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Research Article

EQUIVALENCE OF TWO GENERIC BRANDS OF AMLODIPINE BESYLATE UNDER BIOWAIVER CONDITIONS

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ABSTRACT

Quality of generic medicines should be comparable with the innovator brand and therefore interchangeable with the innovator. Affordable quality tests that assure pharmaceutical and therapeutic equivalence of generics are needed, so that product selection of low priced generics by health practitioner is objective.

Without appropriate tests to assess bioequivalence (BE) in cost effective manners, maximum cost savings accruable to generic use may not be realized, because cheap generics are often associated with poor quality. Based on Biopharmaceutics Classification System (BCS), dissolution testing can be used as surrogates for *in vivo* BE studies (biowaiver). The study objective was to compare dissolution profiles of two generics of a BCS class I drug (amlodipine) with innovator amlodipine under biowaiver conditions.

Method: Assessment of physical parameters which include, uniformity of weight, hardness, friability and disintegration test were done according to British Pharmacopeia (BP) 2007 requirements. Chemical assay was carried out using a validated UV spectrophotometric method. The dissolution profile of Amlodipine tablets were evaluated in three media (pH 1.2, buffer pH4.5 and 6.8) using US Pharmacopoeia dissolution apparatus II.

Result: All the formulations conformed to B.P 2007 pharmacopoeial tests for tablets. The percentage purity of the three brands was within the range of 90 – 110% general tolerance level for tablet formulation in B.P. The results showed that none of the products met biowaiver criteria for very rapidly dissolving tablets. F_2 calculation was used to assess dissolution profile similarity. A generic brand sample B was comparable with the innovator brand in all the media ($f_2 \geq 50$) while the sample A has $f_2 \leq 50$ in one media.

Conclusion: To make objective decision about generic product selection, pharmacists and other health practititoners need adequate information on suitability of generic for substitution from national regulatory bodies.

Keywords: Bioequivalence, Biowaiver, BCS, Generic medicines and Amlodipine.

INTRODUCTION

The essential drug concept adopted in many developing countries promotes use of generic medicines, the main reason for generics is drug price containment through competition to improve access to essential medicines[1]. *A generic medicine is defined as a faithful imitation of a mature drug — no longer protected by a patent — marketed with the chemical name of the active ingredient*[2]. Quality of generic medicines should be comparable with the innovator brand and therefore interchangeable with the innovator. The fear of using generic drugs that are not bioequivalent, with the consequence of therapeutic failure, is the most influential risk that pharmacists reported to perceive in more than one study on generic drug use[3].

The price differentials between generics and innovators are sometimes in the 80% range[4] and depending on the category of generic wide variations exists between prices of generics available in a market. This price differential reinforces the belief among health practitioner and patients that less expensive generic drugs than brand are inferior and less effective [5,6]. The nature and extent of price competition in a patent expired market is influenced by the number of generics entering the market. As the number of competing manufacturers increases the greater the competition on price among firms[7]hence there could be wide variations in generic products prices. Appropriate quality tests that assure pharmaceutical and therapeutic equivalence of generics are needed, so that product selection of low priced generics by health practitioner is objective.

Without appropriate tests to assess bioequivalence (BE) in cost effective manners, maximum cost savings accruable to generic use may not be realized.

