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Full Length Research Paper

Quality of brands of atorvastatin calcium tablets marketed in Lagos, Nigeria

Moshood O. Akinleye[1], Oladipo Idris[2]*, Patricia N. Nwachukwu[1] and Olubukola O. Oyetunde[3]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, College of Medicine, University of Lagos, Idi-araba, Lagos, Nigeria.
[2]Department of Family Medicine, Lagos State University Teaching Hospital, Ikeja, Lagos, Nigeria.
[3]Department of Clinical and Biopharmacy, Faculty of Pharmacy, College of Medicine, University of Lagos, Idi-araba, Lagos, Nigeria.

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This study investigated the quality of atorvastatin calcium tablets marketed in Lagos, Nigeria, by evaluating and comparing their physico-chemical profiles. Evaluation of physico-chemical parameters viz: uniformity of weight, hardness, friability and disintegration test was carried out according to British Pharmacopoeia. Assay of active ingredient and *in-vitro* dissolution evaluation were conducted using USP Apparatus 2 satisfying the general conditions for film tablets as stipulated in official books. Tablets and dissolution samples were analyzed using a modification of the validated High performance liquid chromatographic method developed by Stanisz and Lukas. All the three brands met the standards for the physical qualities of a satisfactory tablet, and all had percentage purities within the 90 to 110% range. Only brands AT and CT had released ≥75% of label claim of atorvastatin calcium within 45 min, as specified in the B.P for conventional tablets. Thus, brand BT which had barely released 70% of its label claim at 60 min failed dissolution test. We concluded that out of the 3 brands of immediate-release atorvastatin calcium tablets available in the market at the time of the study, only 2 passed all the pharmacopoeia tests for satisfactory quality. Thus, only these can be interchanged in clinical practice.

Key words: Atorvastatin, *in-vitro* bioequivalence, switch ability, quality, safety.

INTRODUCTION

Rising prevalence of non-communicable diseases have been observed in Nigeria and other developing countries. A recent publication showed that non-communicable diseases, most importantly cardiovascular diseases (CVD) and cancer, now account for greater proportion of the burden of diseases in the developing countries than previously observed (Dalal et al., 2011). Furthermore, projections from the Global Burden of Disease Project suggest that from 1990 to 2020, the burden of CVD faced by African countries will double (Dalal et al., 2011; World Health Report, 2004).

An important Pharmacoepidemiologic consequence of this trend is the expected increase in consumption of drugs employed in the management of CVD as well as their risk factors. These include drugs employed in the prophylaxis and/or therapy of dyslipidemia, diabetes mellitus, hypertension, stroke, ischaemic heart disease, arrythmias and heart failure. Increased demand in the face of low capacity for local manufacture encourages importation and proliferation of generic brands on the drug market.

In the context of CVD, drugs indicated for dyslipidemia play the dual role of prophylactic and therapeutic agents. Evidence has shown that anti-lipidemic agents are important for the primary and secondary prevention of cardiovascular diseases (Mercuro et al., 2011). Statins are the most commonly prescribed anti-lipidemic agent. Quite a number of statins are on the world drug markets including atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin but the most widely prescribed anti-lipidemic agents is atorvastatin (Arca, 2007). Drugs in this class reduce endogenous synthesis of cholesterol by inhibiting the rate limiting

*Corresponding author. E-mail: holladipo@yahoo.com. Tel: 23418053245481.

enzyme in hepatic cholesterol biosynthesis viz: 3-Hydroxy-3-MethylGlutaryl Coenzyme- A synthase (Brunton et al., 2007). The main indications for the use of atorvastatin are the reduction of total serum cholesterol, triglyceride and LDL, and elevation of high density lipoprotein cholesterol levels. It is marketed as atorvastatin calcium tablets (10 and 20 mg formulations) and prescribed at single nightly dosages ranging from 10 to 40 mg.

The innovator brand and three generic brands are presently marketed in Lagos, Nigeria. The increasing importance of this molecule coupled with the need for lifelong use (for most indications) places a high premium on the assurance of high quality, reliability, and interchangeability of available brands.

Statutorily, all drugs that are marketed in Nigeria are required to be registered by the regulatory agency (National Agency for Food and Drugs Administration and Control- NAFDAC) before marketing approval is granted. An essential aspect of the registration process is evaluation of the safety and quality of the drug. However, research evidence has shown that not only are unregistered drug products marketed in Nigeria, but randomly selected registered drug products do not always pass independent standardized bioequivalence evaluation (Taylor et al., 2001).

