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Quality assessment of various brands of losartan potassium tablets sold in Uyo Metropolis

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ABSTRACT

Background: Losartan potassium is a non-peptide angiotensin II receptor antagonist with high affinity and selectivity for the AT_1 receptor, used for the management of hypertension, diabetic nephropathy as well as hypertension with left ventricular hypertrophy. Various brands of Losartan potassium were assayed to reveal their conformity with compendia requirements and assure that the brands are of acceptable standards for human consumption.

Methods: Qualitative and quantitative analyses of ten (10) brands coded A-J of Losartan potassium sold in Uyo metropolis were carried out using standard physical and ultraviolet (UV) spectrophotometric methods respectively.

Results: All the brands tested met the official requirements for uniformity of weight. Brand I failed the disintegration test by British Pharmacopeia specification (disintegration within15 mins.) but conformed to the United States Pharmacopeia specification (disintegrated within 30 mins.). Only brand J complied with official dissolution specification (>80% at 30 mins.) when 0.1 N HCl was used as the dissolution medium, whereas, all the brands except brand F (<80%) complied when distilled water was used. The calibration curve for reference Losartan potassium in methanol was linear over a concentration range of 0.00-50 µg/mL with correlation coefficient of 0.985. All the brands passed the British Pharmacopoeia (BP) and United States Pharmacopoeia (USP) requirements for percentage drug content of 98.5% to 101.5% and 95.0% to 105.0% respectively.

Conclusion: The brands performed creditably well in their physical characteristics and percentage recoveries. The assay method in this study was simple, inexpensive, and reproducible and can be routinely used to assay Losartan potassium tablets.

Keywords: Angiotensin II receptor antagonist, AT_1 receptor, Assay, Losartan potassium

1. INTRODUCTION

Losartan potassium is a non-peptide angiotensin II receptor antagonist (ARB) used in the treatment of hypertension, diabetic nephropathy, heart failure and left ventricular hypertrophy [1, 2, 3, 4]. It is cardioprotecive and kidney protective [5, 6]. Administration of Losartan results in a decrease of Total Peripheral Resistance (TPR) and Cardiac Venous Return [7]. Unlike the angiotensin-converting enzyme (ACE) inhibitors, ARB does not have the adverse effect of dry cough [8]. A drug must be manufactured to meet laid down specification with respect to quality safety and efficacy. The introduction of generic drug products from multiple sources into the healthcare system of developing countries like Nigeria is aimed at improving the overall healthcare delivery system in such countries. It has been asserted that the use of substandard or fake drug products could result in poor clinical outcome and threat to life and improved surveillance of counterfeit medicine is one way to prevent this menace [9]. Therefore, there is need to ascertain that every drug product meets the pharmacopoeia standards. The results

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of consuming falsified, substandard or counterfeit drugs could be devastating [10]. Due to the fact that different companies manufacture and distribute Losartan potassium, there is the risk of purchasing substandard brands which could result in poor clinical outcome. Therefore, these drugs should be analysed for their chemical and biopharmaceutical equivalence, strength, purity and release profile of the active ingredient in comparison to the innovator brand [11].

2. MATERIALS AND METHODS

2.1 Materials

The electronic balance used was Ohaus, model PA213 and made in China. The Uv-vis spectrophotometer was a China brand, model 1.7. Other materials used included friability test apparatus, Roche Double Wheel Friability apparatus, England; Mosanto Hardness tester, made in England; Digital tablet disintegration test apparatus, model 011021, England and Dissolution test apparatus model DA-6D, Germany. Methanol was from James Borroughs Limited England while hydrochloric acid was from Fisher Scientific International Company.

2.1.1 Drug samples and reagents

Ten different brands of losartan tablets within their shelf-lives were purchased from community pharmacies in Uyo and coded A to J. The reagents used were of analytical grade and used as purchased.

2.2 Methods

2.2.1 Extraction and identification of pure Losartan

Five (5) tablets of losartan of the innovator brand Cozaar were pulverized and extracted with 100 mL of methanol. The melting point of the dried losartan extract was measured and a value of 140 ^{o}C was obtained, which corresponded with the melting point value of losartan in the British Pharmacopoeia (BP) safety data sheet [12].

