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| RESEARCH ARTICLE

Quality Assessment of Brands and Generic in Atorvastatin Tablets Available in Iraq-thi-Qar

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| ABSTRACT

Hypolipidemic agents have been shown to be helpful in the primary and secondary prevention of cardiovascular disease. Statins are frequently administered to treat hyperlipidemia. Although there are many statins on the market today, atorvastatin is the one that is most frequently recommended. The medications must meet the required physical qualities and contain the right quantity of active medicinal components. The primary goal of the study was to assess the value of several brands of atorvastatin calcium tablets sold in Iraq.Methods: In this study, the in vitro dissolving test, disintegration, friability, and hardness tests of the innovator product coded as (AT-1) and the generic brands (coded as AT-2) of atorvastatin tablets 20 mg available in Iraq were assessed. Drug analysis was done using a spectrophotometric technique. At a 240 nm wavelength, atorvastatin was found. The researched products released more than 90% of the atorvastatin in 30 minutes, per the findings of the dissolving testing. In under 30 minutes, the brands AT-1 and AT-2 showed a release of atorvastatin of over 95% and 86%, respectively. Our research revealed that the generic brand AT-2 and the innovator atorvastatin (AT-1) were of high pharmaceutical grade. In vitro dissolution, friability, disintegration, and hardness tests required by the pharmacopoeia were all passed by generic and innovator of atorvastatin tablets sold in the Iraqi market. Therefore, it was concluded that these generics might be utilized interchangeably by focusing on their in vitro release characteristics.

| KEYWORDS

Atorvastatin, Dissolution, Friability test, disintegration test, hardness.

| ARTICLE INFORMATION

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1. Introduction

Statins represent a major portion of the global market for lipid-lowering medications. The drug atorvastatin is the most frequently prescribed of these [Arca, 2007]. The medication consistently ranks at the top of the list of best-selling medications [Taylor, 2015]. Fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin are additional medications in the statin medicine class [Kogawa, 2019; van Leuven, 2005]. The chemical formula for atorvastatin calcium (Fig. 1) is C66H68CaF2N4O10, and its molecular weight is 1155.363 g/mol [Lennernas et al. 2003]. It is very marginally soluble in acetonitrile, distilled water, phosphate buffer with a pH of 6.8, and methanol. It is easily soluble in methanol[Shaker et al. 2020]. It falls under class II due to its strong permeability and low soluble content [Paidi, 2015]. The brand-name medication, known as LipitorTM (atorvastatin calcium), was approved by the "United States Food and Drug Administration (USFDA)" in 2001. It is sold in the market in four strengths (10 mg, 20 mg, 40 mg, and 80 mg) [White, 2015]. Patients with hypercholesterolemia, heterozygous familial hypercholesterolemia, and patients at high risk of experiencing their first cardiovascular incident should take atorvastatin[Schachter, 2005].

These lipid-lowering medications lower blood cholesterol by inhibiting 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, an enzyme that serves as a catalyst in the formation of numerous compounds in the body, including cholesterols, from mevalonates [Chong, 1997]. Statins also serve as an anticancer sensitizing agent by preventing the development, growth, and spread of tumors[Chan et al., 2003].

In the liver, the "cytochrome P450 (CYP)" isoenzyme CYP3A4 mostly breaks down atorvastatin into its two active forms, 2-hydroxy-atorvastatin acid and 4-hydroxy-atorvastatin acid, which have a bioavailability of about 14% [Khan et al. 2011]. Due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, which is its primary site of action, it has poor absolute bioavailability. It has a 98 percent binding affinity for plasma proteins [Posvar, 1996]. In circulation, atorvastatin has a half-life of about 14 hours, but due to the influence of active metabolites, the inhibitory action on HMG-CoA reductase lasts for 20 to 30 hours. Atorvastatin is primarily eliminated in the bile as metabolites[Cilla et al. 1996].

