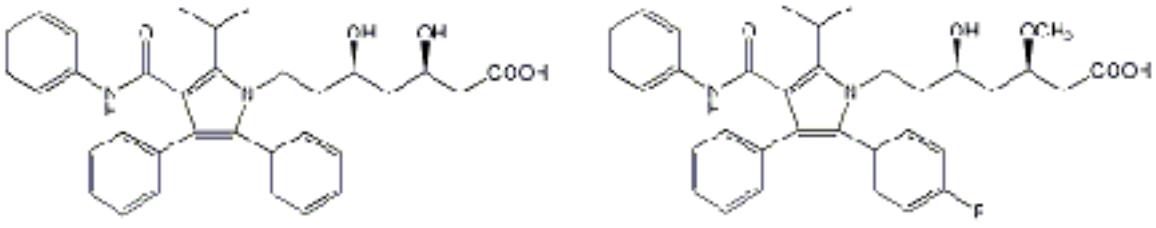
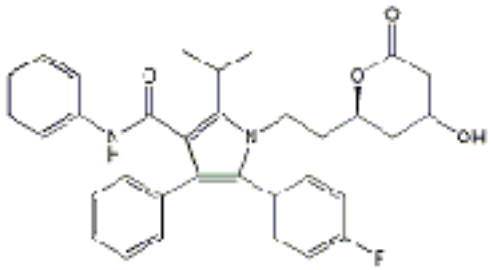
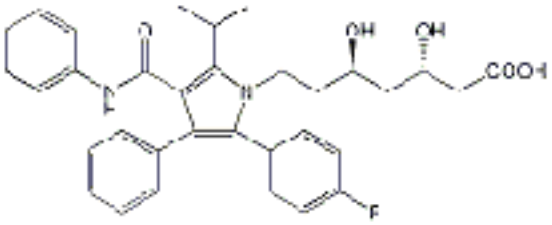
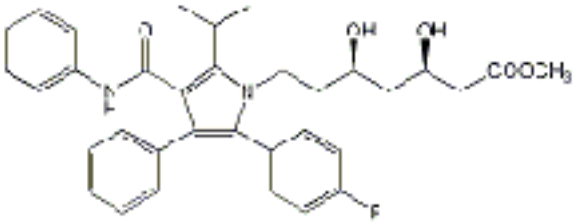


Desfluoro-atorvastatin atorvastatin 3-o-Methyl





Lactone atorvastatin 3S,5R-Atorvastatin



Atorvastatin methyl ester

Materials and Methods

Chemicals: Atorvastatin and its five impurities-desfluoro atorvastatin, distereoisomer, 3-o-methyl atorvastatin, lactone atorvastatin, and diol methyl ester were supplied by Cadila Healthcare Ltd, Ahmedabad, India. HPLC grade acetonitril was purchased from E. Merck (Germany). Tablet DIVASTINTM (20 mg; atorvastatin calcium trihydrate, batch number: TAB/D 153:0509) was supplied by Drug International Ltd, Bangladesh.

Chromatographic condition: The HPLC-UV diode-array system consisted of Agilent model 1200 series solvent delivery pump, degasser, autosampler, column oven and photo diode array detector. Chromatographic data were collected and analyzed using ChemStation software.

A reverse-phase high performance liquid chromatography (HPLC) was used for the determination of atorvastatin both in atorvastatin bulk drug and tablet DIVASTINTM (20 mg) (Ertu¨rk et al., 2003). The chromatographic analyses were performed on an Agilent 5 ?m C18 column (150 x 4.6 mm). The mobile phase used for analysis consisted of 45% acetonitril (HPLC grade; E. Merck, Germany) and 55% sodium di-hydrogen phosphate buffer (pH 4.0, adjusted with o-phosphoric acid) was delivered at a rate of 0.5 mL/min. The phosphate buffer was prepared freshly on each day of experiment and filtered using 0.45 m nylon filter. Separations were achieved at 50℃. The wavelength was set at 248 nm (bandwidth 8 nm). Injection of sample (20 ?L) was done using an autosampler. The peak with retention time and area were defined using software.

Identification of impurities: One milligram of each impurity (desfluoro atorvastatin, distereoisomer, 3-o-methyl atorvastatin, lactone atorvastatin, and diol methyl ester) was dissolve into the mobile phase separately and then diluted into different concentrations. One microgram of each sample was injected into the HPLC system separately to identify the peak using retention time. Then all the above mentioned impurities with atorvastation (1 g each) were mixed in mobile phase of which 20 L was injected.