Previous bioequivalence studies of drugs products marketed in different parts of Nigeria found that some brands (including innovator and generics) did not measure up to pharmacopoeial standards (Babalola et al*.,* 2004; Bamiro et al., 2004; 2007, Adebolagun et al., 2007; Esimone et al., 2008). This underscores the importance of independent evaluation of bioequivalence of marketed drug products by researchers in this environment.

The aim of this study was to evaluate the *in-vitro* bioequivalence of 3 brands of immediate release atorvastatin tablets marketed in Lagos, Nigeria. Our objectives were to determine and compare the physico-chemical characteristics of the 3 brands and assess the switchability of these products.

MATERIALS AND METHODS

The tablets tested were immediate release dosage forms of Atorvastatin calcium 20 mg. Two generic brands of Atorvastatin calcium 20 mg tablets (samples AT and BT) were available and procured from registered pharmacy and innovator brand (Lipitor® 20 mg) was used as the reference sample (CT). Atorvastatin calcium reference standard (USP) was procured from United State Pharmacopoeia, USA.

Reagents used include: high perfomance liquid chromatography (HPLC) grade methanol, 99.9% [Sigma-Aldrich], Acetonitrile 99.9% [Sigma-Aldrich], potassium dihydrogen orthophosphate [BDH Chemicals Limited, Poole, England. 99 to 101%], sodium hydroxide pellet [Merck, Germany. 98%]. Equipment used include: Mettler Toledo® Electronic Analytical weighing balance, Erweka hardness tester®, Charles Ischl AG friabillator® and Manesty® disintegration tester .

Physicochemical

Assessment of physicochemical parameters which include uniformity of weight, hardness, friability and disintegration test were done according to British Pharmacopoeia (BP) 2007 and USP 2004 requirements.

Preparation of media

The medium used in the study for dissolution was Phosphate buffer pH 6.8 prepared based on British Pharmacopoeia 2007.

Instrumentation and chromatographic conditions

All chemical analyses were performed using high performance liquid chromatography (HPLC). Agilent HPLC system (series 1100) equipped with Quartenary pumps, on-line Degasser, Rheodyne injection valve supplied with a 20 µl loop and ultraviolet (UV) absorbance detector with a ChemStation software was employed. The analytical column was a stainless steel Zorbax C18, 150 × 4.6 mm I.D, 5 µm particle size. The system was maintained at ambient temperature. The wavelength of detection was set at 254 nm. The mobile phase was a mixture of water (pH 2.1, adjusted with 80% orthophosphoric acid) and acetonitrile in the ratio of 48:52 (v/v) at a flow rate of 1.0ml/min. The mobile phase was filtered through syringe filter 0.45um. The data collection was performed with Chemstation software.

Preparation of calibration plots and validation of assay method

Graded atorvastatin calcium standard concentrations ranging from 10 to 100 µg/ml were prepared from stock solution (1000 µg/ml). The drug was quantified according to the slightly modified method of Stanisz and Lukas (2006) as described earlier. Calibration samples were then subjected to HPLC analysis in triplicate for the assessment of linearity of the calibrators. The precision of the analytical method was done using three different concentrations, analysed three times a day and for three consecutive days (n = 6). The coeficient of variations were evaluated. The accuracy of the method was also assessed by spiking pre-analyzed samples with known concentration of the standard and percentage recoveries

Table 1. Description and coding of the evaluated brands of atorvastatin tablets.

Brand code	Batch number	Date of manufacture	Date of expiration	Registration number	Country / manufacturer
AT	632060	June 2010	June 2013	A4-60	Ireland / Pfizer
BT	SK 92413	August 2009	July 2011	A4-1608	India/ SUN
CT	VM 001	January 2010	December 2012	A4-0271	India/ Medibios

Table 2. Physical characteristics of the atorvastatin tablets.

Brands	Uniformity of Weight : mean % deviation ± SEM*	Friability: % change in weight after friabillation	Hardness: Mean crushing force (Kg/m^2) mean ±SEM*	Disintegration time (minutes)
AT	1.05 ± 0.24	0.03	5.74 ± 0.59	0.57
BT	1.41 ± 0.26	0.05	9.57 ± 38	3.40
CT	2.21 ± 0.26	0.02	23.41 ± 0.85	6.62

*SEM: Standard error of the mean.

were then calculated.

