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Release Profile of Branded Atorvastatin Calcium Tablet Relative to Commercially Available Counterpart Generics

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ABSTRACT

Atorvastatin, a hypolipidemic medication, is commonly used as oral anti-atherosclerotic and cardiovascular protectant, with multiple marketed tablet brands available. This study aimed to assess critical quality attributes, including in-vitro dissolution characteristics, for five atorvastatin calcium tablet brands (labeled A–E) collected from the Saudi Arabia market. All brands were tested for conformity with the United States Pharmacopoeia (USP) specifications, including evaluation of weight variation, hardness, friability, disintegration time, and dissolution rate. Dissolution profiles were compared with the innovator (brand A) using model-dependent and independent approaches. The samples were compliant with USP specifications for weight variation, disintegration, and dissolution tests; however, brands C and D differed from brand A with respect to disintegration time. All tested tablets showed high hardness and low friability except C, which exhibited a relatively higher friability of 1.38%. All samples had a rapid dissolution profile, with > 89% release rate within 15 min. No significant differences were found with respect to dissolution efficiency and mean dissolution time for all the brands. Although dissolution area under the curve (AUC) values were all in a similar range, brand D AUC was significantly higher than that of A. Lastly, the Weibull model of drug-release kinetics was the best fit for all samples. In conclusion, all atorvastatin calcium tablets examined met USP specifications and reasonably passed the local validation. Only minor variations in critical quality attributes were detected for two brands, suggesting the presence of some differences in tablet manufacturing processes.

KEYWORDS: Atorvastatin calcium, USP tablet testing, Saudi generics, comparative analysis, drug release profile, Weibull model kinetics

INTRODUCTION

Atorvastatin calcium is a synthetic drug that belongs to second-generation lipid lowering agents, statins (*1*). Pharmacologically, this hypolipidemic drug acts via reducing the synthesis of cholesterol in the liver by competitively inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase. Atorvastatin is considered a highly potent statin, exhibiting a half maximal inhibitory concentration (IC_{50}) of 1.16 nM, with efficacy for reducing bad cholesterol fractions of low-density lipoprotein (LDL) around 40–60% (*2*, *3*). This enzymatic HMG-CoA inhibition constitutes the rate-limiting step (de novo) in the mevalonate biosynthetic pathway of cholesterol (*2*). Accordingly, the resultant reduction in intracellular cholesterol comes from the induction of hepatocyte LDL receptor surface expression and increased uptake of LDL from the blood, which together facilitates the therapeutic effect of

atorvastatin in clearing LDL cholesterol from the circulation (*2*). More specifically, atorvastatin lowers apo B100 lipoproteins carrier of the liver, eventually leading to the favorable reduction of both cholesterol and triglyceride concentrations (*2*, *4*).

Like many other drugs, statins use has been associated with certain adverse effects. Critically, myopathy (rhabdomyolysis with muscle pain) linked to creatine kinase elevation and liver toxicity are of considerable risks with statins use (*2*, *5*). Other adverse effects like neurological deficits, possible predisposition to diabetes mellitus, and cataract risk are less frequently encountered (*5*). Additionally, proteinuria and hematuria have also been reported with certain statins, but these are uncommon with atorvastatin due to the low renal elimination pharmacokinetics of this drug (*5*). Nevertheless, the impact of atorvastatin and other statins on lowering LDL cholesterol significantly protects against cardiovascular disease, with remarkable anti-inflammatory and antioxidant (pleiotropic) potential (*2*, *5*). As such, statin therapy is the cornerstone for preventing atherosclerotic plaque build-up and coronary heart disease (*2*, *3*–*5*).

