Journal of Innovations in Pharmaceuticals and Biological Sciences
www.jipbs.com
JIPBS
ISSN: 2349-2759

Research article

In-vitro evaluation of some generic products of atenolol commonly sold in the Saudi market

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Abstract

The specific aim of this study was to evaluate the quality of 6 atenolol generic tablet products available in the Saudi market and to compare them to the originator innovative product that is also available in the Saudi market which is TENORMIN®. This approach will be used to establish a pharmaceutical and chemical equivalence between the generic products and the originator, which can serve as an indicator of pharmacokinetic and therapeutic bioequivalence. Six different generic brands of atenolol were purchased from the retail pharmacy outlets in the city of Riyadh, Saudi Arabia. These brands were investigated according to the *in-vitro* compendial requirements, which include weight variation, content uniformity, tablet thickness, tablet hardness, friability and tablet disintegration and dissolution tests. These tests were performed according to the procedures and methods described by the British Pharmacopoeia (BP).All the investigated 6 generic brands of atenolol passed the standards of the BP regarding hardness, friability, weight variability, and content uniformity. In comparison to the originator product (Tenormin®), all the generic brands passed the pharmacopoeial standards for the disintegration and dissolution tests. There were no significant differences in the percent released of the active ingredient among the different brands as indicated by the results of the dissolution test. All the investigated generic products released more than 80% of the drug within 30 minutes. Based on the obtained results and in comparison with the originator product, all the tested brands are assumed to be chemically and pharmaceutically equivalent. All these products can be used as generic substitutes for the originator product.

Key words: Atenolol, originator, generic, quality, equivalence

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1. Introduction

Post-marketing surveillance study involves all activities undertaken to obtain more information about a product after it had been granted marketing authorization. There are many studies on quality control testing for marketed pharmaceutical brands

that are conducted around the world. In these studies, they found some brands that met the established quality control standards for generic drug products and some of them did not.

According to meta-analysis that evaluated many articles for clinical equivalence in cardiovascular therapies, it has been reported that there was an equivalence among all cardiovascular therapies except for thiazides. It has been found that one out of 12 products was not equivalent, and two out of 7 products of calcium channel blockers were not equivalent in clinical response [1]. On the other hand, there is evidence that shows even with generic products having the same active ingredient; there are differences in their therapeutic outcome. The reasons behind that may be due to a difference in the rate or extent of absorption, purity of the active ingredient, mixing method or granulation processes among other possible reasons [2, 3].

Bioequivalent drug products should be the same in pharmaceutical presentation and should generate the same blood exposure which indicates that they have the same clinical effect and safety profile. *In-vitro* pharmaceutical equivalence indicates that they should be the same in their dosage form, strength, the rate of dissolution, and route of administration. Such properties can be evaluated using *in vitro* testing. In addition, clinical bioequivalence should be proved by having the same clinical response by using *in-vivo* test. Quality control assessment is very important in order to predict bioequivalence in clinical outcome. However, generic drug products may differ in shape, color, inert binder, filler and process of manufacture. Furthermore, the US Food and Drug Administration (US FDA) defined bioequivalence as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study". This definition focuses on the release of the drug and its absorption into the systemic circulation [4, 5].

Atenolol is a beta-blocker agent with high selectivity to beta-receptors where it is classified as β1 receptor antagonist [6]. It works by slowing heart rate, reducing cardiac output and lowering blood pressure by 15–20% when used as a monotherapy. It is used primarily in treatment of cardiovascular diseases like hypertension, heart failure, coronary artery syndrome and arrhythmias [7]. According to the Biopharmaceutics Classification System (BCS), atenolol is classified as BCS Class III drug which indicates that it is a drug with high solubility and low permeability.

The originator brand name of atenolol is TENORMIN® where it is manufactured by AstraZeneca Pharmaceuticals and available in the market as 25, 50 and 100 mg oral tablets. The bioavailability of atenolol is around 50 to 60% after oral administration and it is mainly excreted renally with an elimination half-life of 6 to 8 hours [8]. Atenolol was introduced back in 1976 and approved by the US FDA in 1981 whereas generic products of atenolol were available since 1988.

Generic products are chemically equivalent to the originator brand product in terms of active ingredients, but may differ in peripheral features, like color or shape of tablet, inert binders and fillers, and the specific manufacturing process [9]. Bioequivalence can be established on the basis of quality, strength, purity and safety of the product [10].

