Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **36** (10): 2098-2104 (2017)

Received: July 27, 2017
Revised version: August 30, 2017
Accepted: September 2, 2017

Assessment of Pharmaceutical Equivalence of Different Generic Atorvastatin Tablets available in Pakistan

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***SUMMARY*. The local drug market of Pakistan is overwhelmed by the importation and local manufacturing of many generic products. The present research assessed pharmaceutical equivalence of different atorvastatin tablets procured from different pharmacy stores of Karachi. Sample M1 was considered as innovator brand. Different quality attributes were performed to evaluate their quality including tablet weight uniformity, thickness and diameter, disintegration time, hardness and content of active ingredient. *In-vitro* dissolution profile study was also performed using model dependent and independent approaches. All samples passed pharmaceutical quality testing. Among the brands, M5 and M6 passed f_1, f_2 test and their difference in %DE was within the range of ± 10% in all three FDA recommended dissolution media. Atorvastatin release kinetics followed First order and Weibull model. Two of the seven brands were found to be much similar to the innovator brand and therefore can be interchangeable.**

RESUMEN. El mercado local de drogas de Pakistán está abrumado por la importación y la fabricación local de muchos productos genéricos. La presente investigación evaluó la equivalencia farmacéutica de diferentes tabletas de atorvastatina adquiridas en diferentes farmacias de Karachi. La muestra M1 fue considerada como marca innovadora. Se realizaron diferentes atributos para evaluar su calidad, incluyendo la uniformidad del peso de la tableta, el grosor y el diámetro, el tiempo de desintegración, la dureza y el contenido del ingrediente activo. También se realizó el estudio del perfil de disolución *in vitro* usando métodos modelo-dependientes e independientes. Todas las muestras pasaron la prueba de calidad farmacéutica. Entre las marcas, M5 y M6 pasaron la prueba f_1, f_2 y su diferencia en %DE estaba dentro del rango de ± 10% en los tres medios de disolución recomendados por la FDA. La cinética de liberación de atorvastatina sigue los modelos de primer orden y deWeibull. Se encontró que dos de las siete marcas eran muy similares a la marca innovadora y por lo tanto pueden ser intercambiables.

INTRODUCTION

Quality of pharmaceutical product is very important aspect for achieving the therapeutically active and standard drug. Novel and improved therapeutic agents are being discovered continuously with the passage of time. Nearly 40% of the discovered drug moieties are lipophillic in nature. It is a well-established fact that solubility of lipophillic compound is the most critical factor associated with release of drugs. Therefore, the absorption of the drug from gastro intestinal tract is mainly dependent on the drug dissolution rate. These lipophillic drugs endure inadequate oral bioavailability and is usually associated with high intra subject and inter subject variability [1]. US Pharmacopeia emphasized on carrying out requisite *in vitro* analysis that encompasses content uniformity, assay and dissolution testing. The dissolution profile comparison studies provide more precise results for drug product characterization [2]. Dissolution testing is an extremely key parameter for evaluating the quality of dosage form of different formulation having same therapeutic agent and considered to be the rate limiting step for drug absorption through gastro intestinal tract principally for BCS class II drugs [3,4].

Atorvastatin is a second generation synthetic 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitor that selectively and competitively inhibits of 3-hydroxy-3-methyl glutarylcoenzyme-A enzyme responsible for cholesterol production in the body. There by, reducing levels of VLDL cholesterol, LDL cholesterol and triglycerides and facilitates the augmentation of high-density lipoprotein choles-

KEY WORDS: atorvastatin, *in vitro* dissolution profile, pharmaceutical equivalence.

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ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)

terol concentration in dyslipidemic patients [5]. Therefore, it is prescribed for the treatment of hypercholesterolemia efficiently [1,6]. Atorvastatin is a BCS class II compound [7,8]. Membrane permeability and drug solubility are insistent parameters considered to be the rate limiting parameter in determination of oral bioavailability as well as dissolution rate of formulated drug [1]. Therefore, the solubility and dissolution rate is critical factor for drug's bioavailability [9,10]. It has been reported that different pharmaceutical dosage forms having similar concentration of active pharmaceutical ingredient have shown variation in their therapeutic response [3,4] owing to purity of the active ingredients, types of excipients used and formulation and manufacturing process parameters employed [11].