2.2.2 Weight Uniformity analysis

Twenty (20) tablets selected randomly from each brand of losartan were weighed individually and the average weight determination of each tablet in a brand was obtained. The mean, standard deviation and percentage deviation were calculated and compared to the permitted variations in the official books.

2.2.3 Friability Test

Five (5) tablets from each brand of losartan were de-dusted and weighed together(W_0) and then subjected to friability test in a Roche Friabilator at 25 revolutions per minute for 4 minutes. The tablets were removed from the chamber, de-dusted and reweighed(W_1) and the percentage weight loss was calculated using the formula:

$$\% \text{ weight loss} = \frac{W_0 - W_1}{W_0} \times 100\ \%$$

2.2.4 Hardness Test

Five (5) tablets from each brand of losartan were randomly selected and subjected to crushing test individually using manual Monsanto hardness tester. The average crushing pressure required for each brand was determined.

2.2.5 Disintegration Time test

Five (5) tablets from each brand of losartan were randomly selected and subjected to disintegration in 900 mL of distilled water at a bath temperature of 37 ^{o}C$\pm$0.5 ^{o}C. The time taken for each of the tablet to disintegrate completely was recorded.

2.2.6 Dissolution Test

This test was carried out in two different media of 0.1N HCl (900 mL) and water (900 mL), with bath temperature of 37 ^{o}C$\pm$0.5 ^{o}C for 30 minutes. 10 mL of the dissolution medium were withdrawn at 5 minutes, 10 minutes, 15 minutes, 20 minutes and 30 minutes and were replaced with equal volume of the respective solvents after each withdrawal. The withdrawn samples were filtered using Whatman filter paper and assayed by UV Spectrophotometer at 247.0 nm (0.1 HCl medium) and 246.5 nm (for water medium) against the respective blank medium. The standard solutions of Losartan in the different media were scanned in a UV Spectrophotometer at wavelength range of 200–420 nm. The concentration of each sample was determined from the appropriate calibration curve obtained from standard solution of Losartan. The amount of drug released at each time interval was calculated as concentration (mg/mL) $\times$ dissolution bath volume (mL). The percentage drug released was calculated using the formula:

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$$\frac{\text{Amount of drug released}}{\text{Labelled claim}} \times 100\ \%$$

Using the dissolution data, the difference factor (f1) and the similarity factor (f2) were calculated for the different brands of Losartan in comparison with the innovator brand coded as B, so as to compare their dissolution profiles. The f1 and f2 values were calculated using the formula

$f1 = \Sigma Rt - Tt/\Sigma Rt$
$f2 = 50\log \{[1+1/n(Rt-Tt)^2]^{-0.5}\times 100\}$[13]

2.2.7 Spectroscopic assay
10 mg of losartan powder was dissolved in 10 mL of methanol to give 1 mg/mL concentration.
5 ml of the losartan standard solution was scanned in the range of 200–420 nm to obtain the maximum wavelength. Aliquots of 10 µg/mL, 20 µg/mL, 30 µg/mL, 40 µg/mL, and 50 µg/mL solution in methanol were made and their absorbance values were measured at 268.5 nm against a reagent blank of methanol. A standard graph was prepared by plotting the absorbance values against the concentration of losartan. A portion equivalent to 10 mg of each brand of losartan was weighed and transferred into a 10 mL volumetric flask containing small quantity of methanol. The solution was sonicated for about 5 minutes and then diluted to the mark (10 mL) with methanol, mixed well and filtered using a Whatman filter paper. Aliquots of 10 µg, 20 µg, 30 µg, 40 µg and 50 µg per mL of the standard solution were made. The various aliquots of each drug was measured at 268.5nm for their absorbance values against the reagent blank (figure 5).
Their concentrations were calculated and also extrapolated from the calibration curve of losartan using the formula;

$$\text{Concentration} = \frac{\text{Absorbance}}{\text{slope}}$$

Their percentage recoveries were also calculated

Thus; $\frac{C_1 \times 100}{C}$
Where; C_1 = Extrapolated concentration; C = Calculated concentration

2.3 Statistical Analysis
The weight uniformity test results (table 1) and hardness test results (table 3) were reported as mean±SD (standard deviation)

3. RESULTS
The average weight of tablets of the ten difference brands of Losartan potassium were found to be in the range between 126 mg-317 mg with each brand showing a percentage deviation of less than 5%, as seen in table 1.

