Polish Pharmaceutical Society

Atorvastatin - (3R, 5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-yl pyrrol-1-yl]-3,5-dihydroxyheptanoic acid (Fig. 1) is a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA) which is an early rate limiting step in cholesterol biosynthesis (1).

This inhibition leads to consumption of intracellular cholesterol, which increases the expression of low density lipoprotein (LDL) receptor on hepatocytes resulting in a fall in serum LDL cholesterol concentration to about 40% and high systemic disappearance of LDL cholesterol (1, 2). Statins also cause small reduction in triglyceride levels by 10-20% and increase high density lipoprotein reducing the risks of morbidity and mortality due to cardiovascular events (1). Strokes and coronary heart diseases are major cardiovascular events that lead to death (3). Hypercholesterolemia has been classified as major factor in the development of atherosclerosis and coronary heart disease (3). Currently, atorvastatin is used for the treatment of hypercholesterolemia (1).

Atorvastatin is insoluble in aqueous solutions with pH ≤ 4 and slightly soluble in water and phos-
such data suggest extremely poor dissolution in gastrointestinal tract, especially in the fasted stomach (4). According to the biopharmaceutical classification system (BCS), atorvastatin is a BCS class II (low solubility and high permeability) compound (5). Atorvastatin is rapidly absorbed in upper gastrointestinal tract. Its oral bioavailability is about 14% (4, 6). This low bioavailability might be due to poor dissolution, presystemic clearance in the gut wall and first pass effect (3). Atorvastatin is acid sensitive drug and accordingly the tablet formulation includes calcium carbonate (CaCO₃) in order to maintain alkaline environment around the active pharmaceutical ingredient (API) (3). The maximum plasma concentration of atorvastatin can be obtained within 2-3 h with long half-life of 20 h (7).

Drugs with poor water solubility often show unpredictable intestinal absorption and high intra- and inter-subject variability (8). Therefore, it is necessary for the health regulatory authorities, manufacturers and researchers to keep a continuous surveillance of poorly water-soluble drugs available on the markets to ensure the accessibility of high quality medicines (9). In 2010, the innovator atorvastatin was the top-selling prescription medication in the United States and generated more than $7 billion in total revenue (10). In June 2011, the innovator’s patent expired and since then many generic versions entered the pharmaceutical markets. Despite the attempts to globalize the principles of the World Trade Organization’s Trade Related Aspects of Intellectual Property Rights (WTO-TRIPS), still the laws in many countries do not support patent protection including pharmaceuticals (11, 12). Many generic versions of innovator products existed before the expiration of patent protection. Countries are now given a transition period till 2016 to upgrade their patent protection laws to meet the WTO’s standards.

Generics and innovator products should be equivalents to be used interchangeably. Since 1960s, in vivo bioequivalence studies have emerged as “gold standards” to prove equivalency between a generic and its innovator counterpart (13). Studies showed that the in vivo bioavailability of a drug formulated into an oral dosage form depends on its dissolution and release characteristics (14). Today, dissolution testing is a widely used quality control tool to ensure batch-to-batch consistency and as an in vitro surrogate for in vivo performance (15).

The current study compares the pharmaceutical quality of innovator atorvastatin with its locally available generic versions in Palestine as well as the quality of the drug and to assess the suitability of interchangeability between the innovator and its generics and between generics themselves. All products were assessed against established procedures used to assess the qualitative and quantitative pharmaceutical quality characteristics of atorvastatin tablets.

EXPERIMENTAL

Materials

Atorvastatin calcium working standard was provided by Beit Jala Pharmaceutical Company, Beit Jala, Palestine. Samples of innovator and all four locally manufactured generic atorvastatin products (20 mg tablet formulations) available on the local market were purchased from a local retail pharmacy shop for testing. Purchased tablets were checked for manufacturing license numbers, batch numbers, production and expiration dates. The qualitative compositions of all products was taken from the products’ summary characteristics and compared against the innovator. The products were coded as AS-1 (innovator), AS-2, AS-3, AS-4 and AS-5. All generic products (AS-2 through AS-5) were compared against the innovator (AS-1). All chemicals and reagents used were of HPLC grade.

