

## Quality Assurance and *in-vitro* bioequivalence Analysis of Amlodipine besylate tablets in Bayelsa State, Nigeria

### ABSTRACT

The proliferation of generic brands in the local medication market makes it increasingly difficult for health professionals and patients to choose the optimal drug. The study aims to assess the physicochemical parameters of generic amlodipine besylate tablets from manufacturers utilizing *in vitro* testing to eliminate health hazards and maximize the safety of people's consumption. Five brands (A, B, C, D, and E) of amlodipine besylate tablets (5 mg) marketed in Bayelsa state were examined for six *in vitro* tests, both official and unofficial, including thickness, hardness, friability, uniformity of weight, disintegration, dissolving tests, and thin layer chromatography (TLC). The dissolution test revealed that brand E (103.2%) discharged the medicine from the dosage form the fastest, while brand B (101.2%) did so slowly. The spectrophotometric measurement was carried out at a wavelength of 240 nm. All five products satisfied the British Pharmacopeia standard for uncoated tablet weight homogeneity (less than 5% variance) and disintegration within 15 minutes. Brand A has the longest disintegration time (1.37 minutes), whereas Brand B has the shortest (0.05). All five brands passed the hardness test. Brand E had the maximum hardness of 8.7 kg/cm<sup>2</sup>, and Brand B had the lowest hardness of 3 kg/cm<sup>2</sup>. All five brands had a friability percentage of less than 1%, with brand B having the greatest (0.91%) and brand E having the lowest (0.10%), and they all crumbled after 15 minutes. Brand A has the longest disintegration time (1.37 minutes), whereas Brand B has the shortest (0.05). All five brands passed the thin-layer chromatography test. The assay method used in this study is dependable, simple, and inexpensive, and it can be used consistently to evaluate amlodipine tablets.

**Keywords:** Amlodipine, bio-equivalence, dissolution, disintegration, Friability, weight uniformity, hardness.

### INTRODUCTION

Hypertension is a chronic medical disorder in which the blood pressure (BP) in the arteries is consistently higher than 140/90 mmHg. Long-term high blood pressure raises the likelihood of stroke, coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia. Hypertension is the leading cause of early death worldwide (Oparil et al., 2018). About 90-95% of cases of primary high blood pressure are caused by specific lifestyle and inherited factors such as excessive salt intake, obesity, smoking, and alcohol consumption. Although 5-10% of secondary high blood pressure cases

**Comment [BEM1]:** Please add conclusion to the abstract

**Comment [BEM2]:** Please reduce the number of keywords and make them related to the title

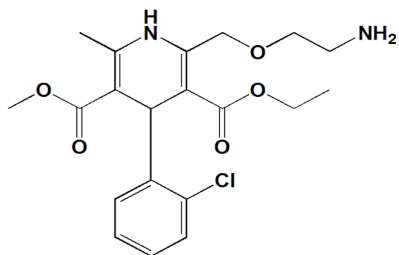
are idiopathic, they are frequently linked to chronic kidney disease, renal artery constriction, an endocrine issue, or contraceptives(Dosh, 2002).

Blood pressure is determined using both diastolic and systolic values. At rest, normal blood pressure ranges from 100 to 130 mmHg systolic and 60 to 80 mmHg diastolic (Brzezinski, 1990). Lifestyle changes and medications can help to control blood pressure and minimize the risk of health problems. Lifestyle improvements include weight loss, more physical exercise, less salt and alcohol intake, and a more balanced diet (Samadian et al., 2016). If lifestyle changes are insufficient, blood pressure medications are used, with combination pharmacotherapy managing blood pressure in 90% of patients (Yang et al., 2017). High blood pressure affects 16–37% of the global population. In 2010, hypertension was deemed to have a role in 18% of all fatalities, or nearly 9.4 million worldwide(Campbell *et al.*,2015).

High blood pressure is treated using a variety of medications (Nelson, 2020), including diuretics (loop diuretics, thiazide, and thiazide-like diuretics, and potassium-sparing diuretics), (James et al., 2014). Calcium channel blockers (Bakris et al., 2004). Angiotensin-converting enzyme (ACE) inhibitors (Wu et al., 2013), angiotensin II receptor antagonists (Verma et al., 2004), beta-adrenergic receptor antagonists (Lindholm et al., 2005), alpha-adrenergic receptor antagonists, mixed alpha-and beta-adrenergic receptor antagonists, vasodilators (Varon et al., 2000), renin inhibitors (Mehta, 2011), alpha-2 or central adrenergic receptor agonists (Chobanian et al., 2003).