Table 1: Weight uniformity test results

Sample	A	B	C	D	E	F	G	H	I	J
Mean weight (mg)	175	317	188	193	126	218	206	157	269	209
±SD (n=10)	2.50	2.45	1.8	2.68	1.84	4.0	2.30	2.63	9.03	2.51
% Deviation	1.43	0.77	0.96	1.39	0.85	1.83	1.12	1.68	3.36	1.20

Permissible percentage deviation is ≤ 5%
All the brands tested for friability had percentage weight loss of less than 1% as shown in Table 2.

Table 2: Friability test results

Sample	A	B	C	D	E	F	G	H	I	J
W_0(g)	0.884	1.558	0.945	0.968	0.629	1.082	1.028	0.786	1.297	1.040
W_1(g)	0.881	1.585	0.944	0.967	0.628	1.081	1.026	0.783	1.295	1.039
W_0-W_1(g)	0.003	0.003	0.001	0.001	0.001	0.001	0.002	0.003	0.002	0.001
% Weight loss	0.34	0.19	0.11	0.10	0.016	0.09	0.19	0.38	0.15	0.10

Permissible percentage weight loss is ≤ 1 %

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The hardness of all the different tested brands ranged from 4.12-7.10 kg/cm^2 as shown in table 3.

Table 3: Hardness test results

Sample	A	B	C	D	E	F	G	H	I	J
Average crushing strength (Kg/cm^2	7.1	6.46	6.16	5.04	4.96	6.46	4.12	6.06	4.20	6.30
±SD (n=10)	0.42	0.37	0.10	0.20	0.29	0.64	0.21	0.59	0.42	0.42

Permissible crushing strength is 4-10 Kg/cm^2
All the brands except I disintegrated within 15 minutes as shown in Table 4.
Table 4: Disintegration test results

Sample	A	B	C	D	E	F	G	H	I	J
Mean disintegration time (min) ±SD (n=10) % Deviation	5.68	11.24	6.42	3.29	3.30	11.93	6.45	8.86	15.18	6.33

Permissible disintegration time is ≤ 15 minutes
Only brand J had up to 80 % dissolution in 30 minutes when 0.1N HCl was used as the dissolution medium whereas all the brands except F had up to 80 % dissolution in 30 minutes when distilled water was used as the dissolution medium as shown in figures 1 and 2.

