Comparative quality assessment of some brands of lisinopril tablets marketed in Lagos, Nigeria

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ABSTRACT

Background: Cardiovascular diseases (CVDs) are number one cause of death across the globe and some classes of drugs are used in its management and treatment. Lisinopril, an angiotensin converting enzyme inhibitor is one of the drugs used to manage the scourge. Quite a large number of Lisinopril brands are spread across Nigeria and there has been reports of loss of efficacy from its use.

Objective: This study was embarked upon to assess the quality of the lisinopril tablets through their physicochemical properties.

Methods: Quality assessment parameters such as hardness, friability, weight uniformity, identification, dissolution profile and assay test were performed on the thirteen different brands of Lisinopril 10 mg tablets. The assay of Active Pharmaceutical Ingredient was done using ultra-violet spectrophotometer and high-performance liquid chromatography. Other tests were conducted based on standard methods of United States Pharmacopeia (USP).

Results: All the brands conformed to USP specifications for weight uniformity and friability. 100 % of the brands passed the hardness test in line with manufacturer's specification. Three out of thirteen brands failed the percentage purity test indicating over 70 % conformity with pharmacopeia purity test. 30.8 % of the brands passed the tablet dissolution profile test.

Conclusion: This study has shown that of all the brands of Lisinopril assessed, only four brands conformed to all the physicochemical tests as specified in the pharmacopoeia monograph hence the need for continuous screening of pharmaceuticals in the open market for quality control assessment and regulatory requirements is imperative.

Key words: Lisinopril, Cardiovascular diseases, physicochemical properties, in-vitro release, quality

Évaluation comparative de la qualité de certaines marques de comprimés de Lisinopril vendus à Lagos, Nigéria

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RÉSUMÉ

Contexte: Les maladies cardiovasculaires (MCV) sont la première cause de mortalité dans le monde et certaines classes de médicaments sont utilisées pour leur gestion et leur traitement. Lisinopril, un inhibiteur de l'enzyme de conversion de l'angiotensine, est l'un des médicaments utilisés pour lutter contre ce fléau. Un nombre assez grand de marques de Lisinopril sont répandues au Nigéria et des cas de perte d'efficacité liés à son utilisation ont été signalés. Cette étude a été entreprise pour évaluer la qualité des comprimés de lisinopril à travers leurs propriétés physicochimiques.

Méthodes: Les paramètres d'évaluation de la qualité tels que la dureté, la friabilité, l'uniformité du poids, l'identification, le profil de dissolution et le test de dosage ont été effectués sur les treize marques différentes de comprimés de Lisinopril 10 mg. Le dosage de l'ingrédient pharmaceutique actif a été effectué à l'aide d'un spectrophotomètre ultraviolet et d'une chromatographie liquide à haute performance. Les autres tests ont été réalisés sur la base des méthodes standard de la Pharmacopée américaine (USP).

Résultats: Toutes les marques étaient conformes aux spécifications USP en matière d'uniformité de poids et de friabilité. 100% des marques ont réussi le test de dureté conformément aux spécifications du fabricant. Trois marques sur treize ont échoué au test de pureté en pourcentage, ce qui indique une conformité de plus de 70% avec le test de pureté de la pharmacopée. 30,8% des marques ont réussi le test du profil de dissolution des comprimés.

Conclusion: Conclusion : Cette étude a montré que sur toutes les marques de Lisinopril évaluées, seules quatre marques étaient conformes à tous les tests physicochimiques spécifiés dans la monographie de la pharmacopée. Il est donc impératif de procéder à un contrôle continu des produits pharmaceutiques sur le marché libre pour l'évaluation du contrôle de la qualité et des exigences réglementaires.

Mots-clés: Lisinopril, maladies cardiovasculaires, propriétés physicochimiques, libération in vitro, qualité

INTRODUCTION

About 20% of countries have well developed and operational medicines regulation. Of the rest approximately half have regulation of varying capacity and level of development, and 30 % have either no or very limited medicines regulation. The reality is that many low-income countries cannot ensure the safety, efficacy and quality of medicines circulating on their markets.[1] However, pharmaceuticals must fulfil regulatory requirements on each formulation before it is called a quality drug.[2] The quality of pharmaceutical products can be evaluated using in vitro or in vivo tests. The superiority of medicines is a subject of global worry, particularly in many developing countries. The occurrence of counterfeit drugs in the global market is getting epidemic magnitude with developing countries affected to a greater degree.[3] Most low- and middle-income countries are affected due to poor facilities, inadequate trained personnel and fragile regulatory systems which fail to ensure the equality of medicines and to carry out regular checking for substandard and misleading products. Substandard drugs can be the result of poor manufacturing practices, counterfeiting, or unsuitable drug storage. There are increased number of infirmary admissions and mortality rate due to quality defects of drugs.[4,5] The use of ineffective and inferior drugs risk therapeutic treatment and may result in treatment failure.