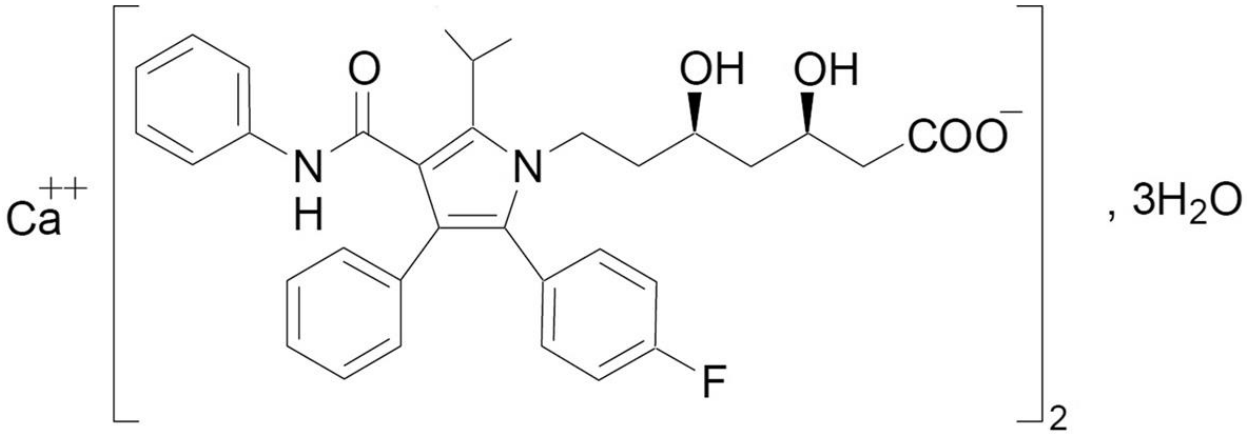

Fig. 1 Chemical structure of atorvastatin calcium

Numerous investigations on the in vitro drug release of various types of commercial tablets in various nations have been reported [Zhou et al., 2021]. However, there is a paucity of literature regarding atorvastatin's marketing in Iraq. Because of its significance in predicting drug bioavailability and product quality, locally available atorvastatin tablets were chosen for the assessment with a focus on the dissolving property.

Ulla et al. (2018) previously evaluated the consistency of generic atorvastatin calcium tablet brands sold in the Asir region of Saudi Arabia. Along with the innovator product, three generic brands were mentioned in the analysis and were put through quality control tests like hardness and friability, as well as assays using UV spectrophotometers at wavelengths of 246 nm. These tests included the disintegration test, invitro dissolution (medium pH 1.2 HCl, 37 0.5 °C, and 100 rpm), and disintegration test. More than 90% of the medicine is released within an hour, according to in vitro drug dissolution profiles of both innovator and generic brands[Rahamathulla, 2018].

In a different study, Tariq et al. (2014) compared the innovator brand's in vitro bioequivalence to that of six generic atorvastatin brands sold in Pakistan. The medium for the dissolution experiment was phosphate buffer pH 6.8 at 37 0.5°C and 75 rpm. The results indicate no resemblance in five of the six generics examined when the similarity factors f1 and f2 are measured. For all of the brands, the drug content was well below acceptable limits. The generic brands evaluated various quality control examinations and found significant variations [Tariq et al. 2014]. An evaluation of three atorvastatin generics available in Bangladesh in comparison to the innovator product was previously published by Popy et al. It comprised an in vitro bioequivalence examination in three distinct media (pH 1.2, pH 4.5, and pH 6.8). Due to the fact that all generic brands released more than 85% of the drug within 15 minutes, the results show that all of the brands demonstrated similarity in pH 6.8 without calculating the similarity factor f2. The results of dissolving research done in a media with a pH of 4.5 reveal a resemblance when using the similarity factor f2; however, the similarity disappears in a medium with a pH of 1.2. There were no differences between innovator and generic products in terms of crushing strength, friability, or weight uniformity, according to the investigation [28]. In the past, Oliveira et al. (2012) established a strategy to contrast an innovator atorvastatin product with a generic version offered in Brazil [de Oliveira, 2012].

