Comparative *in-vitro* Dissolution Assessment of Commercially Available Five Brands of Atorvastatin Tablets in Sri Lanka

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Abstract

Atorvastatin calcium (ATV-Ca) is a synthetic lipid lowering drug which belongs to statin group. It is frequently prescribed for the treatment of hyperlipidemias and cardiovascular diseases. ATV-Ca is an inhibitor of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase. Most of the people think that high price branded drugs are much efficacious than other low price drugs. Therefore it is better to identify whether there is a difference between commercial products of the same item and a difference between effectiveness of different commercially available branded drugs. This study assesses the dissolution profile of five brands of ATV-Ca available in the Sri Lankan market. Standard ATV-Ca powder was received as a gift sample from Astron pvt Ltd (Rathmalana, Sri Lanka). Different brands of ATV-Ca tablet (Atorva®, Atocor®, Aztor®, Atorlip®, and SPC) available in Sri Lanka were collected in Kegalle, Peradeniya and Kandy. The absorbance of the solution of the tablet and the standard was measured by UV-VIS spectrophotometer at 246 nm wavelength. The dissolution test was carried out according to the British Pharmacopoeia (2013) in for 1.0, 4.5, 6.8 buffer solutions. When comparing dissolution efficiency of five samples with 1.0 pH value, A,D samples showed 60% drug releasing and also B,E samples released 71.97% and 82.56% drug respectively. Sample C possesses the highest dissolution efficiency (95.86%) in 1.0 pH solution. All samples except A possess higher dissolution in 4.5 pH. They have released up to more than 90% of the drug. Sample A showed low dissolution compared with other samples. In addition, all samples release up to more than 90% drug with pH 6.8 solution within 40 minutes. There is no significant difference dissolution efficiency among all samples in 6.8 pH medium. In this study it was revealed that sample C have higher dissolution efficiency with 1.0, 4.5, and 6.8 pH medium. It can highly dissolve in low gastric pH conditions and also intestinal pH condition. According to the results obtained in this study conclude that all samples were showed higher dissolution efficiency in 6.8 pH medium. Some differences in the dissolution profile of the drug were observed in 0.1 moldm^{-3} HCl solution and 4.5 pH medium. These differences may be due to factors such as the use of different excipients and manufacturing techniques.

Keywords: *Atorvastatin calcium, Dissolution, Paddle apparatus*

1. Introduction

Atorvastatin calcium (ATV-Ca) is a synthetic lipid lowering drug. It belongs to anti-hyoerlipidemic class. ATV-Ca is frequently prescribed for the treatment of hyperlipidemias and cardiovascular diseases (Thakare et al., 2013). ATV-Ca is an inhibitor of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. It is the early rate-limiting step in the biosynthesis of cholesterol in the human body. ATV-Ca also reduces triglyceride level of the systemic circulation and slightly increases the level of HDL-cholesterol. ATV-Ca is the most effective and frequently used drug for the treatment of hypercholesterolemia (Baribefe et al., 2014).The therapeutic efficacy of a drug depends on the rate and extent of its bioavailability in the systemic circulation (Baribefe et al., 2014).Poorly water-soluble drugs show unpredictable absorption, since their bioavailability depends on dissolution in the gastrointestinal tract (Narasaiah et al., 2010). The solubility and the dissolution rate of a sparingly water soluble drug are critical factors for its oral bioavailability (Baribefe et al., 2014); the intestinal permeability of ATV-Ca is high at the physiologically intestinal pH of 6.0; (Baribefe et al., 2014). Pharmaceutical availability is one aspect of drug bioavailability. The dissolution test is considered to be sensitive, reliable and rational for predicting *in-vivo* drug bioavailability behavior. It is one of the most important quality control tests performed on drugs and drug products (Ozkan et al., 2000). Drug dissolution is crucial factor in drug absorption. Dissolution of solid oral dosage forms varied with different pH values. Therefore, dissolution test is important to develop a

variety of novel or special dosage forms like chewing gums, suspensions, implants and others. Drugs have generic name and brand name. Brand names are familiar to the consumer rather than generic name. Who may only know their prescription by brand name alone. A generic version of a drug indicated for hypercholesterolemia is ATV-Ca. Examples of a brand name for the same drug are Atolip®, Aztor®, Atorva®, Atorcor®, etc. There should not be a significant difference of dose, intended use, effects, route of administration and safety between brand name drugs and generic name drugs. But can be differ in peripheral features of pill color, shape, excipients such as binders, fillers, coloring agents, smoothing agents and the specific manufacturing process. There is a disparity between the prices of different brands of ATV-Ca from different pharmaceutical companies. This may give erroneous impression about the bioequivalence of the products (Baribefe et al., 2014) .In this study assesses the dissolution profile of five brands of ATV-Ca available in the Sri Lankan market.