One tablet DIVASTINTM (20 mg) was powdered and dissolved in 20 mL of mobile phase (1 mg/mL). It was then diluted to 50 g/mL using mobile phase and finally filtered using syringe filter 0.22 m. Twenty microliter of the sample was injected into the HPLC system.

Results and Discussion

The peak of the standard desfluoro atorvastatin appeared first with a retention time of 17.4 min (Figure 1). Other peaks were: distereoisomer (18.7 min), 3-o-methyl atorvastatin (34.9 min), lactone atorvastatin (40.3 min) and diol methyl ester (53.0 min).

When atorvastation bulk drug was injected, all the peaks except diol methyl ester appeared in the chromatogram (Figure 2). Among the impurities highest amount (0.29%) was 3-o-methyl atorvastatin (peak 4, Table I). The total amount of impurities in bulk drug was 0.804%.

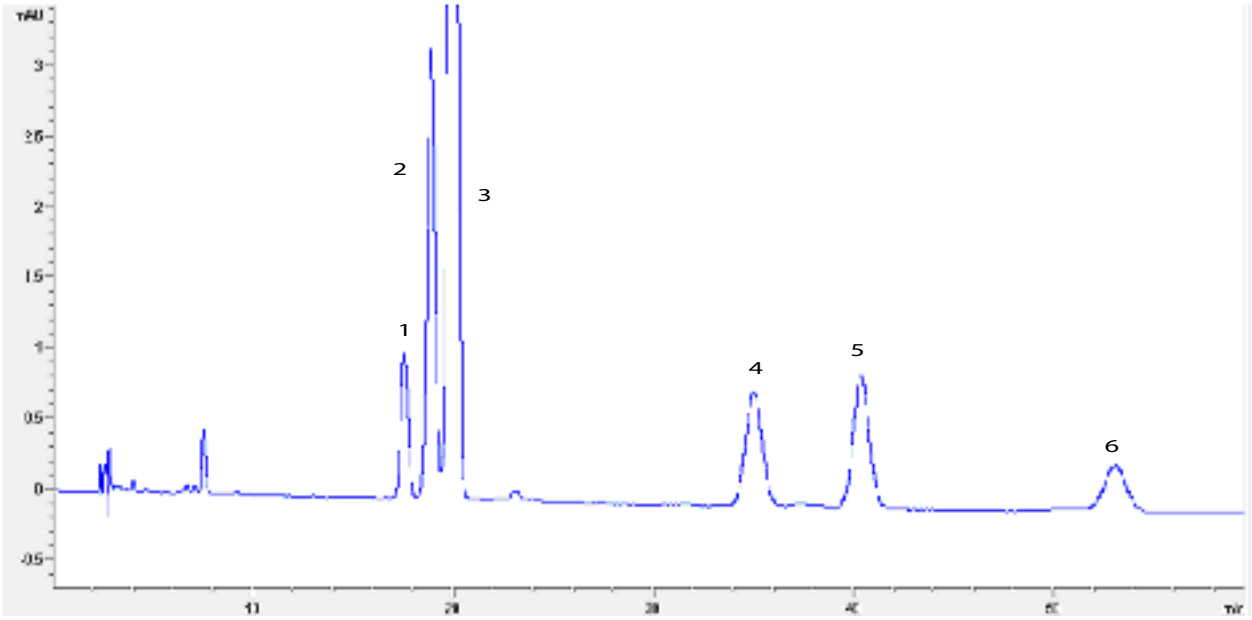


Figure 1: Chromatogram shows peaks of atorvastatin standard and its impurities. Peak 3 was the atorvastatin (19.8 min). Peaks of impurities were desfluoro atorvastatin (peak 1, retention time- 17.4 min), distereoisomer (peak 2, retention time- 18.7 min), 3-o-methyl atorvastatin (peak 4, retention time- 34.9 min), lactone atorvastatin (peak 5, retention time- 40.3 min) and diol methyl ester (peak 6, retention time- 53.0 min). The concentration of each peak was 1 g/mL. The volume of drug injected was 20 L.