The formulation and production processes of pharmaceutical formulation systems largely impact how effective they are; hence dosage system quality may vary. According to earlier research [Akinleye et al., 2012], several atorvastatin generic products did not adhere to pharmacopeial requirements. Therefore, in this setting, it is crucial for researchers to carry out independent bioequivalence assessments of marketed pharmacological products. Product performance tests are intended to evaluate the performance of the product and frequently address dissolution [Dickinson et al., 2008]. Therefore, the goal of the current analysis was to assess how well the innovator AT-1 and the generic AT2 products sold in Iraq performed as drug goods. Friability, hardness, dissolution, and disintegration tests were also taken into account [Hammami, 2020].

2_Materials

Table 1: Materials Used in the Study.

Materials	Supplier
hydrochloric acid	Thomas baker, India
Sodium hydroxide	Merck- Darmstadt, Germany
Potassium dihydrogen	Riedel-De Haen AG- Seeize, Germany,

2.1 Sampled drug products

The products were coded as AT-1 (innovator) and AT-2 (generic). The generic products (AT-2) were compared against the innovator product AT-1.

2.2 In vitro disintegration test

The disintegration time (DT) of the AT was determined using 0.1N HCl as a disintegration medium. The DT was estimated by using special apparatus for disintegration testing (Copley Scientific, UK) with a basket rack assembly containing six open-ended tubes. One tablet was sited in each tube, and the basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in the 900 ml 0.1N HCl kept at 37 ±0.5 ºC. The time wanted for the total disintegration of the tablet in each tube was estimated by using a stopwatch [Lachman, 1987].

2.3 Friability test

The tablet friability tester (Erweka, Germany) was employed in this study to conduct the friability test. The difference between the tablet weights before and after the test was quantified. The friability tester has a 4 minute timer with a 25 rpm speed setting.

2.4 Hardness test

A hardness test was done using YD-1.Beijing. China, an average of hardness test results was obtained, and the standard deviation was calculated.

2.5 Dissolution test

Utilizing potassium dihydrogen phosphate in purified water to create the dissolving media (0.05 M phosphate buffer), sodium hydroxide was used to adjust the pH to 6.8, and a digital PH meter (Hanna-Italy) was used to measure the pH.

For an objective evaluation, choosing the right dissolving medium is essential. The Indian Pharmacopoeia, which specifies phosphate buffer as a dissolving medium, lists atorvastatin calcium as an official component. As a result, dissolving was carried out in 900 cc of pH 6.8 phosphate buffer at 37 0.5 °C and 75 rpm [Popy et al. 2018]. The dissolution equipment was connected to an auto sampler that was set up to remove and replace 5 ml of the dissolution media at 5, 10, 15, 20, 25, and 30 min

3. Results and discussion

3.1 Hardness test

A hardness test showed that all of the brands are resilient enough to withstand pressure without losing any of the tablet's constituent parts during handling and packaging. Our findings showed that the generic product (AT2) displayed hardness values (equal to or more than 4 Kg) that were comparable to the innovator product (Table 2).

3.2 Friability test

To evaluate the tablets' resistance to abrasion, the friability test is used. Friability is currently included as a compendia test in the USP, 1995 [Oishi, 2011]. One percent of compendia is required for the friability test. For all of the atorvastatin brands that were examined in our investigation, the results of the friability test were determined to be less than 1%. (Table 2).

3.3 In vitro disintegration test

Brand and generic products had the fastest in vitro disintegration times, releasing all of the medication within 30 minutes at 0.1 N Hcl (Table 2).

Table 3 Evaluation of disintegration time, Friability and hardness of different products of atorvastatin tablets

Product code	AT1	AT2
disintegration time (min)	1.31	1.55
Frability % Mean (n=20)	0.5	0.9
Hardness Kg Mean ±STD (n=3)	11.78 ±0.29	9.06±0.28

3.4 Dissolution test

Dissolution studies have grown in importance as a technique for analyzing batch-to-batch variance and drug release [Alkufi, 2019]. Drugs that are poorly soluble, like atorvastatin, must dissolve from their solid dose form in order to be bioavailable. Poorly soluble medications will not be as quickly available in the body system for the desired therapeutic effect because they do not have acceptable dissolving profiles, which is the first step in determining the rate of absorption. The amount of medicine that is available for absorption following oral delivery can be determined with the use of dissolution studies [Molavi et al., 2020].