Amlodipine, a vasoselective dihydropyridine calcium channel blocker, has a pharmacokinetic profile that distinguishes it from other calcium antagonists. This includes a gradual onset of action, a protracted effect, high bioavailability, and very minimal variations in peak-to-trough plasma levels, with 24-hour duration of action, and maximal availability 6-12 hours following oral administration. It is removed through the urine after a half-life of 30-50 hours and is metabolized in the liver alongside other inactive pyrimidine metabolites. It is 93% protein-bound and has an oral bioavailability of 64-90%(Van, 1994). It has no cardio-depressant effect at clinically significant doses and does not cause bradycardia due to its vascular selectivity, but it does increase coronary and renal blood flow, leading to a decrease in peripheral vascular resistance (Mukete et al. 2015). The effects it has on heart muscle prevent significant narrowing in coronary arteries(Iyengar et al., 2021).

**Comment [BEM3]:** Please rephrase this statement.



**Fig 1. Structural of Amlodipine**

Amlodipine is readily absorbed orally, with an average oral bioavailability of approximately 60%. It has a half-life of approximately 30 to 50 hours, and steady-state plasma concentrations are achieved after 7 to 8 days of daily treatment. It binds to 97.5% of plasma proteins in the bloodstream. Its long half-life and great bioavailability are mostly due to its high pKa of 8.6, capable of binding proteins when ionized at a normal pH (Abernethy, 1989; Chung et al., 2006). It is metabolized by the CYP3A4 enzyme in the liver, through oxidation of the amine group and hydrolysis of the side ester chain, producing an inactive pyridine metabolite (Zuo et al., 2013). Renal elimination is the predominant excretion mechanism, with over 60% of a given dosage recovered in urine, primarily as inactive pyridine metabolites. However, kidney failure has no significant impact on amlodipine elimination. Approximately 20% to 25% of the medicine is removed through feces (Murdoch et al., 1991).

Amlodipine's most common dose-dependent adverse effects are vasodilation, peripheral edema, dizziness, palpitations, and flushing (Agarwal et al., 2018). Blood issues, impotence, depression, peripheral neuropathy, sleeplessness, tachycardia, gingival expansion, hepatitis, and jaundice are some of the side effects reported in less than 1% of cases (Munoz et al., 2007). Many of these negative reactions are underreported (Miediegha & Bunu, 2020). Amlodipine is available in a variety of salt forms, including maleate, mesylate, and besylate, which help with the drug's solubility and absorption, enhancing overall effectiveness (Sheraz et al., 2016). Amlodipine is well tolerated by most people, with little adverse effects. Its extended half-life ( $t^{1/2}$ ) of 35-50 hours when supplied at a dose of 10 mg daily provides the greatest convenience to the patient (Katzung et al., 2004).

Medication cost has a significant impact on affordability and adherence to any given treatment plan (Rohatgi et al., 2021). The high cost of branded products has promoted the importation of

**Comment [BEM4]:** Few grammatical error please correct them

generic products into Nigeria, which are more affordable and regarded as bioequivalent to the original brand (Osibo, 1998). The influx of generic pharmaceuticals into the country has resulted in complaints of subpar and counterfeit drugs, which are sometimes priced lower to get a bigger market share. Quality control tests are important procedures for determining the authenticity of drug products before considering their potential substitution and/or interchangeability with various multi-source brands (Eichie et al., 2011). The need to constantly assess the equivalence of clinically relevant pharmaceutical multi-brands and generics cannot be overemphasized (Eraga et al., 2014). Various analytical techniques, including physicochemical (Ebeshi et al., 2022; Bunu et al., 2023; Dode et al., 2023), chromatographic (Bunu et al., 2023a; Vaikosen et al., 2023), and ultraviolet-visible spectroscopy (Bunu et al., 2020; Vaikosen et al., 2023a), among others, have been used to assess the in-vitro bioavailability and quality of medicinal agents (Peikova et al., 2013; Oraeluno et al., 2023). The current study aims to investigate the physicochemical attributes and in vitro bioavailability of various commercial brands of Amlodipine tablets.

## MATERIALS AND METHODS

### Materials

Five brands of Amlodipine 5mg, Monsanto hardness tester, Analytical weighing balance, Test tube, The Roche friabilator, Measuring cylinder, Beaker, Thermometer, Filter paper, UV- VIS spectrophotometer, disintegration apparatus, dissolution apparatus, and Thin Layer Chromatographic plate. All procedures were conducted following standard protocols in the British Pharmacopoeia (BP, 1998).

