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(RESEARCH ARTICLE)

Physicochemical analysis and quality assessment of Lisinopril oral formulations used in the management of hypertension

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Abstract

Background: Hypertension (HT) is one of the primary causes of death worldwide, accounting for 13% of all deaths. Most cardiovascular disease (CVD) outbreaks in Africa are driven by hypertension, although global detection, awareness, treatment, and control rates are low.

Aim: the study aimed to analyze the physicochemical parameters and quality assessment of different brands of Lisinopril.

Method: Five (5) brands of Lisinopril oral tablets (10mg) were purchased and coded LSP1, LSP2, LSP3, LSP4, and LSP5. Different test including **w**eight uniformity, standardizations, extraction, titrimetric (aqueous and non-aqueous) analysis, and quality determination of all the brands was conducted using standard procedures outlined in the United States Pharmacopoeia (USP).

Result: All brands of Lisinopril used in the analysis conformed to the weight uniformity test. LSP1 conformed to the standard purity range in aqueous titrimetric analysis (98.5%), while the other brands had a close percentage but did not fall within the stated standard with a percentage purity of 82.2% (LSP2), 75.5% (LSP3), 87.1% (LSP4), and 75.6% (LSP5), respectively. For the non-aqueous titration, LSP 1 and LSP 2, conform to the standard percentage purity outlined in the USP, with 100.65% (LSP1), and 97.55% (LSP2). The brands had a percentage purity of 72.78% (LSP3), 88.26% (LSP4), and 88.26% (LSP 5), respectively.

Conclusion: the method used in this study can be easily employed in the quality assessment and physicochemical analysis of solid dosage formulations commonly utilized by patients because it is rapid, efficient, cost-effective, less technical and reproducible.

Keywords: Lisinopril; Percentage purity; Quality assessment; Physicochemical parameters

1. Introduction

A sustained increase in arterial blood pressure (diastolic and/or systolic) equal to or higher than 140/90mmHg (140/90mmHg) in an adult aged 18 years or older is described as hypertension. The Blood Pressure (BP) goal for the overall population of adults aged 60 years or more (60 years) without diabetes or chronic kidney disease is less than 150/90mmHg and less than 140/90mmHg (140/90mmHg) for an adult aged less than 60 years (60 years), according to the eight Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC8) reports

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(Okwuonu *et al.*, 2015). The blood pressure goal of a general population of all ages with diabetes and absence of chronic kidney disease is a blood pressure less than 140/90mmHg (<140/90mmHg) and blood pressure less than 140/90mmHg (140/90mmHg) also for a general population of all ages and races with chronic kidney disease present with or without diabetes (Nicholas, Vaziri, & Norris, 2013; Passarella *et al.*, 2018).

The prevalence of hypertension varied from 2.8% to 13.9% for males and 0.5% to 12.7% for women in studies that used the BP benchmark of 160/95mmHg. The basic occurrence rate of hypertension ranged from 6.2% to 48.9% for males and 10% to 47.3% for females in studies that used the BP benchmark of 140/90mmHg. Regardless of the BP benchmark, males had higher overall actual prevalence rates than females (22 studies found higher prevalence in males in comparison to females, while 11 studies found higher prevalence in females compared to males). More research, however, indicated that females had a higher actual frequency than males based on the BP benchmark of 160/95mmHg (Akinlua *et al.*, 2015).