The products AT-1 showed 94.06% drug release within 30 minutes of the dissolution research, according to the results of the dissolution test (Fig. 2). ProductAT-2 displays 85.45% (Fig. 2). Every single generic tablet that was tested showed quick disintegration and released more than 85% of the atorvastatin content in within 30 minutes. Regulatory agencies require proof of similarities between the generic and innovator brands before they will give a generic a marketing licence. Tablets that dissolve very quickly are regarded as being substantially similar.

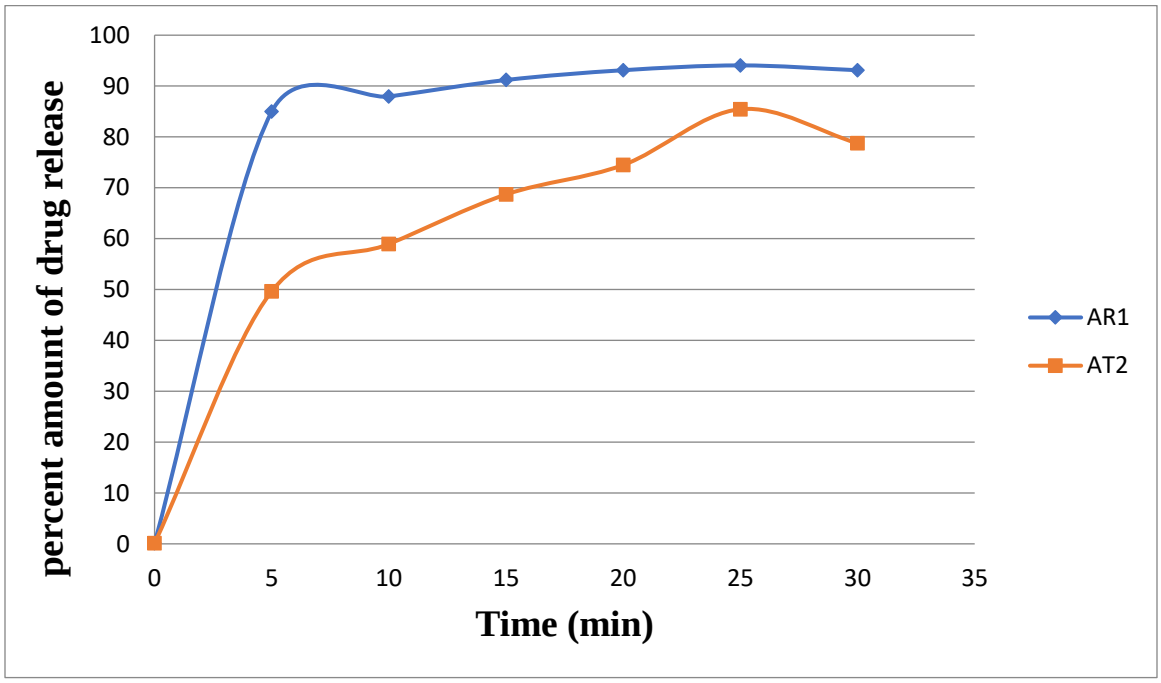

Fig2: Dissolution profiles of the atorvastatin tablets (AT-1) and their generic counterparts (AT-2) at pH 6.8.

4. Conclusion

The findings of the current study showed that the atorvastatin tablet (20 mg) generics under investigation are of good pharmaceutical quality and are comparable to the innovator product. According to the dissolution profile, the innovator product and analyzed generic brand tablets quickly decomposed and released more than 85% of the medication in under 30 minutes. Also, the result obtains from hardness, friability, and disintegration tests give acceptable value for both generic and innovator products. The results of the current investigation demonstrate that generic drugs and innovator products are interchangeable. A generic medicine is typically less expensive than a brand-name medication. Therefore, switching to generic medicines will help patients save a significant amount of money. So you will save an amount of money in the future for the patient and the hospital. In vivo bioavailability studies are essential to confirm whether the results achieved in this investigation can be extrapolated to the in vivo conditions.