Dissolution testing has evolved over years into valuable test to characterize drug product performance and its impact on regulatory practice is increasing. The Biopharmaceutics Classification System (BCS) introduced in 1995 produced a new paradigm in bioequivalence, according to the system drugs are classified on the basis of their aqueous solubility and intestinal permeability[8]. Based on BCS, dissolution testing can be used as surrogates for *in vivo* BE studies (biowaiver). Biowaivers allow for drug product approvals based on *invitro* dissolution tests rather than requiring expensive and invasive bioequivalence studies in human[8]. Biowaivers were granted for BCS Class 1 drugs by FDA[9] and WHO[10]. Class 1 drugs are rapidly dissolving drugs products containing compounds of high solubility and high permeability. These drug products are assumed to behave *invivo* like an oral solution for which bioavailability is considered self evident. Dissolution of class 1 drugs is expected to be very fast, BA/BE studies seem unnecessary for such products [11]. BCS and biowaiver have become important regulatory tools and more so in developing countries, where technology and other resources are very limited to conduct appropriate *in vivo* bioequivalence study. In a study conducted by Somnath et al. 2010[12] Ofloxacin was found to show above 85% drug release within 30 minutes. Hence, the product exhibits rapidly dissolving characteristics within the BCS limits. It has also been proven that drug in class I of BCS can be reformulated by complexation with solubility enhancing substance such as cyclodextrin to improve aqueous solubility with the intent of moving class IV or III drug to class I. Consequently such polymer complexes exhibit higher dissolution rates than the pure drug.[13] All these reiterate the importance of dissolution testing for quality control and regulatory purposes.

The study objective was to compare dissolution profiles of two generics of a BCS class I drug (amlodipine) with innovator amlodipine under biowaiver conditions. The lowest priced generic amlodipine and highest priced generic amlodipine available in Lagos State Nigeria were selected for comparison with the innovator.

Amlodipine is an antihypertensive belonging to dihydropyridine group of calcium channel blocker and is available in Nigeria as 5mg and 10mg dose. According to BCS, amlodipine is highly soluble (D/S ratio ≤250ml). When an active pharmaceutical ingredient is absorbed to an extent of 85% or more, it is considered "highly permeable." Amlodipine's absolute bioavailability is 60–65%, but its

permeability is classified as "high" due to metabolite excretion in urine (90–95%). Amlodipine is highly soluble and has high permeability, therefore belongs to BCS class 1 drug[14].

Amlodipine came off patents recently, thereby allowing for introduction of generic versions. These generic versions came in to Nigeria market with wide price variations. This work is designed to compare the equivalence of the lowest priced and highest priced generics with the innovator brand.

MATERIALS AND METHODS

Materials

The tablets tested were immediate release dosage forms of amlodipine 5mg. Two generic brands of amlodipine 5mg tablets (samples A and B) were selected based on price survey as test samples and procured from registered pharmacy and innovator brand (Norvasc® 5mg) was used as the reference sample (C). Amlodipine besylate reference standard was obtained freely from Lagos State University drug quality control laboratory, Lagos.

Reagents used were of the analytical grade, concentrated hydrochloric acid [May and Baker LTD, Bahenham, England], Methanol AR [Sigma-Aldrich], potassium dihydrogen orthophosphate [BDH Chemicals LTD Poole England, 99-101%] sodium hydroxide pellet [Merck, Germany 98%]. UV/visible spectrophotometer (Agilent 8453) Denver Analytical weighing balance, Pharma hardness tester®, Charles Ischl AG friabilator® and disintegration tester (Erweka®)

Methods

Physicochemical

Assessment of physicochemical parameters which include uniformity of weight, hardness, friability and disintegration test were done according to British Pharmacopeia (BP) 2007 requirements[15].

Preparation of Media

The media used in the study for method validation and dissolution were 0.1N HCL and buffer pH 4.5 and 6.8 prepared based on British Pharmacopoeia 2007.

Preparation of Calibration Plots

Gradient amlodipine standard concentrations ranging from 1.0 to 25 µg/mL were prepared from stock solutions and subjected to Ultra-violet spectrophotometric method at 238nm wavelength. Respective absorbances were taken and lines of regression were determined. The calibrator prepared in methanol was used for assay while that in 0.1N HCl, Buffer pH 4.5 and 6.8 were used for analysis of dissolution samples and assessment of method validation. Validation of UV spectrophotometric method was conducted according to recommendation of International Conference on Harmonization (ICH)[16].

