IJPSR (2015), Vol. 6, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 October, 2014; received in revised form, 20 December, 2014; accepted, 15 February, 2015; published 01 June, 2015

ASSESSMENT OF PHARMACEUTICAL QUALITY CONTROL AND IN VITRO EQUIVALENCE OF VARIOUS BRANDS OF ATENOLOL (100MG) TABLETS AVAILABLE IN SUDANESE MARKET UNDER BIOWAIVER CONDITIONS.

Abdelrhman Abdelkarim *, Abdelkarim Mohammed and Mohammed Abdeen

Azal Pharmaceutical Co. LTD Khartoum, Sudan

Keywords:

Biowaiver,
in vitro equivalence,
generic products, quality control

Correspondence to Author:
Abdelrhman Abdelkarim

R&D Deputy manager, Azal Pharmaceutical Co. LTD Khartoum, Sudan

E-mail: amrhanakarim@gmail.com

ABSTRACT: As Atenolol is one of the first choice medications in the management of hypertension in Sudan, it was very important to carry out post authorization safety studies on some of the brands commercially available on the market. The pharmaceutical equivalence of three Atenolol 100 mg tablets was evaluated using official and non-official standards according to US Pharmacopoeia including weight variation, diameter, hardness, disintegration, and assay. Dissolution profiles were studied using three different buffer solutions: PH 1.2, 4.5, and 6.8 and evaluated using the similarity factor f2 to predict the likely in vivo bioavailability and bioequivalence. The three brands complied with the requirements of the official tests of weight variation, hardness, disintegration, assay and dissolution. The two generics used in this study failed to qualify for biowaivers, as brand (A) did not qualify for the WHO criteria for biowaivers (both the test and reference products are very rapidly dissolving in the three media, ie to release ≥ 85 % in 15 min). The amount released in 15 minutes was less than 85%, while brand (B) released more than 85% in 15 minutes in the three media which means higher rate and extent of absorption than the reference drug. The study shows that the generic drug products assessed do not qualify for biowaivers, therefore *in vivo* bioequivalence studies are required to ascertain bioequivalence.

INTRODUCTION: Hypertension is a common and serious health disorder, the high rates of hypertension in low- and middle-income countries are striking [1]. Patients with hypertension are at an increased risk of the incidence of several CV events (stroke, myocardial infarction, sudden death, heart failure and peripheral arterial disease) and of end stage renal failure [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(6).2390-94

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(6).2390-94

Hypertension has the highest prevalence among the major non-communicable diseases (NCDs) in Sudan (prevalence of 23.6 in Khartoum state). [3] Hypertension accounts for 1.3% of the outpatients visit, it is represented as one of 10 leading diseases treated in health facilities (outpatients) and also one of the 10 leading causes of deaths in Sudan [4], and as Atenolol is one of the first choice medications in the management of hypertension in Sudan, it was very important to carry out post authorization safety studies (ongoing safety monitoring) of the different Atenolol tablet brands available on the market. Bioequivalence is used to assess the expected in *vivo* biological equivalence of two proprietary preparations of a drug, but the

bioavailability and bioequivalence studies of drugs cost up to $ 250,000 to $300,000 each and may require up to 12 months to complete [5].

Biowaiver was adopted by the , Food and Drug Administration (US-FDA), World Health Organization (WHO) and European Medicines Agency(EMA) for implementation in the approval of some generic drug products [6,7,8] to streamline the introduction of the generic drug products and even further reduce the prices in the market place while still assuring (very good) drug product performance.

On the basis of studied biopharmaceutical data, Atenolol could be clearly classified into Biopharmaceutics Classification System (BCS) Class III [9]. In addition, Atenolol is listed in WHO Model List of Essential Medicines. According to WHO Technical Report, Atenolol in vitro equivalence may be evaluated under Biowaiver conditions for BCS Class III [7].