Per tablet price comparison of different atorvastatin products

The price differences between innovator and generic products were compared using per tablet percent price difference which was calculated according to the following equation:

\[
\text{Percent price difference} = \frac{\text{price of innovator} - \text{price of generic product}}{\text{price of innovator}} \times 100\%
\]

Testing physicochemical properties and pharmaceutical quality

Innovator and generic products were evaluated for their organoleptic properties (shape and color), assay, weight uniformity, tablet hardness, disintegration and dissolution. All atorvastatin tablets were visually inspected for shape, color, absence of black spots and/or preched edges.

Assay

The amount of atorvastatin calcium in each product was tested according to the United State Pharmacopeia (USP) (16). Twenty tablets from each product were crushed into a very fine powder using mortar and pestle. An equivalent amount of 114 mg of atorvastatin powder was weighed and dissolved in 60 mL of mobile phase (50% acetonitrile and
The mixture was sonicated for about 15 min and the volume was adjusted using mobile phase. The solution was passed through 0.5 µm filter. The first 10 mL of the filtrate was dismissed. The clear filtrate was injected into the HPLC (Dionex, Sunnyvale, CA) with auto-sampler (QCA 150). The amounts of atorvastatin were analyzed against atorvastatin reference standard USP which was injected separately. Samples were passed through the column (Lichrosphere RP18, 125 × 4 mm, 5 µm, Merck, Germany) at 1.5 mL/min.

The amount of atorvastatin calcium was calculated using the following equation:

\[
\text{% of atorvastatin} = \left( \frac{\text{Area under the curve (AUC) of sample}}{\text{AUC of reference standard}} \right) \times 100%
\]

Weight uniformity

To assess the weight uniformity of atorvastatin tablets, twenty tablets of each innovator and generic products were randomly selected and weighted individually using analytical balance (262 SMA-FR Series, Switzerland). Percentage deviation of each individual tablet from the mean was evaluated according to the USP standard method (16).

Hardness

The hardness test was carried out on tablets to determine the resistance of tablet to breakage. The hardness of 5 tablets of atorvastatin products was measured randomly using hardness tester (Erweka, Germany) and the crushing strength was recorded.

Disintegration

Evaluation of disintegration time of atorvastatin tablets was done according to the procedure described in the USP (16). One tablet was placed in each of the 6 tubes of the basket of the disintegration apparatus (Erweka, Germany). Each tube was filled with water and the temperature was adjusted at 37°C. Disintegration times were noted. According to the USP, immediate release film coated tablets should disintegrate completely in ≤ 30 min.

Dissolution

Dissolution of tested atorvastatin tablets was evaluated using USP paddle 2 dissolution apparatus (Caleva 8ST, Germany). In accordance with the test standards recommended by the FDA, six tablets of each product were tested. In the dissolution apparatus, one tablet was placed in each vessel with a paddle stirrer at 75 rpm filled with 900 mL of dissolution media (0.05 M phosphate buffer, pH 6.8) and the temperature was adjusted at 37 ± 0.5°C. Aliquots of 2 mL from each dissolution vessel were removed after 5, 10, 20, 30, and 45 min. The percents of atorvastatin release were analyzed using HPLC (Dionex, CA).

RESULTS AND DISCUSSION

Price differentials

All atorvastatin tablets were evaluated for their prices and pharmaceutical quality. Comparing prices, the innovator atorvastatin was more expensive than three out of four generic atorvastatin products (Table 1). All visually inspected atorvastatin tablets were of white color and showed oblong shape. Overall, the tablets were of good quality and did not show any signs of defects with respect to shape, color, presence of black spots or preacheld edges. Qualitatively, the composition of all tested tablets was similar. In addition to atorvastatin, tablets contained calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, opadry white Ys-1-7040, polyethylene glycol, polysorbate 80, simethicone emulsion, talc, and titanium dioxide.