2. Objective

To determine the comparative *in-vitro* dissolution assessment of commercially available five brands of Atorvastatin tablets in Sri Lanka.

3. Material and Method

Standard ATV-Ca powder was received as a gift sample from Astron pvt Ltd (Rathmalana, Sri Lanka). Different brands of ATV-Ca tablet available in Sri Lanka were collected in the following areas: Kegalle, Peradeniya and Kandy prior to starting this study. All the samples were purchased from a registered retail pharmacy outlet and the study was carried out within the product expiry dates. All chemicals and reagents were analytical grade. The absorbance of the solution of the tablet and the standard were determined by using UV-Vis spectrophotometer (Thermo Scientific GENESYS 10S, India). The dissolution test was carried out by using a dissolution test apparatus (Veego, India).

3.1 Preparation of Calibration Curve

The method described by Prajapati & Bhandari (2011) was used to prepare the calibration curve. 1000 ppm was prepared by dissolving 50 mg of pure Atorvastatin powder in 50 ml of methanol. Concentration series (5, 10, 15, 20 and 25 ppm) were prepared by using the Atorvastatin stock solution. Then absorbance of the each concentration level was measured at 246 nm wavelength by using UV-Vis spectrophotometer.

3.2 Preparation of buffers (pH 6.8)

The phosphate buffer pH 6.8 prepared based on British Pharmacopoeia (BP) 2013.

3.3 Preparation of Acetate buffer (pH 4.5)

The Acetate buffer pH 4.5 was prepared method based on BP 2013.

3.4 Preparation of pH 1.0 HCl Solution

pH 1.0 HCl solution was prepared according to the method stated on in BP 2013

3.5 Dissolution test

A dissolution study was carried out according to the BP 2013 in 900 ml of each dissolution medium. The speed of the paddle was set at 50 rpm and medium temperature was maintained at 37±0.5 ºC using a water bath. Three samples were taken from three different batches of same brand when they send to market. Samples were taken manually by using a glass pipette at 10, 20, 30 and 40 minutes.

The samples taken were replaced each time with equal volume of fresh medium maintained at the same temperature to maintain a constant dissolution volume.

The samples were filtered using 0.2 um syringe filters (Agilent, USA) and the absorbance measured at 246 nm using UV-Vis spectrophotometer.

The amount of Atorvastatin Calcium was determined using standard calibration curve. The dissolution profiles of different samples were generated from the graph using MS Excel.

4. Results and Discussion

In this study dissolution efficiency was assessed to compare the drug release from five different Atorvastatin samples in Sri Lankan market. Dissolution characteristics were tested in the three pH ranges. 1.0, 4.5 and 6.8. Dissolution studies give an idea about the amount of drug absorption after oral administration. When a drug has poor dissolution profile it will not be available in required amount in the systemic circulation or target organ to give desired therapeutic effect. Manufacturing dates, expiry dates and physical appearance of different Atorvastatin tablets were given in Table 1.

Table 1 Information's of purchased Atorvastatin tablets

Code	Country of origin	Date		Appearance
		Manufactured	Expired	
A	India	Jan-2014	Dec-2016	Light blue circular tablet
B	India	Oct-2013	Sept-2015	White triangular tablet
C	India	Oct-2013	Sept-2016	Brown circular tablet
D	India	Jan-2014	Dec-2016	White oblong tablet
E	India	May-2013	Apr-2016	White oblong tablet

Table 2 Dissolution profile of Atorvastatin tablets in pH 1.0 HCl medium

Time (min)	% Dissolution				
	A	B	C	D	E
0	0.00	0.00	0.00	0.00	0.00
10	22.22	43.89	78.13	37.24	44.38
20	35.02	55.47	85.76	44.63	66.31
30	44.88	67.04	94.88	47.83	75.91
40	47.83	71.97	95.86	56.21	82.56