Pharmacological or pharmacotherapy is the mainstay of hypertension care, as it reduces the risk of cardiovascular disease, renal illness, cerebrovascular disease, and overall death of hypertensive patients. However, identifying the most suitable blood pressure targets, particularly for those aged 60 and above, has shown contentious positive outcomes in hypertensive management (Qaseem *et al.*, 2017). The argument over the target systolic blood pressure (SBP) for persons with hypertension has heated up, especially in light of recent recommendations. Furthermore, while choosing BP objectives for persons aged 60 and above, healthcare providers must consider comorbid diseases that may influence treatment choice (Saiz *et al.*, 2018). The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) cooperated to develop clinical recommendations for hypertension treatment in adults aged 60 and older, based on the benefits and harms of higher versus lower BP targets (Qaseem et al., 2017). Hypertension is treated using angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, calcium channel blockers, beta blockers, selective alpha-blockers, and other medications (Nguyen *et al.*, 2010; Wright, Musini, & Gill, 2018). An oral long-acting ACE inhibitor, lisinopril, is a lysine-derivative of Enalprilate with similarities in structure to its substrate. It differs from captopril in that it lacks the sulfhydryl group. The chemical formula for lisinopril is (*S*)-1-[N2(1-carboxy-3-phenyl propyl)-L-lysyl]-L-proline-dihydrate (Acharya *et al.*, 2003).

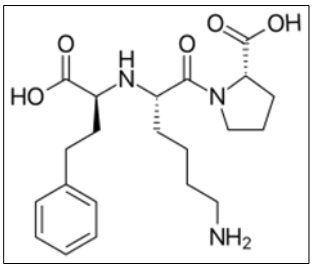

Figure 1 Structure of Lisinopril

Lisinopril has a molecular weight of 441.52g and a molar mass of 40.488 g/mol. It is soluble in water, methanol, and almost insoluble in ethanol, acetone, acetonitrile, and chloroform (Gul et al., 2017). Lisinopril promotes natriuresis in type II diabetes patients and is useful in preventing diabetic retinopathy. It takes approximately 1-2 hours to onset of action after oral administration, that last for about 24 hours. It's absorption in the GIT is gradual and moderate, with a peak plasma concentration after 7 hours. There are no pharmacological or food interactions. Drug dispersion can be as high as 25%. It is completely removed in the urine. The drug's bioavailability is about 25% (Goa *et al.*, 1997).

The assay method for any drug is very important for pharmaceutical industries, and it remains preferable to choose and create a simple, least time-consuming, accurate, reliable, and cost-effective method for determining the level of drugs in active pharmaceutical ingredient (API) in pharmaceutical dosage forms and pathological samples like blood, urine, saliva and plasma. Analytical data is used to screen possible medications in biological samples, support formulation studies, assist in the generation of drug syntheses, monitor API in bulk pharmaceuticals and finished products, and test final products, to predict the pharmacokinetic parameters (Naveed et al., 2014). According to previous research, spectrophotometric, atomic absorption, HPLC, and LC-MS methods for lisinopril estimation have been developed (Shah et al., 2017). The official analytical techniques for Lisinopril are potentiometric titration and HPLC. Other spectrophotometric approaches, chromatographic analytical methods such as micellar electrokinetic chromatography and gas-liquid chromatography, fluoroimmunoassay, capillary electrophoresis, radioimmunoassay, and others have been published. The current approaches have drawbacks such as low reliability due to isomerization, decreased

sensitivity, measuring at a lower wavelength, being pH-dependent, being inaccessible, and requiring expertise (Gul *et al.*, 2017).

Falsified and substandard pharmaceuticals are a global health issue, especially in low and middle-income countries (LMICs) with inadequate pharmacovigilance and drug regulatory regimes. Poor quality medications have major health effects, including the possibility of treatment failure, the development of different kinds of resistance, and serious adverse drug reactions, all of which raise healthcare costs and erode public trust in healthcare systems (Kovacs et al., 2014). Medicine products adulteration can harm both the medicine and the patient (Board on Global Health, 2013). Hence, the study aimed to analyze the physicochemical parameters and quality assessment of different brands of Lisinopril in Yenagoa, Bayelsa State, Nigeria.

2. Material and methods

2.1. Sample procurement

Five (5) commercial products (brands) of Lisinopril, labeled to contain 10mg per tablet, except LSP1 from different pharmacies in Yenagoa were purchased and coded LSP1, LSP2, LSP3, LSP4, and LSP5. All experiments were conducted using standard procedures outlined in the United States Pharmacopoeia (USP, 2013).