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 10 mg of amlodipine was weighed out and transferred into a 10 ml sample bottle. This was dissolved and made up to 5 mls solution with methanol to obtain 1000 µg/ml stock solution. Six replicates, 100 µg/ml solution was prepared for each brand. Samples were sonicated in ultrasonic bath and filtered with syringe filters (0.45 µm). 20 µl of filtrates were injected into HPLC to evaluate the peak areas. The concentrations corresponding to peak areas were extrapolated from the regression line of the calibration plot. The percentage purities of the atorvstatin brands were then assessed.

Dissolution study

The dissolution profiles of Atorvastain calcium tablets were evaluated in 900 mL of phosphate buffer pH 6.8 using US Pharmacopoeia dissolution apparatus II (Electro-Lab, TDT-08 L dissolution tester USP). The temperature and degree of agitation were set at 37 ± 0.5°C and 50 revolutions per minute respectively. Sample (5.0 ml) was withdrawn from the dissolution apparatus at predetermined time intervals 5, 10, 15, 30, 45 and 60 min. 5 ml of fresh medium already equilibrated to 37°C was replaced into dissolution medium after each sampling in order to maintain sink condition. Six tablets per brand were used for the study. The collected samples were filtered with syringe filter 0.45 µm (Millipore®) to remove any insoluble excipients. The filtered samples were analyzed by the HPLC as stated earlier. 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.

RESULTS

Physical parameters

As shown in Table 1, all the 3 brands evaluated in this study were registered with the regulatory agency that is, NAFDAC. As at the time the experimental work was conducted, all were still within their shelf lives.

Results of the assessed physical parameters (Table 2) show that none of the 3 brands deviated more than 10% of the mean weight and all disintegrated within 15 min. Also, none had a post-friabillation weight loss of 1% or mean crushing force less than 4 kg/cm^2. Thus, all the three brands met the standards for the physical qualities of a satisfactory tablet.

Dissolution and chemical assay

Method validation for High-performance liquid chromatography (HPLC) assay

The linearity of atorvastatin is represented by the expression y = 19.853x +63.256 where y and x are peak area and concentration respectively. The correlation coefficient, r equal to 0.99 was obtained. The coefficient of variation which is the parameter for assessing precision was found to be less that 5% while the accuracy which was measured by recovery rate was not