Health care professionals including physicians and pharmacists are routinely exposed to advertising of commercially available therapeutically equivalent branded drug products with variable prices with respect to their bioavailability, quality, safety and interchangeability for better treatment outcomes. Therefore, prescribing physicians face problems in selecting generic substitutes. Current perspective necessitates routine assessment of product quality so that therapeutically effective quality products are available for general public. Therefore, government, pharmaceutical companies, regulatory bodies and independent research groups needs to carry out continuous surveillance studies to assure the accessibility of quality medicines to the patients. Different brands of atorvastatin formulations are manufactured and marketed by local and multinational pharmaceutical companies in Pakistan. Few studies were carried out to evaluate quality of commercially available pharmaceutical products in different parts of the world [12-14]. In the present study, different brands of atorvastatin tablets available locally were assessed to ensure and justify the interchangeability of these therapeutically equivalent atorvastatin brands for their quality parameters with special emphasis on dissolution profile comparison studies. USP buffer solutions of pH 1.2 hydrochloric acid solutions, pH 4.5 phosphate buffer solution, and at pH 6.8 phosphate buffer solutions were used. The outcomes of the present study will be to provide guidance to physician and clinical pharmacist for selecting the most economical product of atorvastatin having better *in vivo* performance.

MATERIAL AND METHODS

Commercial products and reference standards

In the present study, seven different marketed brands containing atorvastatin were purchased from registered pharmacy stores of Karachi, Pakistan. Each sample manufacturing license number, manufacturing date, expiry date and the batch number was noted. Marketed brands of atorvastatin were visually inspected for shape, color, chippings, mottling and black spot. Each of the samples was coded alphanumerically as M1-M7 and was stored appropriately. Sample M1 was considered as innovator brand. The reference standard of atorvastatin was gifted by Getz Pharmaceutical Pvt. limited.

Weight, thickness and diameter Uniformity

Twenty tablets of each sample were weighed accurately using electronic balance (Mettler Toledo B204-S). The average weights of tablets were estimated and the percentage deviation from the mean value was determined. The acceptable limit is ± 7.5% for tablets having average weight of ≤ 130 mg. Tablet thickness and diameter were also evaluated using digital vernier caliper (Seiko Brand, 0 to 150 mm) to find the thickness of ten randomly selected tablets. Results were expressed as mean values ± SD.

Hardness and friability tests

Hardness and friability were determined in accordance with British pharmacopoeial standards [15]. Ten tablets from each brand were individually inserted into the tablet crushing equipment (OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan) and the force at which the splitting occurred was recorded. Ten tablets were weighed and then placed in friabilator (Erweka GmbH D-63150, Husenstamm, Germany). The percent (%) friability determined (note that BP stated that twenty tablets should be used, but due to limited supply of the atorvastatin tablet, this study utilized ten tablets) [15].

Disintegration test

Disintegration test was carried out according to USP specification [16] using the disintegration apparatus (Erweka ZT-2, Huesnstanm, Germany). The time taken for each of the seven tablet tested from each of the brands was recorded.

Drug content

A pre validated method was adopted for determining the drug content. The linearity of method was carried out by making concentrations of 80, 40, 20, 5, 2.5, 1.25, and 0.625 µg/mL from stock solution. The standard calibration curve yields a straight line over a given concentration range. Reference Standard and solutions of each product samples were prepared by dissolving 5 mg standard atorvastatin and powdered tablets equivalent to 5 mg of the drug in 10 mL methanol separately following dilution with mobile phase. The HPLC system consisting of LC-20 AT pumps, SPD-20 UV/visible detector (Shimadzu, Japan). The chromatographic separation was accomplished using C18 column (5 µm, 4.6 × 150 mm, Waters, USA) at 25 °C using a mobile phase consisting of acetonitrile-distilled water (55:45) at pH 4 at a flow rate of 1.5 mL/min. The detection was carried at 261 nm [12]. Potency was calculated for each brand by comparing the standard and sample peak area.

Cost comparison

The difference in the prices of the innovator in comparison with test samples was carried out utilizing Eq. [**1**] [17]:

$$Price\ difference = \frac{Price\ of\ innovator - Price\ of\ test}{Price\ of\ innovator} \times 100 \quad [1]$$

Dissolution studies

In vitro release study for each sample was performed using at 75 rpm USP Apparatus-II (Erweka DT600, Husenstamm, Germany) with six replicates [18]. All brands were evaluated using 900 mL dissolution media maintained at 37 ± 0.5 °C. Dissolution media used were 0.1 N HCl pH 1.2 and buffer solution pH 4.5 and pH 6.8. Aliquots of 10 mL were withdrawn at definite time intervals for 2 h, *i.e.* 5, 10, 15, 20, 25, 30, 45, 60, and 120 min and substituted with fresh dissolution medium. The samples were filtered and assayed using spectrophotometer (Shimadzu Corporation, Kyoto, Japan) at 244 nm. Cumulative percentages of drug dissolved from the tablets were calculated.