Chemically, the molecular formula for atorvastatin calcium is $[C_{33}H_{35}FN_2O_5]_2 \cdot Ca \cdot 3H_2O$, the chemical name is *R*-(*R**,*R**)-2-(4-fluorophenyl)-*β*,*δ*-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1 *H*- pyrrole-1-heptanoic acid, and its molecular weight is 1209.42 g/mol (Fig. 1) (*6*). Solubility characteristics of crystalline atorvastatin calcium powder is inferred as insoluble in aqueous solutions of pH ≤ 4, very slightly soluble in distilled water and pH 7.4 phosphate buffer, slightly soluble in ethanol, and freely soluble in methanol; hence, atorvastatin calcium is considered a poorly soluble drug in the biological system (*7*, *8*). Thus, atorvastatin's ability to cross physiological membranes and cells, together with its first pass liver metabolism (CYP450 3A4), aligns with its 30% absorption rate and absolute bioavailability of 12% following oral intake (*5*, *9*).

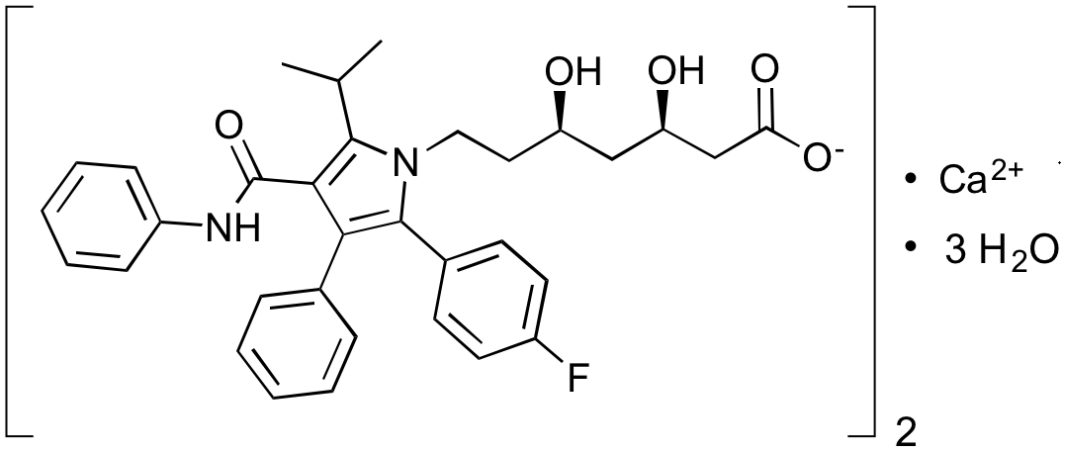

Figure 1. Chemical structure of atorvastatin calcium trihydrate.

Pharmaceutically, due to inadequate dissolution in the gastrointestinal tract, atorvastatin is considered as class II drug in the Biopharmaceutics Classification System (BCS) (*10*, *11*). However, the development of formulation strategies to improve the dissolution rate and oral bioavailability

of this drug are highly successful, resulting in enhanced permeability and rapid oral absorption (*3*, *10*). Therefore, atorvastatin calcium tablets were effectively marketed for cardiovascular events prophylaxis following its approval by the United States Food and Drug Administration (FDA) in 2003 (3, *12–14*). It was first introduced in 1996 under the brand name Lipitor by Warner-Lambert Company (which merged with Pfizer in 2000) (*14*, *15*). The typical dose of atorvastatin is 10–80 mg/day, and is rapidly absorbed after oral administration (*3*, *16, 17*). Lipitor became the world's best-selling drug in the history of pharmaceuticals with accumulated sales of more than US $125 billion over the years (*3*, *14*, *18*). The large market for atorvastatin prompted competition between the innovator and generic drug companies. The Kingdom of Saudi Arabia also has a large pharmaceutical market as a member of G20, a group that accounts for 80% of global economic power (*19*). This market is expected to grow tremendously due to the Kingdom's strategic plan (Vision 2030) to support and grow the healthcare and pharmaceuticals industry for effective delivery of healthcare (*20*). Currently there are 12 registered generic brands of atorvastatin calcium tablets within the Saudi Food and Drug Authority (SFDA) (*21*). Even though many generic brands are widely available in the market, effective monitoring may be inadequate; hence, frequent periodic evaluation of generics is needed to guarantee the therapeutic effects of generic medications (*22*, *23*).