MATERIALS AND METHODS:

Instruments: Analysis of Atenolol was carried out on UV -Vis Spectrophotometer (shimadzu UV-1800, Japan), Dissolution tester (Pharma test D-63512, hainbursg, Germany), Electronic balance (Sartorius Etend ED2245), pH meter (Sartorius professional meter pp-20), Disintegration tester (Mp disintegra0tion test apparatus -1901), and Hardness tester (Pharma test PT B511F-Germany)

Reagents:

- Hydrochloric acid.
- Potassium dihydrogen phosphate.
- Reference Atenolol powder (working standard).

All of these substances were a gift sample from Azal Pharmaceuticals. Atenolol tablet brands were randomly collected from the local Private pharmacies. **Table 1** show brands of Atenolol tablet, their manufacturing and expiry date

Physicochemical parameters:

Active content of generic and innovator brands were assessed using the US Pharmacopeia 2014 method [10], while physicochemical parameters were done using British Pharmacopeia 2013 method. [11]. The result was shown in **Table 2** below:

TABLE 1: ATENOLOL TABLET BRANDS

Item	Batch NO	Mfg	Exp
Innovator	KH121	Apr13	Jan-18
A	TOLO30	2013	2015
B	4080	May14	May-18

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF 3 DIFFERENT BRANDS OF ATENOLOL TABLETS

Item	Weight Uniformity (mg)	diameter (mm)	thickness (mm)	hardness (KP)	disintegration (min)	Assay (%)
(innovator)	420.5±1.45	10.145±0.02	4.92±1.2	9.675±4.01	5.51±0.56	101.18
A	479.4±1.24	11.25±0.09	5.025±0.26	10.3±5.32	9.22±0.42	100.37
B	433±1.71	11.47±0.18	4.69±0.37	3.55±6.7	10.58±.21	102.79

Dissolution study:

The dissolution profile of Atenolol tablets was assessed in 900ml of buffer pH 1.2, 4.5 and 6.8 using US Pharmacopoeia dissolution apparatus II [10] at 75rpm. Dissolution media were USP buffer solutions at pH 1.2 (hydrochloric acid solution), pH 4.5 (acetate buffer solution), and pH 6.8 (phosphate buffer solution) at 37 ± 0.5 °C. Dissolution media volume was 900mL. In all experiments, 5-mL sample aliquots were withdrawn at 5, 10, 15, 30, and 45 min using syringe and immediately replaced with equal volumes of fresh medium at the same temperature to maintain constant total volume during the test. All samples were filtered through 0.45-µm membrane filters. Drug release was assayed spectrophotometrically. Twelve tablets of each preparation were studied to obtain statistically significant result.

Data analysis: Dissolution profiles were evaluated by using Similarity factor which is adopted by the

FDA in its guidance [12] by using the following formula:

$f2=50*\log \{[1+ (1/n) n\Sigma t+1n (R_t-T_t)^2] ^{-0.5}*100\}$

Where Rt and Tt are percent dissolved at each time point for reference and test respectively. Values of 50 or above (50-100) ensure similarity of the curves.

Difference factor (f1): Difference factor can be mathematically computed by using:

$f1= \{[t+1 ^n|R_t-T_t|]/[t+1^nR_t]\} *100$

Difference factor of 0-15 ensures minor difference between two products approach to assess bioequivalent between two formulations.

According to WHO guidance [7], a drug product is considered to be very rapidly released if ≥85% of the drug is dissolved in 15 minutes, which corresponds to gastric emptying half-life (T50%) in fasting conditions.