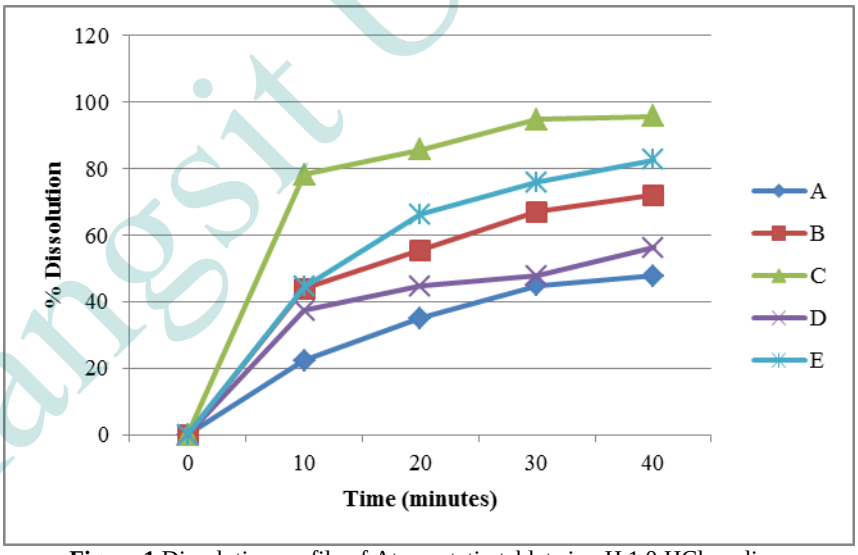

Figure 1 Dissolution profile of Atorvastatin tablets in pH 1.0 HCl medium

Dissolution profile was constructed by taking samples in four intervals (10, 20, 30 and 40 minutes). Dissolution profile of five different brands of Atorvastatin in pH 1.0 HCl solution were given in Table 2 and Figure 1. Sample C released up to more than 85% drug during the first 20 minutes of the dissolution assessment. From the result obtained pointed out that all samples except C released up to less than 85% drug after 40 minutes. Sample C showed significantly higher drug releasing ability than other samples with 0.1 moldm^{-3} HCl solution. Sample A released the least amount of 47.83% drug after 40 minutes. According to the result obtained that sample C showed very rapid dissolving property in 0.1 moldm^{-3} HCl solution. Therefore there are significant differences in dissolution efficiency among five Atorvastatin samples.

Table 3 Dissolution profile of Atorvastatin tablets in 4.5 pH medium

Time (min)	% Dissolution				
	A	B	C	D	E
0	0.00	0.00	0.00	0.00	0.00
10	43.65	83.30	71.97	78.87	82.32
20	58.42	95.86	93.15	88.23	95.37
30	67.54	99.06	98.82	96.11	98.57
40	72.46	101.28	103.00	94.88	99.31

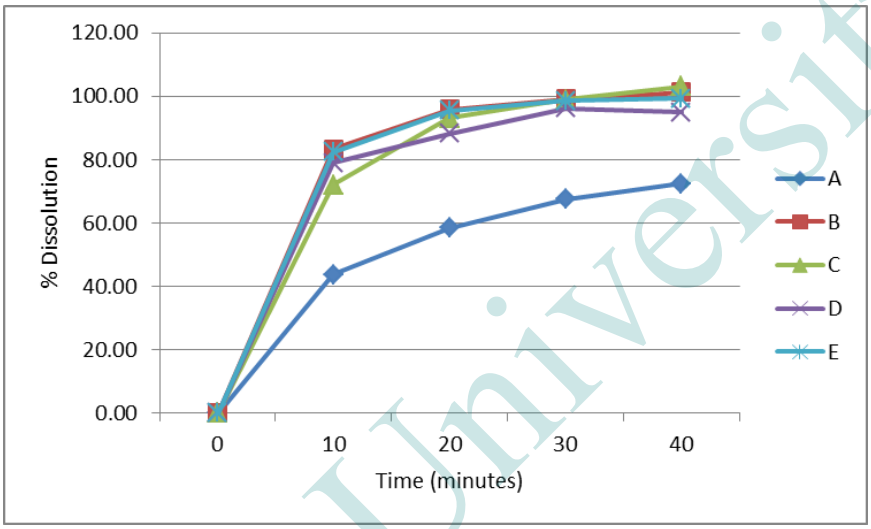

Figure 2 Dissolution profile of Atorvastatin tablets in 4.5 pH medium

Intestinal permeability of ATV-Ca is high at the intestinal pH between 4.0-7.0. Dissolution profile of five brands of atorvastatin with 4.5 pH is shown in Table 3 and Figure 2. All Atorvastatin samples except A released up to more than 85% drug during the first 20 minutes. They showed very high dissolution efficiency in pH 4.5 medium. After 40 minutes, sample A released 72.46% drug. Other all sample released >75% drug within 40 minutes. According to the results, sample A gives lower bioavailability than other samples B, C, D and E dissolution profile, sample A may be showed low bioavailability compared with other brands of Atorvastatin.

