

Comparative Dissolution Study of Atorvastatin Calcium Tablets in Indonesia

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ABSTRACT

Atorvastatin calcium is a prescribed medication for hyperlipidemia that is widely used in Indonesia, both the innovator and its generic products. The performance of each product may vary, but generic products must meet quality standards of bioequivalence with the innovator. This study aimed to reveal the in vitro equivalence of eight atorvastatin calcium generic products from various manufacturers by comparative dissolution testing. Four generic name products (labeled G1–G4) and four branded generic products (coded B1–B4) from the Indonesian market were used to study their pharmaceutical equivalence with the innovator brand (Lipitor). In vitro dissolution testing was performed in gastrointestinal pH (1.2, 4.5, and 6.8) using USP apparatus 2 with 900 mL dissolution medium at 75 rpm and 37 ± 0.5 °C. The percentage of the dissolved drug was evaluated using the similarity (f_2) factor. Atorvastatin calcium content for all products was 94.08–101.10% of the labeled claim. At pH 4.5 and 6.8, all products met the criteria for rapid dissolution (85% in ≤ 30 min). Dissolution percentages at pH 1.2 were more than 80% at 60 min. Based on f_2 values, the dissolution profiles did not have similarity (i.e., $f_2 < 50$) with the innovator at pH 6.8 for product G1 and B1, at pH 4.5 for product B1, and at pH 1.2 for product B2 and B3. Therefore, in vitro bioequivalency with the innovator product was established for four out of eight generic products.

Keywords: atorvastatin calcium, dissolution test, generic comparison, in vitro equivalence

INTRODUCTION

In Southeast Asia, Indonesia is the largest pharmaceutical market. Competition among pharmaceutical companies is inevitable, including innovator and generic products. Generally, the therapeutic efficacy of innovator is more recognized, but the innovator product is usually more expensive than generic products. The generic products should be bioequivalent to the corresponding innovator. They contained the same qualitative and quantitative composition of active pharmaceutical ingredients, in similar dosage form, strength, and identical route of administration (1, 2). The generic products and innovator should be equivalent to be used interchangeably; however, generic products may vary in the quality of components used in formulation. Inequivalent of generic products may have implications for public health (3, 4).

Since the 1960s, bioequivalence studies have emerged as gold standard to prove equivalency between a generic and its innovator product. Studies showed that the bioavailability of a drug formulated into an oral dosage form depends on its dissolution and release characteristics. Today, dissolution testing is a widely used as a quality control parameter to ensure batch-to-batch consistency and as an in vitro surrogate for in vivo performance (5).

Several generic drug products lack bioequivalence with the innovator product based on in vitro dissolution studies. For example, a study in Peru found that a generic product containing 100 mg of phenytoin was equivalent to the innovator brand at pH 1.2, but were not similar at pH 4.5 and 6.8, based on in vitro studies (6). Another study in Peru found that one out of four moxifloxacin tablet products was not equivalent to the innovator (7). In Spain, a study of

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pravastatin products failed to establish in vitro equivalency at pH 1.2, 4.5, and 6.8, but in vivo studies showed bioequivalence. Conversely, products known not to be bioequivalent have shown in vitro equivalence at pH 6.8 (8). In Saudi Arabia, one out of five generic products of amlodipine and acetaminophen were not similar with the reference (9, 10). In Pakistan, two generic brands of co-amoxiclav failed to meet criteria for similarity based on release of amoxicillin (11). However, there are also studies that have established in vitro bioequivalence of generic and innovator tablets, such as furosemide in Ethiopia, losartan in Argentina, and naproxen in Bangladesh (12–14).

Atorvastatin - (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenyl carbamoyl)-5-propan-2-yl pyrrol-1-yl]-3,5-dihydroxy heptanoic acid (Fig. 1), is a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA). This enzyme catalyzes the conversion of HMG-CoA to mevalonate in cholesterol biosynthesis (15). Atorvastatin is used as lipid lowering agent. Currently, atorvastatin calcium (salt form) is used to treat high cholesterol, and many generic products are available in the pharmaceutical markets. According to the Biopharmaceutical Classification System (BCS), atorvastatin calcium belongs to class 2, having low aqueous solubility and high intestinal permeability (16). It is insoluble in aqueous solution at pH less than 4, but it is slightly soluble in water. Atorvastatin calcium is absorbed from the gastrointestinal tract rapidly. Oral bioavailability is low, approximately 14%, owing to poor dissolution, presystemic clearance in the gut wall, and first-pass effect in the liver (17).