There are two ways to conduct a bioequivalence study, which could be either *in-vitro* or *in-vivo*. *In-vivo* bioequivalence study is usually carried out on human subjects by measuring the rate and extent of drug absorption in the blood stream after a drug has been administered. *In-vitro* bioequivalence study is carried out in a dissolution apparatus or in equipment that mimics the biological conditions. *In-vitro* studies reduce the cost and the number of trials required to conduct the study. It also offers benefits in terms of ethical considerations and drug performance [11]. Quality standards and compendial requirements for dosage forms, particularly tablets, include usually testing of the general appearance of the tablet like size, thickness, color and odor [12].

Other tests that are specific for tablet dosage forms include:

1. Hardness test which measures the crushing strength property of the tablets.
2. Friability test which measures the resistance of the tablets to abrasion by tumbling them in a rotating drum.
3. Disintegration test which measures breakage of tablets into smaller fragments and this is an important step prior to dissolution.
4. Dissolution test which measures the release of the drug from the tablet into solution per unit time under standardized conditions that simulate the gastrointestinal environment.
5. Weight variation test to ensure that all tablets have similar weight within an acceptable range limits and this usually indicates uniformity in the content of the active ingredient.
6. Content uniformity test where the tablets are assayed for their content of the active ingredient, according to the specific method described in the individual pharmacopoeial monograph of the drug.

The specific aim of this study is to ensure that the established quality control standards for generic tablet products of atenolol are met and to compare them to the originator product available in the market which is TENORMIN®. Generic brand tablet products of atenolol were selected from the Saudi market and the quality control standards for these products were investigated according to the methods described in the British Pharmacopoeia (BP) [13]. These quality control standards were compared with that for the originator product. The compendial requirements to be investigated include weight variation, content uniformity, tablet thickness, tablet hardness, friability and tablet disintegration and dissolution.

The study was conducted by comparing 6 generic brands of atenolol to the originator brand TENORMIN® using the above mentioned quality control tests. These tests will serve as indicators for bioequivalence of the generic brands compared to the originator product. These tests were performed according to the procedures and methods described by the BP.

2. Materials and Methods

Materials

Seven brands of atenolol tablets were purchased from different retail pharmacy outlets in the city of Riyadh, Saudi Arabia. These include the originator product Tenormin and 6 generic products: Tenol, Tenolol, Atormin, Apo-Atenol, Cardol, and Hypoten. All the purchased products were manufactured within six months prior to the start of the study. Pure atenolol was a

gift sample obtained from Riyadh Pharma for Pharmaceutical Industries, Riyadh, Saudi Arabia. Distilled de-ionized water was used in the study and all solvents used throughout the study were of pharmaceutical grade.

Methods

1. Mechanical Properties (Non-Official Tests)

a. Determination of tablet hardness, diameter, thickness, and weight uniformity

These tests were performed using 10 tablets from the originator product and each generic brand using a multi-check machine (ERWEKA, MultiCheck 5.1, Germany).

b. Determination of friability

Ten tablets from the originator product and each generic brand were weighed and subjected to abrasion by employing a friability test apparatus (PHARMA TEST,PTF 20ER, Germany) operated at 25 rpm for four minutes. Then the tablets were removed, de-dusted, weighed and compared with their initial weight and the percentage friability was calculated according to the following formula:

$$\%friability = \frac{W1 - W2}{W1} \times 100$$

Where: W1 is the initial tablets weight; and W2 is the weight of the tablets after running the test.

2. Official Tests

a. Tablet disintegration test

Six tablets from the originator product and each generic brand were employed to examine their disintegration time in a freshly prepared medium of 0.1 N HCl at 37 °C using disintegration apparatus (ERWEKA, ZT 220 Series, Germany). The disintegration time will be taken to be the time where no particles remained on the screen of the basket carrying the tablet in the disintegration apparatus.

b. Tablet dissolution test

The dissolution test was performed using the USP dissolution apparatus I (ERWEKA, DT 626 Series, Germany) where it employs the basket method in six replicates. Six tablets from the originator product and each generic brand were tested in a 1000 mL dissolution medium of 0.1N HCl that is maintained at 37 °C and stirring speed of 50 rpm. Five mL aliquots from the dissolution medium were withdrawn at predetermined time intervals and replaced with an equal volume of the dissolution medium to maintain sink condition. The samples were filtered and assayed by a UV spectrophotometer at 275 nm (Thermo, Evolution 60S, Thermo Fisher Scientific Inc., China) and the concentration of the drug was determined using a calibration curve constructed using pure atenolol as a reference standard.

c. Determination of content uniformity

The drug content in the tablets has been determined according to the method described in the monograph of atenolol in the BP [13]. Briefly, 20 tablets from each brand were powdered and transferred to a 500 mL flask containing 300 mL methanol, heated up to 60 °C and shaken for 15 min. After cooling down and dilution to 500 mL with methanol, the resulting suspension was filtered and then a suitable volume of the filtrate was diluted with methanol to produce a solution containing 0.01% W/V of atenolol. The content of atenolol in the sample was measured at 275 nm

considering the value of the absorptivity A (1%, 1 cm) to be 53.7.