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References

[1] Arca M. (2007). Atorvastatin: a safety and tolerability profile. Drugs. 67:63–9.

[2] Alkufi, H. K., & Rashid, A. M. (2021). Enhancement of the solubility of famotidine solid dispersion using natural polymer by solvent evaporation. *International Journal of Applied Pharmaceutics, 13,* 193-198.

[3] Abebe S, Ketema G, Kassahun H (2020). In vitro Comparative Quality Assessment of Different Brands of Furosemide Tablets Marketed in Northwest Ethiopia. Drug Des Devel Ther;14:5119–28.

[4] Al-Kazemi R, Al-Basarah Y, Nada A (2019). Dissolution Enhancement of atorvastatin Calcium by Cocrystallization. Adv Pharm Bull. 9:559–70.

[5] Akinleye MO, Idris O, Nwachukwu PN, Oyetunde OO (2012). Quality of brands of atorvastatin calcium tablets marketed in Lagos. Nigeria. Int J Pharm Pharmacol.;1:001–7.

[6] Alkufi, H. K., & Kassab, H. J. (2019). Formulation and evaluation of sustained release sumatriptan mucoadhesive intranasal in-situ gel. Iraqi J Pharm Sci, 28(2), 95-104.

[7] Bagbi BM, Omotoso AE, Chiagozie O (2014). Comparative assessment of quality brands of atorvastatin tablets marketed in Southern Nigeria. J Pharm Biomed Sci;04:318–26.

[8] Chong PH, Seeger JD (1997). Atorvastatin calcium: an addition to HMG-CoA reductase inhibitors. Pharmacotherapy17:1157–77.

[9] Cilla DD, Whitfield LR, Gibson DM, Sedman AJ, Posvar EL (1996). Multiple-dose pharmacokinetics, pharmacodynamics, and safety of atorvastatin, an inhibitor of HMG-CoA reductase, in healthy subjects. Clin Pharmacol Ther;60:687–95.

[10] Chan KK, Oza AM, Siu LL (2003). The statins as anticancer agents. Clin Cancer Res;9:10–9.

[11] Dickinson PA, Lee WW, Stott PW, Townsend AI, Smart JP, Ghahramani P (2008). Clinical relevance of dissolution testing in quality by design. Aaps J;10:380–90.

[12] de Oliveira MA, Lacerda CD, Bonella AF (2012). Developing methods to compare tablet formulations of atorvastatin. Braz J Pharm Sci;48:801–10.

[13] Hammami MM, AlSwayeh R, Hussein RF (2020). Pharmaceutical quality of seven brands of diclofenac tablet on the Saudi market. BMC Res Notes;13:548.

[14] Kogawa AC, Pires A, Salgado HRN (2019). Atorvastatin: A Review of Analytical Methods for Pharmaceutical Quality Control and Monitoring. J AOAC Int. 102:801–9.

[15] Lennernas H (2003). Clinical pharmacokinetics of atorvastatin. Clin Pharmacokinet. 2003;42:1141–60.

[16] Khan FN, Dehghan MH (2011). Enhanced bioavailability of atorvastatin calcium from stabilized gastric resident formulation. AAPS PharmSciTech. 12:1077–86.

[17] Lachman L, Liberman H, Kanig J. (1987). The theory and practice of industrial pharmacy, Mumbai: Varghese Publishing House, 3rd ed: 293-345.

[18] Molavi F, Hamishehkar H, Nokhodchi A (2020). Impact of tablet shape on drug dissolution rate through immediately released tablets. Adv Pharm Bull;10:656–61.

[19] Manani RO, Abuga KO, Chepkwony HK (2017). Pharmaceutical equivalence of clarithromycin oral dosage forms marketed in Nairobi county, Kenya. Sci Pharm;85(2):20. https:// doi. org/ 10. 3390/ sciph arm85 020020.

