Content Uniformity and Invitro Dissolution of Amlodipine Half Tablets

Rene BROWN AMADI[1] and Sarah VUGIGI[1]

1. Department of Pharmaceutical Chemistry & Pharmaceutics, School of Pharmacy, Kabarak University, P.O. Private Bag Kabarak-20157, Kenya

   Correspondence: *ramadi@kabarak.ac.ke*

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ABSTRACT

Tablet splitting technique is a practice that is carried out in hospitals and community pharmacies. The aim is to achieve dose flexibility, reduce tablet size, ease swallowing and save cost. This technique is prone to variation in the weight of split tablets, mass loss and content uniformity. Its effectiveness is subject to the tablet characteristics, method of splitting and patient's knowledge and skill. This practice increases the risk of inaccurate dosing, uneven distribution of drug substances and potential loss of efficacy or adverse effects. This study aimed to determine the effect of splitting amlodipine tablets on weight variation, content uniformity and in-vitro dissolution. Four brands of amlodipine 10mg tablets from the Kenya pharmaceutical market were evaluated. For each brand, weight variation and content uniformity tests were conducted as per the European Pharmacopoeia. Dissolution test was performed on 6 split tablets according to the British Pharmacopoeia. All the brands of amlodipine half tablets tested for weight variation were within acceptable limits. Only one individual mass was outside the 85-115% limit of the average weight, being 83.87%. Three of the four brands complied with the content uniformity test. One brand had 2 split tablets having amlodipine content out of the limit of 85-115%. Three brands complied with the dissolution test requirement for amlodipine tablets at the S1 stage. One brand had at least 75% of the amount of amlodipine (5mg) dissolved for the half tablets that were tested. The study shows variation in content uniformity and dissolution test for one brand each. All the brands met the pharmacopeia requirements for the tablet weight variation test.

Keywords: *Amlodipine, Content, Dissolution, Uniformity, Weight*

INTRODUCTION

Dosage forms, such as tablets, are designed to deliver accurate quantities of the drug substance for desired efficacy (Alexander et al., 2006). Tablet splitting is a common practice with benefits such as dose flexibility, cost-saving effects, and easier swallowing (Verrue et al., 2011). This practice takes into account inter-individual differences and varying dosage ranges for dose flexibility. However, accuracy and precision in tablet splitting can be challenging, leading to variations in weight and content of split tablets (Chaudhri et al., 2019). This may lead to delivery of quantities lower or higher than the desired amount. Factors such as tablet characteristics and splitting techniques can affect accuracy (Tahaineh & Gharaibeh, 2012; Seong et al., 2019). Patient factors also play a role; the knowledge and skills, the patient's state of consciousness, age and vision acuity (Ganzetti et al., 2021; Emagn et al., 2022).

Inaccurate splitting can result in underdosing or overdosing, impacting treatment efficacy and causing adverse reactions (Shah et al., 2010). Studies should investigate the challenges of tablet splitting, including accuracy, precision, and variability, to develop strategies to overcome them (Kanika et al., 2023). Healthcare professionals should provide clear instructions to patients, and regulatory guidelines are necessary for safe and effective tablet splitting (Elliott et al., 2014; FDA, 2013). The effectiveness of tablet splitting is crucial in ensuring the performance of the product.

This study seeks to fill a knowledge gap by examining the uniformity of content and mass in split amlodipine tablets. The findings will inform healthcare providers on appropriate tablet splitting methods, improving dosing accuracy and treatment efficacy. Additionally, the study results will impact patient outcomes by reducing the risk of adverse reactions and drug toxicities associated with inconsistent dosing, potentially leading to interventions to enhance tablet splitting accuracy and consistency.

The United States Pharmacopeia and The European Pharmacopoeia outline quality specifications for scored tablets, including weight variation, content uniformity, disintegration time, friability, hardness, and dissolution, which are crucial for ensuring medication safety and efficacy. Weight variation, content uniformity, and dissolution tests are carried out to assess the quality of split tablets. The specification acceptance criteria is presented in Table 1. Tablet characteristics like hardness, diameter, thickness, and shape are also considered during the study.

