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Quality Assurance and *In-vitro* Bioequivalence Analysis of Amlodipine Besylate Tablets

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The proliferation of generic brands in the local pharmaceutical market makes it increasingly difficult for health professionals and patients to choose the optimal drug. The study aimed to assess the physicochemical parameters of generic amlodipine besylate tablets utilizing in-vitro testing to eliminate health hazards and maximize safety. Five brands (A, B, C, D, and E) of amlodipine besylate tablets (5 mg) were examined for six in-vitro tests; thickness, hardness, friability, uniformity of weight, disintegration, dissolution, and thin layer chromatography (TLC). The dissolution test revealed that Brand D had the highest percentage of drug release at 5 minutes (106.2%), followed by Brand E (103.2%), A (70.7%), B (64.4%), and C (61.0%), respectively. The spectrophotometric measurement was carried out at 240 nm. All five brands 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 (4.37 minutes), whereas Brand B has the

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shortest (3.05). 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 highest (0.91%) and brand E, lowest (0.10%), all tablets crumbled after 15 minutes. All brands passed the quality assessment test. Conclusion: The Quality Assurance and in-vitro bioequivalence assay methods used in this study are dependable, simple, and inexpensive, and they can be used consistently to evaluate amlodipine tablets and other solid-dosage pharmaceutical products.

Keywords: Amlodipine; bioequivalence; dissolution test; quality control; quality assurance; chromatography.

1. 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 [1]. 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, endocrine issues, or contraceptives [2].

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 [3]. 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 [4]. If lifestyle changes are insufficient, blood pressure medications are used, with combination pharmacotherapy for managing blood pressure in about 90% of patients [5]. 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 [6]. High blood pressure is treated using a variety of medications [7], including diuretics (loop diuretics, thiazide, thiazide-like diuretics, and potassium-sparing diuretics), [8]. Calcium channel blockers [9]. Angiotensin-converting enzyme (ACE) inhibitors [10], angiotensin II receptor antagonists [11], beta-adrenergic receptor antagonists [12], alpha-adrenergic receptor antagonists, mixed alpha-and beta-adrenergic receptor antagonists, vasodilators [13], renin inhibitors [14], alpha-2 or central adrenergic receptor agonists [15].

Amlodipine, a vasoselective dihydropyridine calcium channel blocker, has a pharmacokinetic profile that distinguishes it from other calcium antagonists. It has 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 metabolized in the liver and eliminated through the urine after a half-life of 30-50 hours. It is 93% protein-bound and has an oral bioavailability of 64-90% [16], with no cardio-depressant effect 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 [17], and prevents significant narrowing of coronary arteries [18]. 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 [19,20]. 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 [21]. This group of enzymes metabolizes more than 90% of clinically used drugs [22, 23]. It is predominantly eliminated via the renal route, with over 60% recovered in urine as inactive pyridine metabolites. However, kidney failure has no significant impact on elimination. Approximately 20% to 25% is removed through feces [24].

Amlodipine's most common dose-dependent adverse effects are vasodilation, peripheral edema, dizziness, palpitations, and flushing [25]. 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 [26]. Many of these adverse reactions are poorly reported [27].

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 [28].

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 [29].

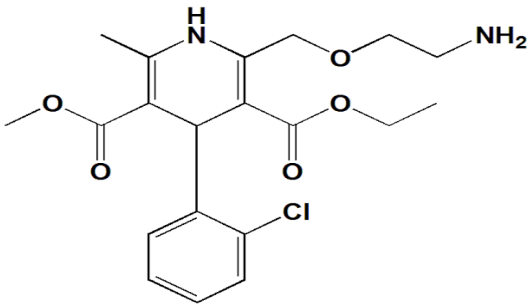

Fig. 1. Structural of Amlodipine

Medication cost has a significant impact on affordability and adherence to any given treatment plan [30]. 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 [31]. 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 [32]. The need to constantly assess the bioequivalence of clinically relevant pharmaceutical multi-brands and generics cannot be overemphasized [33]. Various analytical techniques, including physicochemical [34,35,36], chromatographic [37,38], and ultraviolet-visible spectroscopy [39,40], among others, have been used to assess the in-vitro bioavailability and quality of medicinal agents [41,42]. The current study aimed to assess the physicochemical parameters and in-vitro bioequivalence of various commercial brands of Amlodipine tablets.