### Methods

#### List 1 :Physicochemical Analysis

Test Method	Procedure
Uniformity of weight Determination	An analytical weighing scale was used to weigh twenty (20) tablets from each of the five (5) brands separately. The average weights for each brand, as well as their percentage departure from the mean value, were determined.
Hardness	The crushing strength was evaluated using a tablet hardness tester. Five (5) tablets were randomly chosen from each brand, and the pressure at which they were crushed was recorded.
Friability	Ten (10) tablets of all brands were weighed and abraded using a Roche friabilator set to 25 rev/min for 4 minutes. The tablets were subsequently weighed and compared to their original weights, and their percentage of

Comment [BEM5]: Please elaborate more on the methodology part

	friability was recorded.
Disintegration	Six (6) tablets from each brand were tested in a freshly produced medium containing 0.1 N HCL at 37 °C using educational science equipment. The disintegration time was defined as the time in which no particle remained in the system's basket.
Dissolution	Each brand's dissolving test was performed in 5 replicates using the basket method. The dissolution medium was 900ml of 0.1 N HCL, which was kept at 37±0.5 °C during the experiments. 5ml of dissolution sample was taken at 0, 5, 10, 30, 45, and 60 minutes and replaced with an equal volume to maintain the sink condition. The samples were filtered and analyzed using UV spectrophotometry at 240nm. The sample concentration was measured using a calibration curve produced from pure Amlodipine samples.

#### ***Extraction of pure amlodipine***

Five (5) tablets from the innovator brand E were pulverized and extracted using 50ml methanol, filtered, and the solvent evaporated to obtain the amlodipine powder as crystalline solids.

#### ***UV Spectroscopic analysis***

To prepare the stock solution of 500 µg/ml; 50 mg of amlodipine powder was dissolved in 50 ml of 0.1N HCl and was made up to 100 ml with distilled water. The stock solution was diluted with distilled water to 25 µg/ml and scanned in the ultraviolet (UV) spectrum of 200 - 350 nm. After obtaining the  $\lambda_{max}$ , aliquots amounts of 10µg/ml, 20µg/ml, 30µg/ml, 40 µg/ml, 50 µg/ml, and 60 µg/ml were prepared from the stock solution and used to construct the calibration curve. Their absorbance was measured at  $\lambda_{max}$  of 240 nm against the reagent blank.

#### ***Thin Layer Chromatographic analysis***

The experiment was performed using silica gel 60 F254 (0.2 mm thick) TLC plates (20×10cm). A capillary tube was used to transfer samples to the plates in 8 mm bands, 8 mm apart, and 10 mm from the plate's boundaries. Chloroform, ethanol, toluene, and glacial acetic acid (5:3:3.5:0.5 v/v) were used as the mobile phase. Following the development, TLC plates were allowed to dry and examined in an iodine tank to obtain the R<sub>f</sub> value.

## **RESULTS**

Table 1. Weight Uniformity analysis

S/N	% Weight Deviation (mg)				
	A	B	C	D	E
1	411±0.70	175±0.57	177±0.71	206±1.25	204±0.41
2	408±0.04	178±1.34	170±3.27	206±1.25	203±0.90
3	410±0.45	171±2.84	176±0.14	204±0.27	204±0.41
4	409±0.21	184±4.55	176±0.14	204±0.27	204±0.41
5	403±1.26	172±2.27	171±2.70	202±0.71	206±0.56
6	405±0.79	184±4.55	176±0.14	204±0.27	205±0.07
7	408±0.04	176±0	175±0.43	206±1.25	204±0.41
8	408±0.04	178±1.34	177±0.71	205±0.76	204±0.41
9	405±0.97	179±1.70	178±1.28	203±0.22	203±0.90
10	411±0.70	178±1.34	180±2.42	202±0.71	205±0.07
11	410±0.45	173±1.70	177±0.71	202±0.71	206±0.56
12	410±0.45	174±1.34	170±3.27	204±0.27	205±0.07
13	407±0.28	175±0.57	177±0.71	207±1.74	203±0.90
14	404±1.02	171±2.84	176±0.14	202±0.71	204±0.41
15	412±0.94	176±0	175±0.43	201±1.20	206±0.56
16	408±0.04	178±1.34	178±1.28	202±0.71	203±0.90
17	407±0.28	174±1.34	175±0.43	205±0.76	210±2.51
18	409±0.21	174±1.34	179±1.85	203±0.22	206±0.56
19	413±1.19	174±1.34	177±0.71	198±2.68	206±0.56
20	405±0.77	176±0	175±0.43	203±0.22	206±0.56

As shown in Table 1 all five(5) brands complied with the BP specification for uniformity of weight of uncoated tablets as no tablet has a percentage deviation greater than 5%. The result is presented as the mean of twenty tablets and the standard deviation (Mean ± SD)

Table 2. Disintegration analysis

Samples	A (min)	B (min)	C (min)	D (min)	E (min)
Tab1	1.32	0.05	0.1	0.05	0.05
Tab2	1.36	0.05	0.1	0.1	0.1
Tab3	1.30	0.05	0.1	0.1	0.1
Tab4	1.32	0.05	0.1	0.05	0.05
Tab5	1.50	0.05	0.1	0.1	0.1
Tab6	1.40	0.05	0.1	0.05	0.1
Mean	1.37	0.05	0.1	0.08	0.08

As observed in Table .2, all the tested brands disintegrated within the prescribed time limit of < 15 minutes. Brand A has the highest disintegration time of 1.37minutes while Brand B has the lowest disintegration time of 0.05minutes.