Table 1:

Tablet Parameter Specification and Acceptance Criteria

Specification	Acceptance criteria
Weight variation	85-115% of the average weight of split tablets.
Content uniformity	Not more than one individual weight outside 85-115% No individual unit less than 75% or greater than 125%
Disintegration	Less than 15 minutes
Dissolution	Amount dissolved ≥ 80% of the label claim
Friability	Less than 1%
Hardness, diameter, thickness, and shape	Manufacturers In-house specification

In this study, the effect of splitting of amlodipine tablets was investigated. Amlodipine has a long half-life (30-50 hours) and consistent dosing is crucial for maintaining steady blood pressure control. The tablets are formulated as amlodipine besylate and are used in the management of hypertension and angina (Bulsara & Cassagnol, 2022). Adverse effects of amlodipine include peripheral edema and cardiovascular complications. The drug can be manufactured in 10mg tablets with a score line for splitting (Melisa Puckey, 2022).

METHODOLOGY

Quantitative analysis of amlodipine besylate tablets was performed to assess dose variability in split tablets. Four amlodipine tablet brands were selected from the Kenya pharmaceutical market. The study was carried out at the Pharmaceutical Chemistry and Pharmaceutics laboratories, at Kabarak University, Kenya.

Materials

UV-Vis spectrometer Model; Li-2904 and Dissolution Apparatus Model; UMS-RC8 were used to perform the content uniformity test and dissolution test respectively. Freshly distilled water was prepared in the Kabarak School of Pharmacy Pharmaceutical Chemistry laboratory. HCl, 0.01M medium was prepared in the Kabarak School of Pharmacy, Pharmaceutics laboratory. Solutions were filtered with Whatman filter No. 1 0.45-µm pore size filter.

Method

Weight Variation Test

For every brand, thirty tablets were selected randomly, split into halves, and one split part was weighed from each tablet. The average of the split tablets was calculated. The acceptance criteria of this test; not more than one individual weight can be outside the range of 85-115% of the average weight, and not more than one individual weight can be outside the range of 75-125% of the average weight as per the European Pharmacopoeia (11th Edition).

Content Uniformity Test

Ten tablets were split into halves, from the pool of split halves; ten split tablets were randomly selected. The split tablets were dissolved in 100ml distilled water. Absorbance was measured at 238 nm against a standard solution. The acceptance criteria; not more than one individual weight can be outside the range of 85-115% of the average weight, and not more than one individual weight can be outside the range of 75-125% of the average weight as per the European Pharmacopeia (11th Edition).

Standard preparation

A quantity of amlodipine besylate (equivalent to 1.5mg of amlodipine) was weighed and dissolved in a 100-volumetric flask. The solution was filtered and absorbance was taken at a wavelength of 238 nm using the UV-Visible spectrophotometer.

Dissolution Test

Ten tablets were split into halves, from the pool of split halves; six split tablets were randomly selected. The split tablets were subjected to a dissolution test, the paddle method. The dissolution medium was 0.01M Hydrochloric acid at 37°C, at 50 rpm for 20 minutes. Absorbance was measured at 238 nm. To pass the test at Stage S1, all six split tablets should have an amount of amlodipine dissolved, not less than 80 percent, United States Pharmacopeia, 2020.

Standard Preparation

A solution containing 0.0055mg/ml of amlodipine was prepared in 250 ml of 0.01M HCl, by dissolving 7.626g of Standard amlodipine besylate to 1 liter of 0.01M HCl.
The solution was subjected to a dissolution test, paddle method at 37°C, at 50 rpm for 20 minutes. The solution was filtered and absorbance was taken at a wavelength of 238 nm using the UV-Visible spectrophotometer.

Ethical considerations

In order to attain and assess the study aims, the Kabarak University Research Ethics Committee (KUREC) and Kabarak University School of Pharmacy approved and authorized the research.

RESULTS

Physical Parameters of Amlodipine Tablets

The physical parameters of the amlodipine tablets are described in Table 2. Brand 1 had an average whole tablet thickness of 3.57mm, a cylindrical shape with a diameter of 7.00mm and an average whole tablet hardness of 69.8N
Brand 2 had an average whole tablet thickness of 3.48mm, a cylindrical shape with a diameter of 8.07mm and an average whole tablet hardness of 55.4N
Brand 3 had an average whole tablet thickness of 3.38mm, an oblong shape with a diameter of 10.80mm and an average whole tablet hardness of 73.3N.
Brand 4 had an average whole tablet thickness of 2.77mm, a cylindrical shape with a diameter of 7.96mm and an average whole tablet hardness of 27.2N.

