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Quality Control and Interchangeability of MultisourcedLisinopril Tablets Marketed in Nigeria

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ABSTRACT
The availability of multisource brands of the same drug in Nigeria drug market makes it imperative for the routine monitoring of their quality to guarantee efficacy, safety, quality and interchangeability. The assessment of qualities of three brands of lisinopril tablets marketed in Nigeria (coded LSP A, LSP B and LSP C) was made by evaluating their hardness, friability, weight and content uniformity, disintegration time and dissolution profile via the standard or official methods. Results showed that only one brand (LSP A) passed the hardness test with a force of 5.15 ± 0.35 Kg; two brands (LSP A and LSP B) passed the friability test with a range of 0.14-0.27 %; one brand (LSP C) passed the absolute drug content test with a value of 85.1%, while all the brands passed the weight uniformity (220.85-211.15 mg), disintegration and dissolution tests according to the pharmacopoeial specifications. The dissolution parameters of predicted availability efficiency (PAE) and dissolution efficiency (DE) of the different brands (Brand A and B) were significantly ($p<0.05$) different from those of the reference brand (LSP C). It was concluded that though some of the brands of lisinopril tablets marketed in Nigeria meet some of the pharmacopoeial requirements, they were not considered bioequivalent to the reference brand (LSP C) and are thus not interchangeable.

Keywords
Lisinopril, Interchangeability, Nigeria drug market, Quality control, Tablet.

INTRODUCTION

In order to ensure the availability and affordability of many drugs, there is usually a wide proliferation of many brands of the same drug in many developing countries, in addition to the innovator brand. In most cases, the innovator product is quite expensive but the generics and the newer brands are cheaper and hence more affordable. Herein lies the attraction to substitute them with the innovator brand. Unfortunately, due to factors such as ineffective enforcement of existing laws, involvement of non-professionals in drug distribution, loose control system, high cost of drugs, greed, ignorance and corruption, counterfeit and substandard drugs abound in drug markets of developing countries [1-2].

Given the multiplicity of the various brands and the availability of fake products, prescribers are often faced with the dilemma of selecting a genuine and a suitable brand which is affordable and yet interchangeable with the innovator brand.Babalola [3] has defined interchangeability as the process of dispensing a different brand or unbranded drug product in place of the prescribed drug product. Interchangeable products must contain the same amount of the active ingredients and exhibit similar bioavailability profile [3-4].

The investigation of such interchangeability is based on the quality control (QC) parameters of the different brands. QC has been described as all measures designed to ensure the output of uniform batches of drugs that conform to established specifications of identity, strength, purity and other characteristics [5]. The QC parameters are obtained from the compendial tests- uniformity of content of active ingredient (uniformity of weight & content uniformity),disintegration, dissolution, and friability

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tests as well as the non-compendia tests-tablet thickness and tablet hardness.

Lisinopril (LSP), chemically described as N-[N-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate, is an angiotensin converting enzyme (ACE) II inhibitor used in the treatment of hypertension, congestive heart failure, heart attacks and also in preventing renal and retinal complications of diabetes [6]. There are several brands of commercially available lisinopril in Nigeria but the common forms are 5, 10 and 20 mg tablets. The price differences between the same strengths of different brands are not always wide thus necessitating their evaluation for not only their quality but also their possible interchangeability. To the best of our knowledge, such evaluation studies have not been carried out on lisinopril, though drugs such as metformin HCl tablets, ciprofloxacin HCl tablets, piroxicam capsules, chlorpropamide tablets, ciprofloxacin HCl caplets [7-11], ketoconazole [2] and ofloxacin [4] have been investigated for their quality and interchangeability among different brands. The findings of such studies revealed bioinequivalence in some cases [2]. Therefore, the focus of the present investigation was the assessment of the quality and similarity or otherwise of three brands of lisinopril tablets in Nigeria market through *in vitro* techniques, with the aim of establishing their quality and interchangeability with the reference brand.

Materials and Methods

Materials

In our studies, three brands of commercially available tablets containing 10 mg of LSP were purchased from local pharmacy shops in Nsukka, Enugu State, Nigeria. They were coded as LSP A, LSP B, and LSP C. All the reagents and chemicals were of analytical grade.