Table 3. Friability Test

<b>Friability test</b>	<b>A (g)</b>	<b>B (g)</b>	<b>C (g)</b>	<b>D (g)</b>	<b>E (g)</b>
Initial weight (W <sub>o</sub> )	4.11	1.672	1.744	2.038	2.048
New weight (W)	4.110	1.764	1.738	2.030	2.046
W <sub>o</sub> -W	0.006	0.016	0.006	0.008	0.002
%friability	0.15%	0.91%	0.34%	0.39%	0.10%

Table 3 shows that the five(5) brands have a percentage Friability below 1% of which bread B has the highest percentage Friability of (0.91%) and brand E has the lowest percentage Friability of(0.10%). Hence all the brands passed the test.

Table 4. Hardness(crushing strength) analysis

Tablet No.	Sample Brands				
	A (kg/cm <sup>2</sup> )	B (kg/cm <sup>2</sup> )	C (kg/cm <sup>2</sup> )	D (kg/cm <sup>2</sup> )	E (kg/cm <sup>2</sup> )
Tab 1	6.0	2.5	3.5	4.0	9.0
Tab 2	3.0	3.0	3.5	4.0	8.5
Tab3	5.5	3.5	3.5	4.0	8.5
Tab 4	4.5	3.0	3.5	4.0	8.5
Tab 5	5.0	3.0	3.5	4.0	9.0
Mean	4.8	3.0	3.5	4.0	8.7

According to Table 4, all the brands passed the crushing test. Brand E had a maximum hardness of 8.7kg/cm<sup>2</sup> whereas Brand B had the lowest hardness of 3kg/cm<sup>2</sup> among all the average hardness of the five (5) brands.

Table 5. Dissolution profile

Time (mins)	% Drug Release				
	A (%)	B (%)	C (%)	D (%)	E (%)
0	0	0	0	0	0
5	70.7	64.4	61.0	106.1	103.2
10	89.6	79.4	84.8	114.3	53.5
15	103.7	92.0	106.6	109.0	68.1
30	106.1	101.2	104.1	108.0	62.5
45	95.4	96.4	109.4	99.8	55.7
60	86.7	93.0	102.2	96.9	54.3

As shown in Table .5, all five(5) brands passed the BP specification for dissolution rate. Brand C has the highest percentage of drug release at 109.4% at 45minutes while Brand B has the highest percentage of drug release at 101.2 at 30minutes.