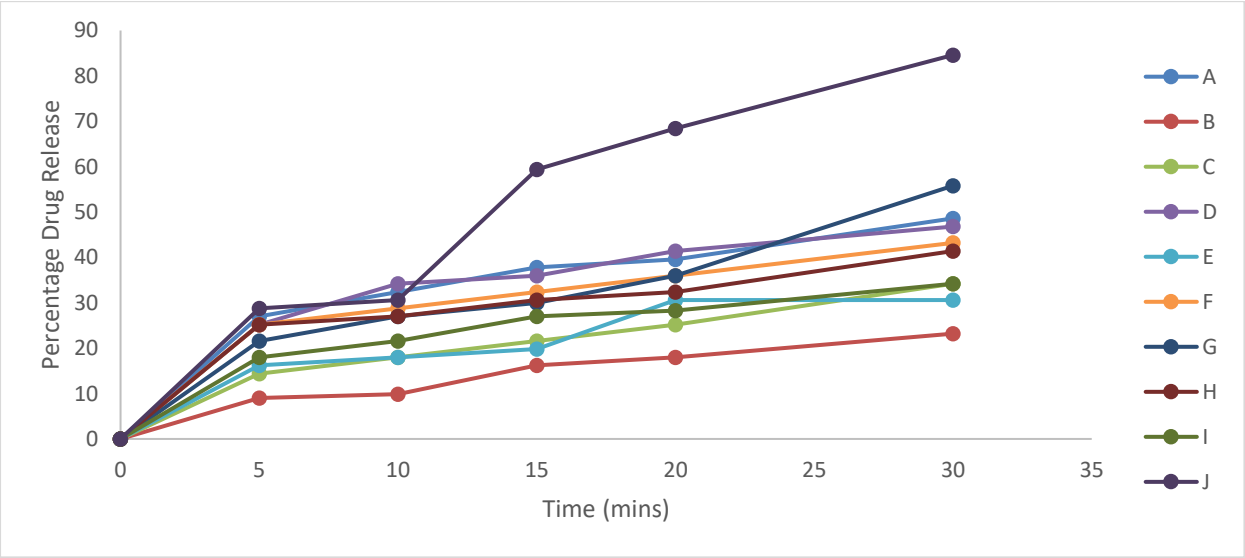

Fig 1: Dissolution Profile of ten brands of losartan potassium tablets in 0.1N HCl

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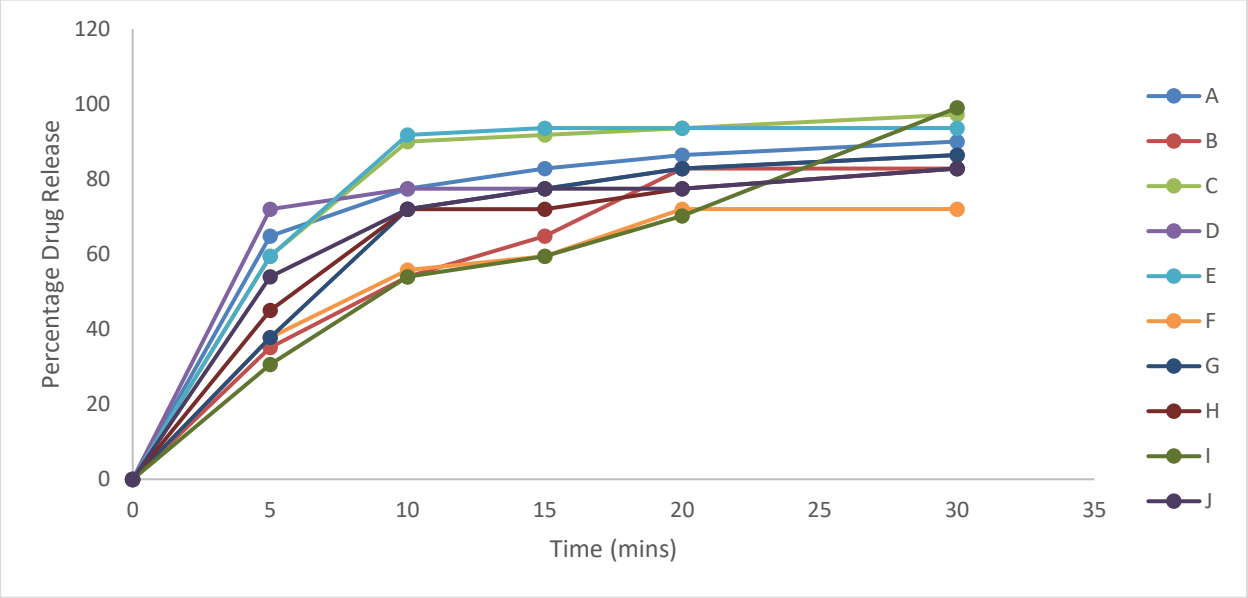

Fig. 2: Dissolution Profile of ten brands of losartan potassium in distilled water.

The differential factor (f1) and similarity factor (f2) gave values as shown in table 5.

Table 5: f1 and f2 values of the various brands of Losartan tablets compared with the innovator brand B.