Table 4: Dissolution profile of Atorvastatin tablets in 6.8 pH medium

Time (min)	% Dissolution				
	A	B	C	D	E
0	0.00	0.00	0.00	0.00	0.00
10	71.72	97.83	83.05	106.70	101.28
20	82.56	101.28	84.78	107.68	104.98
30	87.00	102.02	87.00	108.18	106.21
40	90.94	102.51	88.23	106.21	106.45

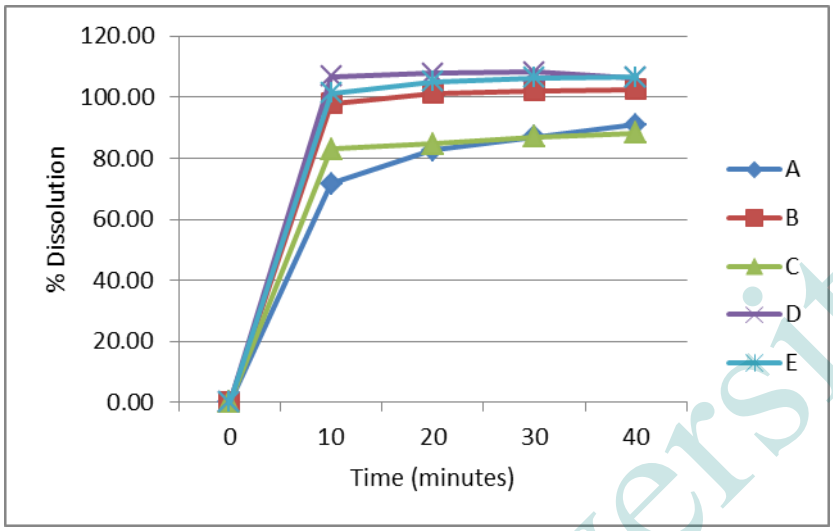

Figure 3 Dissolution profile of Atorvastatin tablets in 6.8 pH medium

Some drugs can be absorbed in the small intestine. pH in the simulated intestine fluid is about 6.8. So pH 6.8 is important in dissolution of drugs. Dissolution profile of five Atorvastatin sample with pH 6.8 was given in Table 4 and Figure 3. Sample B, D and E reached >85% dissolution efficiency within 10 minutes. Sample A and C showed >85% dissolution within 30 minutes. These samples are rapidly dissolving drug samples with pH 6.8. All samples were showed >85% dissolution efficiency after 40 minutes. All drug brands were showed higher bioavailability. In addition, they may give significant therapeutic effect.