3. Results and Discussion

Results

Table 1 summarizes the dimensions of the investigated tablet brands of atenolol in addition to hardness, friability and weight uniformity of the tablets. As indicated by the results, the hardness of the tablets ranges between 67±4 N to 166±14 N. This result is satisfactory where it exceeded the minimum requirement of 39.29 N, which is equivalent to 4 kg. The friability results met the compendial specifications of having a percent loss in the tablet weight of ≤1% where the results of friability of all brands range between 0 and 0.1%. The weight uniformity complies with the compendial standards of having a deviation from the average weight by not more than 5%. The results show that the mean weights of all brands are within the range.

The results of the content of the active ingredient in Tenormin and the generic brands are shown in Table 2 as a percentage of the claimed labeled amount. The values ranged between 91.3% and 114.5%.

Table 1. Dimensions, hardness, friability, and weight uniformity of Tenormin and the generic brands

Brand Name	Thickness (mm±SD)	Diameter (mm±SD)	Hardness (N±SD)	Friability (%)	Weight (mg±SD)
Tenormin	4.92 ± 0.03	10.09 ± 0.02	149 ± 10	0.0	421 ± 4.3
Tenolol	5.35 ± 0.03	11.31 ± 0.05	121 ± 14	0.0	450 ± 2.9
Tenol	4.85 ± 0.04	10.22 ± 0.02	72 ± 8	0.0	377 ± 4.5
Atormin	5.15 ± 0.03	10.11 ± 0.01	155 ± 8	0.0	406 ± 6.1
Apo-Atenol	3.53 ± 0.05	8.8 ± 0.01	67 ± 4	0.1	245 ± 4.3
Hypoten	4.81 ± 0.01	10.65 ± 0.03	145 ± 8	0.0	411 ± 2.7
Cardol	3.77 ± 0.07	9.12 ± 0.02	166 ± 14	0.0	315 ± 6.2

Table 2. The content percentage of atenolol in Tenormin and the generic brands represented as % of labeled amount in each product

Brand	Tenormin	Tenolol	Tenol	Atormin	Apo-Atenol	Hypoten	Cardol
%Content ±SD	114.5 ±5.08	108.1 ±0.04	104.1 ±0.17	91.3 ±0.14	100.7 ±3.9	96.9 ±0.05	107 ±0.17

Table 3. Tablet disintegration times of Tenormin and the generic brands in reference to the standard disintegration times by the BP

Brand Name	Type of Tablet	BP Standard Time (min)	Disintegration Time (min)
Tenormin	Film coated	30	7.72
Atormin	Coated	60	1.92
Tenol	Film coated	30	10.65
Tenolol	Film coated	30	2.75
Apo-Atenol	Uncoated	15	7.83
Cardol	Uncoated	15	5
Hypoten	Coated	60	8.27

Table 3 shows the tablet disintegration times of Tenormin and the generic brands in reference to the standard times as per the BP and according to the type of tablets. All the brands passed the test by registering disintegration times less than the maximum time limits specified by the BP.

The dissolution profiles from the reference product (Tenormin) and the test generic products are combined and presented in Figure 1. It can be observed that all the products released at least 80% of the drug within 30 min. Therefore, all the products passed the acceptance pharmacopoeial criteria.

Discussion

Hardness and friability tests are used to test the mechanical properties of the tablet dosage forms. Hardness or the crushing strength test is an indicator of the ability of the tablets to withstand the stress that they might be subject to during handling, packaging, and transportation. The mechanical properties of the tablet are also related to the disintegration time and the rate of dissolution of the tablets. A minimum crushing force applied on the tablet to pass this test has to be not less than 4 kg (39.29 N) so that the mechanical strength of the tablet is assumed satisfactory. All the tested generic brands of atenolol and the originator product passed this standard by exceeding the minimum limit of crushing force when applying the hardness test.

