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Comparative Quality Control Evaluation of Atenolol Tablets Marketed in Kuala Lumpur, Malaysia

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Authors' contributions

This work was carried out in collaboration between all authors. Author SRD designed the study and wrote the first draft of the manuscript. Author MA had done the all research activity. Authors SS and VSM managed the analyses of the study. Author WPS managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Background: The emergent of many pharmaceutical companies producing their own generic type of drugs after the patent of innovator drugs expired can improve the general healthcare delivery systems as well as decreasing the healthcare costs. But it also raises a few issues with one of it is the widespread of substandard and counterfeit product. Post-surveillance study to assess product parameter of various generics drug marketed is crucial. This kind of monitoring reduces a country's economical burden on health issues from diseases due to fraudulent and substandard drugs usage.
Purpose: The main objective of this study is to perform a comparative evaluation of the physicochemical properties of five commercially available leading brands of Atenolol tablets marketed in Kuala Lumpur.
Method: The quality control parameters of five different brands of atenolol tablets were atenolol tablet assessed included uniformity of content, uniformity of weight, friability, crushing strength, disintegration and dissolution tests as well as content uniformity of the tablets. All the tablets were assessed for conformity with British Pharmacopoeia (BP) standards.
Results: All the five brands of the tablets passed the British Pharmacopoeia (BP)

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standards for weight uniformity, disintegration, friability, content uniformity and hardness tests.
Conclusion: The quality control parameters of all five top selling brands of atenolol tablets marketed in Kuala Lumpur analyzed passed all the BP and USP quality specifications and were physically and chemically equivalent.

Keywords: Quality control; physicochemical anti-hypertensive; generic; innovator.

1. INTRODUCTION

The huge cost and expenses in clinical trials for the development of novel drug by pharmaceutical companies is rewarded through achieving its drug patent for a certain period of time that protects the product from competition in the market [1]. But, when the patent of innovator drug products expired, it gives an opportunity to several pharmaceutical companies to produce their own generic drug brands. In order for generic drug application to obtain approval, the applicants must validate that their generic drugs are bioequivalent and pharmaceutically equivalent compared to the innovator drug [1]. The increasing production of cheaper and affordable generic drugs can improve the general healthcare delivery systems [2] as well as decreasing the healthcare costs [3].

Even though there are many generic drug brands available in the market, effective monitoring of the quality of generic drug products marketed are absent in many developing countries [4]. This matter raise a few issues with one of it is the widespread distribution of substandard or counterfeit drug products [4]. Substandard drug products can be defined as genuine drugs manufactured by authorized manufacturers but do not meet the quality specifications fixed for them by national standards [5].

There are several cases happens related to substandard and counterfeit drug products [6]. Apart from that, survey conducted by World Health Organization (WHO) in 2007 found that 20-90% of antimalarial [7] and 28% of antibiotic [8] drugs failed quality specifications. As per the study conducted by Ministry of Health, Malaysia in 1997, 5.3% of counterfeit or substandard drugs are available in market [9]. Other than that, according to the malaysian pharmaceutical services division, approximately 5.28% of all Over-The-Counter (OTC) drugs marketed in Malaysia were counterfeit or substandard in 2008 [9].

It is believed that substandard drugs contribute far greater threat to public health compared to counterfeit medicines [10]. Currently, there are many literatures and reports of the availability of counterfeit drugs worldwide. But in the majority of these, the terms counterfeit and substandard drugs were used synonymously which contributing to the confusion on the terminology [10]. According to WHO, a counterfeit product is a product that is intentionally and illegally mislabeled [10]. Based on this definition, the quality of the product is not being mentioned since the quality of counterfeit product can be as good as the original one. Bear in mind that this matter does not mean 'good quality' fake product can be tolerated, but that exact problem of substandard products should be eliminated [11].