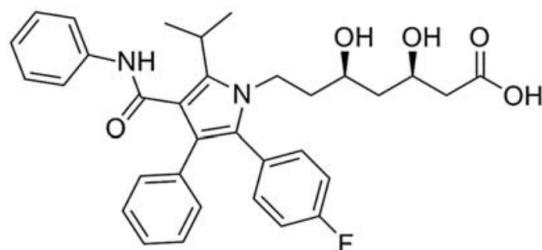


Figure 1. Chemical structure of atorvastatin.

Generic atorvastatin calcium products have been shown to lack in vitro bioequivalence. In Bangladesh, six generic atorvastatin calcium (10 mg) products were

shown to be not equivalent to the standard product (18). Also in Bangladesh, comparative dissolution testing of three branded generic atorvastatin calcium (10 mg) products failed to establish in vitro bioequivalence with the standard product at pH 1.2 but were equivalent at pH 4.5 and 6.8 (19). In Palestine, in vitro bioequivalence with the innovator was established for generic atorvastatin calcium (20 mg) products (20).

Post-marketing in vitro and in vivo performance of atorvastatin calcium tablets has not been assessed in Indonesia. The current study compares the pharmaceutical quality of the innovator brand (Lipitor) with locally available generic versions in Indonesia to assess interchangeability between the innovator and generics and between the generics themselves. Eight generic products of atorvastatin calcium were studied under simulated gastrointestinal conditions at three pH levels, pH 1.2 (hydrochloric acid [HCl]), pH 4.5 (acetate buffer), and pH 6.8 (phosphate buffer), and the dissolution profiles were compared using similarity factor (f_2) analysis.

MATERIALS AND METHODS

Chemicals and Reagents

Atorvastatin calcium working standard was donated by Etercon Pharma, Demak, Indonesia. Reagents used were of analytical grade (Merck), including 37% HCl, sodium acetate trihydrate, glacial acetic acid, sodium hydroxide, and potassium dihydrogen phosphate.

Tablet Samples

The innovator and eight multi-source atorvastatin calcium products (10-mg tablets) were purchased from a retail pharmacy in Semarang, Indonesia. The innovator product was Lipitor (lot no. EM0450, Pfizer). The four non-branded generic products were coded as G1–G4 (lot no. 51J0080, Dexa Medica; 1912053, Guardian Pharmatama; KTATVA06261, Hexpharm Jaya; and LH 0871, Pratapa Nirmala, Indonesia). The branded generic products were coded as B1–B4: Avesco (EX3A138, Dipa Pharmalab, Indonesia), Fastor (T1013, Lapi Laboratories, Indonesia), Litorcom (OEB813, Combiphar, Indonesia), and Tavora (KTTVRA05015, Kalbe Farma, Indonesia). All tests were done at least 3 months prior to expiration.

Standard Curve Preparation

Atorvastatin calcium working standard was prepared as a stock solution (100 µg/mL) in 10 mL of 0.05 M phosphate buffer pH 6.8. Aliquots of the stock solution were further diluted to concentrations range (8–18 µg/mL) and scanned at a maximum wavelength of 240 nm using UV/Visible spectrophotometer (Shimadzu UV-1800 240V). The resultant plot of absorbance versus concentration ($r^2 = 0.99971$) was used for assay and dissolution testing analysis.

Assay

Ten tablets from each product were crushed and dissolved separately in 100 mL of phosphate buffer pH 6.8. It was sonicated in an ultrasonic bath and filtered with a syringe filter (0.45 µm). One mL from the filtered solution was diluted to a volume of 10 mL with phosphate buffer pH 6.8. The absorbance was measured at 240 nm using UV spectrophotometry. The concentration was extrapolated from the standard curve calibration for atorvastatin calcium.

Dissolution

The dissolution test was conducted using USP apparatus 2 (paddle; TDT-08L, Electrolab) with six replicates for each product. Dissolution media were USP buffer solutions of pH 1.2 (0.1 N HCl), pH 4.5 (acetate buffer), and pH 6.8 (0.05 M phosphate buffer). The medium maintained at 37 ± 0.5 °C, the stirring speed was set to 75 rpm. Samples (5 mL) were withdrawn at 5, 15, 30, 45, and 60 minutes and replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The samples were filtered using 0.45-µm membrane filters (Whatman Puradisc), then their absorbance was measured using a UV/Vis spectrophotometer. Absorbance values were correlated with the previously constructed standard curve calibration ($r_2 = 0.9997$) to calculate the concentration of drug released at each time interval.