Table 2:

Physical Parameters of Amlodipine Tablets

Brand	Shape	Average Thickness (mm)	Average Diameter (mm)	Average Hardness (N)
1	Circular shaped	3.57	7.00	69.8
2	Circular shaped	3.48	8.07	55.4
3	Oblong shaped	3.38	10.80	73.3
4	Circular shaped	2.77	7.96	27.2

Weight Variation Test

The weight variation test results for the four brands of amlodipine tablets are presented in Table 3. Four brands of amlodipine tablets were evaluated. Brand 1 had an average whole tablet weight of 162.2mg, an average weight of the split tablet of 93.00mg, and a standard deviation of 7 for the weights of the split tablets.
Brand 2 had an average whole tablet weight of 174.8mg and an average weight of the split tablets of 93.03mg. The standard deviation of the split tablet weight was 6.82.
Brand 3 had an average whole tablet weight of 322.8mg and an average weight of split tablets of 161.00mg. The standard deviation of the split tablet weights was 4.
Brand 4 had an average whole tablet weight of 172.2mg and an average weight of split tablets of 99.00mg. The standard deviation of the split tablet weights was 8.

Table 3:
Weight Variation Test

	Brand 1	Brand 2	Brand 3	Brand 4
Average Weight of Split Tablets (mg)	93.00	93.03	161.00	99.00
Average Weight of the Whole Tablet (mg)	162.2	174.8	322.8	172.2
The standard deviation of the Weights of split tablets	7	6.82	4	8
Compliance with acceptance criteria (85-115)	Yes	Yes	Yes	Yes

Content Uniformity Test

The content uniformity test results for the 4 brands of amlodipine tablets are presented in Table 4.
Brand 1: Out of the ten split tablets tested, nine complied with the content uniformity test within the 85-115 percentage limits. However, one tablet had a lower amlodipine content, 84.955%, within the 75-125%. The standard deviation of amlodipine content was 0.435. Two tablets exceeded the desired dosage of 5mg of 5mg while eight tablets had amounts lower than the desired dosage of 5mg.
Brand 2: All split tablets met the content uniformity test requirements. The standard deviation of amlodipine content was 0.274. All tablets had amlodipine content above the desired dosage of 5mg of 5mg.
Brand 3: All split tablets complied with the content uniformity test. The standard deviation of amlodipine content was 0.288. Three split tablets had amlodipine content higher than the desired dosage of 5mg, while seven were below the desired dosage of 5mg of 5mg.
Brand 4: Eight tablets from brand 4 met the content uniformity test requirements, but two tablets were outside the 85-115% limit. This brand, therefore, did not meet the compliance criteria. The standard deviation of amlodipine content was 0.627.

Table 4:
Content Uniformity Test

	Brand 1	Brand 2	Brand 3	Brand 4
Average Amount of Amlodipine content in the Split Tablets (mg)	4.557	5.520	4.762	5.037
Split tablets with amounts higher than 5mg	8	10	3	6
Split tablets with amounts lower than 5mg	2	0	7	4
The standard deviation of the Weights of split tablets	0.435	0.274	0.288	0.627
Compliance with acceptance criteria	Yes	Yes	Yes	No

Dissolution Test

The dissolution test results for the 4 brands of amlodipine tablets are presented in Table 5.
Brand 1: All tablets met the dissolution test requirements, with amlodipine content dissolved more than 80 percent of the desired dosage of 5mg of 5mg. The average amount of amlodipine dissolved was higher than the 5mg. The standard deviation of the amount of amlodipine dissolved was 0.216.
Brand 2: Five tablets from brand 2 met the dissolution requirements, one tablet fell below the specified limit. The average amount of amlodipine dissolved was lower than the desired dosage of 5mg of 5mg. The standard deviation of the amount of amlodipine dissolved was 0.586.
Brand 3: All tablets met the dissolution requirements. One tablet exceeded the desired dosage of 5mg. The average amount of amlodipine dissolved was lower than the desired dosage of 5mg. The standard deviation of the amount of amlodipine dissolved was 0. 345.

Brand 4: All tablets met the dissolution requirements. The average amount of amlodipine dissolved was lower than the desired dosage of 5mg. The standard deviation of the amount of amlodipine dissolved was 0.218.