2. MATERIALS AND METHODS

2.1 Materials

Five brands of Amlodipine 5mg, (coded A, B, C, D, and E-Innovator brand) purchased from pharmacies in Bayelsa state, 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 [43].

2.2 Methods

Physicochemical methods such as weight uniformity, tablet hardness and friability, disintegration, and dissolution assays, were used to evaluate the in-vitro bioequivalence properties of the amlodipine brands.

2.3 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. This was done for all the other brands used in the analysis. The sample concentration was measured using a calibration curve produced from pure Amlodipine (extracted) samples at 240 nm.

2.4 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.

2.5 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.

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.

3. RESULTS

Table 1 shows that 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).

As observed in Table .2, all the tested brands disintegrated within the prescribed time limit of < 15 minutes. Brand A showed the highest disintegration time of 4.37 minutes while Brand B had the lowest disintegration time of 3.05 minutes.
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.

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.

As shown in Fig. 3, all five (5) brands passed the BP specification for dissolution rate Brand C has the highest percentage of drug release at 109.4% at 45 minutes while Brand B has the highest percentage of drug release at 101.2 at 30 minutes.

4. 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 [43]. 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.

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±0.00	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±0.00	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±0.00	175±0.43	203±0.22	206±0.56

Table 2. Disintegration analysis

Samples	A (min)	B (min)	C (min)	D (min)	E (min)
Tab1	4.32	3.05	3.10	3.05	3.05
Tab2	4.36	3.05	3.10	3.10	3.10
Tab3	4.30	3.05	3.10	3.10	3.10
Tab4	4.32	3.05	3.10	3.05	3.05
Tab5	4.50	3.05	3.10	3.10	3.10
Tab6	4.40	3.05	3.10	3.05	3.10
Mean	4.37	3.05	3.10	3.08	3.08

Table 3. Friability test

Friability test	A (g)	B (g)	C (g)	D (g)	E (g)
Initial weight (W_o)	4.110	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 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