The factor f1 is proportional to the average difference between the two profiles, whereas factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time-points. The factor f2 measures the closeness between the two profiles. [12]

RESULTS:

TABLE 3: DISSOLUTION TEST RESULTS OF THE THREE BRANDS

Medium	Time	Innovator% Released	A % Released ± SD	B % Released ± SD
	5	70.5±6.2	36.83±5.1	24.84±7.2
	10	101.7±4.5	81.35±5.5	52.23±6.2
	15	100±5.2	93.65±2.8	87.56±6.6
pH1.2	30	101±1.2	94.29±3.1	98.43±5.7
	45	101.3±1.6	94.13±1.4	97.45±4.7
	F2	innovator		
	F1			
	5	61.27±2.2	53.01±1.9	36.52±3.1
	10	93.19±2.3	81.27±2.6	70.79±2.4
PH 4.5	15	102.5±1.4	97.53±3.3	95.87±2.5
	30	101±1.1	100.4±2.4	102.6±1.6
	45	101.3±1.6	99.04±1.1	103.9±1.9
	F2	innovator		
	F1			
	5	27.48±3.1	24.47±3.5	37.68±4.1
	10	53.51±2.9	64.17±2.4	75.77±3.6
	15	78.81±3.1	82.39±2.2	93.48±3.5
pH 6.8	30	89.54±3.2	87.95±3.1	104.2±2.4
	45	95.4±3.2	86.59±2.2	103.3±3.8
	F2	innovator	57	39
	F1		8	20

