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Quality Assessment of Various Brands of Lisinopril Tablets sold in Uyo Metropolis using UV Spectrophotometry

Arnold C. Igboasoiyi *, Amarachi P. Egeolu and Blessing Godwin Amos

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Uyo, Uyo, Akwa Ibom State, Nigeria.

Lisinopril is an angiotensin-converting enzyme inhibitor (ACEI) used for the management of hypertension. The danger of use of substandard and/or fake lisinopril tablets for management of hypertension cannot be over-emphasised. It will lead to negative treatment outcomes. This necessitates the quality assessment of the different brands of lisinopril marketed and the provision of simple and cost-effective method of assay that will encourage regular and quick sampling. Ten brands of lisinopril tablets were qualitatively assessed for uniformity of weight, friability, hardness, disintegration and dissolution rate using standard physical methods. Quantitative assay was carried out using spectrophotometric method. The spectrophotometric measurement was done at a wavelength of 340nm. Seven brands met the official requirements for uniformity of weight; eight passed the friability test and the hardness tests. All the brands tested passed the disintegration test while only four brands passed the dissolution test. The calibration curve for reference lisinopril in methanol was linear over a concentration range of 0.00-0.1µg/ml. The variation of absorbance with concentration showed correlation with coefficient of correlation (r) of 0.994 and coefficient of determination (r^2) of value 0.985. Seven brands passed the British Pharmacopoeia (BP) requirement for percentage drug content of lisinopril (92.5-105.0%). The assay method used in this study is reliable, simple and cost-effective and can be routinely used to assay lisinopril tablets.

Keywords: Lisinopril, antihypertensive, methanol, spectrophotometric assay.

INTRODUCTION

Lisinopril is an oral long-acting angiotensin-converting enzyme inhibitor used in the management of high blood pressure, heart failure and acute myocardial infarction. It was introduced into clinical therapy in the late 1980s after it was synthesised by structural modifications of enalaprilate and found to be useful in the management of high blood pressure (Menard and Patchett, 2001). It is known to be particularly useful in diabetic co-morbidities for the management of diabetic nephropathy (Arauz-Pacheco *et al*., 2002; Lüscher *et al*., 2003; Gross *et al*., 2005) and has an insulin-sensitivity-enhancing effect when given together with antidiabetic agents (Lüscher *et al*., 2003). It acts by suppressing the renin-angiotensin-aldosterone system through inhibition of the angiotensin converting enzyme which catalyses the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor and also stimulates aldosterone secretion by the adrenal cortex (Atlas, 2007; Katzung and Bertram, 2012; Noro *et al*., 2018). It is safe for administration in hypertensive children of 6 years and older (Soffer *et al*., 2003; Hogg *et al*., 2007; Lurbe *et al*., 2009). It is available in different brands and different doses of 2.5mg, 5mg, 10mg and 20mg. It is also available in fixed-dose combinations with hydrochlorothiazide. Lisinopril exists in an anhydrous form with the chemical formula $C_{21}H_{31}N_3O_5$ and the dihydrate form with the chemical formula $C_{21}H_{31}N_3O_5.2H_2O$. It is a white/off-white crystalline odourless hygroscopic powder. It is soluble in water, less soluble in methanol and insoluble in ethanol and most other organic solvents. It is slowly and incompletely absorbed enterally and reaches a peak plasma concentration after about 7 hours. It is not significantly bound to plasma proteins. It is excreted unchanged in urine. It has a half-life of about 12 hours in patients with normal renal function. As with ACE inhibitors, lisinopril is contra-indicated in pregnancy (Wikipedia, 2019; Astra Zeneca, 2008). Common side effects associated with lisinopril therapy include hypotension, angioedema, dizziness, fatigue, headache, cough, skin rash and gastrointestinal upset. Excessive hypotension can occur when lisinopril is used with diuretics, other antihypertensive drugs and alcohol. Non-steroidal anti-inflammatory drugs have been reported to reduce or abolish the hypotensive action of lisinopril (Brown, 2000; Fogari *et al*., 2002, Norman *et al*., 2013). Lisinopril is manufactured and distributed by different companies under various brand names. Therefore, there is a high probability of purchasing a substandard brand.

This could be as a result of failure of the entire manufacturing process or the use of substandard raw materials and can result in poor patient clinical outcomes.