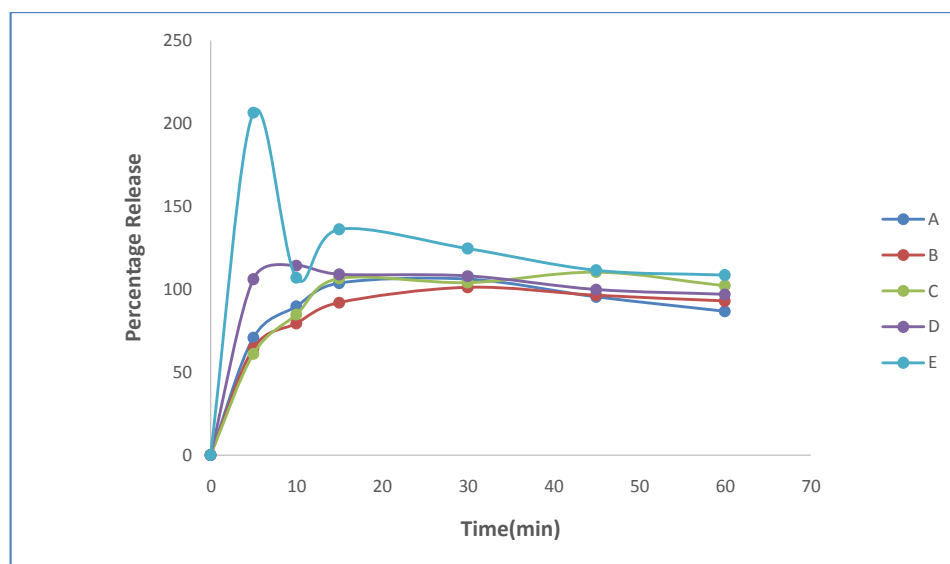


Figure 2. Dissolution rate of different brands of Amlodipine

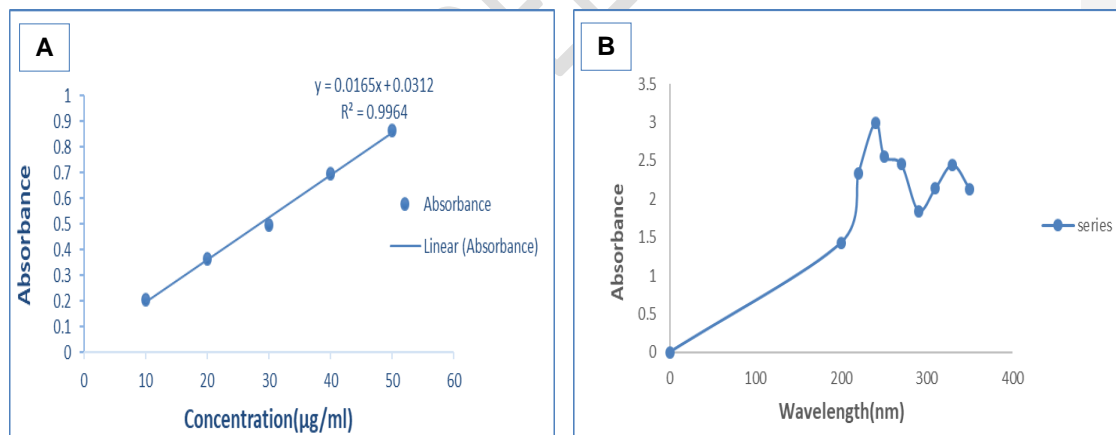


Figure 3. Calibration curve of Amlodipine (A):  $y = 0.0165x + 0.0312$ ; and Absorbance spectrum of Amlodipine (B): The wavelength maximum absorbance of Amlodipine in 0.1N HCl was obtained at 240nm.

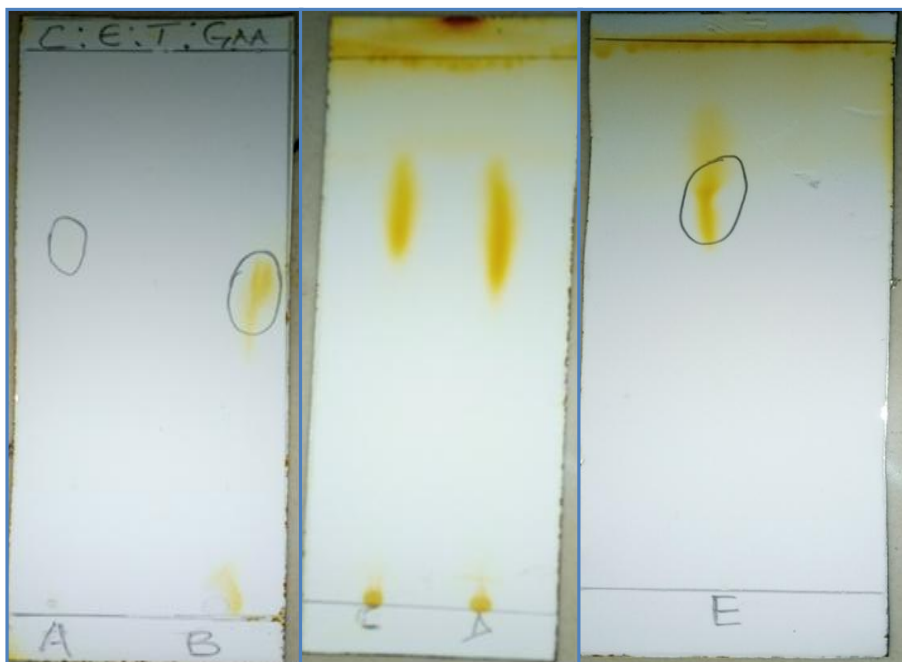


Figure 4. TLC Plate of test samples A – E.

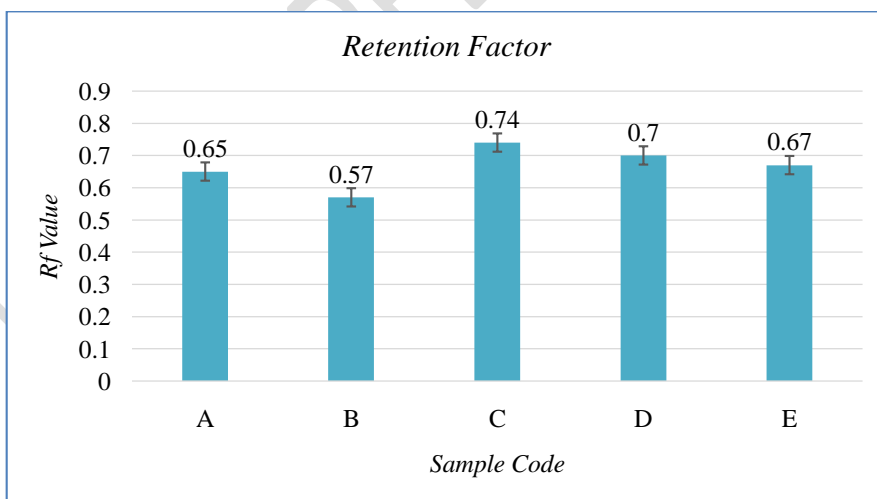


Fig 5. Thin layer chromatographic analysis: Brand C has the highest Rf value of 0.74 while Brand B has the lowest Rf of 0.57.