There are many causes and problems associated with substandard drugs. The common problems may include wrong concentration of active ingredient, poor quality of both excipients and active ingredients, contamination of the product, problems in packaging as well as decomposition of active ingredients [10]. The decomposition of active ingredients is

possible when the product is kept in environment that is prone chemical degradation, especially in tropical countries where humidity plays is relatively high [11].

Thus, monitoring of generic drugs in the market is vital. WHO has issued many guidelines for global standard and requirements for the assessment, authorization, registration, marketing as well as quality assurance of the generic drug products [4]. Monitoring marketed drugs can lessens a country's economical problem on health issues from diseases due to fraud and substandard drugs usage [12].

Initial quality control evaluation of the generic drugs is essential and in vitro dissolution testing can be a valuable predictor of the in vivo bioavailability and bioequivalence of tablet dosage forms [4]. Quality control methods of assessment are useful to monitor quality characteristics of various marketed brands and product consistency of batch-to-batch drug release [13]. In addition, drugs that having three or more generic brand must be assessed and monitored to ensure its interchangeability with innovator brand [14].

Atenolol belongs to anti-hypertensive class called beta-adrenoceptor blocker. This drug is indicated for hypertension, arrhythmias as well as in combination with other class of anti-hypertensive for long-term management of angina pectoris [15]. Atenolol works by competing with sympathomimetic neurotransmitters for binding at beta-adrenergic receptors inhibiting the sympathetic stimulation. This action can reduce cardiac output, heart rate, systolic and diastolic blood pressure [16]. Currently, there are about 9 brands of atenolol including its innovator brand available in Malaysia market [17].

The main objective of this study is to perform the comparative evaluation of quality control of some commercially available five leading brands of atenolol tablets marketed in Kuala Lumpur. The basic purpose was to establish their quality prior to determining interchangeability with the innovator product.

2. METHODOLOGY

2.1 Materials

Top five brands of Atenolol tablets 50mg (A to E) were purchased from different retail pharmacies in Kuala Lumpur. The top five selling brands were determined by survey to random 65 retail pharmacies in Kuala Lumpur. Atenolol, working reference standard with purity of 98.5% is supplied Sigma Aldrich, Malaysia. The aim of the survey is to determine the top five (5) leading atenolol tablet brands marketed in Kuala Lumpur. The research survey was done based on prospective cross-sectional study using a preset questionnaire.

2.2 Physical Measurement

All the atenolol tablets involve in this investigation were evaluated based on British Pharmacopoeia and compared with innovator tablet, brand C and were assessed whether they are within the standard limits or not. Before proceeding to the tablet quality control evaluations, visual inspection of the tablets were done by examined the size, shape and colour of the tablets visually.

2.3 Friability Test

Twenty tablets were randomly selected from each five atenolol brands. The tablets were weighed and subjected to abrasion and shock using a Roche Friabilator at 25 revolutions for four minute. Then the tablets were weighed again and the percentage of weight loss was calculated. Calculations are based on formula below:

$$\text{F (\%)} = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight}\ X\ 100\%$$

2.4 Weight Uniformity Test

Twenty tablets from each five atenolol brands were weighed individually by using digital analytical balance and their average weight were calculated. The percentage deviation of individual tablet from the mean was determined.

2.5 Content Uniformity Test

Ten tablets selected at random from each brand were weighed together, crushed in a mortar together, crushed in a mortar with a pestle and the quantity of powder equivalent to the average weight per tablet of each brand was placed in a 100ml capacity beakers. Freshly prepared methanol was added with shaking to the flask to make 100ml. The mixture was filtered and appropriate dilution made with methanol. The absorbance of the filtered samples was read at 275nm using a Shimadzu UV-160 UV-Visible spectrophotometer. The concentration of each brandwas determined from the calibration curve previously obtained with a pure sample of atenolol.