*Corresponding Author: Tel: +2348033228771; Email: igboasoiyiarnold@yahoo.com

The results of consuming falsified, substandard or counterfeit drugs could be devastating (Ubajaka *et al.*, 2016). There is a need to ascertain that every drug product meets the Pharmacopoeia standards so as to ensure optimal clinical outcomes. Counterfeit drugs are a global problem with significant and well documented consequences for global health and patient safety, including drug resistance and patient deaths (Mackey and Liang, 2011). Regular monitoring of drugs in circulation is one way of improving surveillance (Igboasoiyi *et al*., 2018). It serves as a means for post market surveillance which is essential to ensure products quality. This monitoring could be encouraged by provision of simple, easy to use, accurate and reproducible analytical assay procedures.

EXPERIMENTAL

Materials: Ten different brands of lisinopril 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. Extraction of pure lisinopril: Ten tablets of the innovator brand J were pulverized and extracted using 100ml methanol, filtered and the solvent evaporated. The residue was recrystallized using chloroform:methanol mixture ($1:1^{v}/_{v}$) to obtain pure lisinopril (Olalowo *et al.*, 2015). This was subjected to melting point identification. Weight Analysis: Twenty tablets of each brand were randomly selected and weighed individually using electronic weighing balance (Shimadzu, Japan). The mean weight, standard deviation and percentage deviation of each brand were calculated.

Friability Test: Five tablets of each brand were randomly selected and weighed together to obtain weight Wo. Each brand was subjected to friability test in a Roche friabilator at 25 revolutions per minute for 4 minutes after which each batch was reweighed to obtain weight W. The weight loss and percentage weight loss were calculated.

Hardness Test: Five tablets of each brand were randomly selected and each tablet subjected to crushing force using a Mosanto hardness tester. The average pressure at which each brand crushed was calculated.

Disintegration Test: Five tablets of each brand were randomly selected and put in a digital tablet disintegration test apparatus using 900mL distilled water as the disintegration medium at a bath temperature of 37^{o}C. The time taken for each brand to disintegrate completely was recorded.

Dissolution Test: The dissolution profile of each brand of ciprofloxacin was measured according to the method described in the British Pharmacopoeia (2008) using a digital tablet dissolution apparatus in 900mL of 0.1N HCl at 37^{o}C.

Spectroscopic assay: Pure sample of lisinopril (10mg) was dissolved in 10mL of methanol to obtain a standard solution of lisinopril. 5mL of the lisinopril standard solution was transferred into a 10mL measuring cylinder, made up to mark using methanol and the resulting solution scanned in a UV-Vis Spectrophotometer at wavelength range of 200-420nm to obtain the wavelength of maximum absorption (λmax) which was found to be at 340nm.

Aliquots of the lisinopril standard solutions (0.02mL, 0.04mL, 0.06mL, 0.08mL and 0.1mL) were transferred into 5mL volumetric flasks and made up to mark using methanol. The absorbance of each concentration was measured at the λmax of 340nm against a reagent blank of methanol to obtain the calibration curve of lisinopril. Twenty tablets of each brand of lisinopril were pulverised and portions equivalent to 20mg of drug extracted with 50mL of methanol and their respective absorbance measured at 340nm against the reagent blank. These were extrapolated on the standard curve to obtain the respective extrapolated concentrations. The percentage recoveries were obtained by comparing the extrapolated concentrations with the expected concentrations.

RESULTS AND DISCUSSION

The melting point of the compound extracted from the innovator brand of lisinopril was found to be 146^{o}C. This figure corresponded to the literature value of the melting point of lisinopril.

Uniformity of weight is an indication of adherence to Good Manufacturing Practice during the granulation and compression stages. British Pharmacopoeia (2008) specification for uniformity of weight of uncoated tablets is 5% deviation of each tablet from the mean value. Seven brands complied with the British Pharmacopoeia specification for uniformity of weight of uncoated tablets (Table 1). Friability measures the resistance of tablets to abrasion and evaluates the conditions that the tablets will be exposed to during transportation. Good friability property ensures tablets do not chip during transportation as a result of abrasion and is an evidence of a good finished product. It is expected that a batch gives a weight loss of less than 1%. Eight brands passed the friability test as they had a weight loss of less than 1% (Table 2). Crushing/hardness test measures the ability of tablets to withstand handling without chipping which can influence friability and

disintegration. The harder a tablet is the less friable with longer disintegration time, and vice-versa. A crushing force of between 4 Kg/cm^2 and 10 Kg/cm^2 is the recommended requirement. Eight brands passed the crushing test as they gave crushing value within the required range (Table 3).