Having a huge number of brands in circulation, the health care providers are in a tight spot to pick a suitable brand for the cost-effective treatment with the same effectiveness as that of innovator product. Consistency and reproducibility of a drug product from batch to batch is assured by show of safety and efficacy. Since the use of generic drugs is at lower cost than the innovator brands, great savings in health care payment can be made. Nevertheless, lot of medical doctors have a doubt of quality of generic drugs and their dependability in replacing a particular drug.[6] To reduce the medicines expenditure burden on a health care system, the World Health Organization (WHO) has continuously advocated the use of generic products but this should be supported with sufficient evidence for the substitution of one brand for another. This could not be achieved without proving its efficacy through bioequivalence studies.[7] Thus, the quality, safety, and efficacy of multisource products should be demonstrated together with their possible interchangeability.[8] However, the availability of multisource drugs have been accompanied by the widespread distribution of counterfeit and substandard drug products.[9]

The spread of substandard drugs remains a major problem in developing countries in sub- Saharan Africa, where most of the drugs available are imported. Medicines sold in these markets are often found to contain ingredients at concentrations that are too high or too low.[10] For example, in a study conducted in 10 African countries on drug quality, nearly a quarter of generic antihypertensive medicines were of low quality.[11] In Nigeria, a quality check of an antihypertensive medicine - nifedipine was reported on a total of 14 brands; of 102 samples, 29.3, 74.5 and 76.5% were found to be falsely labelled, substandard and of poor quality respectively.[12]

According to a report on the pharmacopeial quality of medications given by Nigerian pharmacies that was released in 2001, 48% of the pharmaceuticals tested failed the standard set by the pharmacopeial, which serves as the standard for assessing the quality of pharmaceutical preparations.[13] A further study on the effectiveness of antimalarials sold in retail establishments in Tanzania indicated that 12.2% of the samples were ineffective and of inferior quality.[14] This information highlights the significance of maintaining drug quality control to protect the government's system for delivering healthcare to the country's thronging population.

Determining the chemical and biologic equivalence of any medication products is the first step in determining their therapeutic equivalence.[15] The strength, quality, purity, active ingredient release profile and dosage form of a drug product must all be the same for it to be considered chemically and bio pharmaceutically equivalent. To ensure consistent medication release from batch to batch, dissolution testing of pharmaceutical goods is a crucial quality control method to monitor batch to batch consistency of drug release[16] and also for prediction of in-vivo bioavailability in most oral preparations.[17,18]

Most drugs commonly used in management of different cardiovascular diseases are Angiotesin-converting enzyme (ACE) inhibitors. Angiotensin-converting-enzyme inhibitors are a class of medication used primarily for the treatment of hypertension and heart failure. Generally, they are used to lessen cardiac oxygen consumption and lower blood pressure.[19] ACE inhibitors

are frequently the first medication prescribed for the treatment of high blood pressure particularly when diabetes is present. However, as people age, their needs may change, and it is typical to require multiple medications to achieve the desired improvement. Lisinopril is one of the numerous angiotensin converting enzyme inhibitors used in the management of hypertension and other cardiovascular disease conditions. There is high prevalence of Lisinopril generics being marketed in cosmopolitan Lagos, Nigeria and the need to monitor the quality of these brands becomes very critical and imperative.

MA TERIALS AND METHODS

Samples

Thirteen (13) different brands of Lisinopril 10 mg tablets purchased from Lagos drug market areas were labelled as in table 1 and tested for identification, uniformity of weight, hardness, friability, dissolution and assay according to procedures described in United States pharmacopeia[20] and British Pharmacopeia[21].