Chemical Assay

Twenty tablets of each brand were weighed to determine the average weight. The tablets were triturated in a porcelain mortar into fine powder. The equivalence of 5mg of amlodipine was weighed out and transferred into a 5ml sample bottle. This was dissolved and made up to 5mls solution with methanol, to obtain 1000µg/ml stock solution. Six replicates, 10µg/ml solution was prepared for each brand. The sample was sonicated in ultrasonic bath and filtered with syringe filter (0.45µm). The absorbances of the filtrates were read in UV/visible spectrophotometer and the concentrations were determined from the calibration plot of the standard.

Dissolution Study

The dissolution profile of Amlodipine tablets were evaluated in 900mL of 0.1NHCl and buffer pH4.5 and 6.8 using US Pharmacopoeia dissolution apparatus II. In order to avoid degradation of amlodipine and to maintain optimum dissolution values, the experiments were carried out by wrapping the dissolution vessels in aluminium foil to exclude effect of light. The temperature and degree of agitation were set at 37°C±0.5 and 50 revolutions per minute respectively. Sample (5.0ml) was collected at predetermined time intervals 5, 10, 15, 30 and 50minutes. 5ml of fresh medium already equilibriated to 37°C was replaced into dissolution medium after each sampling in order to maintain sink condition. Twelve tablets per brand were used for the study. The collected samples were filtered with syringe filter 0.45µm (Millipore) to remove any insoluble excipients. The filtered samples were analyzed by the validated Ultra-violet spectrophotometric method (UV) at 238nm wavelength. The concentration and the percentage release in each time interval was determined using the equation of the line of the calibration plot obtained from the reference standard in the respective medium.

Data analysis

The dissolution profiles were estimated by plotting the percent drug released versus time and were compared using a model independent approach, similarity factor f_2 as described by the US FDA and presented in the following equation:

$$F_2 = 50\log\{[1 + 1/n\sum^{n=1}(R_t - T_t)^2]^{-0.5} \times 100\}$$

where R_t and T_t are percent dissolved at each time point for reference and test respectively. Dissolution profiles were considered similar if $f_2 \geq 50$.

RESULTS

The tablets tested were immediate release dosage forms of amlodipine 5mg that were within their stated expiration date and with National Agency for Food and Drug Administration Control (NAFDAC) registration numbers (table 1).

The percentage price differentials (table 1) were calculated by using the formula below

(Price of innovator – Price of generic) ÷Price of innovator X 100

The price differential between the two generic tested was 76.9% which was calculated by

(Price of generic A – Price of generic B) ÷ Price of generic A X 100

Result of UV Spectrophotometric validation

Linearity of amlodipine gave following linear equations in different media

y = 0.024x- 0.016 in 0.1N HCL
y = 0.029x – 0.002 in buffer pH 4.5
y = 0.025x – 0.012 in buffer pH 6.8

where y and x are absorbance and concentration respectively ;

Correlation coefficient, r^2 of 0.997, 0.996 and 0.998 and the limit of detection were 0.3, 0.1 and 0.3 µg/ml in pH 1.2, 4.5 and 6.8 respectively.

The relative standard deviation was found to be less than 10%. The accuracy was found not to be less than 80.3% in the three formulations examined.

Result of UV Physico-chemical tests

All the formulations conformed to B.P 2007 regulations on pharmacopoeial tests. The percentage purity of the three brands is shown in table 2 which is also within the range of 90 – 110% general tolerance level for tablet formulation in B.P.

Comparison of Dissolution profiles

Figures 1-3 and table 3 represent the dissolution profiles comparison and corresponding data of the three formulations in dissolution medium pH 1.2, 4.5 and 6.8. According to FDA, a drug product is considered to be very rapidly released if ≥85% of the drug is dissolved in 15minute, which corresponds to gastric emptying half-life ($T_{50\%}$) in fasting conditions. The results showed that none of the products met these criteria. Table 3 shows the statistical result for similarity factor, f_2 using innovator product C as the reference. The products were not rapidly dissolving but f_2 calculation were done since the innovator brand was also not rapidly dissolving in this work.