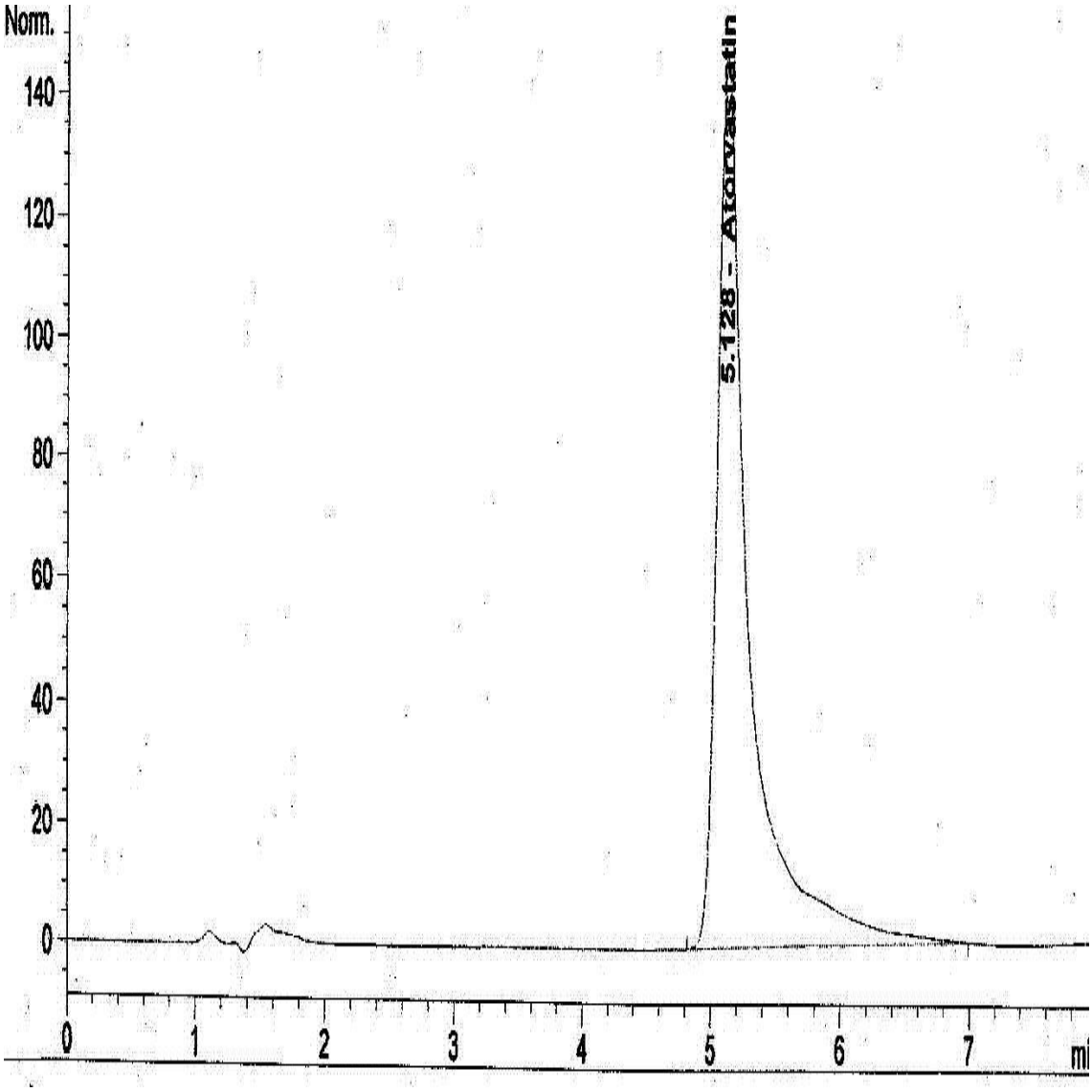

Figure 1. Chromatogram of atorvastatin standard in mobile phase.

less than 90%. Figures 1 to 3 respresent typical chromatograms of atorvastatin standard, atorvastatin in tablet formulation and atorvastatin in dissolution samples.

Dissolution profiles and drug purity.

The dissolution profiles of the 3 brands are shown in Figure 4. Only brands AT and CT had release equal to or greater than 75% of label claim of atorvastatin calcium within 45 min, as specified in the B.P for conventional tablets. Thus, brand BT which had barely released 70% of its label claim at 60 min failed dissolution test. Table 3 shows that all the 3 brands had percentage purities within the 90 to 110% range as specified in the general requirements for tablets in B.P.

DISCUSSION

At the time we conducted this study, 3 generic brands of atorvastatin calcium tablets were marketed in Lagos, Nigeria, along with Lipitor®; the innovator brand. Two of the generic products were selected for the study because they are in the same immediate release dosage form as the innovator brand. The third generic brand is in a modified-release dosage form.

Our findings show that the innovator brand with only one of the two generics evaluated met all the pharmacopoeial standards for satisfactory tablet formulation. Thus, only this generic brand and the innovator brand can be said to have *in vitro* bioequivalence based on these data and may be interchangeable.