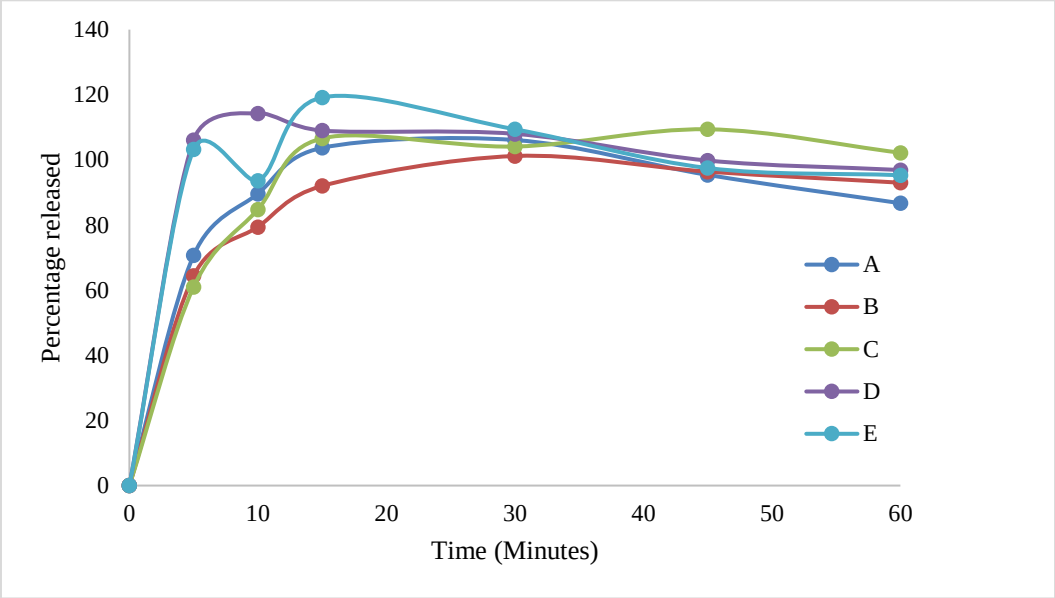

Fig 2: Dissolution profile for different brands of amlodipine

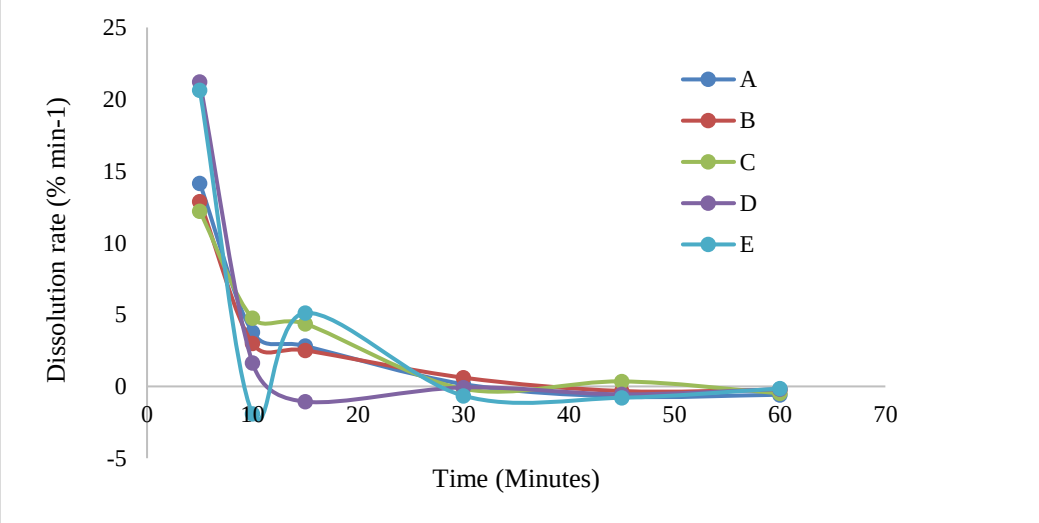

Fig. 3. Dissolution rate of different brands of Amlodipine

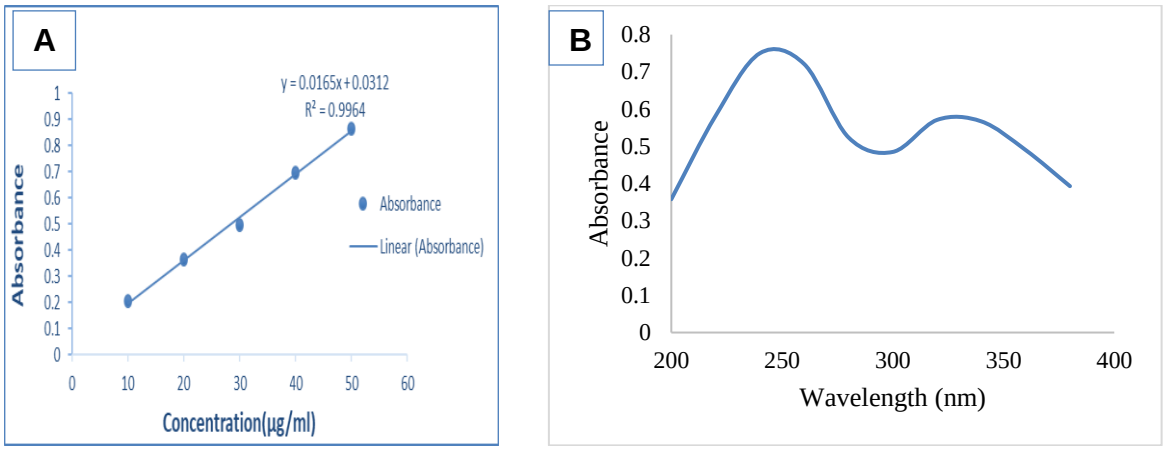

Fig. 4. (A): Calibration curve of Amlodipine (y = 0.0165x + 0.0312, R2=0.9964); (B): UV-Spectrum of Amlodipine in 0.1 M HCl with maximum absorbance at 240nm (λmax)