Sample	A	C	D	E	F	G	H	I	J
f1	25.63	35.21	23.94	35.21	9.86	11.55	12.68	12.11	17.18
f2	35.95	30.75	42.57	30.24	56.37	49.83	49.83	50.54	43.93

The calibration curve for extracted pure sample of Losartan potassium in 0.1N HCl and water were linear over concentration ranges of 10 – 50 µg/mL as shown in Figures 3 and 4.

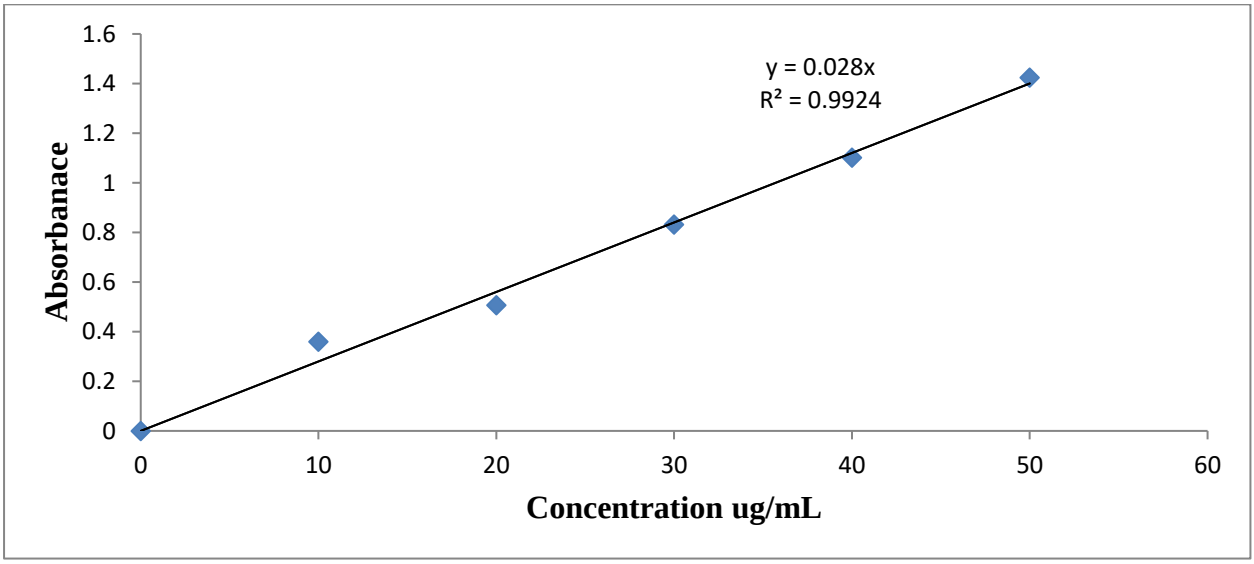

Figure 3: Calibration Curve of Losartan (Medium 0.1N HCl)

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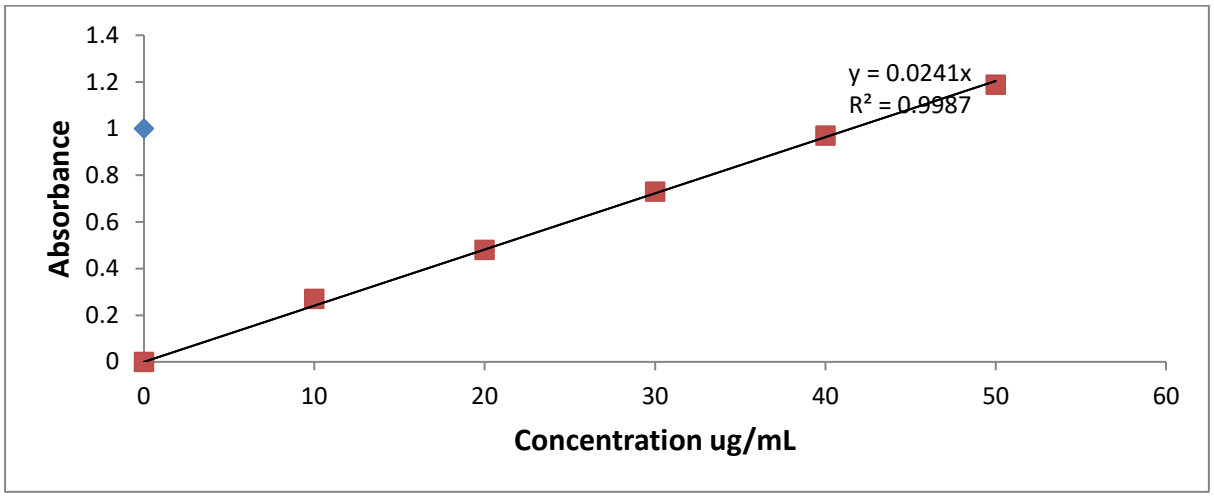