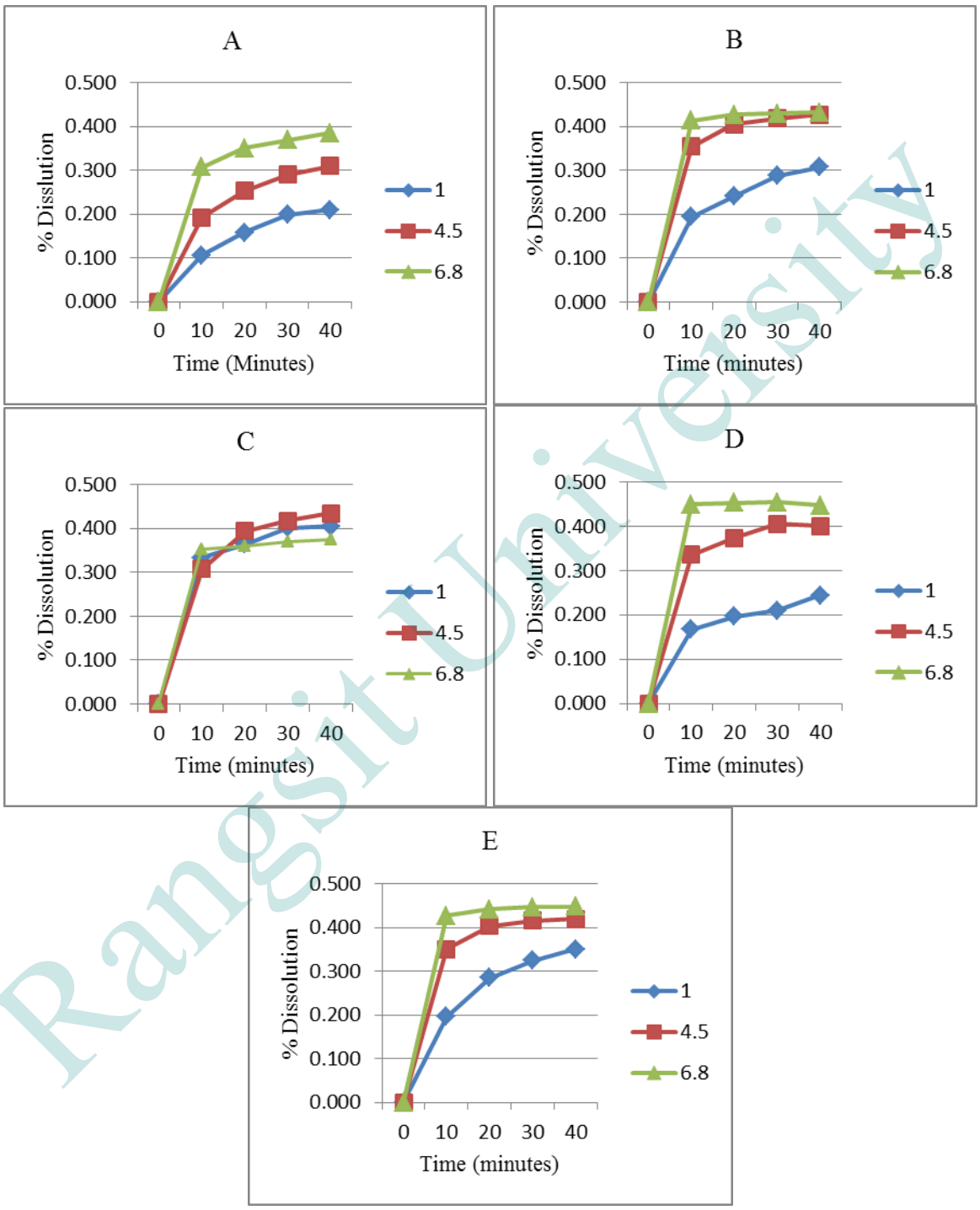

Figure 4 Dissolution profile of each Atorvastatin samples in different pH medium

Figure 4 showed comparative dissolution efficiency of each drug brand with different pH values in one graph. When comparing dissolution efficiency of five samples with 1.0 pH value, Aand D samples showed 60% drug release and also B and E samples released 71.97% and 82.56% drug respectively. Sample C possesses the highest dissolution efficiency (95.86%) in 1.0 pH solution. It gave higher therapeutic effect than other Atorvastatin samples with low gastric pH conditions. All samples except A possess higher

dissolution in 4.5 pH. They have released up to more than 90% of the drug. Sample A showed low dissolution compared with other samples. In addition, all samples released up to more than 90% drug with pH 6.8 solution within 40 minutes. Absorption of Atorvastatin was high at the physiological intestinal pH (6.0-6.5). There is no significant difference dissolution efficiency among all samples in 6.8 pH medium. In this study was revealed that sample C have higher dissolution efficiency with 1.0, 4.5 and 6.8 pH medium. It can highly dissolve in low gastric pH conditions and also intestinal pH condition.

The active pharmaceutical ingredient (API) is the chemical that has the desired biological effect. There may be a dozen ingredients in a tablet, for example, fillers, colors, binders, etc. But the API is the ingredient we are concerned. Most dosage forms (e.g., tablets and capsules) are designed to deliver the API to the site of action. More over the dissolution profile of different brand in different pH could be vary due to using various excipients and API.

5. Conclusion

The *in-vitro* dissolution rate is important for bioequivalence studies. According to the result obtained that sample C showed very rapid dissolving property in 0.1 moldm^{-3} HCl solution. There is no significant difference of dissolution rate of sample B, C, and E in 4.5 pH medium. According to the results obtained in this study, it can be concluded that all samples showed higher dissolution efficiency in 6.8 pH medium. Some differences in the dissolution profile of the drug were observed in pH 1.0 HCl solution and 4.5 pH medium. These differences may be due to factors such as the use of different excipients and manufacturing techniques. Though dissolution profile is an important parameter of a drug ,we cannot decide better brand of a drug depending only upon the dissolution profile. In order to determine a better brand, other parameters should be considered.

6. References

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