METHODS

Analytical method for the assay of LSP

In order to determine the standard calibration curve of LSP, a stock solution of 100 µg/ml was prepared in distilled water. Then dilutions were made to prepare a series of solutions containing LSP in different concentrations. For those solutions, absorbance values at 320 nm (λ_{max}) were determined spectrophotometrically and by plotting the concentration values (x) versus absorbance (y), a calibration curve of LSP in distilled water was obtained [12].

LOD and LOQ determination

The limit of detection (LOD) and the limit of quantitation (LOQ) were determined by using the following equations:

$$LOD = {}^{3SD}/_{m} \quad \text{... ... ...Eqn. 1}$$

$$LOQ = {}^{10SD}/_{m} \quad \text{... ... ...Eqn. 2}$$

Where SD is the standard deviation of the absorbance values (n=3) of the second smallest concentration, m is the slope of the calibration curve [12].

Quality Control tests

Tablet hardness test

Ten tablets were randomly selected from each brand of LSP. The hardness of each tablet selected was determined using the Mosanto hardness tester.

Weight variation

Each tablet (n=20) belonging to each brand was weighed with an electronic balance (OHAUS). The mean weight as well as the deviations (standard deviation) of the individual tablets from the mean weight was calculated.

Absolute drug content determination

Ten tablets were selected at random from each brand of LSP and were collectively weighed and crushed. The quantity equivalent to the mean weight of the brand was dissolved with 0.1N HCl and made up to 100 ml with the dilute acid. It was filtered and the absorbance determined using UV-VIS spectrophotometer (Jenway 6505, England). The experiment was repeated thrice for each brand of drug and concentration and hence the amount of LSP present in each sample calculated from the Beer's plot.

test

Ten (10) tablets from each brand were weighed and put into the friabilitor (Roche Friabilitor). Tablets were rotated at 25 rpm for 4 minutes and weighed again. The friability percentage was calculated for each batch according to Eqn. 3 [13]:

Disintegration test

Six (6) tablets were selected at random from each brand. One tablet was placed in each of the six tubes contained in each unit of the Erweka multiple unit disintegrating apparatus (900 ml of 0.1 N

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HClmaintained at 37 ºC was the disintegrating medium). The time taken for each tablet to completely breakdown to particles and pass through the wire mesh was determined.

Dissolution study

The dissolution rate studies on LSP tablets were carried out according to the basket method using the USP XXII dissolution apparatus type I (Electrolab, Mumbai, India) at a stirring rate of 100 rpm [15]. The dissolution medium was 600 ml of 0.1 N HClthermostated at 37 ± 1 ºC. The drug samples (2 ml) were withdrawn at definite time intervals for one hour (2, 5, 10, 15, 20, 25, 30 and 40 minutes) and replaced with equal volume of fresh dissolution medium. The samples were assayed spectrophotometrically as described previously. The percentage of cumulative LSP amount released from the tablets was calculated thus:

$$\%\ Drug\ dissolved = A \times \frac{100}{B} \ldots\ldots\ldots\ldots\ldots Eqn.\ 4,$$

where A is the amount of drug released (mg) calculated from the standard calibration and B is the amount (mg) of LSP in each tablet taken for the dissolution study.

Comparison of the dissolution profiles

For the comparison of the dissolution parameters to assess the pharmaceutical equivalence of the different brands of LSP tablets, the concepts of AUC (area under the curve), DE (dissolution efficiency) and PAE (predicted availability efficiency) were used. AUC was calculated using the trapezoid rule (Eqn. 5) [2].

$$[AUC]_{t_{n-1}}^{t_n} = \frac{C_{n-1}+C_n}{2} \times (t_n - tn{-}1 \ldots\ldots\ldots\ldots Eqn.\ 5,$$

where C_n and t_n refer to the concentration and time for the nth sample.

DE and PAE were calculated from the following relations [2, 4]:

$$DE_t = {AUC_t}/{AUC_{total}} \ldots\ldots\ldots\ldots \text{Eqn. 6;}$$

$$PAE = {AUC_b}/{AUC_{inv}} \times 100 \ldots\ldots\ldots\ldots \text{Eqn.7;}$$

DE_t ,AUC_t refer to dissolution efficiency and AUC_t at time t respectively while AUC_{total} refers to the AUC over the entire release period. AUC_b and AUC_{inv} refer to AUC of a brand and AUC of the reference brand respectively.

Statistical analysis

Data were plotted and evaluated using a statistical package program (Microsoft Excel & SPSS 16.0). Where necessary, the statistical significance between differences amongst brands was analyzed using the student's t – test. $P < 0.05$ was considered significant [16].