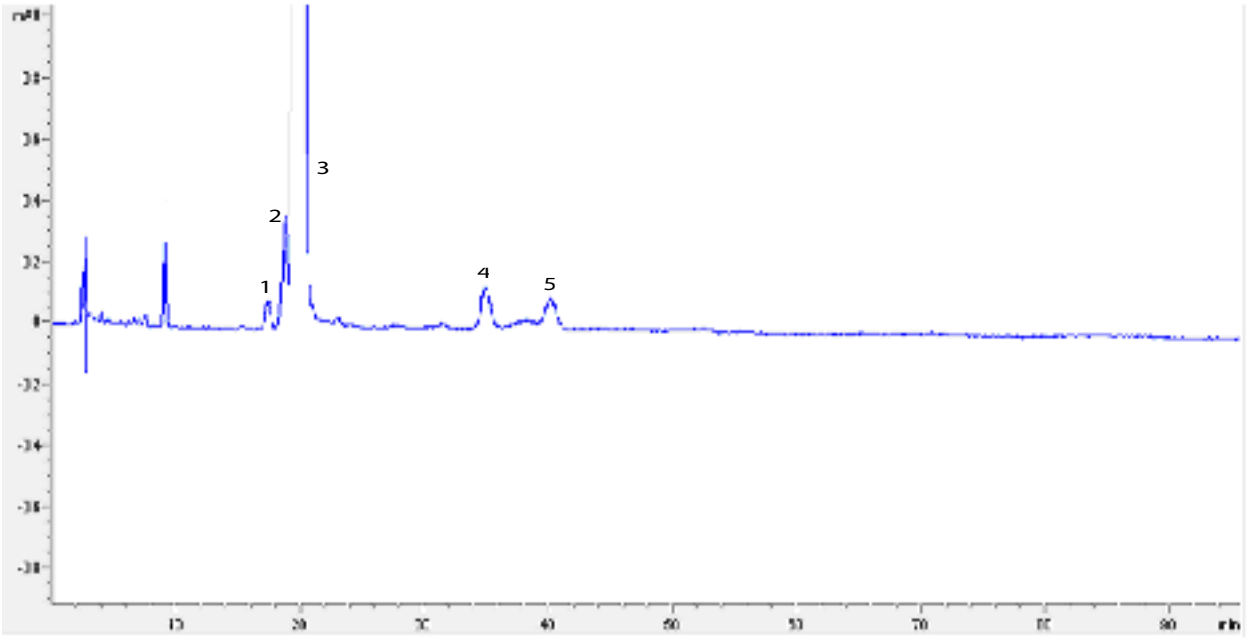


Figure 2: Chromatogram shows peaks of atorvastatin and its impurities in atorvastatin bulk drug. Peak 3 was the atorvastatin (19.7 min). Peaks of impurities were desfluoro atorvastatin (peak 1, retention time- 17.3 min), distereoisomer (peak 2, retention time- 18.6 min), 3-o-methyl atorvastatin (peak 4, retention time- 34.9 min) and lactone atorvastatin (peak 5, retention time- 40.1 min). The volume of drug injected was 20 L.

