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Effect of acid, base and heat on five brands of Atorvastatin tablet available in Bangladesh

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Abstract

Different brands available for atorvastatin calcium, is a most prescribed oral 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that is mainly used to treat primary hyperlipidemia. The objective of this study was to develop the degradation studies of five different brands of Atorvastatin 10 mg tablets. This drug was subjected to different stress conditions as per International Conference on Harmonization guidelines (ICH). An ultraviolet UV spectroscopic method was developed for analysis of the drug in the presence of the degradation products. Methanol was used as a solvent. The amount of degraded drugs was calculated by taking the absorbance at 244nm. According to the assay specified limit of USP that the content should not be less than 95% and not more than 105% of labelled amount. All brands were degraded by after the heat exposure. In addition to basic pH and acidic pH, all brands also degraded. The method was found to be simple and less time consuming and cost effective. It was concluded that all brands degraded from ranges for all the stresses applied for degradation studies.

Keywords: Atorvastatin 10 mg, HMG-CoA reductase, Degradation studies, Assay.

Introduction

Atorvastatin calcium is a drug of statins class. Therapeutically, it is used in elevated blood cholesterol levels. It is chemically[R-(R*, R*)]-2-(4-fluorophenyl)-b,d-dihydroxy-5-(1-methylethyl)-3-pheny1-4 [(phenyl amino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate (Fig. 1). Its molecular formula is $C_{66}H_{68}CaF_2N_4O_{10}$ and its molecular weight is 1209.42.[1] Pharmacologically, it is an inhibitor of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Atorvastatin tablet is administered as the calcium salt of the active hydroxyl acid and between 10 and 80 mg per day is used to decrease the raised lipid levels in patients with primary hyperlipidemia (familial and non-familial) or combined hyperlipidemia.[2-4]

Forced degradation may be defined as a process whereby the natural degradation rate of a drug product or drug substance is accelerated by the application of an additional stress. Understanding of these products qualitatively, can assist in predicting toxicity of these degradation products and also in deciding the shelf life of the drug. According to the ICH guideline that stress testing is designed to determine the stability of the molecule by knowing degradation pathway in order to identify the likely degradation the products. The degradation products are those formed under different conditions like effect of temperature, humidity, oxidation, photolysis and susceptibility of hydrolysis across a wide range of pH value. Even though, ICH and FDA ask to include this study at phase III level. It is recommended to start this study as early as possible to provide valuable information to assess inherent stability of a drug and to improve the formulation process. Literature survey revealed that various analytical methods such as

Spectrophotometry[5- 6], Extractive Spectrophotometry[7], HPLC[8-9], HPTLC[10] and LC-MS[11] methods have been reported for estimation of atorvastatin calcium in formulations and biological fluids. It was decided to develop UV spectroscopic method for simultaneous estimation of atorvastatin in a tablet formulation. The aim of present work was to develop and validate a simple UV spectrophotometric method to be applied for analysis of atorvastatin calcium degradation in tablets as per ICH guidelines, which serves as a tool for the quality control of pharmaceutical dosage forms.[12] These types of degradation studies of drugs and these are very helpful for health care professionals.[13-17]

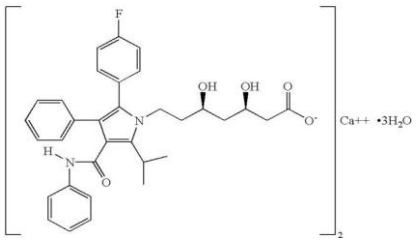

Figure 1: Atrovastatin structure

Materials and Methods

Reagents

Analytical grade reagents were used 0.1N sodium hydroxide, 0.1N hydrochloric acid, methanol, de-mineralized water and distilled water.

Glassware

Volumetric flask, funnel, beakers, measuring cylinder, pipette, and stirrer used were of Pyrex type and were washed with chromic acid followed by thorough washing with water and finally rinsed with distilled or de-mineralized water which was freshly prepared in the laboratory.

Instruments

These include Spectrophometer (UV-vis spectrophotometer), Weighing Balance (Precision balance, LF224DR, Shinko Denshi Co., ltd.), Water Bath (Stainless-steel, thermo station, HH-S).

Wavelength Selection

About 100 ppm of atorvastatin was accurately prepared in methanol. The wavelength maxima (λmax) were observed at 244nm and this wavelength was adopted for absorbance measurement.

Preparation of 0.1N Sodium Hydroxide

0.4 grams of sodium hydroxide was taken and transferred it in 100ml volumetric flask and dissolve it in small quantity of water and finally make up the volume up to the mark of the flask with de-mineralized water.

Preparation of 0.1N Hydrochloric Acid

8.36 ml analytical grade hydrochloric acid (37%, 12N) was taken in a volumetric flask and de-mineralized water was added to make up the volume.