Data Analysis

Dissolution profiles were compared using the similarity factor (f_2). A f_2 value of 50–100 ensures that the two products have similar dissolution profiles.

RESULTS AND DISCUSSION

The content of atorvastatin calcium in the innovator product was 99.1% and the generic products had 94.08–101.10% of the declared amount (Table 1). The acceptance range is 94.5–105.0% of the declared amount according to USP or 90.0–110.0% according to Indonesian Pharmacopeia (21, 22). All products except G1 satisfied the quality requirement for content for USP, and all products met the requirement for Indonesian Pharmacopeia.

Table 1. Assay of 10-mg Atorvastatin Calcium Content in Multi-Source (G1–B4) and Reference Products

Product Code	Mean Drug Content (%)
Ref	99.10 ± 1.76
G1	94.08 ± 2.34
G2	97.53 ± 1.26
G3	99.51 ± 3.16
G4	98.46 ± 2.51
B1	98.53 ± 4.40
B2	96.37 ± 1.80
B3	96.91 ± 2.80
B4	101.10 ± 0.80

Figure 2 shows the dissolution profiles of the studied products. At pH 1.2, all products released more than 80% within 60 minutes. At higher pH levels, the dissolution rate increased, with more than 85% of drugs dissolved in less than 30 minutes (and within 15 minutes at pH 6.8). All atorvastatin calcium products showed rapid dissolution at pH 4.5 and 6.8. This study shows that the solubility of atorvastatin calcium depends on the pH of the medium. In a medium with low pH, the solubility is only 0.02 mg/mL, but at pH 6.8, the solubility is 1.23 mg/mL (19). The percentage of atorvastatin calcium dissolved should not be less than 80% within 30 min (Q) per USP, or 70% per Indonesian Pharmacopeia, in phosphate buffer pH 6.8 (21, 22). All products satisfied the dissolution requirement for USP and Indonesian compendia. Minor differences in dissolution profiles might be related to differences in the physical characteristics (shape and size), manufacturing processes, and the amount and type of excipients used in each formulation.

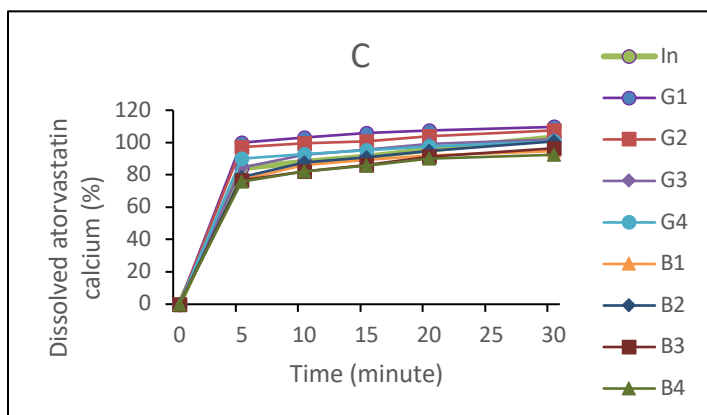
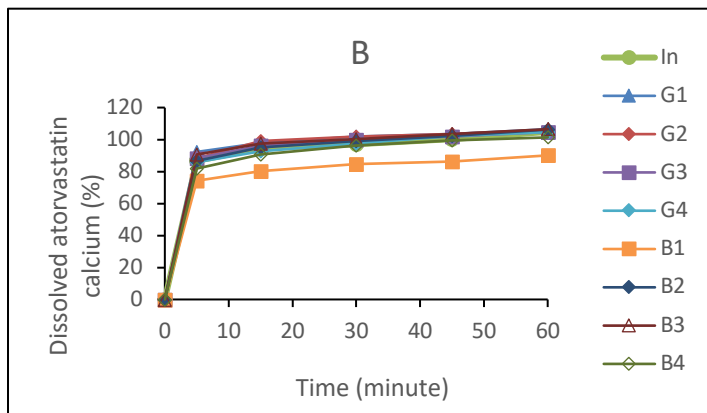
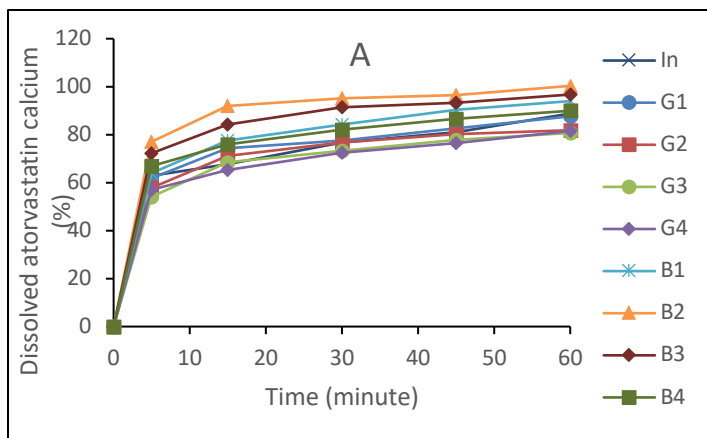