For any tablet dosage form, unintended chemical breakdown or interaction between constituents may alter the physicochemical properties, thereby potentially disturbing bioavailability of the tablet formulation (*12*, *24*). Thus, evaluating critical quality parameters such as tablet mechanical strength and consistency for weight and content of the active pharmaceutical ingredient (API) is important (*22*). Testing these parameters can be evaluated by performing tests for friability, hardness, and uniformity (*22*, *25–29*). For immediate-release (IR) tablet dosage forms, disintegration time reflects the initial phase that drives the release of API into the surrounding solution (*22*, *30*, *31*). In-vitro dissolution data can be correlated with the in-vivo bioavailability of various oral drug systems, so dissolution testing and drug release kinetics are the main tools for obtaining marketing approval for many new generic medicines (*22*, *32*, *33*). Quality control tests are essential to certify the safety and efficacy of pharmaceutical products and provide data to bodies like the SFDA for post-market monitoring. Differences between innovator and generic brands may impact the patient's experience and contribute to significant variability in the predicted therapeutic response (*34*).

The objectives of the present investigation are to examine the in-vitro quality parameters of five commercially available atorvastatin calcium tablets and evaluate their conformity with the United States Pharmacopeia (USP) standards. Furthermore, this research aimed to explore drug-release kinetics for the selected brands of atorvastatin and determine their pharmaceutical equivalence with the innovator brand (Lipitor).

MATERIALS AND METHODS

Chemicals and Reagents

Atorvastatin calcium reference standard (RS) was a gift from Hikma Pharmaceuticals (Riyadh, Saudi Arabia). Analytical grade potassium dihydrogen phosphate, disodium hydrogen phosphate, and sodium hydroxide were purchased from Sigma-Aldrich, USA.

Tablet Samples

Five brands of atorvastatin calcium 40-mg strength tablets were purchased from different retail pharmacies in Riyadh, Saudi Arabia. These brands were as follows: Lipitor (innovator brand) (lot FE6867, Pfizer, USA), Lorvast (lot 1NM137, Tabuk Pharmaceuticals, Saudi Arabia), Astatin (lot XK0139, Jamjoom Pharmaceuticals, Saudi Arabia), Atorva (lot 3426, Jazeera Pharmaceutical Industries, Saudi Arabia), and Lipicure (lot 00336, Dammam Pharma, Saudi Arabia). Atorvastatin brands were labelled from A to E, with A being the innovator and the others were arbitrarily distributed generic products (Table 1). All tests in this study were done at least 6 months before the product expiration dates on the medication packages.

Standard Curve Preparation

The RS of atorvastatin calcium was used to prepare a stock solution of 100 µg/mL in 0.05 M phosphate buffer. A calibration curve with a concentration range of 2-36 µg/mL (Beer-Lambert's range) was prepared by diluting aliquots of the stock solution in phosphate buffer. Concentration of atorvastatin calcium was measured by UV/Visible spectrophotometer (Jenway 6705, UK) at a wavelength of 244 nm. Special polystyrene micro 2-mL cuvettes were purchased from LP Italiana SPA (Italy). The calibration curve (r^2 = 0.9994) was plotted for further analysis (*22*).

Mechanical Calibration and Performance Verification of Dissolution Apparatus and UV/Visible Spectrophotometer

The instrument was installed and qualified by the vendor in a limited vibration workstation where the bench surface inclination is not more than 1°, followed by twice yearly routine checks of the apparatus assembly following procedures for mechanical calibration and performance verification according to *USP* <711> (*35*). The dimensions, inclination alignment, rotation speed, temperature control, and presence of gross defects are checked for all the vessels.