Table 1: Brands and Codes of the Experimental Drugs

Codes	**Country of make**	**Batch number**	**Manufacturing date**	**Expiry date**
ZTY	India	AF85001	03/2020	02/2024
ZIL	United Kingdom	RP002	07/2020	06/2024
AFB	Nigeria	19208	06/2019	06/2022
LIL	India	F3190	03/2019	02/2022
ZCM	India	ASL-294	08/2021	07/2024
TVA	United Kingdom	S000007	08/2019	07/2022
OAL	India	A19514	08/2019	07/2022
PAX	India	(10)G010653	02/2021	01/2024
FRN	India	AL06107	05/2021	04/2024
SVO	India	GT20264	06/2020	05/2023
PCO	India	XTIH019	08/2021	07/2024
PIL	China	200868	8/2020	07/2023
LAB	India	LIA002	12/2020	11/2023

Uniformity of weight

Metler Toledo® analytical weighing balance was used to weigh twenty tablets of Lisinopril 10 mg from each brand individually. The weight of the twenty tablets were summed to obtain the total weight. The average weight, the deviation and percentage deviation of each tablet from the mean weight were determined per brand.

Hardness test

The tablet hardness was determined using Monsanto® hardness tester. A total of ten (10) tablets were individually placed between the spindle of the hardness tester, and pressure was applied by turning the knurled knot just sufficient enough to hold the tablet in position. The pressure was increased as uniformly as possible until the tablet breaks and the pressure required to break the tablet was read from the instrument and recorded. This was repeated for the remaining 12 brands of Lisinopril 10 mg tablets.

Friability test

The friability of the tablet was determined using Erweka® friabilator. A total of ten (10) tablets were weighed together and transferred to the friabilator which was operated at 25 revolutions per minute for 4 minutes; making a total of 100 revolutions, dropping the tablet at height of 6 inches in each revolution. After 4 minutes, the tablets were removed, dusted and weighed together again. This procedure was repeated for the remaining brands.

Preparation of lisinopril standard stock solution and construction of calibration curve for HPLC Analysis

Lisinopril reference standard (10 mg) was weighed into a 10 mL volumetric flask and dissolved with the diluent [water: methanol, 4:1] to the mark to obtain a concentration of 1.0 mg/mL stock solution. Gradient concentrations (50-400 µg/mL) were prepared and injected into the HPLC to obtain calibration plot and regression equation.

Chromatographic conditions

Chromatographic analysis was done using Agilent Technologies® HPLC 1200 series, Binary pump, micro-vacuum Degasser, Standard and Preparative Autosampler, Thermostated Column Compartment, Diode Array and multiple Detector with ChemStation software. The Column used was Agilent® Eclipse XDB-C18, 4.6 x 150 mm, 5µm diameter particle size. The mobile phase was 0.1 % hexane-sulfonate in 30 mM KH2PO4 (pH 2.0) in and acetonitrile (80:20). The mobile phase was filtered through a 0.45µm membrane filter, then de-aerated ultrasonically prior to use. The flow rate, injection volume and wavelength were 1.0 mL/minute, 20 µL and 215 nm respectively.

Identification of lisinopril in the tablet brands

Lisinopril standard (200 µg/mL) prepared in the diluent and same strength was also prepared from each of the brands of Lisinopril tablets. For identification and authentication, the retention time of lisinopril in the reference standard was compared with that of the lisinopril in tablets.

Preparation of lisinopril from tablet samples for HPLC analysis

Lisinopril tablets (20) was weighed together and average weight was calculated. An equivalent weight of Lisinopril 10 mg was weighed and dissolved in 10 mL volumetric flask with the diluent. The resulting solution was sonicated, filtered with 0.45 µm syringe filter and 200 µL of the filtered solution was made up to 1000 µL to obtain 200 µg/mL of Lisinopril in sample brand. The sample was injected into the HPLC to obtain the peak area. The equivalent concentration was obtained from the regression line from calibration plot. This process was repeated on the remaining brands.

Preparation of lisinopril standard stock solution for assay of dissolution samples using UV spectrophotometer

Lisinopril standard (10 mg) was accurately weighed and transferred into a 100 mL volumetric flask. This was dissolved and made up to mark with 0.1N HCl solution to prepare a stock solution of 0.1 mg/mL. Gradient concentrations (1.25 - 15 µg/mL) were prepared for the calibration plot and quantified using ultra-violet spectrophotometer at 210 nm wavelength. The absorbance of each concentration was taken and a graph of absorbance against concentration was plotted to obtain the regression equation.

