**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/cm², and Brand B had the lowest hardness of 3 kg/cm².All five brands had a friability percentage of less than 1%, with bread 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

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).

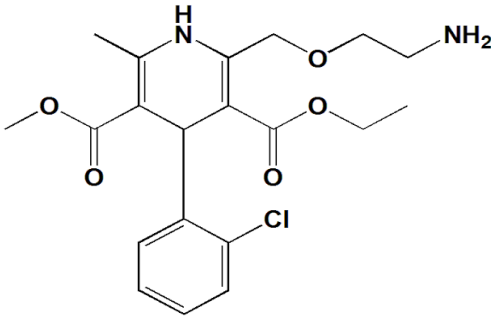


**Fig 1.Structural of Amlodipine**

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

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 |

| | |
|---|---|
| | friability was recorded. |
| Disintegration | Six (6) tablets from each brand were tested in a freshly produced medium containing 0.1 N HCL at 37 0C 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 λmax, aliquots amounts of 10µg/ml, 20µg/ml, 30µg/ml, 40 mg/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 λmax 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 Rf 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 hasa 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

| **Friability test** | **A (g)** | **B (g)** | **C (g)** | **D (g)** | **E (g)** |
|---|---|---|---|---|---|
| Initial weight ($W_o$) | 4.11 | 1.672 | 1.744 | 2.038 | 2.048 |
| New weight (W) | 4.110 | 1.764 | 1.738 | 2.030 | 2.046 |
| $W_o$-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 ($kg/cm^2$) | B ($kg/cm^2$) | C ($kg/cm^2$) | D ($kg/cm^2$) | E ($kg/cm^2$) |
| 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/cm² whereas Brand B had the lowest hardness of 3kg/cm² 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.*