Table 5:
Dissolution Test

	Brand 1	Brand 2	Brand 3	Brand 4
Average Weight of Split Tablets (mg)	93.00	93.03	161.00	99.00
Split tablets with amounts higher than 5mg	6	2	1	2
Split tablets with amounts lower than 5mg	0	4	5	4
Split tablets with amounts higher than 80 percent of the desired dosage of 5mg, (4mg)	6	6	6	5
The standard deviation of the Weights of split tablets	0.216	0.586	0.345	0.218
Compliance with acceptance criteria	Yes	Yes	Yes	No

DISCUSSION

Weight Variation Test

Based on the weight variation test results, all four evaluated brands of tablets met the compliance criteria set by pharmacopeial standards. Brand 3 exhibited the highest consistency and consequently lowest standard deviation, 4, in split tablet weights. Brand 1 and brand 4 showed relatively higher variability. Factors such as tablet shape, size, hardness, and thickness influenced the weight variation. Brand 3 had the largest whole tablet size and diameter, and an oblong shape. This may have led to better splitting accuracy demonstrated by the lower standard deviation and highest consistency. Overall, the tablets demonstrated acceptable weight uniformity, indicating compliance with quality standards for pharmaceutical tablets.

Content Uniformity Test

Based on the content uniformity test results, brand 2 and brand 3 demonstrated better consistency and compliance with the specified limits compared to brand 1 and brand 4. Brand 1 and brand 4 exhibited higher variation (standard deviation of 0.435 and 0.627) in amlodipine content, with some tablets deviating from the desired dosage of 5mg. The two had cylindrical shaped tablets, a relatively smaller diameter, 162.2mm and 72.2mm. Brand 2 had a higher percentage of tablets exceeding the desired dosage of 5mg, while brand 3 showed smaller deviations from the desired dosage of 5mg with a lower standard deviation. Overall, brand 3 exhibited the best performance in terms of content uniformity, followed by brand 2, while brand 1 and brand 4 showed relatively higher variability. Brand 3, still had better results in this test. The tablet characteristics can be attributed to having influenced the results; being the largest in size, oblong-shaped and with a deeper score line. The results obtained were consistent with the weight variation test, with the tablet brand having a better consistency in the tests. Brand 4 did not meet the acceptance criteria as only eight of the ten tablets were within the 85-115% limit. This brand exhibited the highest variation in amlodipine content. The inconsistency is also attributed to the tablet features; smaller tablet size and lower diameter.

Dissolution Test

Based on the dissolution test results, three of the four brands met the dissolution requirements. However, there were variations in the dissolution test and the amount of amlodipine dissolved among the brands. Brand 1 had a higher average amount of amlodipine dissolved and met the requirements, while brand 2 had one tablet below the limit and a higher variation in dissolution rate. This brand had harder tablets and the highest thickness, in addition to being smaller in size and lower in diameter. These parameters contributed to lower accuracy and precision during the split, with a standard deviation of 0.586. Brand 3 and brand 4 met the dissolution requirements, but the average amount of amlodipine dissolved was lower than the desired dosage of 5mg. The variation in the dissolution test for brand 3 was moderate, standard deviation of 0.345. Tablet characteristics, including oblong shape and largest size, contributed to better performance for this test as well. Overall, the dissolution performance varied among the brands, potentially influenced by tablet characteristics such as size, shape, hardness, and thickness.

Conclusion (s)

The study found that physical characteristics like size, shape, hardness, and thickness affect how accurately amlodipine tablets can be split, impacting weight variation, content uniformity, and dissolution. The oblong shape in brand 3 made it easier to split compared to the cylindrical-shaped tablets. Brand 3 had the largest whole tablet size and diameter. This made it have consistently better results in all three tests. All brands met the weight variation test requirements, but brand 4 had the highest variation, standard deviation of 8. Three brands met the content uniformity criteria, while brand 4 did not. The dissolution test results varied among the brands, with brand 1 consistently exceeding the desired dosage of 5mg, brand 2 having the lowest amount dissolved, brand 3 showing moderate variation, and brand 4 having the second-highest amount of drug substance dissolved. These findings highlight the importance of conducting quality tests to ensure consistent dosing in split tablets. Patients and healthcare professionals should be aware of the potential dose variations caused by tablet characteristics, pharmaceutical manufacturers, and Drug Regulatory Authorities should ensure compliance with quality standards for scored tablets.

Recommendation (s)

To enhance patient safety, healthcare providers should educate patients about the potential risks of tablet splitting and advise them to do it only when necessary and under professional guidance. Regulatory agencies should ensure split tablets meet the required quality standard for weight variation, content uniformity, and dissolution. Further research should investigate the impact of tablet splitting on the bioavailability and pharmacokinetics of amlodipine and other drugs to improve understanding of patient outcomes. Implementing these recommendations will improve the quality and safety of tablet splitting; ensuring patients receive accurate medication doses and achieve optimal therapeutic results.

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