2.2. Weight uniformity tests

The balance was restored to zero after a clean white paper was placed on it. Twenty LSP1 tablets were chosen at random and weighed individually on an analytical balance, with their weights recorded. The same technique was then followed for LSP2, LSP3, LSP4, and LSP5 tablets, and the mean and standard deviation were computed for each.

2.3. Extraction procedure

Standardized Perchloric acid ($HCLO_4$), and Sodium hydroxide (NaOH) were used for the percentage purity determination. Twenty tablets were weighed and pulverized into fine powder. A portion of the powder equivalent to 100 mg of Lisinopril was accurately weighed and transferred into a 100 mL volumetric flask, and extraction was performed by shaking for half an hour with 50ml of the solvent specified under each method (glacial acetic acid for non-aqueous titration and distilled water for aqueous titration), then made up to volume (100ml) with their respective solvents, mixed well, and filtered using filter paper. The first 20ml of the filtrate was discarded, and the succeeding sample extract solution was submitted to titration.

2.4. Aqueous titration

About 10 ml of LSP1 solution (from the previously prepared 100 ml stock solution) was pipetted into a conical flask, and three (3) drops of colorless Phenolphthalein were added. It was then titrated in the burette with 0.1N sodium hydroxide until a pink tint was detected. The titration was repeated four times, and the average titer value was calculated. The same steps were taken for LSP2, LSP3, LSP4, and LSP5 solutions. The weights and percentage purity were then computed.

2.5. Non-aqueous titration

Pipetting 10ml of LSP1 solution into a conical flask, three (3) drops of crystal violet were added, resulting in a purple tint. It was then titrated with 0.1M Perchloric acid until the hue changed to blue. The titration was repeated four times, and the average titer value was calculated. The same steps were taken for LSP2, LSP3, LSP4, and LSP5 solutions. The weight and purity percentage were then determined.

3. Results

3.1. Uniformity of weight

Table 1 Weight uniformity test of various Lisinopril tablets brands, their respective total weight, average value, and percentage deviation range

Sample	The total weight (g)	Mean weight (g)	Percentage deviation range (%)	No. of tablets deviating by ±5%	NO. of tablets deviating by ±10%

LSP 1	4.56	0.228	-1.32 – 0.88	Nil	Nil
LSP 2	4.44	0.222	-1.80 – 0.9	Nil	Nil
LSP3	2.48	0.124	-3.23 – 4.84	Nil	Nil
LSP 4	2.92	0.146	-2.05 – 2.74	Nil	Nil
LSP 5	3.16	0.158	-1.27 – 3.16	Nil	Nil

Table 2 Titer volume, percentage purity obtained from the aqueous titration of Sample LSP 1 – LSP 5

Sample code	Titer volume (ml)	Milliequivalent (g/ml)	Calculated Weight (mg)	Percentage purity (%)
LSP1	0.6	0.009858	9.858	98.6
LSP2	0.5	0.008215	8.215	82.2
LSP3	0.46	0.007558	7.558	75.6
LSP4	0.53	0.008708	8.708	87.1
LSP5	0.46	0.007558	7.558	75.6

- 405.488g of $C_{21}H_{31}N_3O_5$ = 1000ml 1M NaOH
- 0.405488g of $C_{21}H_{31}N_3O_5$ = 1ml 1M NaOH
- 0.0405488g of $C_{21}H_{31}N_3O_5$ = 1ml 0.1 NaOH
- LSP 1: Calculated weight = 0.0405488 x 0.6 x 0.4052 = 0.009858g = 9.858mg
- Percentage purity = 9.858 mg x 100%/10mg = 98.6%

Table 3 Titer volume, percentage purity obtained from the non-aqueous titration of LSP 1 -LSP 5

Sample code	Titer volume (ml)	Milliequivalent (g/ml)	Calculated Weight (mg)	Percentage purity (%)
LSP1	1.625	0.010065	10.065	100.65
LSP2	1.575	0.009755	9.755	97.55
LSP3	1.175	0.007278	7.278	72.78
LSP4	1.425	0.008826	8.826	88.26
LSP5	1.425	0.008826	8.826	88.26