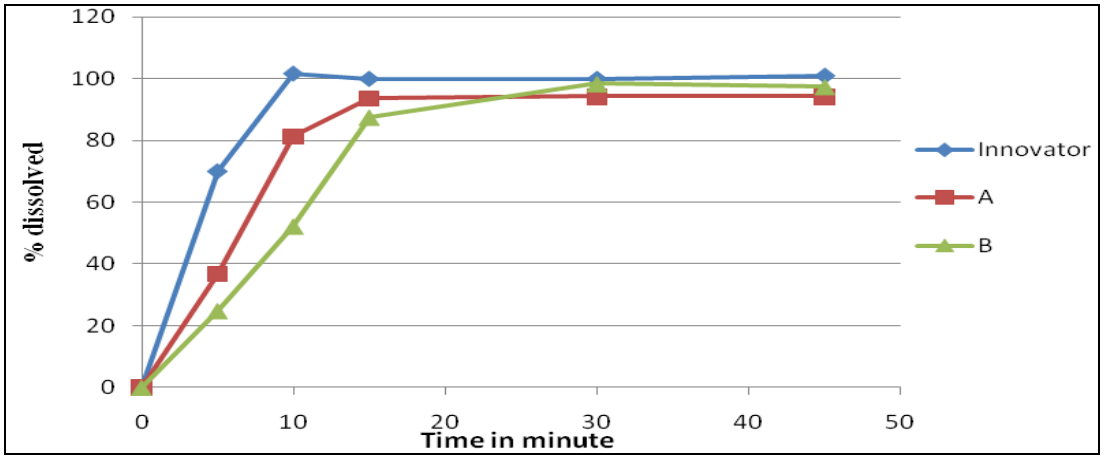

FIG. 1: DISSOLUTION PROFILE AT pH 1.2 BUFFER SOLUTION

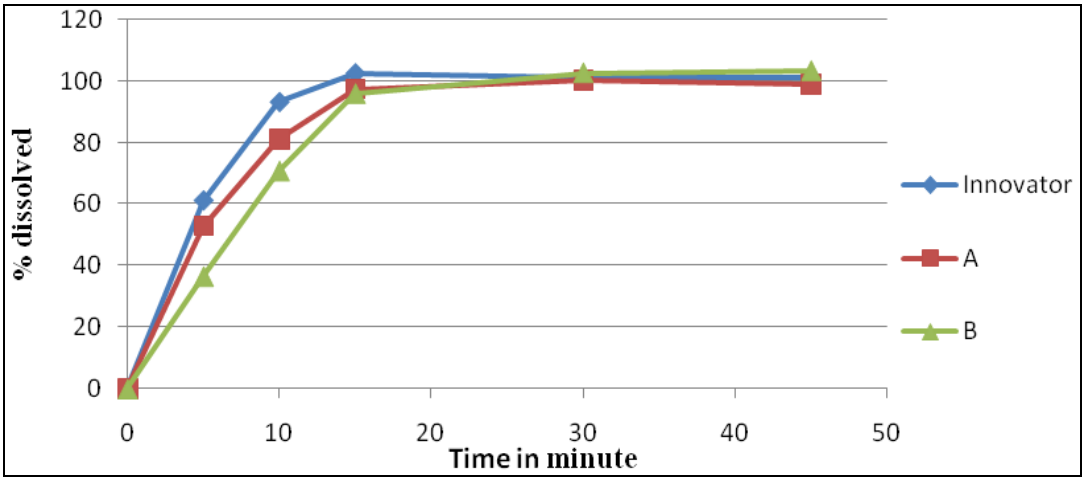

FIG.2: DISSOLUTION PROFILE AT pH 4.5 BUFFER SOLUTION.

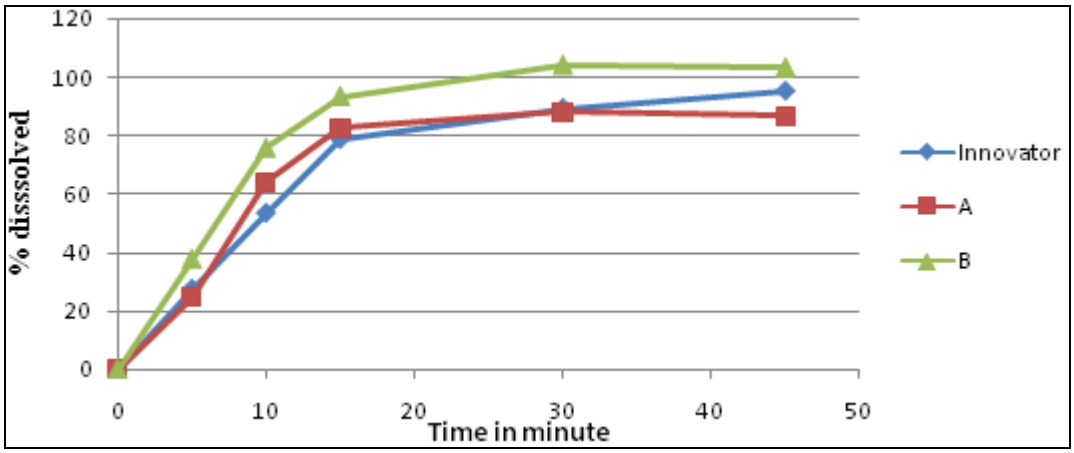

FIG.3: DISSOLUTION PROFILE AT pH 6.8 BUFFER SOLUTION.

DISCUSSION AND CONCLUSION: The aim of the present study was to collect information on the safety, efficacy, and possible interchangeability of the different generic Atenolol tablet brands with the Innovator by using simple and cost effective *in vitro* dissolution method. For the purpose of the study, 2 generic Atenolol tablet brands were randomly selected and collected from the market, and their physicochemical properties and release profiles compared with the innovator. (**Table 2**) shows that all the brands studied fulfill the compendia specification for uniformity of weight, diameter, thickness, hardness, disintegration, and content of active ingredient, although there is significant difference in the hardness of brand B but this test is considered not official[10, 11].

The three brands within their expiry dates. Dissolution test was carried out for the three products to establish bioequivalence between different brands. The test was carried out in three different mediums (pH 1.2, 4.5, and 6.8) to cover the whole GIT environment of different pH (**Table 3**) and (**Fig. 1, 2, 3**).

Drugs of class 3 are considered acceptable for bio waivers under WHO criteria (i.e., both the test and reference products are very rapidly dissolving).This means that dissolution of 85% or more of the labeled amount of API should be achieved within 15 min under all physiological conditions [6].