Dissolution profiles comparison

Model independent and dependent approaches were applied to compare the dissolution profiles of different atorvastatin samples using DDSolver® an excel based add-in program [19].

Model independent method

FDA recommends model independent approach utilizing similarity factor (f_2) for determination of equivalence dissolution data. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of similarity in the dissolution % of two curves as in Eq. [**2**].

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{N}\right)\sum (Ri - Ti)^2\right]^{-0,5}\right\} \times 100 \quad [2]$$

where N = number of dissolution sample times; Rt and Tt = individual or mean percents dissolved at each time point for the reference and test products, respectively.

The difference factor was calculated with Eq. [**3**].

$$f_t = \frac{\sum_{f=1}^{n} |R_j - T_j|}{\sum_{f=1}^{n} R_j} \times 100 \quad [3]$$

where Rt and Tt = percentage release of reference and test brands, respectively.

The FDA suggests that f_2 values of 50-100 % ensure equivalence and f_1 values less than 15 ensure the difference of two dissolution profiles.

Dissolution efficiency (%DE) is considered as the area under the dissolution curve obtained during a time interval of (t_1-t_2). Dissolution efficiency was calculated by Eq. [**4**]:

$$AUC = \sum_{i=1}^{i=n} \left(\frac{(t_1 - t_{i-1})\ (y_{i-1} + y_i)}{2} \right) \quad [4]$$

where y is the drug dissolved expressed in percentage. The sample are considered equivalent to the reference if the dissolution efficiencies differential is within ±10% [20].

Model-dependent methods

The drug release mechanism can be determined using different mathematical models. The mathematical models applied to dissolution profile during the time duration of 60 min included zero order kinetics, first order kinetics, Weibull and Hixson-Crowell models.

RESULTS AND DISCUSSION

The quality of pharmaceutical product is very important for achieving the desired therapeutic outcomes. Pharmaceutical product must have consistent and predictable performance to ensure quality, safety and bioavailability. Post market surveillance program helps in continued supply of good quality pharmaceutical products. Economic condition has a substantial impact on drug budgets and has resulted in an expansion of generic drug utilization globally. The cost of generic products are considerably lower than innovator brands thus minimizes the health care expenditure [21]. Physicians are generally very

concerned about the generics drug quality and usually have trust issues in prescribing drug interchangeably. Even though generic drugs production also follows good manufacturing practices [22]. They are assumed to be considered as inferior in their quality and therapeutic efficacy. This concept of generic substitution will definitely work in developing countries like Pakistan, where public solely bears their health care expenses. Atorvastatin is prescribed for chronic diseases for a longer period of time, therefore, its cost become more important. The innovator brand (sample M1) is a highly expensive product (PKR 66.28/unit dosage form). The cost of generic products was in the range of PKR 6.5-PKR 18. A great price differential was observed when cost was compared with the cost of innovator (price differential more than 72.84%) (Table 1). Therefore, it is now very important to judge the quality of these generic products so that a low-cost generic product can substitute confidently the innovator brand where there is an issue of affordability.

Selected marketed brands information including strength, the price of package, the price per unit dosage form, expiry date and manufacturing date is summarized in Table 1. All seven

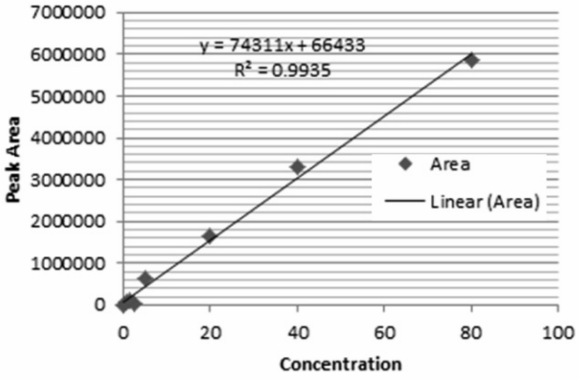

Figure 1. Calibration curve sowing linearity. Graph between drug concentration and peak area.