Price differentials between innovator products and their generic versions and between generics

<table>
<thead>
<tr>
<th>Product code</th>
<th>Number of tablets in each package</th>
<th>Price of the package (JD)</th>
<th>Per tablet percent price difference with innovator (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS-1 (innovator)</td>
<td>30</td>
<td>10.7</td>
<td>-</td>
</tr>
<tr>
<td>AS-2</td>
<td>30</td>
<td>7.3</td>
<td>32.5</td>
</tr>
<tr>
<td>AS-3</td>
<td>28</td>
<td>9.1</td>
<td>9.14</td>
</tr>
<tr>
<td>AS-4</td>
<td>30</td>
<td>9.1</td>
<td>15.7</td>
</tr>
<tr>
<td>AS-5</td>
<td>30</td>
<td>12.7</td>
<td>-18.3</td>
</tr>
</tbody>
</table>

JD = Jordanian Dinar
themselves existed in poor, middle and high income countries. Studies showed that on average, an innovator product is 2.6-folds more expensive than the lowest priced generic version, although the difference may vary by more than 10-fold (17, 18). Our results were in line with these findings, since three out of four generics were less expensive than the innovator product (Table 1).

This is particularly important since a considerable segment of the population in developing countries cannot afford expensive brands and paradoxically patients prefer imported medications as they believe that these products have superior activity and safety profiles compared with the locally manufactured generics (19). Our study showed that one locally manufactured generic was more expensive than the innovator. We do not know if this has implications on the market-share of this product compared to the innovator. Previous reports showed that lack of incentives to physicians, pharmacists and higher prices disfavored the sales of generics (17, 18). Healthcare expenditures are on the rise worldwide and financially constrained systems are under pressure to seek ways to cut costs in a safe and effective manner (10). In the US, switching from the innovator atorvastatin to generics is estimated to save $4.5 billion annually by 2014 (10). Similarly in developing countries, switching to affordable generics can improve access to medicines when needed and can bring significant savings to healthcare systems and general public.

Pharmaceutical quality

All atorvastatin containing products tested were within the ±10% limit difference set by the USP and passed the weight uniformity test as shown in Table 2. Atorvastatin containing products were tested for their drug contents. All tested products (AS-1 through AS-5) passed the test and variations were within specifications (92-105%). The lowest amount was observed in AS-3 and the highest amount was found in AS-5 (Table 2). Hardness of all tested tablets was in the range of 102-197.4 kg as shown in Table 2. The disintegration time for all brands was within 3 min with an average of 2.5 min. The highest disintegration time (3 min) was observed for AS-4.

All tablet products were subjected to dissolution testing using dissolution media at pH 6.8. The dissolution profiles of the five tested products are shown in Figure 2. All tested products showed very rapid dissolution and released ≥85% of their atorvastatin contents in ≤15 min. Very rapid dissolving tablets are considered essentially similar without a need for similarity (f2) and difference (f1) factors.

Regulatory authorities require a proof of similarity between a generic and innovator products in order to grant the generic a marketing authorization (13).

Interchangeability between an innovator and its generic versions is based on the proof of similarity provided. Assessing the pharmaceutical quality of locally manufactured generics is particularly important for determining their suitability for interchangeability with innovator products. In this study, we used compendial and non-compendial tests to assess the pharmaceutical quality of innovator and generic versions of atorvastatin. Our results showed that all tested products lack physical defects in shape, color or presence of other flaws. Absence of such flaws is particularly important for consumer acceptability and patient compliance (20). The weight uniformity and assay tests showed that products contain the same amount of atorvastatin which can ensure the dose uniformity and that all products contain the labeled atorvastatin amounts. Hardness testing showed that all products possess sufficient strength to withstand stress without losing any parts of their components of tablets during packaging and handling of these products. Our results showed that the generic product (AS-4) showed higher hardness value compared to the innovator which explained its relatively delayed disintegration compared to the innovator (21). Other products disintegrated in less than 3 min.