Dissolution profile studies

This was carried out using ElectroLab® dissolution tester coupled with paddle (USP apparatus II) vessels bathed in a water bath and operated at 37^{O}C and 50 revolutions per minute. Dissolution studies were carried out in 900 mL medium; 0.1 N Hydrochloric acid. Dissolution samples (5 mL) was withdrawn at predetermined sampling time interval of 5, 10, 15, 30, 45 and 60 minutes and 5 mL of

blank 0.1N HCl solution was replaced in order to maintain sink condition. Each 5 mL sample was filtered with a Millipore syringe filter (0.45 µm). The collected samples were analysed using UV spectrophotometer. The actual concentration of Lisinopril in the predetermined sampling time interval for each of the 13 brands were determined using the regression equation obtained from the calibration curve.

Statistical analysis

The results obtained were expressed as a mean value ± standard deviation calculated using Microsoft excel 2010 software. The results obtained were compared with compendia specifications.[20,21]

RESULTS

All the brands tested passed the uniformity of weight, Hardness and friability tests in accordance with pharmacopoeia specifications. The calibration plot equations used for estimation of assay of the tablets and that of dissolution samples are y = 11.535x and y = 0.0555x + 0.0421 with coefficient of determinations (R^2) 1.000 and 0.9969 respectively where y is peak area or absorbance and x is the concentration. Both calibrations showed perfect correlation between the concentrations prepared and the responses being measured. Ten out of the thirteen brands passed the assay of the active pharmaceutical ingredient while nine failed the dissolution release test at 30 minutes as show in Table 2. The retention time of Lisinopril in standard preparations gave a retention time of 3.487 minute while lisinopril found in the tablet samples was eluted at retention time of 3.483 minute as shown in figures 1a and 1b. These chromatograms authenticated the presence of lisinopril in the tablet of the examined brands as found in the lisinopril standard. Figure 2 represents the dissolution profiles of the thirteen brands of lisinopril tablets used. Only 4 brands (AFD, LIL, OAL and PCO) out of thirteen conformed to the dissolution tolerance of not less than 80 % of lisinopril dissolved in 30 minutes.