[20] Oishi TS, Haque MA, Dewan I, Islam SMA (2011). Comparative in vitro dissolution study of some ciprofloxacin generic tablets under biowaiver conditions by RP-HPLC. Int J Pharm Sci Res;2:3129–35.

[21] Oishi TS, Nimmi I, Islam SMA (2011). Comparative in vitro bioequivalence analysis of some generic tablets of atorvastatin, a BCS class II compound. Bangladesh Pharm J;14:61–5.

[22] Palem CR, Patel S, Pokharkar VB (2009). Solubility and stability enhancement of atorvastatin by cyclodextrin complexation. PDA J Pharm Sci Technol. 63:217–25.

[23] Paidi SK, Jena SK, Ahuja BK, Devasari N, Suresh S (2015). Preparation, in-vitro and in-vivo evaluation of spray-dried ternary solid dispersion of biopharmaceutics classification system class II model drug. J Pharm Pharmacol. 2015;67:616–29.

[24] Perez-Calahorra S, Laclaustra M, Marco-Benedi V, Pinto X, Sanchez- Hernandez RM, Plana N (2019). Comparative efficacy between atorvastatin and rosuvastatin in the prevention of cardiovascular disease recurrence. Lipids Health Dis. 18:216.

[25] Posvar EL, Radulovic LL, Cilla DD Jr, Whitfield LR, Sedman AJ (1996). Tolerance and pharmacokinetics of single-dose atorvastatin, a potent inhibitor of HMG-CoA reductase, in healthy subjects. J Clin Pharmacol;36:728–31.

[26] Popy FA, Dewan I, Parvin MN, Islam SMA (2012). Evaluation of in vitro equivalence for tablets containing the poorly water-soluble compound atorvastatin. Dissolution Technologies. 2012;19:30–3.

[27] Rodde MS, Divase GT, Devkar TB, Tekade AR (2014). Solubility and bioavailability enhancement of poorly aqueous soluble atorvastatin: in vitro, ex vivo, and in vivo studies. Biomed Res Int. 20:463895.

[28] Rahamathulla M (2018). Comparative assessment of different marketed brands of atorvastatin tablets in Asir region, Saudi Arabia. MOJ Drug Des Develop Ther;2:9–13.

[29] Rohmani S, Yugatama A, Suryadi BB, Lady FF, Ainurofiq A, Prihapsara F (2020). Evaluation of compared dissolution profile of atorvastatin tablets in markets. J Adv Pharm Edu Res;10:107–15

[30] Shaker MA, Elbadawy HM (2020). Improved solubility, dissolution, and oral bioavailability for atorvastatin-Pluronic(R) solid dispersions. Int J Pharm;574:118891.

[31] Schachter M (2005). Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol;19:117–25.

[32] Tariq MH, Khan IU, Ahmad B, Raheem A. (2014). Yasmeen M. Evaluation of in-vitro bioequivalence of commonly prescribed generics of poorly water-soluble drug-atorvastatin calcium in Pakistan. J Pharmacy Res. 8:420–2.

[33] Taylor D (2015). The Pharmaceutical Industry and the Future of Drug Development. In: Pharmaceuticals in the Environment. 1–33.

[34] van Leuven SI, Kastelein JJ (2005). Atorvastatin. Expert Opin Pharmacother;6:1191–203.

[35] Veronin MA, Nguyen NT (2008). Comparison of simvastatin tablets from the US and international markets obtained via the Internet. Ann Pharmacother. 42:613–20.

[36] White R, Bradnam V (2015). Atorvastatin. in Handbook of drug administration via enteral feeding tubes 2015, 3rd Edition. London, UK: Pharmaceutical Press. p.
[37] Xie F, Ding X, Zhang QY (2016). An update on the role of intestinal cytochrome P450 enzymes in drug disposition. Acta Pharm Sin B;6:374–83.
[38] Zhou Z, Wang C, Li M, Lan Q, Yu C, Yu G (2021). In vitro dissolution and in vivo bioequivalence evaluation of two metformin extended-release tablets. Clin Pharmacol Drug Dev;10:414–9.