2.6 Disintegration Test

Six tablets were individually placed inside the basket of disintegration test apparatus (DST-3, Logan Instruments Ltd, USA). The media temperature were maintained at 37ºC±2ºC. If there is no cracking of coat; continue the test by replacing the medium with 0.1M Hydrochloric Acid. As for uncoated tablet, the test needs to be run for 15min.

2.7 Dissolution Rate Determination

The dissolution rate of the tablets were determined by placing tablet at bottom part in the Electrolab Dissolution tester with 500mL dissolution media of 0.1N Acetate buffer pH 4.6 at 37ºC±0.5ºC. The apparatus was set at 50 rotations per minute using paddle method. Samples from the dissolution medium (5ml) was drawn at 5 minutes interval for 30 minutes. After each withdrawal of sample, 5ml of fresh dissolution medium was added. Each withdrawal samples was filtered by using membrane filter (0.45µm). The absorbance was be measured by using UV/Visible Spectrophotometer at wavelength of 275nm and amount of drug dissolve were calculated using standard plot.

The regression equation for the calibration curves prepared in 0.1N Acetate buffer pH 4.6 as below:

$$y = 0.047x + 0.0248,\ r^2 = 0.9997$$

The graph of the amount of atenolol dissolved versus time was plotted from and amount dissolved at 30min were obtained for each brand.

2.8 Hardness Test

The tablet hardness (crushing strength) was determined by using Monsanto's Hardness tester. Ten tablets were randomly selected from each five atenolol brands and force required to crush the tablet were recorded. The results were expressed in Newton as the mean, minimum and maximum values of the forces measured.

3. RESULTS AND DISCUSSION

All the atenolol samples drug taken for the evaluation were within their shelf life at the time of investigation. The results of the quality control properties of the various brands of Atenolol are presented in Table 1. The visual organoleptic properties testing found that all the five brands in good condition where each individual tablets were free from cracks, depression and pinholes. In addition, the tablets color, surface roughness and polish were uniform on whole surface for the sample batch tested.

Table 1. Physicochemical properties of five brands of atenolol tablets

Parameter	Weight uniformity test, % deviation (mean±sd)	Friability, % loss	Crushing strength (mean±sd)	Disintegration time
Brand A (Uncoated)	1.95±1.32	0.30	2.04±0.15	240 seconds
Brand B (film-coated)	0.55±0.51	0.02	4.74±0.21	1320 seconds
Brand C (Uncoated)	0.63±0.38	0.12	4.04±0.17	30 seconds
Brand D (Uncoated)	0.46±0.30	0.51	1.57±0.36	20 seconds
Brand E (film-coated)	1.06±0.91	0.03	4.02±0.19	120 seconds

Friability test will induce abrasions and shock in the tablets. A good formulation tablet should be able to withstand any abrasion and shock during its handling, packaging and transportation [2]. British Pharmacopoeia (2009) stated that conventional compressed tablets that lose less than 1% of weight are considered acceptable. The result showed that all the five brands conformed to the BP standard limits, where maximum weight lost attained is only 0.51% by brand D.

Other than ability to withstand shock during handling, tablet hardness can also indirectly affect the rate of disintegration and dissolution of a tablet [2]. If the tablet is too hard, it will not achieve the specified dissolution rate and it also will not disintegrate completely within the specified time [18].

The tablet hardness may vary between brand depending on the binding agents and compression force. Normally, a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets [18].

But, it does not mean that all good formulation tablets must have a crushing strength of 4kg, since this is non-compendial test; none of the standard pharmacopoeia put any limits for it. Even though there are variation in crushing strength of both brand A and D, the friability test, disintegration test and dissolution test showed that both brand still meet the BP limits thus portrayed a good formulation tablet.

Disintegration test is used to measure the time required for a group of tablets disintegrate completely into particle. Out of five atenolol brands used, two of it was film-coated tablet and the other three were uncoated tablet. Based on BP (2009), the film-coated tablet needs to disintegrate completely within 30 minutes and uncoated table needs to disintegrate completely within 15 minutes.