Disintegration is a crucial test for immediate release oral dosage forms because the rate of disintegration affects the dissolution and subsequently absorption of the drug. The presence of suitable disintegrants in adequate proportions ensures the production of tablets which are free from disintegration problems (Jantratid *et al*., 2008). The British Pharmacopoeia (2008) specifies that uncoated tablets should disintegrate within 15 minutes and film coated tablets disintegrate within 30 minutes. All the tested brands disintegrated within the prescribed time limit (Table 4). Dissolution test is used to determine the rate of release of oral dosage forms. It is a necessary criterion for determination of drug bioavailability. It serves as a useful tool in assessing the probable *in vivo* performance of a drug as well as in identifying unacceptable and substandard drug products (Shah, 2001; Jaman *et al*., 2015). The British Pharmacopoeia (2015) specifies at least 85% dissolution in 30 minutes for uncoated tablets. Four brands (B, C, E and H) passed the British Pharmacopoeia specification for dissolution rate (Figure 2). Incidentally, the innovator product failed the dissolution rate test, underlining the justification for post-market surveillance.The calibration curve for the extracted pure sample of lisinopril was linear over a concentration range of 0.02 to 0.1 ug/mL with the regression line equation obtained as y = 1.3743x + 0.0036 which is in conformity with Beer Lamberts Law (Figure 3). From the assay results only seven out of the ten brands (70%) met the British Pharmacopoeia (B.P, 2015) specification of 92.5 % to 105.0 % active drug content. However, applying United States Pharmacopoeia specification of 90.0-110.0% (USP, 2014), which is a wider range; nine out of the ten brands (90%) passed the test (Table 5). Igboasoiyi *et al*. (2018), observed the need to harmonise BP and USP specifications on content of active ingredient(s).

CONCLUSION

Post-market surveillance is very crucial to assure that dosage forms meet the required standards so as to ensure effective clinical outcomes. The assay method adopted in this study can be routinely used for quick post-market surveillance of lisinopril as it is simple, cost-effective and reproducible.

Table 1: Weight uniformity analysis of different brands of lisinopril tablets

Sample	A	B	C	D	E	F	G	H	I	J
Mean weight(mg)	100.1	176.4	215.1	218.5	120.6	222.0	204.95	220.6	163.3	215.0
SD (n=10)	±1.87	±26.8	±1.5	±2.1	±20.6	±1.5	±1.32	±2.6	±27.1	±1.1
% Deviation	1.87	26.8	1.5	2.1	20.6	1.5	1.32	1.2	27.1	0.5

Permissible percentage deviation is 5%

Table 2: Friability analysis of different brands of lisinopril tablets

Sample	A	B	C	D	E	F	G	H	I	J
W_0(g)	0.880	0.786	1.063	1.079	0.922	1.109	1.044	0.787	0.735	1.067
W(g)	0.520	0.782	1.055	1.078	0.562	1.107	1.043	0.783	0.731	1.066
W_0-W	0.360	0.004	0.008	0.001	0.360	0.002	0.001	0.004	0.004	0.001
% Weight loss	40.91	0.51	0.75	0.09	39.04	0.18	0.09	0.51	0.54	0.09

Permissible percentage weight loss is 1%

Table 3: Hardness analysis of different brands of lisinopril tablets

Sample	A	B	C	D	E	F	G	H	I	J
Average crushing strength (Kg/cm^2)	4.78	4.04	4.04	5.36	4.00	7.40	3.60	4.58	2.84	4.84

Permissible crushing strength is 4-10 Kg/cm^2

Table 4: Disintegration analysis of different brands of lisinopril tablets

Sample	A	B	C	D	E	F	G	H	I	J
Mean disintegration time (min)	2.37	0.75	0.65	0.30	0.62	1.07	0.50	0.98	0.50	0.05

Permissible disintegration time is <15 minutes

Table 5: Percentage recovery of lisinopril tablets

Sample	A	B	C	D	E	F	G	H	I	J
(%)	101.2	90.2	102.2	101.0	98.0	94.8	89.8	92.3	94.4	96.2