Standard Stock Solution

The five different brands were purchased from a local drug shop located in Bayezid Bostami, Chittagong. All tablets of brand were labeled to contain atorvastatin 10 mg per tablet. Shows manufacturing and expire date of brands (Table 1). Weigh and finally crushed tablets accurately for making primary solutions of atorvastatin 10 mg, Anzitor (0.1665gm) Square Pharmaceuticals Ltd., Avas (0.1879 gm) Opsonin Pharma Limited, Atova (0.1521 gm) Beximco Pharmaceuticals Ltd., Divastin (0.1789 gm) Drug International Ltd., Tiginor (0.1568 gm) Incepta Pharmaceuticals Ltd. were weighed accurately and introduced in 100 ml volumetric flasks. Methanol was added and shaken with vigorously. The final solution was making up the volume up to 100 ml to make the strength of the solution 100ppm in 100 ml.

Table 1: Manufacturing and expire date of different brands

S No.	Brand name	Mfg. Date	Exp. Date
1.	Anzitor	October, 2014	January, 2016
2.	Avas	September, 2014	September, 2016
3.	Atova	September, 2014	September, 2016
4.	Divastin	December, 2014	October, 2016
5.	Tiginor	March, 2014	February, 2019

For Acid

To study the effect of acidic pH, 5 ml of 100ppm solution of each brand was taken in five separated test tubes then 5ml of 0.1N HCl was added in each test tube. They were then left for a period of 1 hour. Upon completion of time period, solutions were transferred to a cuvette separately and then absorbance of the solutions was recorded at the wavelength of 244nm.

For Base

To study the effect of basic pH, 5 ml of 100 ppm solution of each brand was taken in five separated test tubes then 5 ml of 0.1N NaOH was added in each test tube. The samples were then left for a period of 1 hour. Upon completion of time period, solutions were transferred to a cuvette separately and then absorbance of the solutions was recorded at the wavelength of 244nm.

For Heat

To study the effect of heat, 5 ml of 100 ppm solution of each brand was taken in five separated test tubes each containing 5 ml of water, than place these solutions in water bath for 1 hour and absorbance of the solutions was recorded at the wavelength of 244 nm.

Result

This research was performed with the purpose to compare the degree of degradation in five different brands of atorvastatin 10 mg tablet. Table 2 shows the variation in absorbance after the effect of different degradation parameters. After acidic pH and as well as basic pH effect, percent of assay was found 129.92%-159.98% (Table 3 and 4). In addition to heat exposure percent of assay was found 140.17%-172.46% (Table 5).

Table 2: Absorbance of drug in different parameters

S No.	Brand name	Absorbance of standard	Absorbance after acidic pH effect	Absorbance after basic pH effect	Absorbance after heat effect
1.	Anzitor	1.872	2.87	2.873	2.624
2.	Avas	1.862	2.728	2.73	2.827
3.	Atova	1.872	2.728	2.995	3.05
4.	Divastin	1.868	2.603	2.427	2.95
5.	Tiginor	1.696	2.472	2.572	2.925

Table 3: Effect of acidic pH

S No.	Brands	% Assay
1.	Anzitor	153.31%
2.	Avas	146.50%
3.	Atova	145.72%
4.	Divastin	139.34%
5.	Tiginor	145.75%

Table 4: Effect of basic pH

S No.	Brands	% Assay
1.	Anzitor	153.47%
2.	Avas	146.61%
3.	Atova	159.98%
4.	Divastin	129.92%
5.	Tiginor	151.65%

Table 5: Effect of heat

S No.	Brands	% Assay
1.	Anzitor	140.17%
2.	Avas	151.82%
3.	Atova	162.92%
4.	Divastin	157.92%
5.	Tiginor	172.46%

Discussion

The forced degradation study is a popular test method to analyze the stability of tablets. Hence, in this present study we analyze degradation of different brands of atorvastatin tablet by using three different means like acid, base and heat. In this analysis, percent of the assay was calculated. USP specified the limit of the assay that the content should not be less than 95% and not more than 105% of labeled amount. According to this USP specified limit, all brands were mostly degraded in acidic and basic pH. In addition to heat exposure, all brands were also mostly degraded. The effect of acidic pH, basic pH or heat exposure no brands of atorvastatin do comply with this USP specified limit.

Conclusion

This analytical study was used to the stress degradation studies as per ICH guidelines. The subjected drug atorvastatin was found to be degraded in almost all types of stress conditions and also to be less stable. The method was used is accurate and precise as well as reproducible and economical and can be successfully used degradation studies of different dosage form. It was concluded that all brands degraded from ranges for all the stresses applied for degradation studies.

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Conflict of Interest

None

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