Performance verification was performed with USP Standard Prednisone Tablets RS, where the dissolution test is carried out for 30 minutes in USP apparatus 2 (paddle) with 500 mL deaerated purified water at 50 rpm and 37 ± 0.5 °C. Samples were withdrawn and filtrated (0.45-µm membrane filters, Merck, USA) then quantified using UV spectrophotometry at 242 nm and compared with reference standard preparations.

The UV-Visible spectrophotometer was validated and monitored following the standard operation procedure. Monthly monitoring includes verification of the following parameters/processes: noise, stability, wavelength accuracy, absorbance accuracy, stray light limit, resolution power, baseline flatness, and reproducibility.

Friability Test

The friability test was carried out using a randomly selected sample of 20 tablets according to *USP* <1216> (*36*). These tablets were weighed (KERN PFB 300-3 analytical scale, Germany) and placed into a friabilator chamber (Roche Friabilator, Germany) at 25 rpm for 4 min (100 revolutions). The tablets were weighed again, and differences in weight were calculated as percentage friability (*22*). The same procedure was repeated for all atorvastatin calcium tablet brands. Requirements are met if weight loss is within 1.0% (*22, 36*).

Hardness Test

The hardness test was performed using 20 tablet samples (*37*) in accordance with *USP* <1217>. Randomly selected tablets from each brand were tested individually between the two plungers of hardness tester (Erweka TBH 125, Germany). Crushing force was recorded in kiloponds (Kp) for each tablet (*22*).

Uniformity of Dosage Unit Test

The weight variation test was conducted using randomly selected sample of 20 tablets in compliance with *USP* <905> (*38*). Tablets were weighed individually using an analytical scale (KERN PFB 300-3, Germany). The average weights and deviation from the mean were calculated for each brand (*22*). Compliance is confirmed if the weights of no more than two tablets deviate from the mean of the same brand by more than 5% and no tablet differs in weight by more than 10% (*22*, *38*).

Disintegration Test

The disintegration test was performed before the dissolution procedure to identify any abnormal disintegration times, which can impact the dissolution parameters. Six tablets of each brand were individually placed inside the six tubes of the basket of the disintegration test apparatus (ED 2L, Electrolab, Mumbai, India), as described in *USP* <701> (*39*). Then 800 mL of simulated gastric fluid (SGF) was filled into a beaker containing the disintegration basket, and media temperature was maintained at 37 ± 2 °C. Tests started immediately after the basket assembly was completed. Disintegration time was recorded when no particles remained in the system's basket. If all six tablets disintegrate, the brand passes the test. If 1 or 2 tablets do not fully disintegrate, then 12 additional tablets are tested; only two tablets out of the 18 are permitted to fail the disintegration process (*39*).

Dissolution Test

The dissolution test was carried out with USP apparatus 2 (paddle) containing phosphate buffer of pH 6.8 as the dissolution medium (n = 6 vessels) (*22, 40*). The temperature of the medium was maintained at 37 ± 0.5 °C and the stirring speed was set to 75 rpm (*40*). Samples (5 mL) were withdrawn from each vessel at time intervals of 5, 10, 15, 30, 45, and 60 min and replaced with equal volumes of fresh dissolution medium. Samples were filtered using 0.45-µm membrane filters (Merck, USA), diluted as required, and their absorbance was measured by UV/Vis spectrophotometry (*35*). Absorbance values were then correlated with the previously constructed standard curve (r^2 = 0.9994) to calculate the concentration of drug released at each time interval.

Data Analysis

Drug release profiles were plotted using the zero-order, first-order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas, and Weibull mathematical models. To identify a linear relationship between the actual drug release profile and kinetic models, the highest coefficient of determination (r^2) represents the best fit (*22, 41*).

In addition, dissolution profiles were compared based on area under the curve (AUC) values, dissolution efficiency (DE), mean dissolution time (MDT), difference factor (f_1), similarity factor

(f_2), and Akaike Information Criteria (AIC), in which the smallest AIC value represents the best fit (*22*, *42*, *43*).