marketed brands of atorvastatin tablets passed pharmaceutical quality test that included weight, thickness and diameter variation test having a coefficient of variation ≤ 5%. Tablet hardness was in the recommended range of 4-9 Kg. Two samples showed highest hardness i.e., M3 (11.52 kg) and M2 (14.02 kg). Friability was within the range of < 1% except for M7 (1.63%). Immediate release tablets must be disintegrated within 30 min. Reference brand M1 was disintegrated within 1 min and all others were disintegrated in the range of 2-25 min. Assay results of

Sample code	Lot no./ batch no	Manufacture date	Expiry date	Price/ Package (PKR)	Price/ Unit Dosage (PKR)	Price differential (%)	Manufacture
M1	119	10-2013	10-2016	662.81	66.281	Innovator	Multi-national
M2	3006	11-2013	11-2016	105.88	10.588	84.026	Local
M3	16	10-2013	10-2016	180	18	72.84	Local
M4	14513	4-2014	3-2017	224	8	90.193	Local
M5	IV	2-2014	8-2016	110	11	83.404	Local
M6	18	8-2014	8-2016	65	6.5	75.257	Local
M7	180f10	6-2014	6-2017	164	16.4	87.93	Local

Table 1. Label information of selected marketed brands of atorvastatin tablets.

Sample code	Weight Variation (mg)	Diameter Variation (mm)	Thickness Variation (mm)	Hardness (kg)	Disintegration Time (min)	Friability (%)	Assay (%)	Dissolution (%)
M1	159.1 ± 5.82	10.35 ± 0.01	4.34 ± 0.02	4.26 ± 0.37	<1 min	0.28	100.46 ± 0.338	100.935 ± 0.077
M2	254.5 ± 3.78	12.06 ± 0.03	4.39 ± 0.02	14.02 ± 0.31	2.3	0	100.45 ± 0.466	100.595 ± 0.558
M3	268.6 ± 5.08	15.06 ± 0.08	4.18 ± 0.09	11.52 ± 1.83	25	0.6	102.995 ± 0.007	102.995 ± 0.007
M4	142 ± 1.56	8.05 ± 0.012	3.151 ± 0.01	6.585 ± 0	11.1	0	101.11 ± 0.141	102.21 ± 1.428
M5	246.1 ± 3.25	11.15 ± 0.01	4.052 ± 0.01	8.9 ± 0.14	14	0.01	100.15 ± 0.778	102.065 ± 1.93
M6	149.9 ± 2.28	8.11 ± 0.01	2.367 ± 0.01	3.28 ± 0.71	2	1	100.145 ± 0.361	100.97 ± 0.891
M7	194.5 ± 7.34	9.43 ± 0.021	3.034 ± 0.01	5.88 ± 0.042	4.8	1.63	100.225 ± 0.361	102.065 ± 0.700

Table 2. Pharmaceutical evaluation of different marketed brands of atorvastatin tablets.

all the selected marketed brands were in the BP recommended range of 97-102% (Table 2 and Fig. 1).

Dissolution test assists in characterization of drug's dissolution properties as well as drug release from formulations. It is important to obtain rapid drug dissolution from the dosage form in order to achieve high peak blood levels of a drug. *In vitro* drug release profile predicts *in vivo* performance of oral solid dosage forms. During the study, samples were subjected to drug release profile study in FDA recommended dissolution media (0.1 N HCl at pH 1.2, phosphate buffer at pH 4.5, and pH 6.8) (Fig. 2).

Dissolution profile of the test and reference products obtained in pH 6.8 showed cumulative drug release was ≥ 85% within 15 min that was similar to the study conducted by Popy *et al.* [13]. Dissolution profiles obtained in different media are represented in Fig. 3.

Zhang *et al.* [19] introduced DDSolver® an excel based add-in program utilized to assess atorvastatin release from samples. Dissolution profile comparison of selected marketed brands of atorvastatin tablets were executed using two recent approaches *i.e.* model independent and dependent approaches. Model independent approach was introduced by Moore & Flanner [23]. The results showed that most of the marketed brands passed f_2 test in dissolution medium of phosphate buffer at pH 4.5 and pH 6.8 except sample M2 failed the test in all three dissolution media. Atorvastatin has low solubility in acidic medium. Therefore, its release from tablets in acidic pH 1.2 is also compromised [13] and all sample failed in f_2 test except marketed brand M5 and M6. Least f_2 and maximum f_1 values were for marketed brand M2 confirmed that it's dissolution profile is far from that of reference brand. F_1 values were in the range of 1.63-4.65 (Table 3).