Figure 4: Calibration Curve of Losartan (Medium – Water)

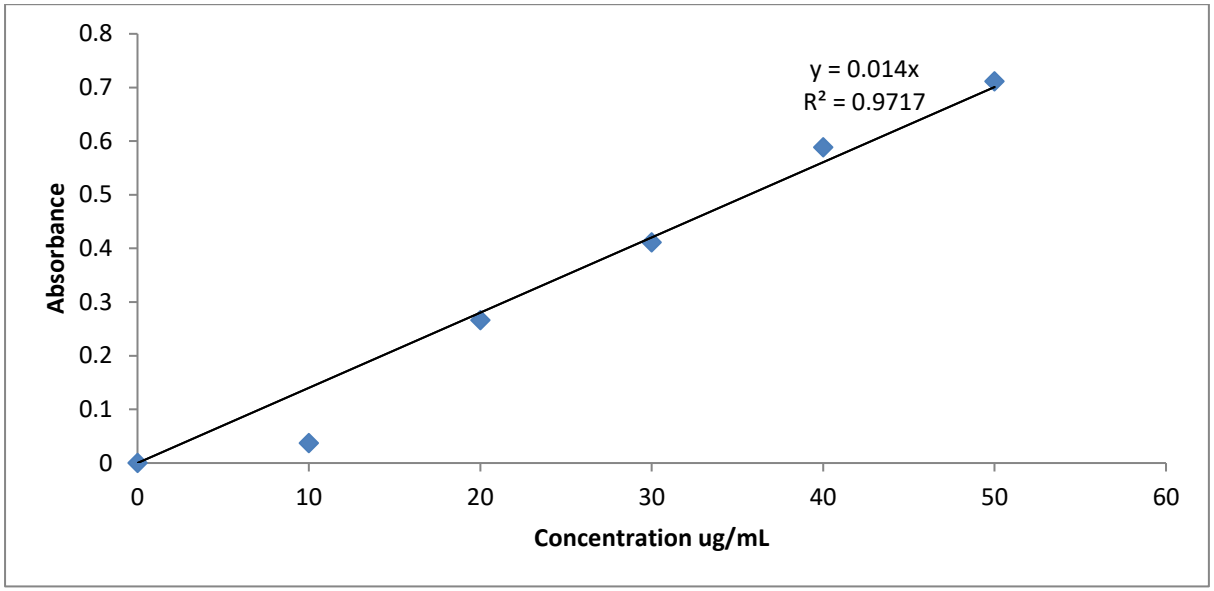

Figure 5: Calibration Curve of Losartan (Medium - Methanol)

From the assay results of percentage recovery shown in table 6, all the ten brands gave 98.5 % to 101.5 % active drug content.

Table 6: Percentage recovery of different brands of losartan

Sample	A	B	C	D	E	F	G	H	I	J
Percentage content ±SD (n=5)	98.64 0.65	99.16 0.93	99.83 1.59	99.64 1.14	98.59 2.12	99.62 1.41	100.31 1.16	99.60 1.88	100.08 0.69	99.20 1.27

4. DISCUSSION

Uniformity of weight is an indication of adherence to good manufacturing practice (GMP). All the brands complied with the USP compendium specification for uniformity of weight which states that for tablet weighing 324 mg or less, the weight of not more than 2 tablets should differ from the average weight by more than 7.5 % [14].