Friability is another indicator or tablet property that is related to crushing strength. Friability test is used to evaluate the ability of the tablets to resist abrasion during handling, packaging, and transportation. The compendial standards stipulate that the loss in the tablet weight should not exceed 1% of the original tablet's weight after applying the friability test. Our results showed that all the tested generic brands and the originator product passed this standard by having the values of friability almost close to 0%.

Hardness and friability tests are well correlated since they are used to examine the mechanical properties of the tablets. The hardness or the crushing test examines the bulk deformation of the tablets while the friability test examines the surface deformation of the tablets. Such properties can be enhanced by the morphology of the tablets in addition to formulation factors like the type of binder and the granulation method used in preparing the tablets. Although these properties are necessary to evaluate the mechanical properties of the tablets and they may affect the disintegration time and the dissolution rate, however, they are not official tests [14].

The weight variation test or the uniformity of weight is an official test that is outlined by the pharmacopoeias in addition to others like content uniformity, disintegration and dissolution tests. All the tested brands in this study comply with the specifications of weight uniformity according to the BP. As shown in Table 1, none of them deviated from the mean weight by more than 5%. Therefore, the results of the weight uniformity are satisfactory. The significance of this test is to indicate that all the tablets in each batch are within the appropriate weight range.

The assessment of the percentage content of the active ingredient in Tenormin and the generic brands is presented in Table 2. According to the official standards of the BP, the content of the active ingredient should lie within 85–115% of the claimed labeled amount by the manufacturer and the standard deviation should be less than 6% [13]. According to our results, all the products gave values within the indicated range where they are assumed satisfactory.

The significance of this test is to ensure that all the tablets will deliver the same amount of the drug in the body, and hence, producing similar and reproducible bioavailability.

The disintegration test measures the time needed for the tablets to disintegrate into small particles. According to our results presented in Table 3, all the tablets examined from Tenormin and the generic brands passed this test. They all registered disintegration times less than the maximum time limits indicated by the BP and according to the type of the tablet whether coated or uncoated.

Disintegration process is prior to the dissolution of the tablet where the active ingredient has to be fully available for absorption. According to the BP, tablets must disintegrate within the time limit set forth in the individual monograph which is usually ranging between 15 min for uncoated tablets up to 60 min for coated tablets. If one or more tablets failed the test, additional prescribed tests by the pharmacopoeia must be performed [13].

The active ingredient becomes available for absorption from oral dosage forms, particularly solid dosage forms, after the process of disintegration and dissolution. Dissolution testing and consequently comparing the dissolution profiles can be used to establish similarity of the generic brands to the originator product. This test is employed to distinguish the effect of manufacturing variables, including the binder type, excipient type, mixing process, and granulation procedure. Therefore, this test can serve as a tool to predict the *in-vivo* behavior of the product [15]. The dissolution results shown in Figure 1 indicate that all the investigated generic brands passed the dissolution test generating profiles similar to that produced by the originator product without any noticeable significant difference. All of them released more than 80% of the drug within 30 min of the test time, which is assumed a satisfactory result in reference to the pharmacopoeial standards. Atenolol is a highly soluble drug; therefore, it is expected to show rapid dissolution.

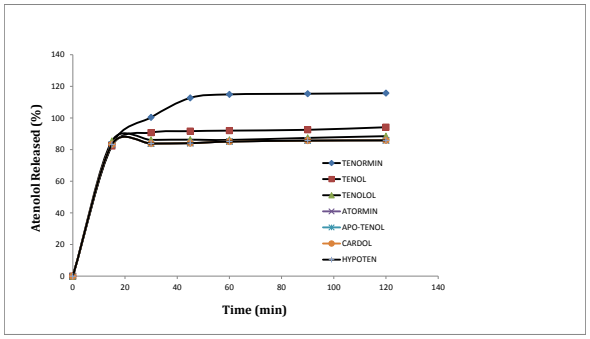

Figure 1. Comparative dissolution profiles of Tenormin tablets and the test generic brands

Conclusion

The conventional official and non-official tests employed in this study indicated that all the generic brands of atenolol selected from the Saudi market are chemically and pharmaceutically equivalent to the originator brand. Thus, it can be extrapolated that they are bioequivalent and expected to produce a similar therapeutic outcome like the originator product. They can all be used as generic substitutes to the originator brand. Such tests are less complicated, time and cost effective, and can serve as useful quality control indicators for evaluation of generic brands. This approach can be used in investigating substandard drug products before conducting tedious *in-vivo* bioequivalence studies.

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