Letters in Applied NanoBioScience
Open-Access Journal (ISSN: 2284-6808)

Article
Volume 13, Issue 1, 2024, 10
https://doi.org/10.33263/LIANBS131.010

In vitro Study of Pharmaceutical Equivalence of Atenolol Tablets

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Scopus Author ID 57194442499
Received: 8.11.2022; Accepted: 5.01.2023; Published: 23.04.2023

Abstract: Atenolol is one of the cardioselective β-blocker drugs widely used to treat cardiovascular disease. Atenolol is available under different trade names and marketed by several generic pharmaceutical manufacturers. The aim of the present work was to evaluate the pharmaceutical equivalence of the generic atenolol tablet (50 mg) available in Algeria and to compare it to the originator brand utilizing *in vitro* dissolution survey. The dissolution study was realized utilizing the paddle apparatus in compliance with the guidelines of US Pharmacopoeia (USP). Results revealed no significant differences in the percent released of the pharmaceutic active ingredient. All tablets released more than 85% of the drug within 15 minutes, which means that the dissolution profiles may be assumed as similar without furthermore mathematical evaluation. Other features, such as weight uniformity, tablet hardness, friability, content uniformity, and tablet disintegration, were also evaluated. All tablets conformed to the official specifications. The tested brand is assumed chemically and pharmaceutically equivalent based on the obtained results. This study indicated that the generic tablet could be prescribed interchangeably.

Keywords: Atenolol; *in vitro* dissolution; paddle method; generic; quality control.

1. Introduction

The food and drug administration (FDA) approved the use of Atenolol in 1981, and it is currently available as an oral table [1], whereas generic products have been available since 1988. Atenolol is a cardioselective β-blocker [2-6] (Table 1). It is widely prescribed for diverse cardiovascular diseases such as hypertension, angina pectoris, and acute myocardial infarction [7-8]. The product information of Atenolol is given in Table 1.

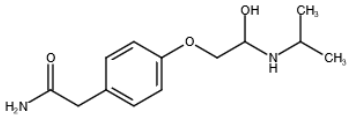
World Health Organization (WHO) promotes the use of generic medicaments in order to decrease healthcare costs and enhance healthcare delivery systems [9]. Generic drugs are chemically identical to their brand-name counterparts in terms of active ingredients. However, the peripheral features may differ, such as inert binders and fillers, shape, color, and the specific manufacturing process [9-12].

Therapeutic equivalence must be ensured by ascertaining the biopharmaceutical equivalency of such drug products [13-14]. However, *in vivo* bioequivalence studies are time-consuming, difficult, and very expensive. Therefore, *in vitro* bioequivalence studies are established to check the bioequivalence among generics and brands [15]. In accordance with Biopharmaceutics Classification System (BCS), Atenolol can be categorized as a class III drug substance [16]. In class III, *in vitro* – *in vivo* correlation can be expected only for rapidly

dissolving drug substances. Atenolol is regarded as a rapidly dissolving drug; therefore *in vitro* bioequivalence studies through dissolution profiles can be applied in order to waive *in vivo* bioequivalence studies [17-22].

In-vitro pharmaceutical equivalence indicates that drug products should be the same in their dosage form, strength, rate of dissolution, and route of administration. Such properties can be evaluated using *in vitro* testing [23-24]. Dissolution testing has become an essential tool in the pharmaceutical industry at various stages of development, manufacturing, and marketing [25-27].

Table 1. Product information.

Product name	Atenolol
Molecular weight	266.336 g/mol.
Molecular formula	$C_{14}H_2N_2O_3$
Chemical name	2-[4-[2-hydroxy-3-(isopropyl-2-amino)propoxy]phenyl]acetamide.
Chemical structure	

The present study aims to evaluate and compare the dissolution profiles of a generic product of atenolol tablet marketed in Algeria with that of the original product of the same dosage form to examine whether the generic is bioequivalent to the pioneer drug.

2. Materials and Methods

Before conducting the dissolution test of the drug, it is crucial to analyze the physicochemical properties of the finished product. Any variation from the physical parameters can lead to a significant difference in the dissolution profiles [19].

2.1. Visual inspection.

The atenolol tablets involved in this investigation were evaluated based on US Pharmacopoeia and compared with the innovator tablets. Before proceeding to the tablet quality control evaluations, a visual inspection of the tablets was done by visually examining the size, shape, and color of the tablets.

2.2. Physicochemical parameters.

Physicochemical parameters were evaluated, such as weight uniformity, hardness, friability, disintegration test, and content uniformity.