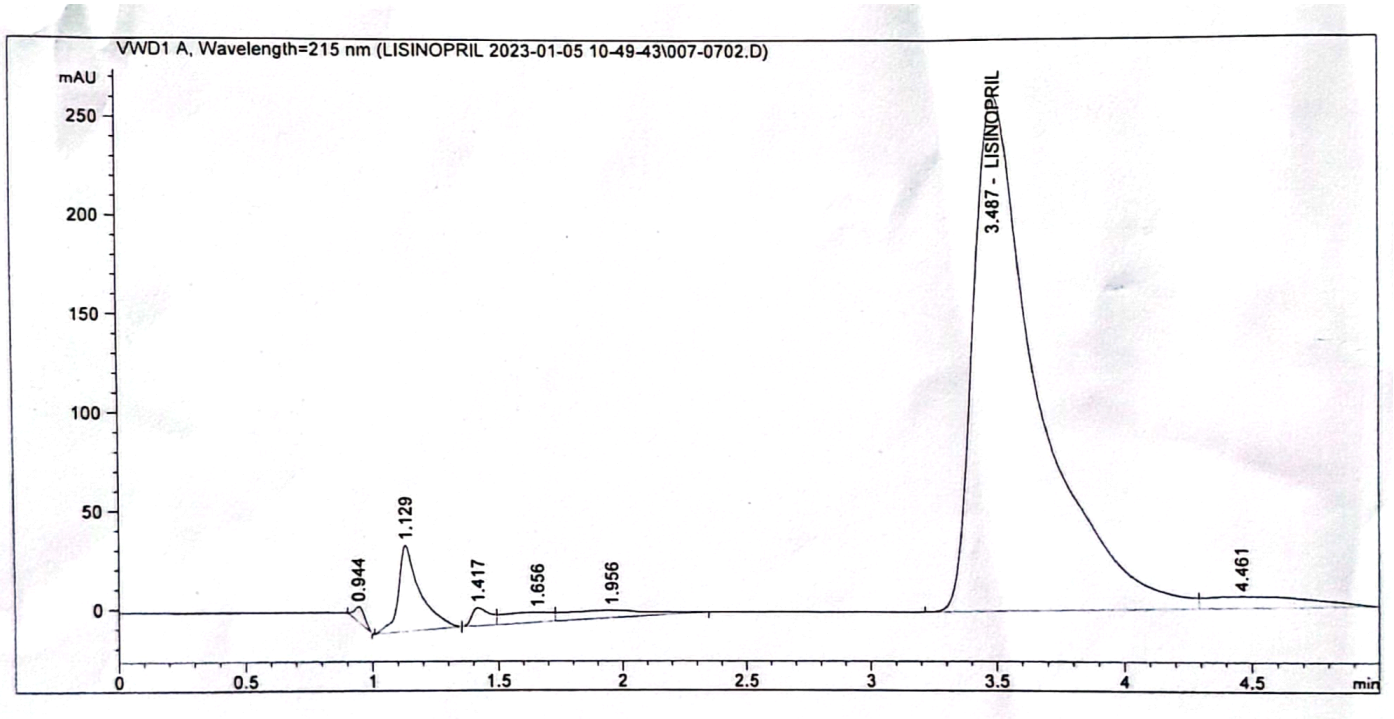

Figure 1a: Chromatogram of lisinopril standard with retention time of 3.487 minute.

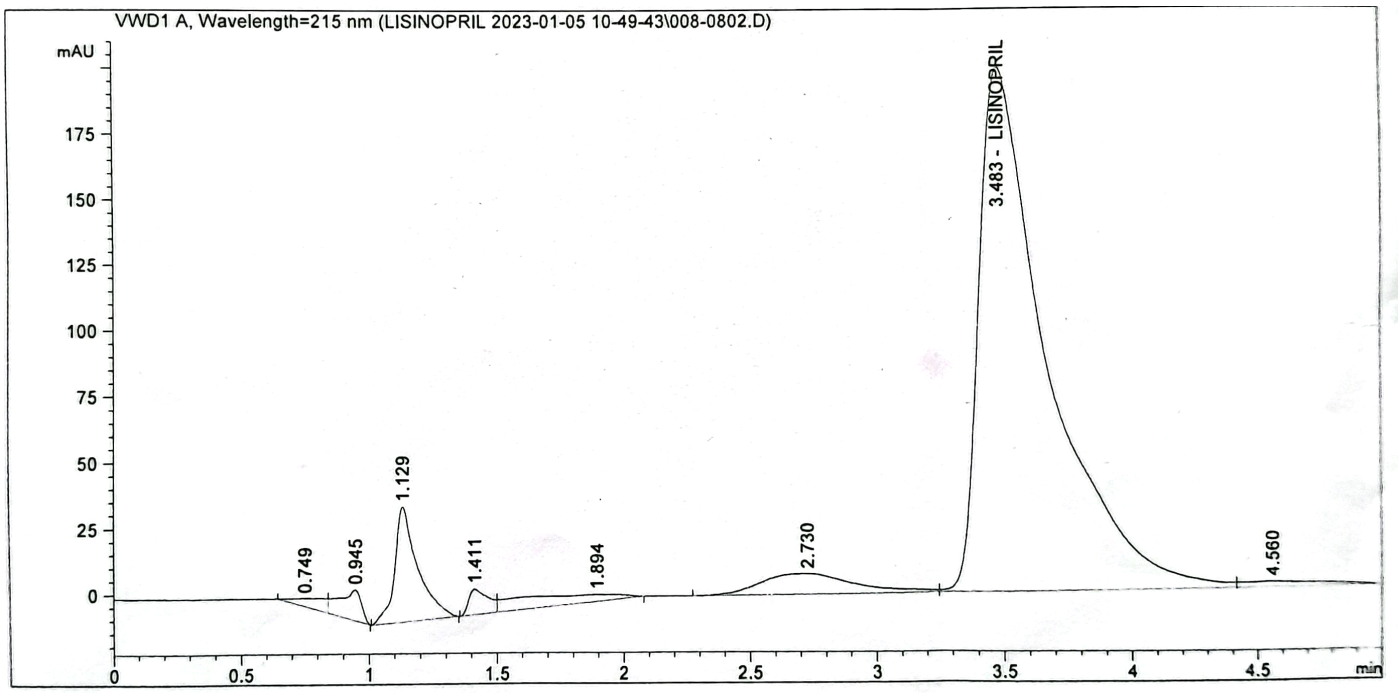

Figure 1b: Chromatogram of lisinopril in one of the tested tablet brands showing retention time of 3.483 minute.