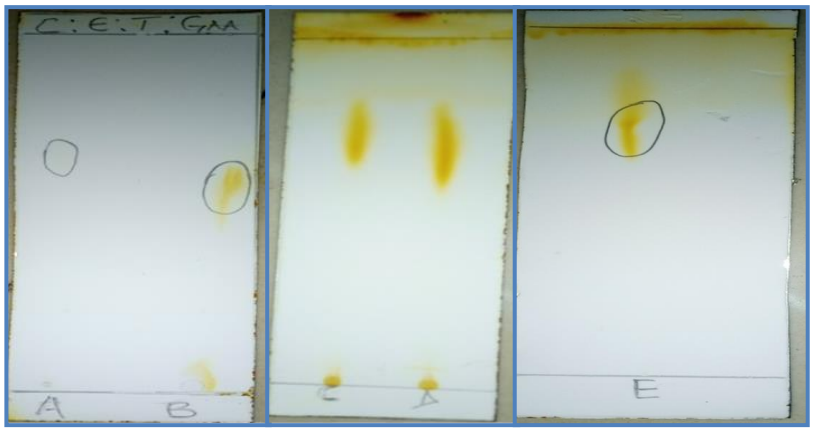

Fig. 5. TLC Plate of test samples A – E

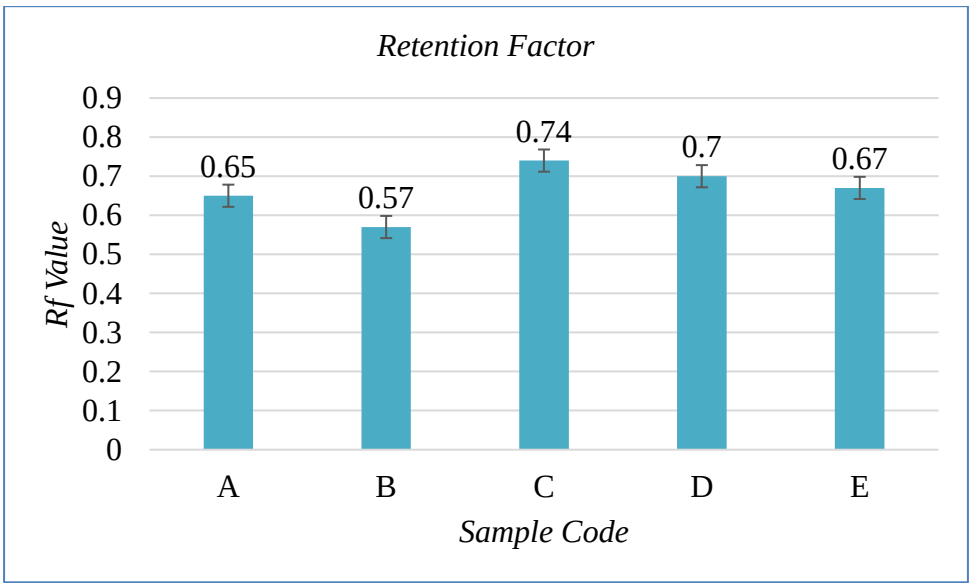

Fig. 6. Thin layer chromatographic analysis: Brand C has the highest Rf value of 0.74 while Brand B has the lowest Rf of 0.57

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 all the brands complied with the standard (Table 2) [43]. A dissolution test determines the rate at which oral dosage 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 [44]. The in-vitro dissolution profile for the release of five brands of Amlodipine is presented in Fig. 2.

The results showed that Brand D had the highest percentage of drug release at 5 minutes (106.2%), followed by Brand E (103.2%), while the order of release for other brands was as follows - A (70.7%), B (64.4%) and C (61.0%). All brands had a percentage release ⩾90% at 15 minutes. This implied that all brands were formulated by manufacturers as quick-releasing drugs. In addition, the aforementioned revealed that all 5 brands released almost 100% amlodipine within 60 minutes - indicating that the drug release pattern is consistent for all brands, despite the investigated brands being manufactured by different companies using different excipients in different proportions and based on the observed releasing factors, they can be used interchangeably. Also, Figure 3, shows the zero-order dissolution rate at different sampling times (t_5- t_{60}).

The calibration curve for the extracted pure sample of amlodipine is linear from 10 to 50 µg/ml (Fig. 4A), which complies with Beer's Law and was obeyed within this concentration range [45]. The samples were evaluated using TLC (Figs. 5 and 6) and were found comparable to that of the reference standard in the British Pharmacopeia [46], - all samples were adjudged to be pure as only a spot-on TLC was observed per spotted sample. It is a common perception that drug items manufactured by mid- or small-scale production companies may be inferior to those produced by top companies in the market [47,48].

5. CONCLUSION

This study demonstrates that good manufacturing practices may have been adhered to – thus resulting in the production of quality medications by local manufacturers (generic brands). The in-vitro examination of amlodipine tablets has generally revealed good quality, satisfactory uniformity of weights, hardness, friability, disintegration, and dissolution rate when compared to the innovator brand. Hence, the evaluated brands can be used interchangeably with innovator brands, and the assay procedures can be used routinely to control and ensure the quality of pharmaceutical solid dosage formulations.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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