RESULTS AND DISCUSSION

Table 1 presents the analytical parameters for the validation of the spectrophotometric analysis and calibration of LSP. The linearity range for the calibration was 10-40 µg/ml while the equation of the line was y = 0.0015x + 0.0078 (r^2= 0.9511). The parameters indicate that the spectrophotometric method was quite suitable for the analysis of the drug.

Table 1: Regression analysis of calibration curve and summary of validation parameters

Parameter	Result
Wavelength (nm)	320
Linearity/ Beer's law limit (µg/ml)	20-50
LOD (µg/ml)	2.0
LOQ (µg/ml)	6.7
Regression equation	y= a + bx, x is the concentration of the analyte and y is the absorbance value
Slope (b)	0.0015
Intercept (a)	0.0078
Correlation coefficient (r^2)	0.9511

Results showed that LSP A passed the test of hardness, requiring a mean force of 5.15 ± 0.35 KgF to break each tablet (Table 2). Hardness of the tablet is controlled (or is affected) by the degree of the pressure applied during the compression stage. The test measures crushing strength property defined as the compression force applied diametrically to a tablet which just fracture (break) it. A force of about 4 KgF is considered the minimum requirement for a satisfactory tablet. The other two brands, LSP B and LSP C, did not meet the requirement of a minimum of 4.0 KgF hence these two brands may not likely possess the ability to withstand fracture and erosion during manufacturing

and handling since hardness is a post-manufacturing parameter which gives an indication of the mechanical strength of the tablet. Although there is no official test for hardness, this property must be controlled to ensure that the product is firm enough to withstand handling without breaking or crumbling and not so hard that the disintegration time is unduly prolonged [14]. Furthermore, there was a significant difference ($p<0.05$) between the hardness of LSP A, LSP B and that of the reference brand, LSP C. Thus the three brands are not interchangeable in terms of hardness.

Results of friability tests are presented in Table 2. Friability is the tendency of the tablet to crumble. In addition, it detects incipient capping or lamination of the tablets. While LSP C did not pass the friability test [1.28 ± 0.09], LSP A and LSP B complied with the requirement of 1% (maximum) [17-18]. In combination with the hardness test results above, LSP C brand does not possess enough mechanical strength to withstand stresses during packaging, transportation and handling.

The result of weight uniformity test of the three brands showed that they all passed the test as, in all the brands, no tablet deviated by more than the compendial requirement of 7.5 % for a tablet weight (X): 80 mg< X<250 mg (Table 2) [3]. Since LSP is a potent drug, however, weight uniformity alone is not an accurate measure of the uniformity of active ingredient as there is a poor correlation between the tablet weight and the active ingredient, hence the need for absolute drug content test.

Table 2 shows that only LSP C complied with the compendial requirement of more than 85% of active ingredient per tablet. The low active drug content of batches LSP A and LSP B could be due to poor manufacturing procedure especially use of insufficient active ingredients during granulation since the tablets have good weight uniformity.

The results of disintegration time are shown in Table 2. For uncoated tablet, the maximum limit for disintegration is 30 minutes [3] and all the batches complied with the compendial requirement. Though all the brands passed the test, LSP A disintegrated more rapidly than the others. Rapid disintegration could be as a result of the nature or quantity of disintegrants used or it could be due to the method of manufacture [5]. Also, there was a low variation in the disintegration time among the tablets in each batch of LSP A and LSP B. According to Rawlings [19], the nature and method of incorporation of lubricants, the action of disintegrants and the degree of compaction and reduction of inter-particle bond strength in the presence of water are some of the factors that affect disintegration time of tablets.

Table 2.Results of QC tests of three brands of LSP tablet marketed in Nigeria[a]

Brand	Hardness (KgF) (mean ± SD)	Friability (%)	Weight (mg) (mean ± SD)	Drug content (%)	Disintegration time (min) (mean ± SD)
LSP A	5.15 ± 0.35	0.14 ± 0.02	220.85 ± 2.48	74.2 ± 2.45	1.13 ± 0.01
LSP B	3.34 ± 0.37	0.27 ± 0.03	222.95 ± 2.42	84.0 ± 4.56	1.05 ± 0.03
LSP C	2.93 ± 0.58	1.28 ± 0.09	211.15 ± 2.39	85.1 ± 8.90	4.63 ± 0.37

a=Data are presented as mean ± SD (n=3)

The results of dissolution rate studies showed that all the brands complied with the compendial requirement since each batch released over 85% of its active drug within 30 minutes [5] (Figure 1). Dissolution rate studies provide an estimate of the extent to which the drug substance is released from the dosage form. As in the case of disintegration, batch LSP A released its drug content more rapidly than the others. This could still be attributed to the composition or method of preparation of the dosage form. Furthermore, a strong correlation was observed between the disintegration time and dissolution rate of the drug in all the brands, in line with previous reports [4, 20-21].