All comparisons were run using GraphPad Prism software, version 6.01. Two-way analysis of variance (ANOVA) followed by Dunnett post-hoc analysis was used to compare dissolution profiles. DDSolver version 1.0 (Microsoft Excel add-in) was used for kinetic modeling and pairwise comparison of dissolution profiles. The best fitting drug-release model was selected based on comparisons of fit parameters, r^2, and AIC provided by DDSolver (*44*). Results of AUC, DE, MDT, and disintegration times were compared by one-way ANOVA and Dunnett tests (*22*).

RESULTS AND DISCUSSION

Table 1 presents the organoleptic properties of each brand's tablet. All tablets had the same color and shape (white, elliptical), with a diameter range of 14.20–16.90 mm and thickness range of 4.00–5.92 mm. This excludes any unexpected effect due to tablet shape or dimensions because all brands were similar.

Table 2 shows the weight variation, hardness, friability, and disintegration time results. Weights were within the range of 489–617 mg with low deviations from average weight (SD: 0.004–0.006), which was within the USP limits of < 5% deviation (*45*). Hardness values were in the range of 15.60–22.94 Kp and were similar for all products except brand C (15.60 Kp). Although there is no USP limit for tablet hardness, the industrial acceptable limit for an immediate-release tablet is > 4 Kp (*46*). Friability tests revealed that all the samples were within the acceptable range of < 1% except brand C (1.3% weight loss), which is above the acceptable USP limit (*36*). The correlation between the lowest hardness and the highest friability for brand C was reported previously; similar factors affect tablet hardness and friability and are mainly related to non-API ingredients like binders (*47*, *48*). High friability may result in weight or content variation as well as tablet appearance variation and consequently, consumer acceptance (*49*).

As shown in Table 2, all brands had disintegration times within the acceptable USP limit (*39*). Brand D had a mean disintegration time of 103 sec, almost half of the innovator brand A, which was 201 sec. Although brand C had low hardness and high friability, mean disintegration time was 389 sec, which was significantly different from the innovator A. These properties of brand C may be related to the presence of high concentration of magnesium stearate, which can reduce the cohesive forces and increase the disintegration time of the tablet system (*47*).

Table 1. Characteristics of 40-mg Atorvastatin Calcium Tablet Formulations

Brand Code	Price[b]	Appearance	Diameter, mm (mean ± SD)	Thickness, mm (mean ± SD)
A[a]	28.08	White, elliptical	15.50 ± 0.07	5.92 ± 0.04
B	23.12	White, elliptical	16.90 ± 0.00	4.00 ± 0.00
C	23.12	White, elliptical	15.60 ± 0.00	4.40 ± 0.00
D	23.12	White, elliptical	14.20 ± 0.00	4.66 ± 0.05
E	23.12	White, elliptical	16.10 ± 0.00	5.21 ± 0.03

[a]*Innovator atorvastatin brand (Lipitor, Pfizer).*

[b]*Latest price per packet in USD.*

Table 2. Weight, Hardness, Friability, and Disintegration Results of Atorvastatin Calcium Tablets

Brand Code	Weight, g (mean ± SD)	Hardness, kp (mean ± SD)	Friability, loss %	Disintegration Time, s[b] (mean ± SD)
A[a]	0.617 ± 0.005	22.94 ± 0.731	0.081	201.17 ± 44.33
B	0.515 ± 0.006	24.80 ± 4.344	0.495	186.33 ± 43.53
C	0.489 ± 0.005	15.60 ± 1.784	1.380	389.83 ± 55.88*
D	0.513 ± 0.004	24.82 ± 1.461	0.283	103.00 ± 28.40*
E	0.613 ± 0.005	19.81 ± 7.479	0.082	246.33 ± 68.91

[a]*Innovator atorvastatin calcium brand (Lipitor, Pfizer).*

[b]*Maximum time registered for complete disintegration.*

**Statistically significant difference ($p < 0.05$) vs innovator per ANOVA and Dunnett tests.*

Figure 2 displays the cumulative drug release profiles. All samples exhibited a rapid release profile with > 89% release in 15 min, which complied with USP specifications (*35*). This aligns with the solubility properties of atorvastatin calcium (highly soluble at acidic pH), reflecting no limitation in atorvastatin solubility in dissolution media at pH 6.8 (*7*).