## DISCUSSION

Weight uniformity/homogeneity implies that good manufacturing practices were used during the granulation and compression procedures. The British Pharmacopoeia's standard for consistent weight of uncoated tablets is a 5% difference from the mean. All five (5) brands satisfied the standard uniformity criterion (Table 1). Friability is used to determine tablet resistance to abrasion during shipment and packaging. It is a measure of how easily the tablets break into tiny pieces when in touch, especially when rubbing. The high friability quality ensures that tablets do not chip during transportation owing to abrasion and demonstrates adherence to competent manufacturing practices (Table 3). It is predicted that a batch delivers a weight loss of less than one percent, and all five brands passed the test (BP,1998).

The crushing or hardness test assesses the tablets' resistance to chipping during handling, which may impair friability and disintegration. The tougher a tablet, the less friable it is and hence takes a longer disintegration time, and vice versa. The suggested crushing force is 4-10 Kg/cm, and the testing results demonstrate that all five brands passed the hardness test (Table 4). The disintegration test is a quality control procedure that examines the ability of solid dosage forms to deteriorate within the required time when immersed in a suitable liquid medium. The rate of disintegration affects the drug's solubility and, eventually, absorption. A sufficient amount of suitable disintegrants in adequate levels allows for the production of tablets free of disintegration issues. The British Pharmacopoeia states that uncoated pills should disintegrate within 15 minutes. The results of the investigation suggested that brands complied with the standard (Table 2)(BP,1998).

A dissolving or dissolution test determines the rate at which oral dose forms are released. It is a necessary parameter for estimating drug bioavailability. It is a useful method for predicting a medicine's in vivo performance as well as identifying inappropriate and inferior drug items. Amlodipine must be dissolved at least 75% in 30 minutes, according to the United States Pharmacopoeia (2014). The results showed that Brand E had the highest percentage of drug release at 5 minutes (103.2%), which subsequently reduced to 54.3% at 60 minutes. Brands A and B have the largest percentages of drug release at 30 minutes, with 106.1% and 101.2% respectively. Brands C and D exhibit the highest percentages of drug release, 109.4% and 109.0% at 45 and 15 minutes, respectively (Table 5 and Fig. 2). The evaluation revealed that almost all 5 brands dissolved 100% or more within 60 minutes, indicating that the drug release pattern is consistent. Even though the brands were manufactured by different companies using

different excipients in different ratios based on releasing factors, they can be used interchangeably.

The calibration curve for the extracted pure sample of amlodipine is linear from 10 to 50 µg/ml (Fig. 3A), which complies with Beer Lambert's Law (Beer, 1852). The samples were evaluated using TLC (Figs. 4 and 5) and compared to a standard utilizing the British Pharmacopoeia (Zhang et al., 2022), and all were found to be pure (Fig. 3B). It is a common perception that drug items manufactured by mid- or small-scale enterprises may be inferior to those produced by top companies in the market. This study depicts the current state of many quality metrics for drug items manufactured by local enterprises.

## CONCLUSION

In today's pharmaceutical industry, in-vitro testing is critical for comparing to multi-brand generic molecules and ensuring acceptable therapeutic activity of the dosage form. The results of the in-vitro examination of amlodipine brands showed good overall quality, a satisfactory dissolving rate, and bioequivalence. As a result, the analyzed brands could be utilized interchangeably with brands.

## REFERENCE

- Abernethy D. R. (1989). The pharmacokinetic profile of amlodipine. *American Heart Journal*, 118(5 Pt 2), 1100–1103. [https://doi.org/10.1016/0002-8703\(89\)90834-x](https://doi.org/10.1016/0002-8703(89)90834-x).
- Agarwal MA, Flatt D, Khouzam RN (2018). The potential detrimental effects of calcium channel blockers' overdose and current available management. *Journal of Annal of Translational Medicine*. 6(1):16.
- Ananchenko G, Novakovic J, Lewis J (2012). Profiles of Drug Substances, Excipients, and Related Methodology. *Academic Press*. 37: 31–77.
- Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A (2004). Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Journal of Kidney International*. 65 (6): 1991–2002.
- Beer (1852). Determination of the absorption of red light in colored liquids. *Journal of Annalen der Physik und Chemie* 162 (5): 78–88.
- British Pharmacopoeia (BP), 1998. volume II, page 1451.
- Brzezinski WA (1990). Blood Pressure. In: Walker HK, Hall WD, Hurst JW, editors. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd edition. Boston: Butterworths; 1990. Chapter 16. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK268/>.
- Bunu JS, Alfred-Ugbenbo D, Dode E, Lambert FK (2023). In-vitro bioequivalence analysis of some Artemether-Lumefantrine-based combination Formulations utilized in Nigeria. *Mod App in pharmacy & Pharma Sci* 1(1)- 2023.