- 405.488g of $C_{21}H_{31}N_3O_5$ = 1000ml 2M $HCLO_4$
- 0.405488g of $C_{21}H_{31}N_3O_5$ = 1ml 2M $HCLO_4$
- 0.202744g of $C_{21}H_{31}N_3O_5$ = 1ml 1M $HCLO_4$
- 0.0202744g of $C_{21}H_{31}N_3O_5$ = 1ml 0.1M $HCLO_4$
- LSP 1: Calculated weight = 0.0202744 * 1.625 * 0.3055 = 0.010065g/ml = 10.065mg
- Percentage purity = 10.065 mg x 100%/10mg = 100.65%.

3.2. Comparison of results obtained from aqueous and non-aqueous titration

Table 4 Weight and Percentage purity of the Lisinopril brands

Brands	Aqueous titration		Non-aqueous titration	
	Weight(mg)	Percentage purity(%w/w)	Weight(mg)	Percentage purity(%w/w)
LSP1	9.858	98.6	10.065	100.65

LSP 2	8.215	82.2	9.755	97.55
LSP 3	7.558	75.6	7.278	72.78
LSP 4	8.708	87.1	8.826	88.26
LSP 5	7.558	75.6	8.826	88.26

4. Discussion

All brands of Lisinopril used in the analysis conformed to the weight uniformity test, as there was no percentage deviation of the tablets as shown in Table 3.1. No tablet exceeded the required range stated in the United States Pharmacopoeia (USP), which states that not more than one tablet should have a percentage deviation exceeding ±5% and no tablet should have a percentage deviation exceeding ±10%. The purity of all brands was determined. The official percentage purity of Lisinopril oral tablets as stated in BP is between 90% - 110% (USP, 2013). from the analyzed products, LSP1 conformed to the standard purity range in aqueous titrimetric analysis (98.5%), while the other brands had a close percentage but did not fall within the stated standard with a percentage purity of 82.2% (LSP2), 75.5% (LSP3), 87.1% (LSP4), and 75.6% (LSP5), respectively (Table 3.2). This could be an external contaminant or impurities during the experimental procedures (Fahelelbom *et al.*, 2016).

For the non-aqueous titration, LSP 1 and LSP 2, conform to the standard percentage purity outlined in the USP, with 100.65% (LSP1), and 97.55% (LSP2). The brands had a percentage purity of 72.78% (LSP3), 88.26% (LSP4), and 88.26% (LSP 5), respectively (Table 3.3). LSP3, LSP4, and LSP5 all had a percentage purity less than the official range for both aqueous and non-aqueous titration, therefore, falls below the standards requirement stipulated in the official monographs (USP, 2013). From the results obtained, the non-aqueous analytical method of lisinopril gave more useful results, when compared to the aqueous analytical methods of estimation of lisinopril (Table 3.4). In contrast to earlier research, a new simple fluorimetric analytical approach that is accurate, exact, and specific for the detection of Lisinopril was developed (Jamakhandi et al., 2010). Another accurate, simple, fast, and cost-effective spectrophotometric method for assessing lisinopril in pharmaceutical pure and dosage forms was developed, based on the interaction of Alizarin with the primary amine present in lisinopril in the presence of 80% ethyl alcohol. This reaction produces a complex red product with the highest absorbance at 434 nm (Shraitah & Okdeh, 2016). Therefore, the method used in this study can be easily employed in the quality assessment and physicochemical analysis of solid dosage formulations commonly utilized by patients, because it is rapid, efficient, cost-effective, and less technical.

5. Conclusion

The proposed method of analysis was effectively implemented and effective for Lisinopril solid oral dosage formulation. Thus, the proposed method can be used as an alternative for regular analysis of lisinopril in single or fixed dosage forms.

Compliance with ethical standards

Acknowledgments

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Disclosure of Conflict of Interest

The authors hereby declare no conflict of interest.

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