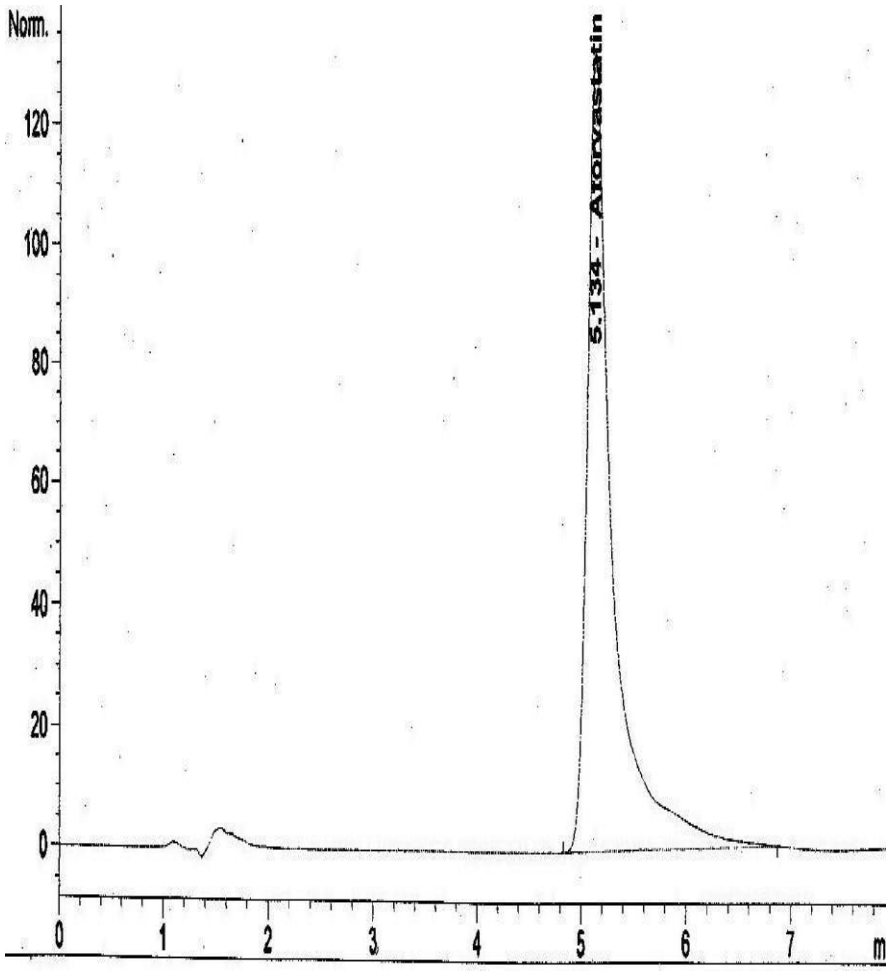

Figure 2. Chromatogram of atorvastatin in tablet formulation.

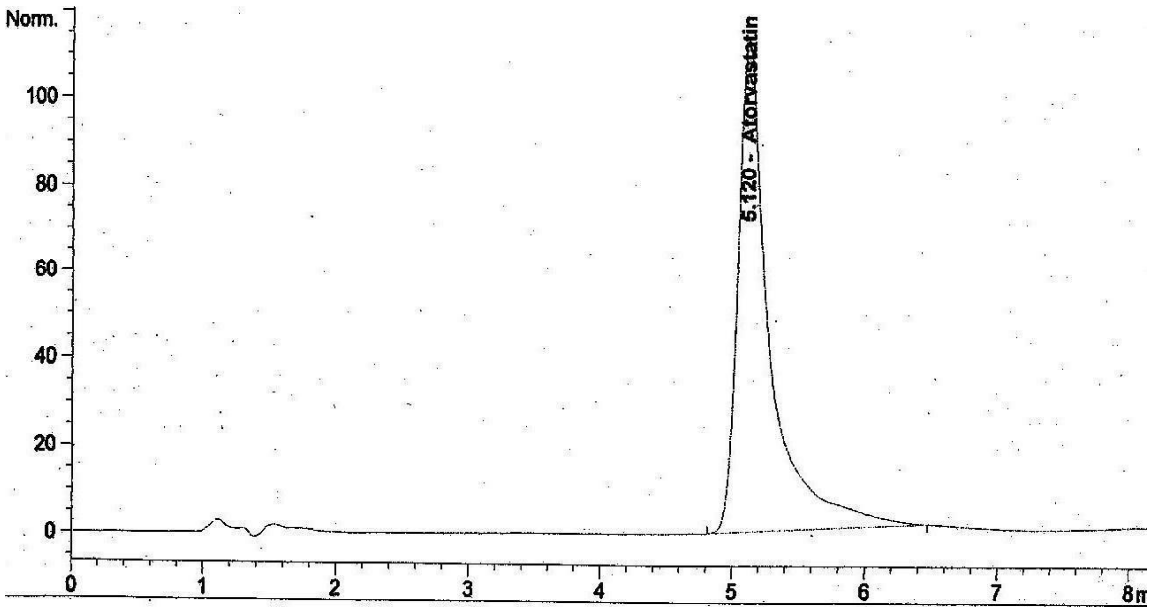

Figure 3. Chromatogram of atorvastatin tablet at dissolution time of 50 min.