The present study is in compliance with the study conducted in Bangladesh for *in vitro* equivalence of tablets containing a poorly water-soluble compound, atorvastatin and drug release was compared with reference brand [12,13]. The percentage dissolution efficiency (%DE) was applied to evaluate drug release from the samples. The difference in %DE of brands M5 and M6 was in the recommended range of ±10% [20].

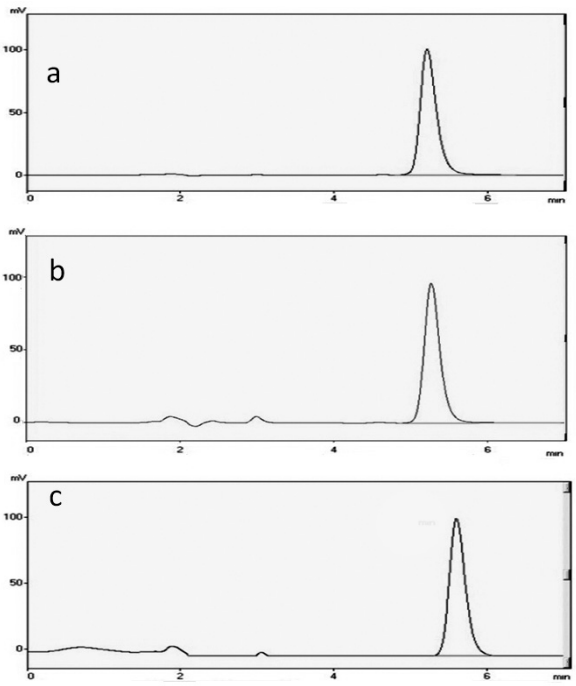

Figure 2. HPLC chromatogram of (**a**) atorvastatin standard, (**b**) atorvastatin tablet brand D, and (**c**) brand E.

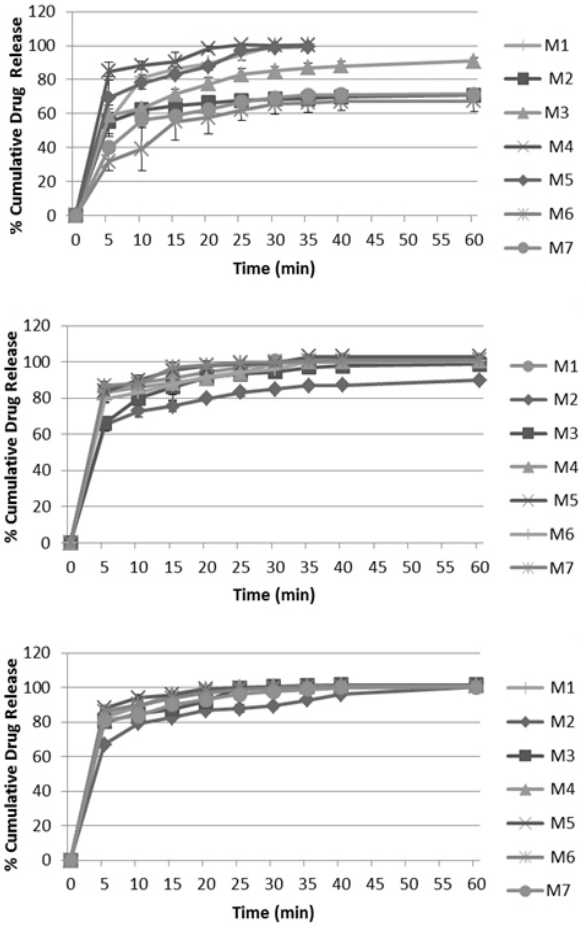

Figure 3. Dissolution profiles of marketed brands of atorvastatin in FDA recommended media (**a**) 0.1 N HCL (pH 1.2) (**b**) phosphate buffer (pH 4.5) and (**c**) phosphate buffer (pH 6.8).

Sample code	pH 1.2			pH 4.5			pH 6.8		
	f_1	f_2	% D.E	f_1	f_2	% D.E	f_1	f_2	% D.E
M1	-	-	79.75	-	-	95.12	-	-	96.79
M2	28.35	30.06	59.9*	14.82	40.69	81.71*	10.4	48.01	89.96
M3	14.81	46.14	68.95*	3.96	59.61	88.39	2.94	68.65	91.91
M4	10.55	43.45	82.50	4.65	61.66	89.50	2.19	77.62	93.39
M5	6.36	51.34	83.95	1.86	81.05	95.17	1.68	82.06	96.38
M6	5.56	65.32	69.90	3.49	71.05	91.75	1.63	81.79	95.48
M7	25.22	31.18	62.37*	2.66	72.70	93.95	3.06	73.56	94.39

Table 3. Model independent release kinetics of marketed brands of atorvastatin in 0.1 N HCL at pH 1.2, phosphate buffer pH 4.5 and phosphate buffer at pH 6.8. FDA recommended ranges of f_2 and f_1 are 50 -100 and 1-15 (Moore & Flanner [23]). *Difference in % DE is not within the range of ±10% (Anderson *et al*. [20]).