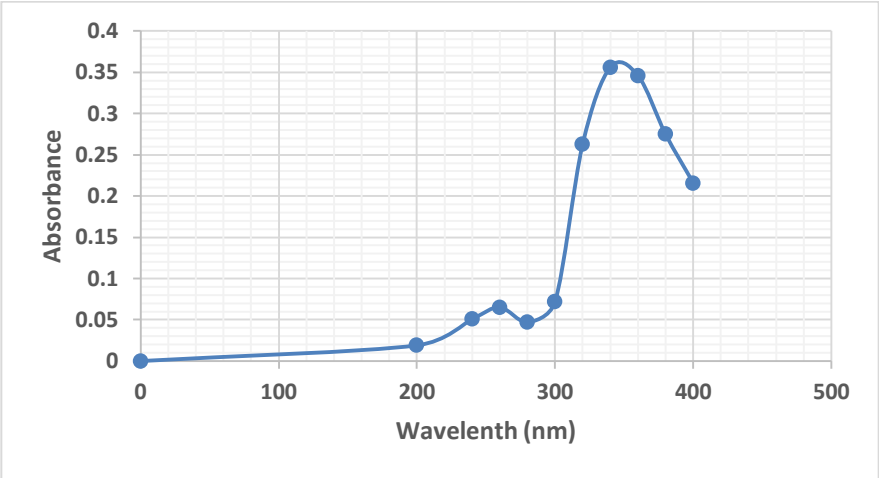

Figure 1: Absorbance spectrum of lisinopril

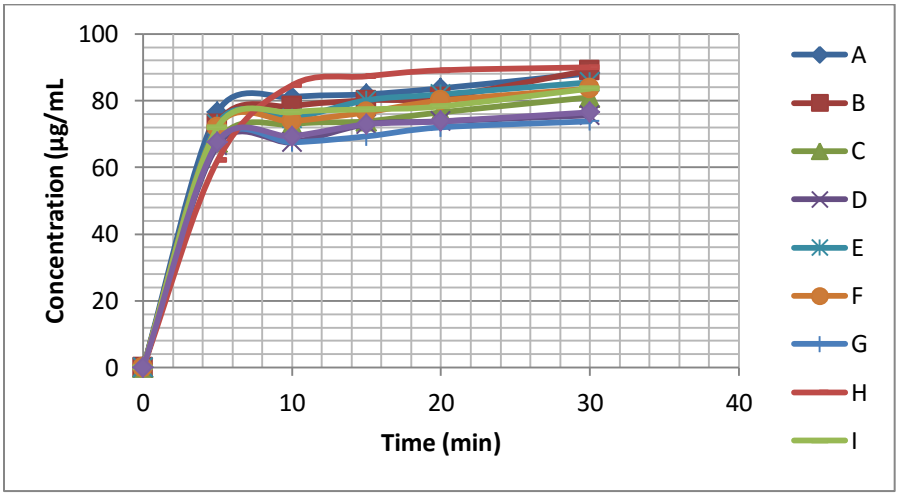

Figure 2: Graph of dissolution test results of different brands of lisinopril tablets

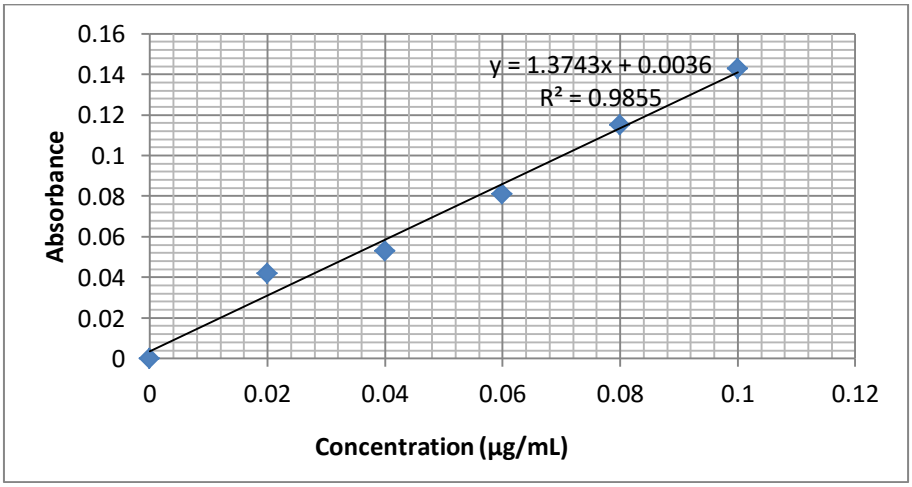

Figure 3: Calibration curve of lisinopril.

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