Table 2: Summary of physicochemical characteristics of the tested brands

Code for Brands	Weight Uniformity % Deviation n=20	Hardness KgF n=10	Friability % n=10	Assay % (HPLC) n=20	Dissolution % 0.1N HCl, t=30 mins n=3
ZTY	0.96 ± 0.54	0.93 ± 0.35	0.121	108.54	70.1
ZIL	0.79 ± 0.60	0.98 ± 0.40	0.154	99.99	68.9
AFB	2.12 ± 1.21	0.92 ± 0.35	0.085	108.49	80.0
LIL	1.07 ± 0.75	2.3 ± 0.44	0.456	63.94	105.8
ZCM	1.97 ± 0.81	3.0 ± 0.55	0.063	105.35	68.9
TVA	0.78 ± 0.69	1.48 ± 0.28	0.334	112.95	74.5
OAL	1.40 ± 1.47	1.38 ± 0.18	0.043	102.81	80.0
PAX	1.13 ± 0.70	1.55 ± 0.31	0.062	109.13	65.5
FRN	1.92 ± 1.36	1.65 ± 0.24	0.052	108.50	76.0
SVO	1.77 ± 1.20	0.4 ± 0.13	0.046	68.83	68.6
PCO	0.78 ± 0.74	1.15 ± 0.17	0.207	109.24	102.0
PIL	1.12 ± 1.15	3.15 ± 0.41	0.005	54.03	75.0
LAB	0.89 ± 0.54	2.18 ± 0.21	0.058	92.73	75.0