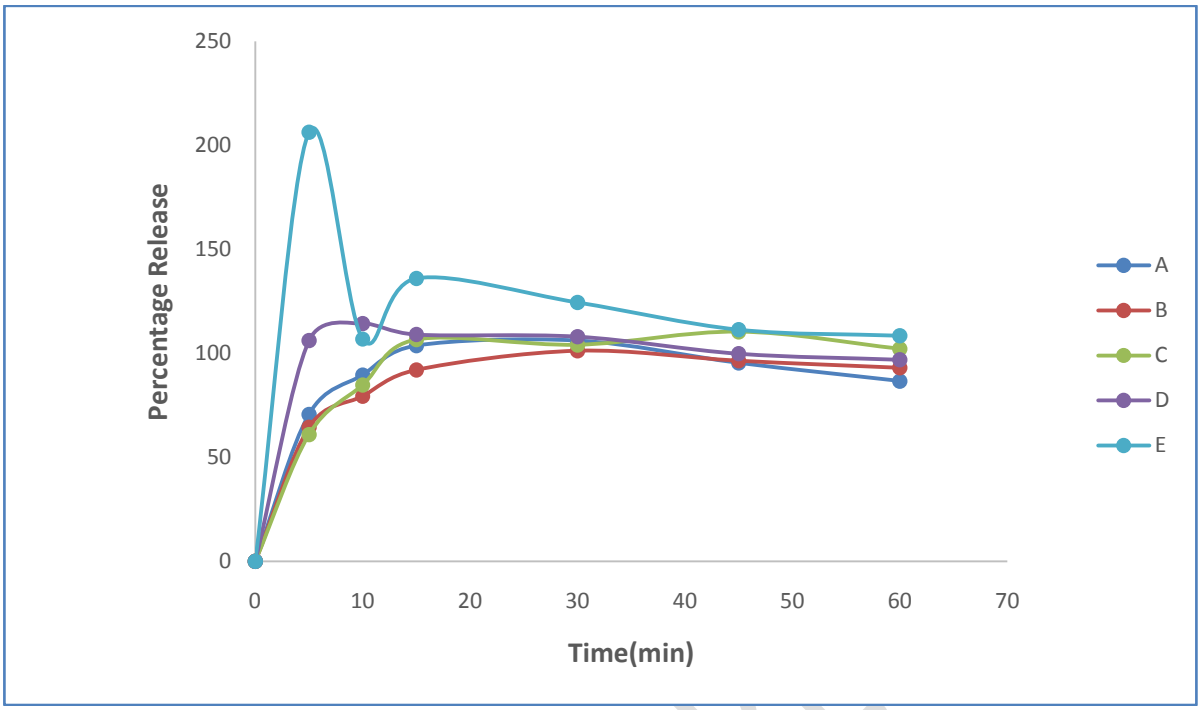


*Figure 2. Dissolution rate of different brands of Amlodipine*

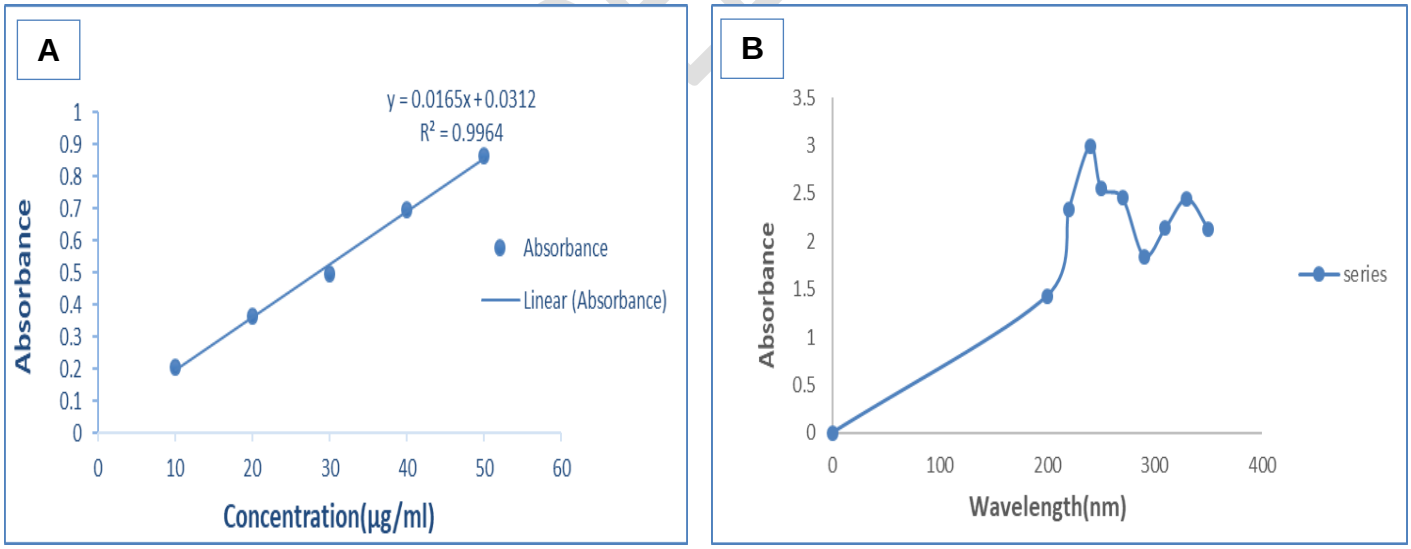


*Figure 3. Calibration curve of Amlodipine (A):* y = 0.0165x + 0.0312; *and Absorbance spectrum of Amlodipine (B): The wavelength maximum absorbance of Amlodipine in 0.1N HCl was obtained at 240nm.*