2.2.1. Weight uniformity test.

Twenty tablets from the originator product and generic brand were weighed individually using a digital analytical balance. The mean weight was calculated, and the percentage deviation from the mean was determined.

2.2.2. Hardness test or crushing strength

The hardness test was carried out by an Erweka tester THB28. Ten tablets from the originator product and generic brand were chosen at random, and the pressure at which each tablet was crushed was recorded. The results were expressed in Newton as the mean, minimum and maximum values of the forces measured.

2.2.3. Friability test.

Twenty tablets were randomly selected from the originator product. The generic brand was weighed and subjected to abrasion and shock by employing a friability test apparatus Apparatebeau-Jel Friabilator at 25 rev/min for four minutes. The weight loss percentage was then computed after a subsequent weighing of the tablets. Calculations are based on the formula below:

$$F(\%) = \frac{(w_i - w_f)}{w_i} \times 1000$$

where w_i is the initial tablets' weight, and w_f is the weight of the tablets after running the test.

2.2.4. Disintegration test.

Tablet disintegration was determined in distilled water at 37ºC±2ºC using ERWEKA ZT3 Disintegration tester of randomly selected six tablets from the originator product and generic brand in distilled water. The tablet disintegration time was taken when no particles remain on the basket of the tester.

2.2.5. Content uniformity test.

A uniformity test for drug content was carried out by selecting twenty tablets randomly from the originator product and generic brand. The tablets were crushed in a mortar, and a quantity of the powder that contained the claimed weight of the active pharmaceutical ingredients (API) was dissolved in 50 ml of methanol. The resulting suspension was shaken for 20 min. Then, the mixture was filtered, and appropriate dilution was made with methanol. The absorbance was measured at 275 nm using Safas UV - VIS spectrophotometer.

2.3. In vitro dissolution test.

The dissolution test was carried out using an Erweka dissolution tester with the paddle setting (USP apparatus 2). All dissolution measurements were performed at 37 ± 0.5 °C in 900 mL distilled water (dissolution media) with a stirring speed of 50 rpm. The concentration and quantity of the active pharmaceutical ingredients in each sample were determined using a UV - VIS spectrophotometer (SAFAS) at 275 nm.

3. Results and Discussion

Both Atenolol samples drug taken for the evaluation were within their shelf life at the time of the investigation.

The visual inspection found that the tablets were in good condition, and each individual tablets were free from cracks and depression. In addition, the tablets' color, surface, and roughness were uniform on the whole surface and showed no sign of defects.

The physicochemical parameters of the tested atenolol 50 mg tablets are listed in Table 1. The data were expressed as mean ± standard deviation (SD).

Hardness is referred to as a non-compendial test [28]. However, appropriate tablet hardness is necessary since it may affect friability and disintegration of tablets [2], whichis to say the less hard a tablet is, the more friable it is, and the less time it takes to disintegrate[29]. It is also conducted to confirm a tablet's quality and determine its strength during chipping,

abrasion damage under storage, shipping or handling before usage [28]. The crushing strength of about 4 kg cm^{-2} is the minimum requirement for a standard tablet. As shown in Table 1, the hardness of the generic brand was found to be 4.91 kg cm^{-2} which fulfilled the limits of the hardness test. If the hardness of a tablet outdoes a certain limit, it increases the disintegration time [30], which impacts the bioavailability [29].

Table 2. Physicochemical properties of the originator product and generic brand of atenolol tablets.

Brand	Average weight (mean ±sd) (mg)	Friability (%)	Hardness (mean±sd) (kg cm^{-2})	Disintegration Time (s)	Drug content (%)
Generic brand	197 ±5	0.12	4.91±0.48	60	97.96
Reference	212 ±1	0.02	5.60±0.69	120	98.9

The friability results met the pharmacopeial specifications of having a percent loss in the tablet weight of ≤1%. As shown in Table 2, the percentage friability of atenolol tablets was 0.02% for the reference product and 0.12% for the generic product, indicating that the tablets have sufficient strength to withstand physical abrasion [31-32]. A good manufacturing tablet should be able to withstand any abrasion and shock during its handling, packaging, and transportation.

The weight uniformity revealed that the investigated atenolol tablets contained the labeled amount of the drug and ensured dosage uniformity.

Drug content estimation helps ensure the consistency of dosage units, in which each unit in a batch should have drug content as per the limits of USP [33]. Therefore, an assay of atenolol tablets was conducted with the help of a UV-Visible Spectrophotometer, and the content was estimated. Drug content for the two brands' batches was found in the range of 97.96– 98.9 for Atenolol (Table 2), and the values were obtained as per USP.