Table 1: History of selected brands of amlodipine tablets

Name of drug	Lot. No.	ExpirationDate	NAFDACReg. No.	Price per tablet ($)	% Price differential with innovator
Generic (A)	ABGH0011	03/2013	A4-0445	0.39	65
Generic (B)	90105001	08/2012	A4-0333	0.09	92
Innovator (C)	910276631	06/2013	04-5354	1.12	

Table 2: Physicochemical characteristics of selected brands of amlodipine tablets

Brand	Uniformity of weight (%) ±SEM	Friability (%)	Hardness/ (kg/cm²) ±SEM	Disintegration (seconds) ±SEM	Assay (%) ±SEM
A	1.31 ± 0.14	0.104	4.40 ± 0.30	19 ± 0.4	99.74±0.91
B	1.06 ± 0.09	0.580	5.43 ± 0.72	24 ± 0.7	99.73±0.72
C	1.17± 0.11	0.074	8.54 ± 1.10	17 ± 0.6	99.04±0.36

Table 3: Dissolution data and dissolution profile comparison using f_2

Medium	Time(min)	Test Products		Reference Product
		A	B	C
		% Dissolvedx ±SEM	x ± SEM	% Dissolvedx ± SEM
pH 1.2	5	69.9±4.6	71.0±0.2	68.2±3.0
	10	75.6±4.6	72.0±0.7	73.3±2.3
	15	76.7±2.4	73.4±0.9	79.2±0.8
	30	76.6±2.0	74.6±0.8	81.7±1.7
	50	84.6±3.1	76.1±1.0	86.7±2.9
F_2		**75.0**	**59.4**	
pH 4.5	5	78.7±4.0	64.4±3.6	65.8±1.3
	10	81.2±0.8	73.6±3.1	74.6±0.5
	15	84.2±0.8	78.0±2.5	75.6±0.9
	30	85.8±1.8	80.5±1.4	75.0±0.8
	50	94.4±4.2	83.9±3.0	76.6±0.6
F_2		**46.0**	**67.8**	
pH 6.8	5	75.7±2.7	55.3±0.7	60.3±0.7
	10	78.6±0.4	62.6±3.0	74.8±1.2
	15	79.1±0.5	78.5±1.9	76.6±0.9
	30	80.1±1.3	82.7±1.3	81.3±1.4
	50	81.3±0.8	87.9±2.7	84.8±2.4
F_2		**59.4**	**60.3**	