Figure 2. Dissolution profiles for atorvastatin calcium tablets in pH 1.2 (A), 4.5 (B), pH 6.8 (C). In: innovator product.

Dissolution profiles are used to estimate in vivo bioavailability and confirm interchangeability between innovator and generic products. The U.S. FDA acknowledges dissolution testing to be more discriminating than an in vivo test. The similarity factor (f_2) has been used to compare dissolution profiles of two products to determine their similarity. This test has been used to differentiate the effect of manufacturing variables, including the excipient type, mixing process, and other procedures and preparation. It is a rapid and inexpensive technique to

estimate the in-vivo bioequivalence of pharmaceutical dosage forms. In vitro dissolution testing promotes the interchangeability of the products, ensures the same efficacy, and the lower cost of generic products is a benefit to patients (23).

The f_2 calculation is calculated based on the amount of active substance dissolved from each sampling time point. The f_2 value is more sensitive to estimating differences between two dissolution curves than the f_1 value (dissimilarity factor), but both factors depend on the number of sampling time points. According to the FDA, $f_2 > 50$ should ensure equivalence among the dissolution curves (5).

Results of the similarity factor calculations are shown in Table 2. The f_2 value of products G2, G3, G4, and B4 were more than 50 at all three pH levels, so these products are similar with innovator product and can be used interchangeably. Products with $f_2 < 50$ include G1 and B1 at pH 6.8, B1 at pH 4.5, and B2 and B3 at pH 1.2. Therefore, these products (G1, B1, B2, and B3) cannot be considered interchangeable with the innovator brand based on differences in their dissolution profiles as certain pH levels. Product B2 and B3 may have contained alkalizing agents that possibly improved atorvastatin calcium solubility, causing dissimilarity in the pH 1.2 medium (18). Products G1 and B1 had dissimilarity with the innovator product at pH 6.8, which requires further evaluation because this is the biorelevant dissolution medium for this drug. However, both products met the USP dissolution limit of Q_{30} . Dissimilarity in the dissolution profiles at different pH levels indicates a lack of in vitro bioequivalence with the innovator brand for four out of eight generic products. This result should be confirmed with in vivo bioequivalence studies.

Table 2. Similarity Factors (f_2) for Multi-Source Products (G1–B4)

Product	pH 1.2	pH 4.5	pH 6.8
G1	74.06	54.05	31.26*
G2	68.32	72.38	50.01
G3	62.15	84.53	73.82
G4	64.06	89.40	68.91
B1	56.38	25.95*	41.75*
B2	37.95*	88.08	77.34
B3	45.08*	74.97	60.49
B4	62.87	73.27	56.07

*: f_2 value < 50

Although all products met the compendial standards for dissolution rate, not all products showed an equivalent dissolution profile in biorelevant (gastrointestinal) conditions. Only four out of eight products showed in vitro equivalence with the innovator. These findings are similar to a study conducted in Bangladesh in 2011 (18). Differences in the characteristics of raw materials used in the formulation and manufacturing process or method can affect pharmaceutical quality. Only those products that show bioequivalence should be interchangeable as therapeutic alternatives, not just pharmaceutical alternatives. Differences in regulatory policies in each country may also impact the quality of medicinal products. The differences observed in this study indicate that dissolution of atorvastatin calcium tablets is formulation dependent. This study will help inform policy and regulations of the Indonesian Food and Drug Authority regarding the quality and effectiveness of generic drug products.

CONCLUSIONS

Eight samples of atorvastatin calcium generic products on the Indonesian market met the acceptance criteria for content and dissolution rate. Four products are bioequivalent and considered interchangeable with the innovator product. Four out of eight generic products did not have similar dissolution profiles with the innovator at all pH levels.

DISCLOSURES

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The authors have no conflicts of interest.

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