The dissolution test measured the time required for a given percentage of a drugs substance in a tablet to go into solution under specific set of conditions. The procedure and materials for this test is following the specific United State Pharmacopoeia (USP) specific monographs for Atenolol tablets. The USP specification for Atenolol tablets that not less than 80% dissolved in 30min the dissolution profiles of atenolol tablet in all brands are presented in Fig. 1. The amounts of drug released at 30min are presented in Table 2. Based on the result obtained, all five (5) selected brands of atenolol marketed in Kuala Lumpur passed the test based on USP standard. All of them have more than 90% of dissolve drugs after 30 minutes.

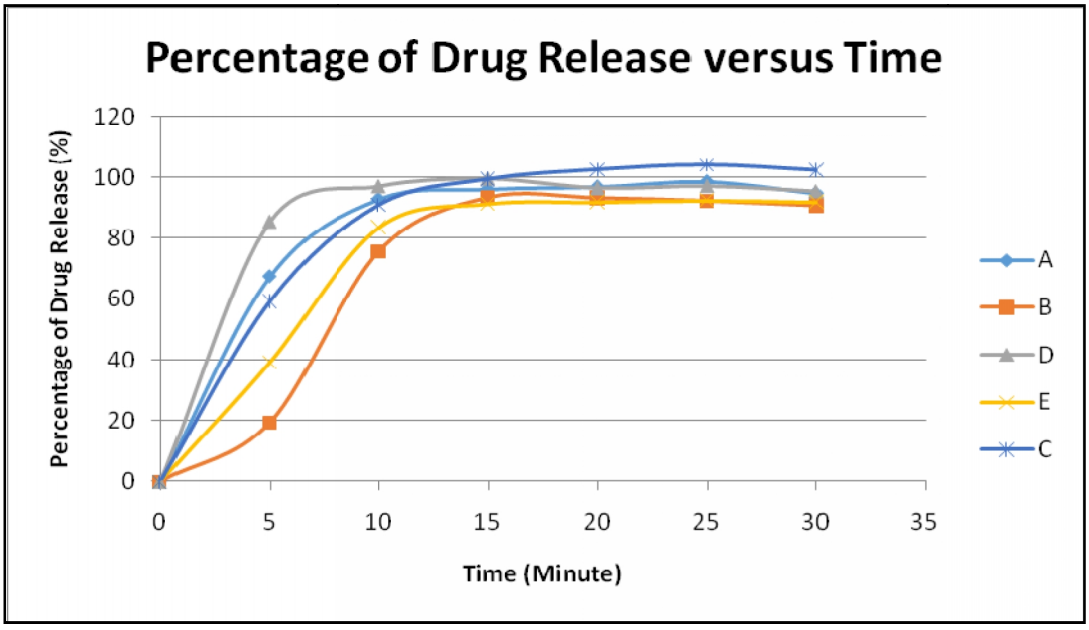

Fig. 1. Dissolution profiles from five different brands of atenolol tablets in 0.1N acetate buffer pH 4.6

Content uniformity test ensure that all the tablets contains the amount active ingredient intended. It is important for all the tablets from each batch to have uniform and intended content of active ingredient as inconsistencies amount of active ingredient will affect the therapeutic outcome. The content uniformity test of single-dose preparations is based on the assay of the individual contents of active ingredient of a number of single-dose units to

investigate whether the individual contents are within the limits set. British Pharmacopoeia stated that for single-dose preparation of tablets, the preparation will complies with the test if each individual drug content is between 85 percent and 115 percent of the average content which is ±15%. Based on the result obtained, all the tablets are within ±15% drug variation.