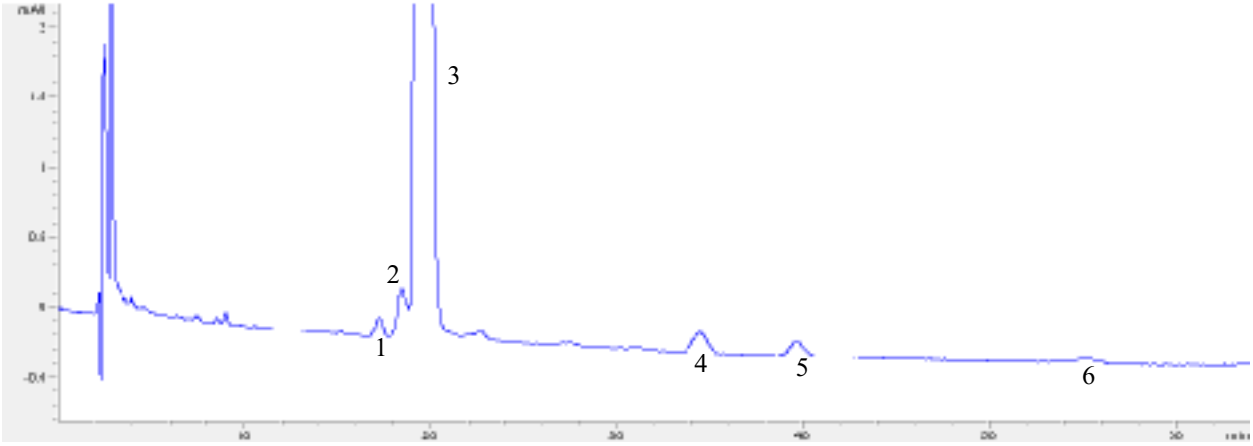


Figure 3: Chromatogram shows peaks of atorvastatin and its impurities in tablet DIVASTINTM (20 mg). Peak 3 was the atorvastatin (19.5 min). Peaks of impurities were desfluoro atorvastatin (peak 1, retention time- 17.1 min), distereoisomer (peak 2, retention time- 18.4 min), 3-o-methyl atorvastatin (peak 4, retention time- 34.4 min), lactone atorvastatin (peak 5, retention time- 39.5 min) and diol methyl ester (peak 6, retention time- 54.9 min). The volume of drug injected was 20 L.

In case of tablet DIVASTINTM (20 mg) all the peaks including diol methyl ester peak were detected (Figure 3). No unknown impurity was detected. Among the impurities 3-o-methyl atorvastatin showed highest amount (0.338%). The total amount of these impurities was 0.983%. Only 0.179% impurity was increased during the production of tablet.

According to ICH guidelines on impurities in drug products, identification of impurities below the 0.1% level is not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic (International Conferences on Harmonization, 2000) . The maximum daily dose qualification threshold is considered to be less than 1 mg/day.

In conclusion, the amount of impurities in finished product (Tab. DIVASTINTM) was less than 1% which is acceptable.

Acknowledgement

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Table I: Percentage of impurities of atorvastatin present in bulk drug and tablet DIVASTIN^{TM}

Peak	Impurities	Retention time (min)	% Present	
			Bulk drug*	Tab. DIVASTIN ^{TM} (20 mg)*
1	Desfluoro atorvastatin	17.4	0.185	0.224
2	Distereoisomer	18.7	0.207	0.186
4	3-o-methyl atorvastatin	34.9	0.290	0.338
5	Lactone atorvastatin	40.3	0.122	0.100
6	Diol methyl ester	53.0	Not detectable	0.135
	Total amount of impurities		0.804	0.983

*Data are mean of three samples

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Original Article

High Blood Pressure can be Controlled by Reducing Extra Table Salt Intake

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Abstract

Background: This quasi-experimental community trial was done through door-to-door health education to find out effect of reducing extra table salt intake on patients with high blood pressure.

Material and Method: This study was conducted among 4,930 respondents out of 7,474 population (response rate was 65.96%). Respondents had age 18 years or above living in Mohammadpur area of Dhaka city in Bangladesh. Study period was from August 2005 to February 2009. Intervention was for 18 months on 282 (male 69.5% and female 30.5%) respondents with stage-I hypertension. Respondents on trial had no co-morbidity and they were neither aware about their hypertension nor were ever treated for it. The intervention was given person-to-person to quit extra table salt after signing the informed consent form. Follow-up for selected parameters were done after 6, 12 and 18 month of intervention. Data analysis and interpretation were done through SPSS. Result: Mean Blood Pressure of the respondents was found to be 121/78 mmHg. Overall prevalence of hypertension is 20.1% (JNC-7 criteria). After 18m intervention percent reduction of SBP is -7.0% and DBP is -9.9%. Blood pressure of 14.9% (n=42) went up in spite of behavioural risk reduction. Normal blood pressure was found among 7.8% respondents having stage-I hypertension while 17.7% remained at stage-I but their blood pressure is reduced. Multinominal regression analysis showed chi-square value of 25.8 df 13 p=0.018 between use of extra table salt and systolic blood pressure while the value was 28.684 df 11 p= 0.003 for diastolic blood pressure in a -2 Log Likelihood reduced model. At beginning 44% respondents used extra salt while eating. After 6m, 12m and 18m of intervention, extra salt intake was found among 20.6%, 5.0% and 1.8% respondents respectively. Quantitatively extra salt intake reduced from 63±6.5g per week at beginning to 29±4.6g per week after 18m intervention. Change of salt intake was significantly related to change of both SBP (F= 9.688; p=0.000) and DBP (F=6.544; p=0.002). Quality of life was evaluated for both subjective and objective indices. Conclusion: Reversal of hypertension was 56.7% by lifestyle modification and behavioural changes including salt intake reduction. This study confirmed relation of salt with hypertension and also confirmed reduction of blood pressure after reducing salt intake. This study recommended no extra salt intake for patients at risk or with high blood pressure.

Key words: Salt and Hypertension, Prevalence of Hypertension in Bangladesh.