One of the two brands of Atenolol tested did not meet this requirement and the innovator product did not achieve 85% dissolution in 15 min (**Table 3**), however, the generic formulation (B) had over 85% dissolution within 15 min in the three media. Since B went into solution faster than the innovator product, there is the possibility of differences in the rate and extent of absorption with B having a higher extent of absorption. Brand A was not very rapidly dissolving (< 85%/15min). Brand A like the innovator (Tenormin)®, had rapidly dissolved by 30 min in pH 6.8 medium, and the f2 value was 57,

showing a similarity in dissolution profiles (**Table 3**).

Brand A would most likely be similar to the Innovator in rate and extent of dissolution; however, it failed to meet the requirement 2of very rapid dissolution (more than 85% release in 15min).

The possible effect of excipients on the dissolution of the generic drugs was not evaluated because only the innovator Product (Tenormin) ® listed excipients on its packaging. Based upon the above results it can be concluded that the generic drugs assessed were pharmaceutically equivalent to the innovator products but were not qualified for Biowaiver, therefore, in vivo bioequivalence studies are required to ascertain their bioequivalence.

ACKNOWLEDGEMENTS: The author is thankful to Azal company for providing tools and chemicals.

REFERANCES:

1. Peter Lloyd-Sherlock, John Beard , Nadia Minicuci ,Shah Ebrahim and Somnath Chatterji Hypertension among older adults in low- and middle-income countries: prevalence, awareness and control Int. J. Epidemiol. (2014);1-13
2. Jan Filipovský ,Jiří Widimský Jr., Jindřich Špinar Summary of 2013 ESH/ESC Guidelines for the management of arterial hypertension Prepared By the Czech Society of hypertension/ Czech Society of Cardiology December 2014 Volume 56, Issue 6, Pages e494–e518
3. Khartoum RF survey 2005-2006
4. Annual health statistical report (2008).
5. Shahnaz Usman, Aftab Alam, Nadda Nadeem, Rameesha Khawar and Zainab Intesar: Biowaiver Studies of Atenolol Tablets (100mg) An Alternative to In Vivo Bioequivalence Studies. Nat Prod Chem Res, 2014.Volume 2. Issue 1.10001258-
6. Guidances for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System. U.S., Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Available from:http://www.fda.gov/CDER/GUIDANCE/3618fnl.pdf.
7. World Health Organization (WHO): Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Technical Report Series, No 937,40th Report, Annex 8 of WHO Expert Committee on Specifications for Pharmaceutical Preparations. Available from: http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf.)
8. European Medicines Agency, Committee for Medicinal Products for Human Use Guideline on the investigation of bioequivalence. 2010. Available from: http://www.ema.europa.eu/docs/en GB/document library/Scientific guideline/2010/01/WC500070039.pdf.
9. Vogelpoel H, Welink J, Amidon GL, Junginger HE, Midha KK, Moeller H, Olling M, Shah VP, Barends DM Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System (BCS) Literature Data: Verapamil Hydrochloride, Propranolol Hydrochloride, and Atenolol. J Pharm Sci.2004,93 (6) 1945-1956
10. The United States Pharmacopeia and National Formulary USP 37–NF 32.The United States Pharmacopeial Convention, 12601 twin brook parkway, Rockville MD 20852, 2014.
11. British Pharmacopoeia Appendix: XII, Disintegration of tablets and capsules. London, 2013.
12. Guidance for Industry Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Accessed at: http://www.fda.gov/ OHRMS/DOCKETS/98fr/3657gd3.pdf.

How to cite this article:
Abdelkarim A, Mohd. Abdelkarim and Mohd. Abdeen: Assessment of Pharmaceutical Quality Control and *In Vitro* Equivalence of Various Brands of Atenolol (100mg) Tablets Available In Sudanese Market Under Biowaiver Conditions. Int J Pharm Sci Res 2015; 6(6): 2390-94.doi: 10.13040/IJPSR.0975-8232.6(6).2390-94.