Table 2. Dissolution parameters of the five brands of atenolol tablets

Brand	Percentage of drug release at 30min (%)	% Content (w/w) of atenolol (mean±sd)
A	94.79±1.39	96.55±4.76
B	90.63±3.24	91.24±2.73
C	102.49±2.65	102.60±4.97
D	95.33±1.94	94.10±1.61
E	91.89±2.86	96.36±3.32

4. CONCLUSION

Physicochemical properties of all five top selling brands of Atenolol tablets marketed in Kuala Lumpur analyzed passed all the BP and USP quality specifications and were physically and chemically equivalent.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Center for Drug Evaluation and Research. Critical Path Opportunities for Generic Drugs. 2007. Accessed 03 Dec 2013. Available:http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077250.htm.
2. Adegbolagun OA, Olalade OA, Osumah SE. Comparative evaluation of biopharmaceutical and chemical equivalence of some commercially available brands of ciprofloxacin hydrochloride tablets, Dept. of Pharmaceutical Chemistry, University of Ibadan, Ibadan. Tropical J Pharm Res. 2007;6(3):737-745.
3. Hailu GS, Gutema GB, Asefaw AA, Hussen DA, Hadera MG. Comparative assessment of the physicochemical and *In vitro* bioavailability equivalence of Co-Trimoxazole tablets marketed in Tigray, Ethiopia. Int J Pharm Sci Res. 2011;2(12): 3210-3218.
4. Michael A Odeniyi MA, Olajire AA, Remilekun BA, Oluwatoyin AO, Oludele AL. Comparative analysis of eight brands of sulfadoxine-pyrimethamine tablets. Tropical J Pharm Res. 2003;2(1):161-167.

5. World Health Organization. What Are Substandard Medicine? 2013. Accessed 20 Nov 2013. Available: http://www.who.int/medicines/services/counterfeit/faqs/06/en/.
6. Kaur M. Beware of fake medicine. 2007 Accessed 25 Nov 2013. Available:http://www.mps.org.my/newsmaster.cfm?&menuid=36&action=view&retrieveid=944.
7. World Health Organization (2007): Survey of the quality of antiretroviral medicines circulating in selected African countries. 2007. Accessed 15 Sep 2013. Available: http://apps.who.int/prequal/info_general/ documents/ARV_survey.pdf.
8. Ahmad K. WHO fights fake pharmaceuticals. Lancet Infect Dis. 2006;6:195.
9. Clinical Practice Guidelines (CPG) on Management of Hypertension: Ministry of Health Malaysia, 3rd edition; 2008.
10. Caudron JM, Ford N, Henkens M, Mace C, Kiddell Monroe R, Pinel J. Substandard medicines in resource-poor settings: A problem that can no longer be ignored. Tropical Med Int Health. 2008;13(8):1062-1072.
11. Shakoor O, Taylor R, Behrens R. Assessment of the incidence of substandard drugs in developing Countries. Tropical Med Int Health. 1997;2(9):839–845.
12. Musa H, Sule YZ, Gwarzo MS. Assessment of physicochemical properties of metronidazole tablets marketed in Zaria, Nigeria. Int J Pharm Pharm. 2011;3(3):27-29.
13. Awofisayo SO, Awofisayo OA, Eyen N, Udoh IE. Comparative assessment of the quality control measures of multisource ofloxacin tablets marketed in Nigeria. Dissolution. 2007;17.
14. Babu GD, Devi SA, Swetha A, Teja GA. Comparative assessment of the quality control measurements of multisource ofloxacin tablets marketed in India. Int J App Pharmaceutics. 2011;3(3):31-33.
15. British National Formulary. 57 ed. London: BMJ Group and RPS Publishing; 2009.
16. Drug Bank. Atenolol: Open Data Drug & Drug Target Database; 2005 Accessed 09 July 2013. Available: http://www.drugbank.ca/drugs/DB00335.
17. MIMS Malaysia. 127th ed. Malaysia: UBM Medica; 2011.
18. David BT, Paul B. Remington: The Science and Practice of Pharmacy. 21st ed. United States of America: Lippincott Williams & Wilkins; 2006.

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