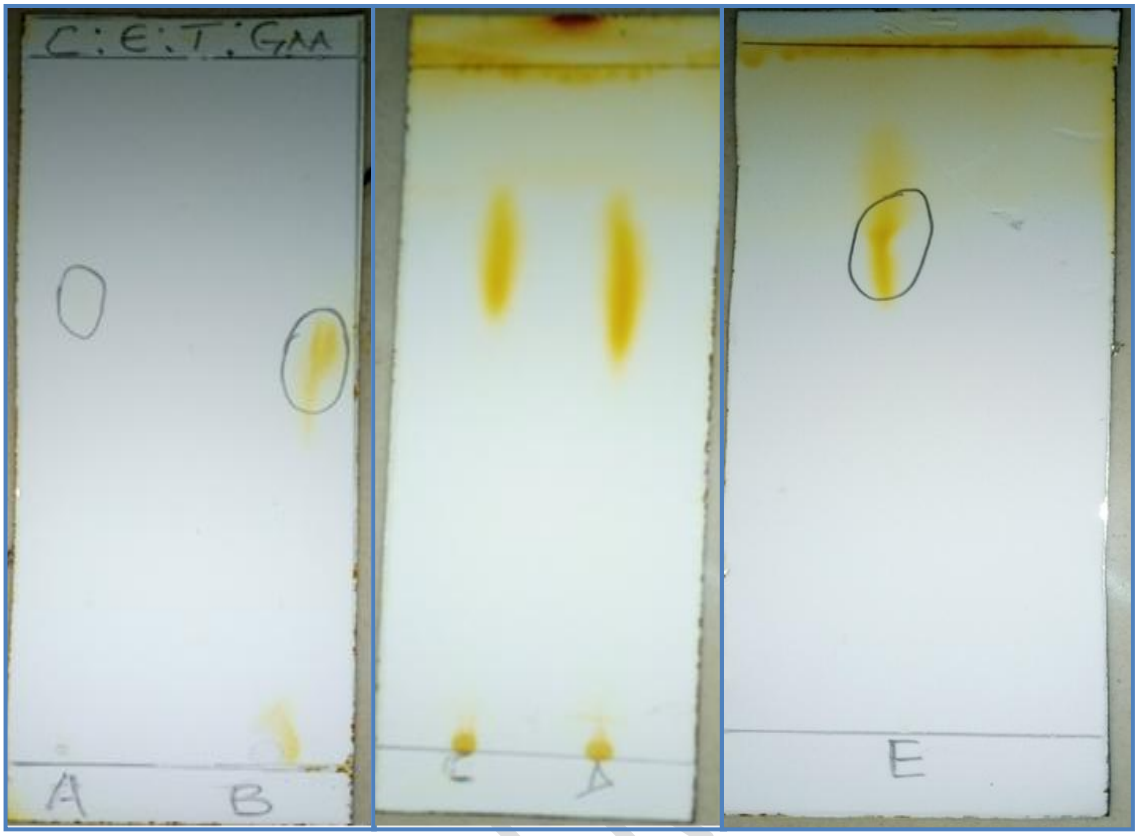


Figure 4. TLC Plate of test samples A – E.

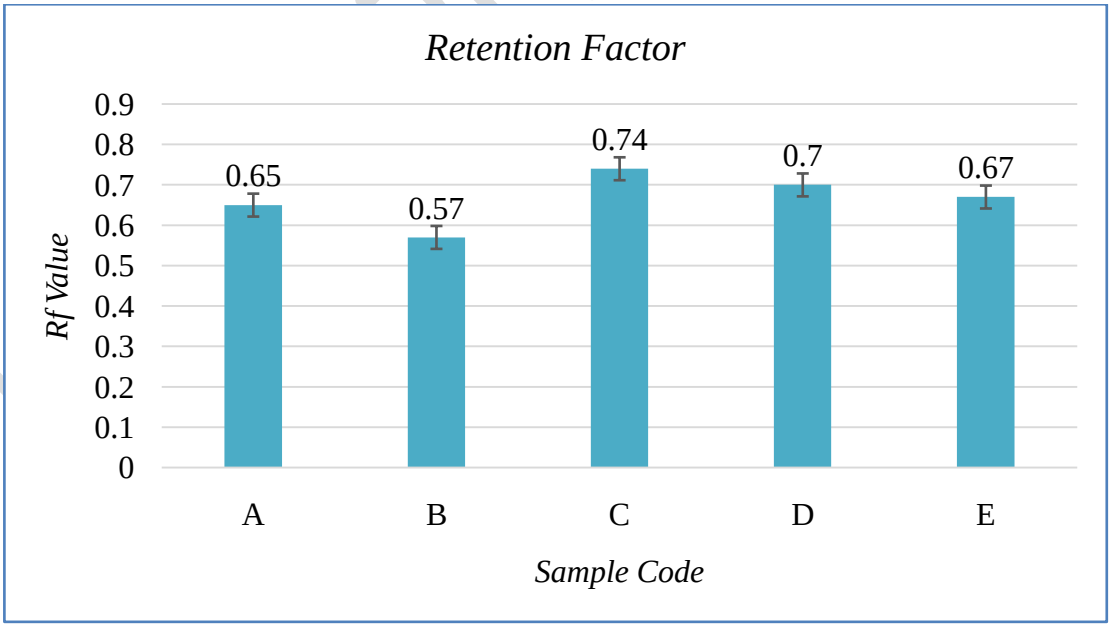


Fig 5. Thin layer chromatographic analysis*: Brand C has the highest Rf value of 0.74 while Brand B has the lowest Rf of 0.57.*

## 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 Lamberts Law (Beer, 1852). The samples were evaluated using TLC (Figs. 4 and 5) and compared to a standard utilizing the British Pharmacopeia (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.

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