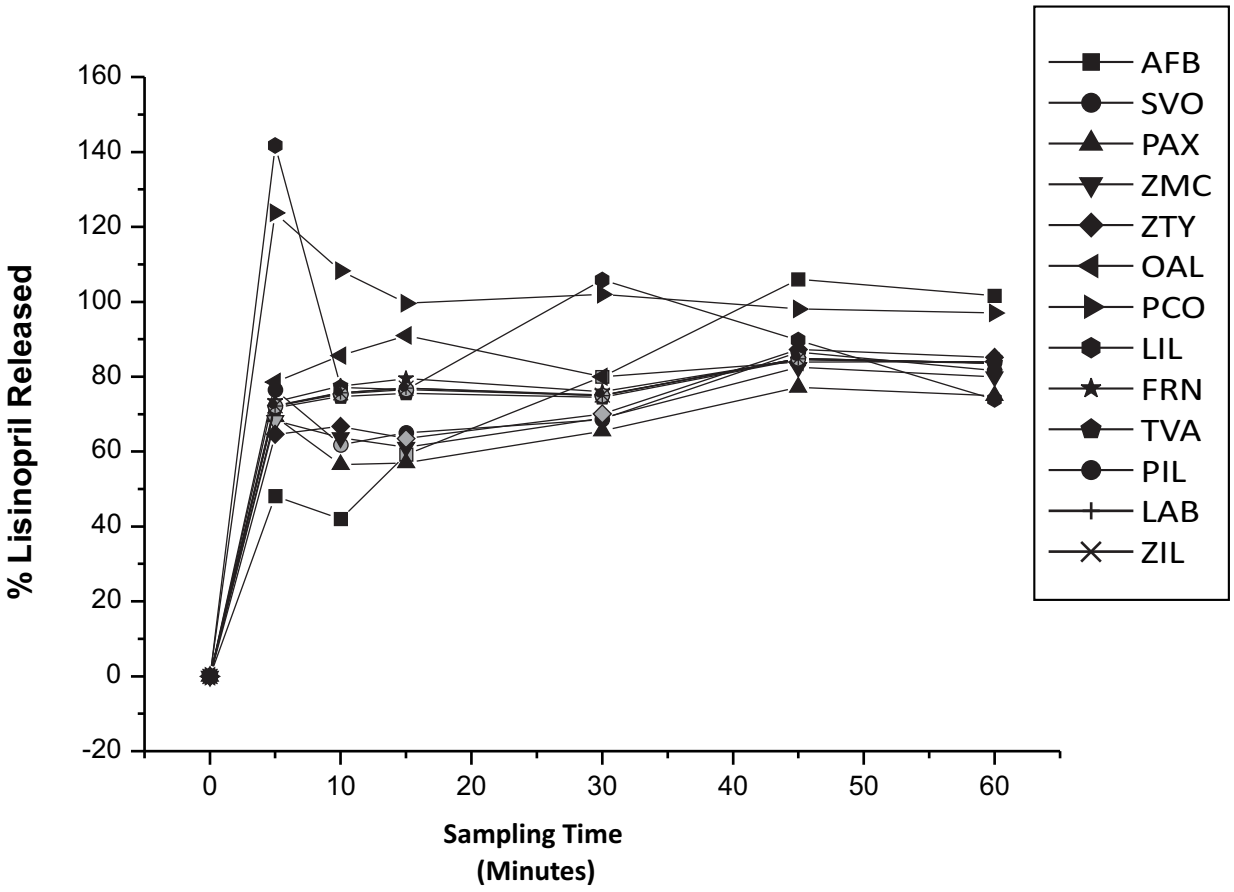

Figure 2: Dissolution profile plots for lisinopril tablet brands

DISCUSSION

Nigerian health experts are worried over the influx of fake and substandard drugs into the country, which they complain is endangering the public's health. Dr Dora Akunyili, one time, director general of the National Agency for Food and Drug Administration and Control, said that fake drugs are responsible for the growing number of cases of hypertension, heart failure, stroke, and other illnesses in Nigeria.[22] So, to lower the chance of having low-quality medicines in the supply chain, it is crucial to continually evaluate the quality of the medicines that are currently being marketed. In this study, we evaluated the pharmaceutical quality of popular brands of lisinopril tablets detailed and marketed in the Lagos, Nigeria. To ensure that pharmaceuticals or medicines are safe, effective, and potent when they reach patients, assessment of the brand quality are done using standard procedures.[23] In this study several quality control tests were performed on all lisinopril brands to evaluate their *in-vitro* release profiles as well as other quality tests such as uniformity of weight, friability, hardness, and assay of lisinopril, the active pharmaceutical ingredient.

Tablet weight homogeneity is guaranteed by strict adherence to Good Manufacturing Practice (GMP) during the granulation and compression steps. None of the tablets' weights varied by more than 10%, as required by the US pharmacopoeia,[20] proving that all were consistent and in line with the approved requirements. This suggests that the active pharmaceutical ingredient and excipients are distributed fairly and with little variation among the manufactured tablets.

The results obtained from the friability test indicates 100 % conformity as none of the tablets lost more than 1.0 % of their weight, demonstrating that they could all withstand abrasion and be transported without losing tablet integrity. This means that the tablets will be physically stable despite the abrasive forces that may be encountered during handling. Strip packaging, dispensing from bulk packs, and other conditions that could cause the tablets to rub against one other are examples of such tensions. As a result, neither the

refinement nor the general appearance of the tablet, nor its integrity in terms of the active medicinal component content, will be compromised.

Even though the hardness test is not a pharmacopeial method for evaluating tablet quality, it is nonetheless useful in assessing the integrity of tablet dosage form. Tablet hardness should be within limits since soft tablets, with hardness ranges below limits, will not tolerate handling during packing and shipping activities during their shelf life.[24] Significant changes in machine speed, excessive binding agent and changes in particle size distribution of the granulation mix are all factors that might affect tablet hardness. During hardness testing, tablet size, shape, and orientation in the tester can all alter the measured hardness value for a particular formulation. All the brands are in consonant with the manufacturer's specification limit.

The dissolution profile test is a measure of the amount of drug released into the dissolution medium over a predetermined time. It is a standard method used to measure the batch-to-batch conformity of oral dosage forms and can also predict bioavailability. The dissolution was carried out using USP paddle method to measure the amount of the active ingredient released into the dissolution medium at different time interval. Of all the thirteen brands tested for dissolution, only four passed by having percentage lisinopril release that are not less than 80 % dissolved at 30 minutes indicating over 60 % dissolution failure. Products LIL and PCO had a fast rise in release of over 100 % within 6 minutes of the dissolution. Over 76 % of the brands passed the assay test in line with percentage purity specified by United States Pharmacopeia limit of not less than 90 % and not more than 110 % of the label claims.[20] Pharmaceutical product assay is a vital quality parameter required to validate that the labelled amount of drug is present in a specific dosage form, and failure to achieve the standard will result in poor quality medicines. Inadequate amounts of Active Pharmaceutical Ingredient (API) will result in under-dosed medication, leading to poor treatment outcomes while excessive amounts of API cause over-dosage of medication, leading to increased adverse drug reactions and treatment failure.

CONCLUSION

All the 13 brands of Lisinopril assessed passed uniformity of weight, hardness and friability tests while 10 and 4 brands passed assay and dissolution tests respectively. In all, only four brands can be said to have fulfilled all the pharmacopeia standards and can be used as substitutes for innovator product.

The authors declare no conflicts of interest.

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