Disintegration times of all the brands were within the limit—both of the atenolol tablets disintegrated in less than 2 minutes.

Table 3 summarizes the mean percentage of dissolved tablets at each time point, the relative standard deviation (RSD), and the upper and lower limits. The percent dissolutions of the generic sample and reference brand were graphed versus time in Figure 1. Both tested brands released more than 85% of drugs within 10 minutes. Due to its low permeability, the rapid dissolution of class III drugs is desirable in order to maximize the time of contact between the dissolved drug and intestinal mucosa, favoring the increase of its bioavailability. The two brands of Atenolol meet the desired quality and efficacy according to the USP standards.

Table 3. Dissolution data of atenolol tablets.

Time	Brand	Mean %	Lower limit	Upper limit	RSD
10	G	87.62	84.34	93.01	3.47
	R	86.62	80.65	88.70	3.29
15	G	91.88	86.38	96.40	3.02
	R	90.37	88.04	92.95	1.80
20	G	93.99	88.12	97.72	2.22
	R	92.38	89.88	94.81	2.22
25	G	94.44	88.53	98.41	2.55
	R	94.64	91.69	97.32	2.84
30	G	95.60	89.11	99.12	1.01
	R	97.67	95.98	99.05	1.20
45	G	97.53	90.79	103.43	2.49
	R	98.75	96.80	100.41	1.29

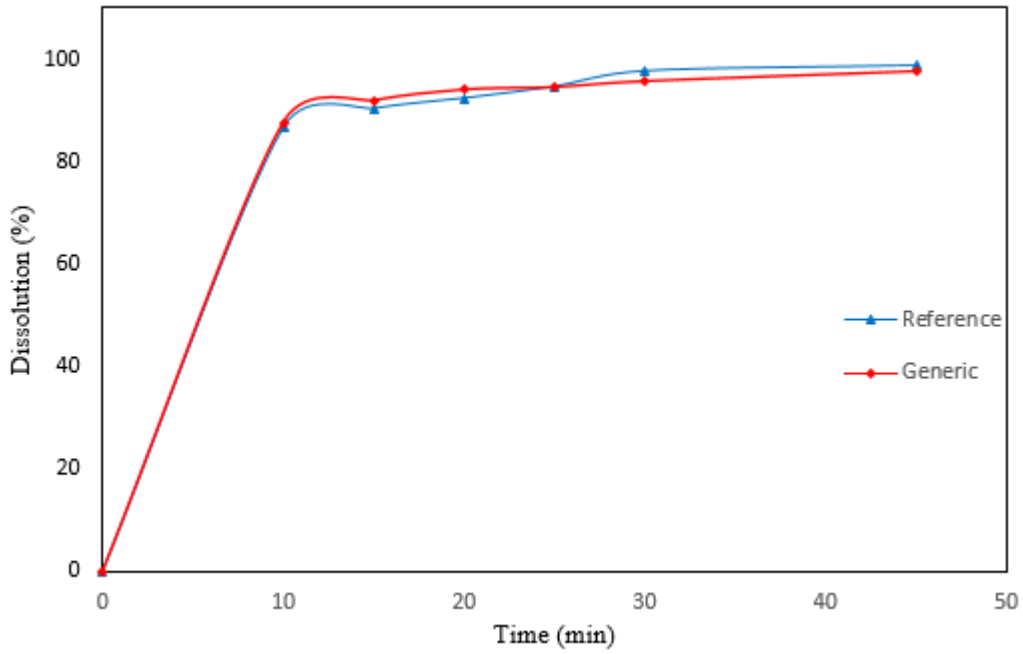


Figure 1. Dissolution profiles of atenolol tablets.

For pharmaceuticals dissolving to 85% or greater within 15 minutes, the profile comparison is not necessary [34].

4. Conclusions

The quality assessment is an important criterion required for any pharmaceutical preparation to assure its efficacy and whether the generic and branded drugs are pharmaceutically equivalent or not. The results obtained from the *in vitro* pharmaceutical equivalence survey showed that the atenolol tablet (50 mg) marketed in Algeria was equivalent to the brand of the reference product. It can be inferred that these brands may have similar bioavailability and may be prescribed interchangeably.

Funding

Not applicable.

Acknowledgments

I sincerely thank Dr.Mouloud Kheireddine of the University of Blida1 for his guidance.

Conflicts of Interest

The author declares no conflict of interest

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