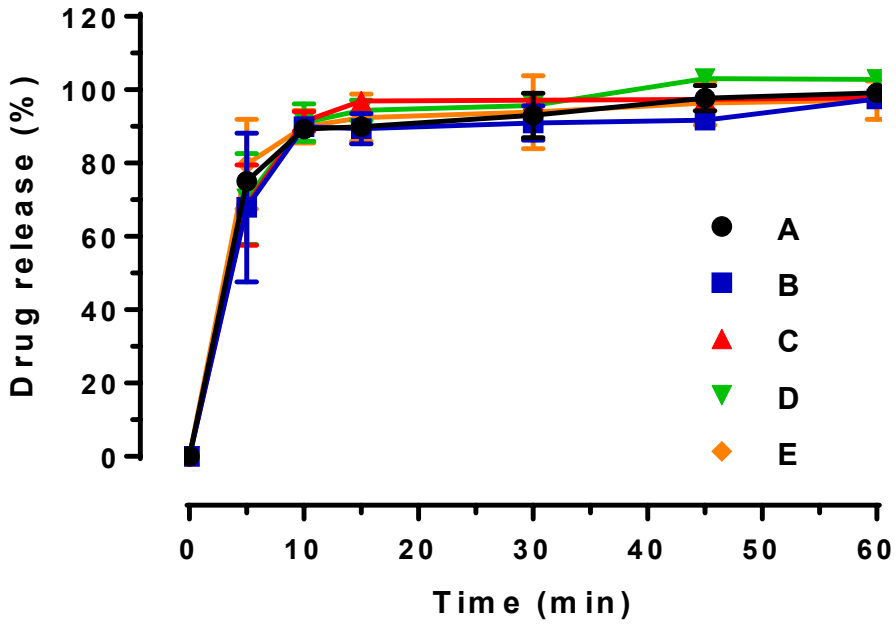

Figure 2. Dissolution profiles of commercially available atorvastatin calcium 40-mg tablet brands (A–E). Data points are mean ± SD percentage of labeled amount dissolved (n = 6).

Table 3 presents the dissolution parameters including AUC, MDT, DE, f_2, and f_1 for all tested brands. Analyses for MDT and DE revealed no significant differences, indicating conformity of the release profile in which all the tested brands displayed a similar fast release behavior compared with the innovator brand. Statistical analysis of AUC values revealed no significant differences with the exception of brand D, which was significantly higher (5503.7) than the innovator (5326.8). Thus, it seems that the markedly fast disintegration time of brand D (103 sec) compared to brand A (201 sec) had a significant impact on AUC values. The significant difference in disintegration time had no impact on MDT or DE. The overall similarity of the dissolution profiles

was further analyzed using fit factors f_2 and f_1 values, which also is endorsed by FDA guidance (*50*). These factors were determined using all release data on the concentration-time dissolution curve to detect any differences between the innovator and generic brands (i.e., f_1 values of < 15 and f_2 values of > 50 indicate similarity with the innovator). For all tested brands, f_1 was 2.2–4.12 and f_2 was 69.00–80.68, indicating similarity of the dissolution profiles for the generic brands with the innovator brand.