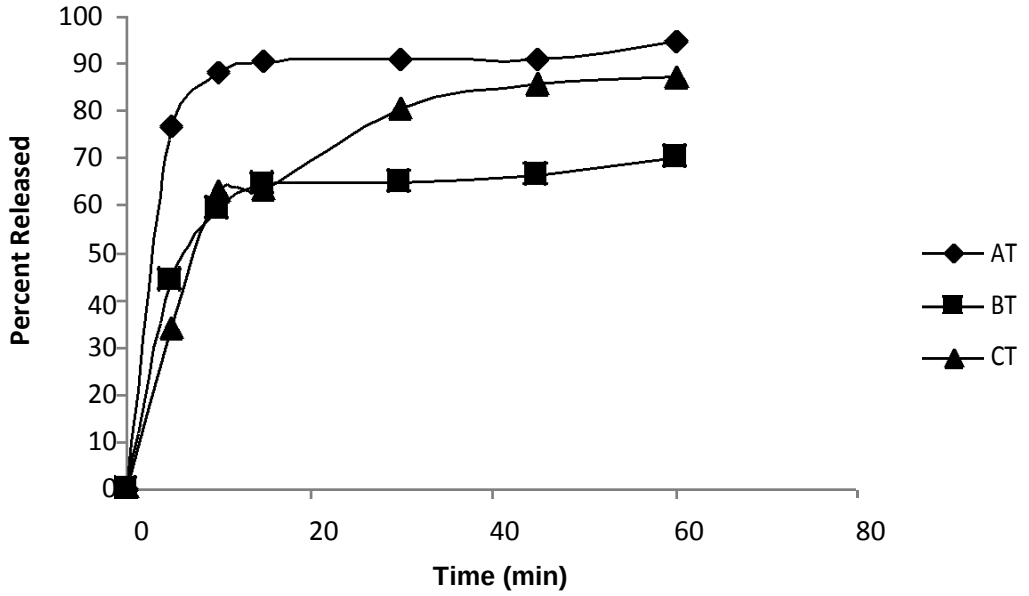

Figure 4. Dissolution profiles of the 3 brands of atorvastatin calcium tablets.

Table 3. Chemical assay of atorvastatin calcium tablets using high performance liquid chromatography (HPLC).

Brand codes	Label claim mg	Detected (mean±SEM) (%)
AT	20	104.2 ± 1.0
BT	20	91.3 ± 0.9
CT	20	90.9 ± 0.2

The relatively slow ability of brand BT to release the active compound gives cause for therapeutic concern as this can have negative impact on the pharmacokinetics and therapeutic efficacy of this formulation. Interestingly, this brand was shown to contain adequate level of pure atorvastatin calcium in the tablets during the chemical assay experiments; suggesting that a re-evaluation of the formulation of this brand may be necessary to improve its ability to release the active compound at a more acceptable rate.

Studies evaluating in-vitro bioequivalence of atorvastatin calcium tablets are scant in the biomedical literature. No previous publication on the in-vitro or in-vivo bioequivalence of brands of atorvastatin calcium marketed in African countries was available for comparison with our data. Studies conducted in Europe and Asia compared the innovator brand with generic brands using pharmacokinetic indices and assessment of therapeutic equivalence.

A multi-centre study conducted in Europe showed therapeutic equivalence of generic and reference atorvastatin in patients with increased coronary risks (Boh et al., 2011). In a similar study conducted among Korean patients with hypercholesterolemia, the innovator and generic brands were found to be equivalent (Kim et al., 2010). A comparison between the innovator and a generic brand of atorvastatin conducted in Czech Republic also found no difference in the bioavailability of the 2 brands (Mendoza et al., 2006).

Trends in the findings of published bioequivalence studies of drug products on the Nigerian market have shown mixed results regarding the interchangeability between generic products and innovator drugs, switchability among generics, and general attainment of pharmacopoeial standards by drug products dispensed to the populace (Babalola et al*.,* 2004; Bamiro et al., 2004; 2007; Adebolagun et al., 2007; Esimone et al., 2008).

The findings of this study indicate that despite the relative paucity of generic formulations of atorvastatin calcium in Nigeria, the early arrivals among the generics are already having challenges with standard. This justifies the need for continuous evaluation of the quality of drug products marketed in Nigeria. It also suggests that as more brands of any drug product are available in the country, the regulatory authorities would have to be more vigilant and alert to the possibility of post-registration decline in drug quality. This possibility requires pro-active interventions to avert the adverse public health consequences.

Conclusion

Of the three immediate release formulations of atorvastatin calcium tablets that were available on the market at the time this study was conducted, only 2 brands met all the pharmacopoeial standards for

satisfactory tablets.

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