### Table 2. Pharmaceutical characteristics of atorvastatin (20 mg) containing products.

<table>
<thead>
<tr>
<th>Product code</th>
<th>Average weight (mg) ± SD; (%RSD)</th>
<th>Hardness (kg) ± SD</th>
<th>Assay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS-1 (innovator)</td>
<td>206.25 ± 2.84; (1.38)</td>
<td>122 ± 11.19</td>
<td>97.6</td>
</tr>
<tr>
<td>AS-2</td>
<td>206.6 ± 8.40; (3.23)</td>
<td>112 ± 13.63</td>
<td>102.5</td>
</tr>
<tr>
<td>AS-3</td>
<td>315.8 ± 1.22; (0.39)</td>
<td>102 ± 1.41</td>
<td>92.2</td>
</tr>
<tr>
<td>AS-4</td>
<td>306.75 ± 7.18; (2.17)</td>
<td>197.4 ± 6.88</td>
<td>104.2</td>
</tr>
<tr>
<td>AS-5</td>
<td>330 ± 3.92; (1.28)</td>
<td>110.4 ± 21.91</td>
<td>105.3</td>
</tr>
</tbody>
</table>
than 3 min which might suggest similar disintegrant contents. Previous studies showed that disintegration time is particularly important in predicting dissolution and subsequent release of drug contents (21). Dissolution testing has emerged as crucial tool in ensuring the release characteristics and batch to batch variability. The dissolution profile of all generics were tested in simulated intestinal fluid and compared with the innovator. All tablets showed very rapid dissolution and the drug released from the innovator and locally manufactured atorvastatin tablets was greater than 85% in ≤ 15 min. These results predict that all tested products can release their atorvastatin contents in a comparable manner. In fact, Amidon et al. showed that if a drug from two different dosage forms is presented at the intestinal lumen at the same molar concentration, there should be no difference in the absorption and any difference may come from within subject pathophysiological variability (22).

Our results can be interpreted considering the limitation of lacking in vivo investigations. Despite the emergence of the biopharmaceutical classification system and the concept of biowaiver and the wide adaptation by regulatory authorities in the US, Europe and Japan, still, authorities see that in vivo pharmacokinetic bioequivalence studies are pivotal in establishing bioequivalence and interchangeability between oral dosage forms containing atorvastatin. Using the FDA official dissolution method to establish the release profiles of different formulations containing atorvastatin in three pH media of 1.2, 4.5 and 6.8 was another major limitation. In this study, we did not use a biorelevant discriminative dissolution method (23). However, the official FDA method was reportedly used in evaluating the in vitro equivalence of tablets containing atorvastatin (9).

CONCLUSION

In conclusion, our results showed that generally, generic atorvastatin are offered to the consumers at lower cost than innovator. Switching to generic prescription can bring significant cost reduction for the public consumers and the healthcare authorities. This could be important for local health authorities to procure high quality medications at lower costs. Furthermore, our results indicate that locally manufactured generics containing atorvastatin (20 mg) are of good pharmaceutical quality compared to the innovator product. Despite the lack of in vivo evaluation, our results indicate that these products are equivalents in vitro. Considering the in vitro release characteristics, these products might be used interchangeably. However, based on the concept of biowaiver, regulatory authorities permit the use of in vitro data in establishing similarity between immediate release oral dosage forms containing BCS class I and III drugs only.

Competing interests

All authors declare that this study was conducted for the purpose of scientific research only. All authors declare no competing interests.

Figure 2. Mean (n = 6) dissolution profiles of the branded atorvastatin tablets (AS-1) and its generic counterparts (AS-2 through AS-5) at pH 6.8
REFERENCES


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