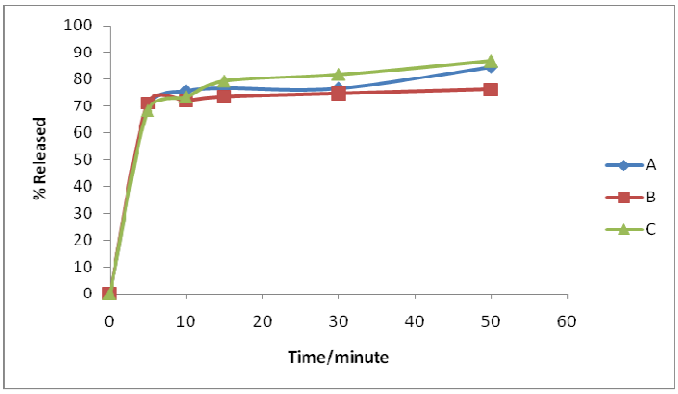

Fig. 1: Dissolution profiles of product A, B and C at pH 1.2 dissolution medium

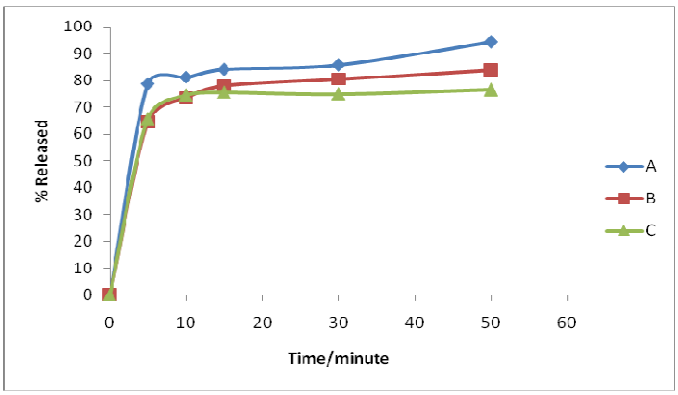

Fig. 2: Dissolution profiles of product A, B and C in dissolution medium of pH 4.5

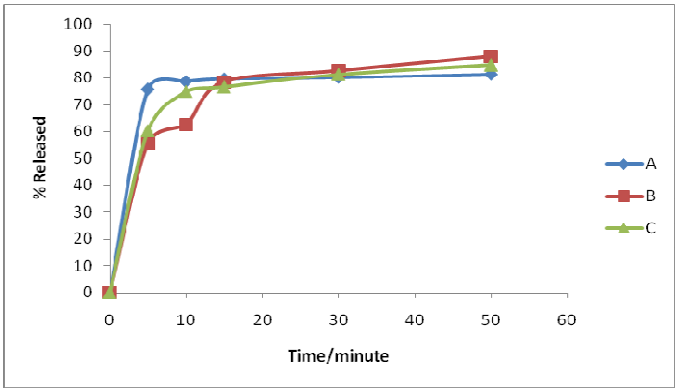

Fig. 2: Dissolution profiles of product A, B and C in dissolution medium of pH 6.8

DISCUSSION

The physicochemical characteristics of the two generic brands tested were comparable with the innovator brand. They were all within the BP limits for immediate release dosage forms, these assure pharmaceutical equivalence of generics tested with the innovator. Although there is no compendia monograph for amlodipine tablets yet, as such the general tablets requirements for dissolution of uncoated tablets was used for assessment. The two generic samples and the innovator brand made the 75% release in 30minutes specification as stated in British Pharmacopoeia.

Amlodipine is classified according to BCS as a Class I drug therefore qualifies for biowaiver. The samples tested did not meet biowiaver criteria for very rapidly or rapidly dissolving tablets, however since the innovator did not meet the criteria also, dissolution profile comparison was carried out using similarity factor,f_2. The cheaper generic brand sample B was comparable with the innovator brand in all the media ($f_2 \geq 50$) while the sample A has $f_2 \leq 50$ in one media. Under the biowaivers the sample B is interchangable with the innovator, they are therapeutically equivalent. Generic susbstitution of generic B for the innovator is appropriate despite the high price differential (92%) between the two. It is important that facts about suitability of generic for susbstitution be avaliable so that product selection is objective, for example in the US the FDA provides the orange book which form basis for product selection. Product selection between generics is rarely based on price but quality in contrast to decision between generic and innovator that is based solely on price. Product quality is the key issue for selection between generics, how quality is assessed by pharmacists or other health practitioners is not very clear.[17] Product selection is not just about generic and innovator but also between generics so that maximum cost saving achieveable from generics are realized.

Based on biowaiver conditions, sample A is not interchangable with the innovator, an in vivo BE study is needed. In vivo BE studies are more expensive and requires invasive procedures. Excipients used in manufacturing tablets have effects on their dissolution, therefore to enjoy biowaiver for regulatory purposes, good manfacturing practice and careful selection of excipients are required on the part of manufacturers.

CONCLUSION

Price differential between generics does not necessarily mean poor quality for the cheaper brand. In order to make objective decision about generic product selection, pharmacists and other health practititoners need adequate information on suitability of generic for substitution from national regulatory bodies.

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