Table 3. Pairwise Comparison of Atorvastatin Calcium Tablets Dissolution Profiles

Brand Code	Area under the curve, min %	Dissolution Time, min (mean)	Dissolution efficiency, %	Similarity factor (f_2)	Difference factor (f_1)
A[a]	5326.8	6.28	88.8	NA	NA
B	5154.4	7.13	85.9	70.90	3.33
C	5421.5	4.58	90.4	69.00	3.93
D	5503.7*	6.46	91.7	70.87	4.18
E	5355.3	4.87	89.3	80.68	2.20

[a]*Innovator atorvastatin brand (Lipitor, Pfizer).*

** Statistically significant difference ($p < 0.05$) vs innovator (A) per ANOVA and Dunnett tests.*

Table 4. Kinetic Modeling of Atorvastatin Calcium Tablets Drug Release

Model		Brand A	Brand B	Brand C	Brand D	Brand E
Zero-order	K_0	0.981	0.956	0.981	1.079	0.910
	r^2	0.386	0.382	0.367	0.427	0.334
	AIC	62.97	62.75	63.58	63.12	63.51
First-order	K_1	0.252	0.217	0.235	0.238	0.290
	r^2	0.982	0.971	0.997	0.995	0.983
	AIC	36.21	39.23	23.02	28.39	36.01
Higuchi	K_h	16.558	16.067	16.734	17.108	16.569
	r^2	0.393	0.401	0.396	0.482	0.293
	AIC	60.90	60.53	61.25	60.41	61.93
Hixson-Crowell	K_{hc}	0.026	0.026	0.026	0.027	0.026
	r^2	0.582	0.615	0.619	0.655	0.501
	AIC	58.29	57.44	58.02	57.58	59.49
Korsmeyer-Peppas	K_{kp}	68.257	64.843	66.990	63.973	74.654
	r^2	0.994	0.977	0.968	0.983	0.996
	AIC	30.71	39.78	42.62	38.43	27.57
Weibull	α	0.748	0.550	0.536	0.954	0.595
	β	0.251	0.111	0.202	0.434	0.176
	r^2	**0.998**	**0.997**	**0.999**	**0.996**	**1.000**
	AIC	**23.80**	**26.92**	**18.77**	**30.26**	**7.89**

***Bold** print indicates the best fit.*

K_0: zero-order release constant; r^2: regression constant; AIC: Akaike Information Criteria; K_1: first-order release constant; K_h: Higuchi release constant; K_{hc}: Hixson-Crowell release constant; K_{kp}: Korsmeyer-Peppas release constant; α: Weibull time dependence scale parameter; β: Weibull dissolution curve progression shape scale parameter.

Table 4 presents the correlation of drug release profiles for each brand against each dissolution kinetic model, in which the highest r^2 value and lowest AIC value represent the best correlation. The zero-order, Higuchi, and Hixson-Crowell models did fit the release profile for any of the brands

(r^2 = 0.3–0.6). On the other hand, the first-order, Korsmeyer-Peppas, and Weibull models strongly correlated with the actual release profiles for all brands (r^2 > 0.9). The Weibull model was considered the best fit, exhibiting the highest r^2 (0.996–1) and lowest AIC (7.98–30.26) for all the brands investigated. Furthermore, the exponent of shape β overall was < 1 in the Weibull model, exhibiting parabolic drug release curves for all tested brands (*51*). Additionally, for better consolidation of drug release mechanisms, the release exponent *n* in the Korsmeyer-Peppas model was < 0.45, indicating a Fickian diffusion release pattern, for all products except brand C. Brand C had an *n* value of 0.87, suggesting a non-Fickian release mechanism (*52*).

CONCLUSION

Comparative post-marketing quality testing for oral atorvastatin brands relative to innovator is critical to examine. This study revealed that four generic brands of 40-mg atorvastatin calcium oral tablets sold in Saudi Arabia (i.e., Lorvast, Astatin, Atorva, and Lipicure) are equivalent to the innovator brand (Lipitor). The data revealed no significant differences in quality parameters and dissolution profiles. Minor differences detected in brand C (low hardness, high friability, high disintegration time) and D (high AUC) can be related to the presence of minor manufacturing differences in the tablet formulation. All brands studied exhibited a drug release profile that best fit the Weibull model. Lastly, these results support pharmaco-equivalence and interchangeability of the innovator and generic brand atorvastatin tablets in the Saudi market.

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CONFLICTS OF INTEREST

The author declares no conflict of interest related to this study.

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