**Comment [BEM6]:** Conclusion is not clear please elaborate more on this part

**Comment [BEM7]:** A lot of references are more than 10 years backdated please update the references

- Bunu JS, Aniako V, Karade VP, Vaikosen EN, Ebeshi BU (2023a), Thin-Layer Chromatographic and UV-Spectrophotometric Analysis of Frequently Utilized Oral Macrolide Antibiotics, *International Journal in Pharmaceutical Sciences*, 1(9), 265-274.
- Bunu JS, Ere D. & Wilson OD (2020). Simple thin-layer chromatographic and UV-spectrophotometric analysis of Promethazine and its N-demethylation metabolites from biological fluids. *International Journal of PharmTech Research*. 13 (4): 316-324.
- Campbell NR, Lackland DT, Lisheng L, Niebylski ML, Nilsson PM, Zhang XH (March 2015). Using the Global Burden of Disease study to assist the development of nation-specific fact sheets to promote prevention and control of hypertension and reduction in dietary salt: a resource from the World Hypertension League. *Journal of Clinical Hypertension*. 17(3): 165–167.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 289 (19): 2560–72.
- Chung, M., Calcagni, A., Glue, P., & Bramson, C. (2006). Bioavailability of amlodipine besylate/atorvastatin calcium combination tablet. *Journal of Clinical Pharmacology*, 46(9), 1030–1037. <https://doi.org/10.1177/0091270006291031>.
- Dode E, Alfred-Ugbenbo D, Bunu JS, & Marcus A (2023). Physicochemical analysis and quality assessment of Lisinopril oral formulations used in the management of hypertension. *International Journal of Biological and Pharmaceutical Sciences Archive*, 05(02), 043–048.
- Dosh S. A. (2002). The treatment of adults with essential hypertension. *The Journal of Family Practice*, 51(1), 74–80.
- Ebeshi UB, Bunu JS, Kpun HF, Ezebube CO (2022). Analysis of gastrointestinal acid-neutralizing potency of some commercial antacid tablet formulations. *GSC Biological and Pharmaceutical Sciences*, 19(02), 008–013.
- Eichie FE, Arhewoh MI, Isesele JE, Olatunji KT (2011). In vitro assessment of quality control parameters of some commercially available generics of amlodipine besylate in the Nigerian drug market. *International Journal of Health*. 4 Suppl 1:57-61.
- Eraga SO, Uzochukwu OC, Iwuagwu MA (2014). Pharmaceutical equivalence of some brands of 5 mg amlodipine besylate tablets available in southern Nigeria. *West Africa Journal Pharmacology*; 25 Suppl 1:38-45.
- Iyengar, S. S., Mohan, J. C., Ray, S., Rao, M. S., Khan, M. Y., Patted, U. R. H., & Gaurav, K. (2021). Effect of Amlodipine in Stroke and Myocardial infarction: A Systematic Review and Meta-analysis. *Cardiology and therapy*, 10(2), 429–444. <https://doi.org/10.1007/s40119-021-00239-1>.
- James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Svetkey LP, Taler SJ, Townsend RR, Wright JT, Narva AS, Ortiz E (2014). 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 311 (5): 507–20.
- Katzung BG, Chatterjee K. (2004). Vasodilators and the treatment of angina pectoris. *Basic and Clinical Pharmacology*. 9th ed. New York: McGraw Hill Companies; p. 184-99.
- Lindholm LH, Carlberg B, Samuelsson O (2005). Should beta blockers remain the first choice in the treatment of primary hypertension? A meta-analysis. *Lancet*. 366 (9496): 1545–53.