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Friability test evaluated the ability of tablets to withstand abrasion, packaging, handling and shipping. It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition [15]. The compendia specification for friability is a percentage loss of not more than 1 %, and all the tested brands conformed to this specification. The hardness or crushing strength measures the ability of tablets to withstand handling without chipping. The hardness of all the brands ranged from 4.12–7.10 kg/cm^2, which were within the official limits of 4–10 kg/cm^2. The tablets of different brands possessed good mechanical strength with sufficient hardness. Disintegration test is a crucial step for immediate-release dosage forms because the rate of disintegration affects the dissolution and subsequently the bioavailability of the medicine. All the brands except I complied with the British Pharmacopoeia compendium specification for disintegration. The BP (2009) specification is that uncoated tablets should disintegrate within 15 minutes and film-coated within 30 minutes [16]. On the other hand, United States pharmacopoeia (USP, 2014) specifies that both uncoated and film-coated tablets should disintegrate within 30 minutes [14]. By this latter specification all the brands tested disintegrated within the USP prescribed time limit of 30 minutes (Table 4). The presences of suitable disintegrants in adequate proportion ensure the production of tablets free of disintegration problems [17]. In the pharmaceutical industry, drug dissolution test is routinely used to provide critical *in vitro* drug release information for both quality control purposes and drug development [18]. The USP and BP specify that the amount of drug in solution after 30 minutes should not be less than 80%. Only brand J met the specification when 0.1N HCl was used as the dissolution medium whereas all the brands except F complied when distilled water was used as the dissolution medium (Figures 1 and 2). The dissolution profiles of two brands are considered similar and bioequivalent if the difference factor (f1) and similarity factor (f2) are between 0-15 and 50-100 respectively [18]. Only brand I gave values within the range and is therefore considered bioequivalent to the innovator brand B (Table 5). The calibration curve for extracted pure sample of Losartan potassium in water was linear over concentration ranges of 10–50 µg/mL, which is in conformity with Beer Lambert's Law. The resulting solution of the pure sample scanned in a Uv–vis spectrophotometer at wavelength range of 200–420 nm to obtain the wavelength of maximum absorption (λmax) was found to be 268.5 nm. All the ten brands met the British Pharmacopoeia [19] specification of 98.5 % to 101.5 % active drug content as well as the United States Pharmacopoeia specification of 95.0 % to 105.0 % which is a wider range.

5. CONCLUSION

Purchasing substandard brands could result in poor clinical outcome and threat to life; hence, there is need for regular monitoring of drugs as a way of improving surveillance. In the research work, all the brands passed the weight uniformity test having percentage deviation of less than 7.5 %. All the ten (10) brands passed the crushing test as they gave crushing value within the required range (4-10 kg/cm^2). Also, all the ten (10) brands passed the friability test as they had weight losses of less than 1 %. Considering the USP specification all the tested brands disintegrated within the prescribed time limit of 30 minutes. On the other hand, going by BP specification brand I failed the disintegrations test having time limit greater than fifteen (15) minutes. For dissolution, only brand J met the specification of not less than 80 % of the labelled amount at 30 minutes when 0.1 N HCl was used as the dissolution medium whereas all the brands, except F (72 %), complied when distilled water was used as the dissolution medium. Also, brand I can be considered bioequivalent to the innovator brand (brand B) because it gave f1 and f2 values that are within the required range. The quantitative assay results showed that all the ten brands met the British pharmacopoeia specification for drug content of the range 98.5 % to 101.5 % as well as the United States pharmacopeia specification of the range 95.0 % to 105.0 %.

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Conflict of Interest
There is no conflict of interest among the authors.

Contribution of the Authors
Author ACI designed the work and supervised IEM who did the bench work. Author APE worked out the f1 (differential factor) and f2 (similarity factor) value and assisted in preparing the manuscript. Authors ACI and IEM collaborated in providing the references. Author ACI wrote the final manuscript.

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