Sample Code	Zero Order		First order		Weibull Model			Hixson-Crowell Model	
	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	A	β	r^2	K_{HC} ($h^{-1/3}$)	r^2
pH 1.2									
M1	6.812	0.864	0.159	0.985	0.938	0.262	0.982	0.042	0.988
M2	5.339	0.668	0.101	0.878	1.361	0.126	0.996	0.003	0.824
M3	5.712	0.646	0.114	0.896	1.840	1.840	0.990	0.031	0.839
M4	7.906	0.672	0.343	0.991	1.191	0.378	0.983	0.081	0.980
M5	6.780	0.736	0.191	0.973	1.374	0.307	0.982	0.053	0.936
M6	4.188	0.919	0.062	0.964	3.077	0.269	0.998	0.018	0.959
M7	4.702	0.7869	0.076	0.935	1.397	0.091	0.994	0.022	0.899
pH 4.5									
M1	7.643	0.511	0.331	0.982	0.618	0.140	0.982	0.081	0.958
M2	6.248	0.650	0.147	0.939	0.970	0.119	0.993	0.038	0.886
M3	6.924	0.749	0.181	0.992	1.879	0.496	0.981	0.048	0.969
M4	7.435	0.505	0.297	0.966	0.753	0.177	0.992	0.077	0.945
M5	7.844	0.588	0.336	0.993	1.121	0.433	0.995	0.081	0.982
M6	7.257	0.624	0.255	0.978	0.993	0.226	0.992	0.071	0.955
M7	7.907	0.558	0.364	0.985	0.873	0.333	0.988	0.086	0.971
pH 6.8									
M1	7.798	0.561	0.335	0.989	0.957	0.351	0.982	0.082	0.977
M2	6.760	0.646	0.177	0.957	1.121	0.231	0.991	0.047	0.912
M3	7.307	0.527	0.265	0.969	0.759	0.164	0.999	0.073	0.948
M4	7.841	0.599	0.316	0.989	1.236	0.471	0.998	0.080	0.977
M5	8.050	0.533	0.404	0.996	0.565	0.195	0.997	0.087	0.985
M6	7.818	0.535	0.359	0.990	0.803	0.284	0.998	0.084	0.977
M7	7.407	0.560	0.272	0.962	0.936	0.261	0.992	0.074	0.935

Table 4. Model dependent release kinetics of marketed brands of atorvastatin in 0.1 N HCL at pH 1.2, phosphate buffer at pH 4.5 and phosphate buffer at pH 6.8.

Sample M5 and M6 were equivalent to innovator brand showing difference in percentage within the range in all dissolution media. The difference in dissolution efficiency at pH 4.5 and 6.8 are comparable to the study in 2012 [13]. Table 3 presents dissolution efficiency of the coded marketed brand's sample observed during the dissolution profile study. The Model dependent approach includes application of different mathematical models to express drug release kinetics from dosage forms. The best goodness of fit was the criterion of selecting the most appropriate model. Correlation coefficient (R^2) of marketed brand is mentioned in Table 4.

The release of the drug from its dosage form is dependent on the drug concentration remaining. Therefore, the first order kinetic model best explained the drug release from all the samples of marketed brands. Drug released kinetics also followed Weibull model Therefore, it can be concluded that drug release followed first order kinetic model and Weibull model. Many other researchers also suggested these models for immediate release tablets [24,25].

CONCLUSION

During the study, seven samples of atorvastatin tablets available in the market of Karachi, Pakistan were successfully analyzed. Marketed brands passed the uniformity of weight test, disintegration test and hardness test as per pharmacopoeial standard. f_1, f_2 and %DE were applied to dissolution profile that clearly depicted that drug release was found to be dependent on pH. Drug release kinetics followed First order and Weibull model among other release kinetics models. Marketed brand M5 and M6 of the atorvastatin tablets tested were pharmaceutically equivalent and therefore they could be used as substitute for reference brand which was highly expensive. However, bioequivalence studies are recommended for further evidence of exhibiting similar *in vivo* performance.

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