- Mehta A (2011). Direct Renin Inhibitors as Antihypertensive Drugs. <https://pharmaxchange.info/2011/01/direct-renin-inhibitors-as-antihypertensive-drugs/> (Accessed 12/3/2022)
- Miediegha O, &Bunu JS, (2020). Pharmacovigilance framework and extent of medications adverse reaction surveillance in Southern Nigeria. *World Journal of Pharmaceutical Research*. 9 (6), 2009 – 2017.
- Mukete BN, Cassidy M, Ferdinand KC, Le Jemtel TH (August 2015). Long-Term Anti-Hypertensive Therapy and Stroke Prevention: A Meta-Analysis. *American Journal of Cardiovascular Drugs*. 15 (4): 243–257.
- Munoz R, Vetterly CG, Rother SJ, Da Cruz EM (2007). Handbook of Pediatric Cardiovascular Drugs. *Springer Science & Business Media*. p. 96.
- Murdoch D, Heel RC (1991). Amlodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. *Drugs*. 41 (3): 478–505.
- Nelson M (2010). Drug treatment of elevated blood pressure. *Journal of Australian Prescriber*. 33 (4): 108–12.
- Nwodo N, Uzochukwu I, Omeje E (2007). Quality control assessment and the possibility of interchangeability between multi-sourced norfloxacin tablets marketed in Nigeria. *Academic Journal 2 Suppl 8*:348-52.
- Oparil, S., Acelajado, M. C., Bakris, G. L., Berlowitz, D. R., Cífková, R., Dominiczak, A. F., Grassi, G., Jordan, J., Poulter, N. R., Rodgers, A., & Whelton, P. K. (2018). Hypertension. *Nature reviews. Disease primers*, 4, 18014. <https://doi.org/10.1038/nrdp.2018.14>.
- Oraeluno JN, Obasi JC, Bunu JS, Bamigbola E, Vaikosen, EN, Igwe, FU (2023). In vitro quality assessment of five different brands of cefuroxime axetil suspension sold in Amassoma, Nigeria. *Journal of Biological Pharmaceutical and Chemical Research*, 10(3): 31-39.
- Osibo OO (1998). Faking and Counterfeiting of Drugs. *West Africa Journal of Pharmacology*;12 Suppl 1:53-7.
- Peikova LP, Tsvetkova BG, Kostova BD, Rachev DR. (2013). Investigations and HPLC assay of model formulations containing amlodipine besylate and lisinopril. 20(1, Suppl 3):11-5.
- Rohatgi, K. W., Humble, S., McQueen, A., Hunleth, J. M., Chang, S. H., Herrick, C. J., & James, A. S. (2021). Medication Adherence and Characteristics of Patients Who Spend Less on Basic Needs to Afford Medications. *Journal of the American Board of Family Medicine: JABFM*, 34(3), 561–570. <https://doi.org/10.3122/jabfm.2021.03.200361>.
- Samadian, F., Dalili, N., &Jamalian, A. (2016). Lifestyle Modifications to Prevent and Control Hypertension. *Iranian journal of kidney diseases*, 10(5), 237–263.
- Sheraz, M. A., Ahsan, S. F., Khan, M. F., Ahmed, S., & Ahmad, I. (2016). Formulations of Amlodipine: A Review. *Journal of pharmaceuticals*, 2016, 8961621. <https://doi.org/10.1155/2016/8961621>.
- United States Pharmacopoeia (2014). National Formulary. Vol. 2. Rockville (MD). United States Pharmacopoeial Convention. Amlodipine; P. 2466-2467.
- Vaikosen EN, Bunu SJ, Dode E, Efidi RB (2023). spectrophotometric fingerprinting and chemical determination of streptomycin, amikacin, neomycin, and gentamycin sulphate

- by condensing with ninhydrin reagent. *International Journal of Chemistry Research* 7 (3), 5 – 10.
- Vaikosen EN, Worlu RC, Bunu JS, Dode E, Doctor M (2023a). Liquid-Liquid Separation and Determination of Betamethasone, Clotrimazole, and Neomycin in Topical Cream By UV-Visible Spectrophotometry. *International Journal in Pharmaceutical Sciences*, 1(4): 170-179.
- Van Zwieten PA (Sep 1994). Amlodipine an overview of its pharmacodynamic and pharmacokinetic properties. *Journal of the national library of medicine*. *Clin Cardiol.* ;17(9 Suppl 3): III3-6
- Varon J, Marik PE (2000). The diagnosis and management of hypertensive crises. *Chest*. 118 (1): 214–27.
- Verma S, Strauss M (2004). Angiotensin receptor blockers and myocardial infarction. *British Medical Journal*. 329 (7477): 1248–9.
- Wu HY, Huang JW, Lin HJ, Liao WC, Peng YS, Hung KY, Wu KD, Tu YK, Chien KL (2013). Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and Bayesian network meta-analysis. *British Medical Journal*. 1136(10): 347.
- Yang, M. H., Kang, S. Y., Lee, J. A., Kim, Y. S., Sung, E. J., Lee, K. Y., Kim, J. S., Oh, H. J., Kang, H. C., & Lee, S. Y. (2017). The Effect of Lifestyle Changes on Blood Pressure Control among Hypertensive Patients. *Korean journal of family medicine*, 38(4), 173–180. <https://doi.org/10.4082/kjfm.2017.38.4.173>.
- Zhang, Meizhen; Yu, Qian; Guo, Jiaqi; Wu, Bo; Kong, Xianming (2022). Review of Thin-Layer Chromatography Tandem with Surface-Enhanced Raman Spectroscopy for Detection of Analytes in Mixture Samples. *Journal of National Library of Medicine*. 12 (11): 937.
- Zuo, Xiao-cong; Zhou, Ya-nan; Zhang, Bi-kui; Yang, Guo-ping; Cheng, Ze-neng; Yuan, Hong; Ouyang, Dong-sheng; Liu, Shi-kun; Barrett, Jeffrey S. (2013). Effect of CYP3A5\*3 Polymorphism on Pharmacokinetic Drug Interaction between Tacrolimus and Amlodipine. *Drug Metabolism and Pharmacokinetics*. 28 (5): 398–405.