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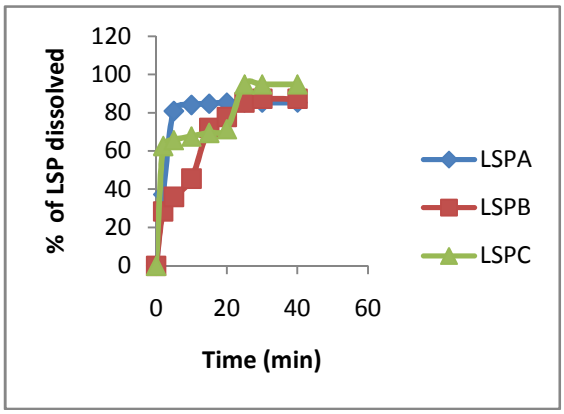

Figure 1: Dissolution profile of three brands of LSP tablets marketed in Nigeria

Out of the *in vitro* techniques, dissolution test is considered the most discriminating in *vitro test* with which to establish the *in vitro- in vivo* correlations and it may often be used to document equivalence between two or multi-sourced products [5]. AUC, DE and PAE tests were applied to the dissolution data in order to compare the predicted bioequivalence of the different brands of LSP tablets. These parameters were calculated using Eqn. 5-7. The results of the PAE and DE for LSP A and B showed that these parameters were significantly different ($p<0.05$) from those of the reference brand, LSP C (Tables 3 and 4). The different brands investigated were considered bioinequivalent and non interchangeable with the reference brand. As stated earlier, inequivalence has been demonstrated for a number of drugs marketed in Nigeria [2, 5]. Beside intentional adulteration, factors which have been identified as responsible for inequivalency of pharmaceutical products include physicochemical properties of the drug, formulation factors, manufacturing procedure, among others [5]. The therapeutic inequivalence of different brands of same drug is of great concern to the physician, pharmacist and all the stakeholders in healthcare delivery. This study has demonstrated that label claim alone is not a guarantee of bioequivalence of the pharmaceutical products; there is need for proof through routine testing.

Table 3: AUC values of the three brands of LSP tablets marketed in Nigeria

Time (min)	Time (h)	T_n-T_{n-1}	Brand A		Brand B		Brand C	
			Conc. (µg/ml)	AUC (µg/ml.h)	Conc. (µg/ml)	AUC (µg/ml.h)	Conc. (µg/ml)	AUC (µg/ml.h)
2	0.03	-	34.13	-	24.80	-	60.80	-
5	0.08	0.05	80.13	2.86	32.80	1.44	64.13	3.12
10	0.17	0.09	83.47	7.36	42.80	3.40	66.13	5.86
15	0.25	0.08	84.13	6.70	70.80	4.54	68.13	5.37
20	0.33	0.08	84.80	6.76	76.80	5.90	70.13	5.53
25	0.42	0.09	84.80	7.63	84.80	7.27	94.80	7.42
30	0.50	0.08	84.80	6.78	86.80	6.86	94.80	7.58
40	0.67	0.17	84.80	14.42	86.80	14.76	94.80	16.12
∑				52.51		44.17		51.00

Table 4: Dissolution parameters of the three brands of LSP tablets marketed in Nigeria

Batch	AUC (µg/ml.h)	DE_{30}**	PAE
A*	52.51	72.54	102.96
B*	44.17	66.58	86.61
C	51.00	68.39	100.00

*Brand A and B were significantly different ($p<0.05$) from brand C;

**DE_{30}=dissolution efficiency at 30 mins

Conclusion

Though the various brands complied with the compendial requirement in weight uniformity test and release rate studies, some of them did not possess the required mechanical strength and absolute drug content. From the comparison of the dissolution parameters, brands LSP A and LSP B were not considered bioequivalent and hence not interchangeable with the reference brand LSP A. It

is recommended that these tests could still be extended to other brands of lisinopril tablets not covered in this work.

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