Misurata Medical Sciences Journal (MMSJ)
Vol.6 Issue 2 (Winter 2024)
https://doi.org/10.36602/mmsj/2024.n11.01
http://www.misuratau.edu.ly/journal/mmsj

Research Article

IN VITRO COMPARATIVE QUALITY ASSESSMENT OF FUROSEMIDE BRANDS MARKETED IN MISURATA CITY

By
Ali Rafieda; Mohamed Daghman; Abdelkarim Sasi; Basma Hendi; Reetag Erhoma; Halima Abuhbeil
Faculty of Pharmacy, Misurata University

ABSTRACT

Choosing the proper drug product is becoming increasingly complicated for health professionals and patients due to the abundance of generic brands in the local drug market. This study aimed to evaluate the different physicochemical parameters of furosemide (FSM) tablets from various manufacturers using in vitro tests to minimize health risk factors and maximize the safety of consumers. Four brands (X1, X2, X3, X4) of furosemide tablets were evaluated using both official and unofficial *in vitro* Quality control tests, including both official and unofficial methods: visual inspection, uniformity of weight, thickness and diameter test, hardness test, friability test, disintegration test, dissolution test, and uniformity content assay. The results showed that all four brands of the (FSM) tablets are meet the British Pharmacopeia (BP) and United State Pharmacopeia (USP) standard specifications for *in vitro* evaluation Quality control tests. Physicians can recommend any of these four products to patients, as they all demonstrated reliable results. The studied products were of good quality and can be used to achieve the desired therapeutic effect.

KEYWORDS: Furosemide, Tablet, Quality control tests.

INTRODUCTION

The selection of drugs is typically based on their pharmacological properties such as potency, selectivity, duration of action, and safety or toxicology assessments. however, even when these pharmacological factors are satisfactory, a candidate drug must also possess suitable pharmaceutical properties. These include good aqueous solubility, crystallinity, non-hygroscopicity, and stability. Importantly, a drug's solid-state properties such as particle size, powder flow, compression, and polymorphism play a crucial role during the preformulation stage. Moreover, cost is a significant barrier to accessing essential medicines, especially in low-income countries. Generic medicines offer a partial solution as they are typically cheaper than their counterpart innovator medicines [1]. Governments and third-party payers have increasingly promoted the use of generics to control healthcare and medication costs. However, the push to reduce healthcare expenses by incorporating generics into the system has led to concerns about

Corresponding author: Ali Rafieda
Email: a.rafieda@phar.misuratau.edu.ly
ORCID: 0009-0002-1368-8919
Received 2 September 2024
Accepted 20 October 2024
Published 30 November 2024

substandard, counterfeit, and mislabelled medicines [2].

To ensure overall suitability, drugs undergo initial physicochemical testing to measure parameters like particle size, true density, bulk density, tapped density, surface area, compression, and powder flow properties. Tablets and capsules are the most frequently used solid dosage forms. These forms combine a mixture of ingredients into a single rigid entity, typically containing an accurate dose of the drug. Tablets, categorized as either compressed or molded, are largely manufactured by compression. Solid dosage forms offer several benefits due to their unique applications and convenience. They are considered the least invasive method of drug delivery and can be self-administered by patients. For manufacturers, solid oral dosage forms offer competitive advantages including cost effectiveness, compactness, aesthetic value for brand identification, and stability [1]. Approximately 70% of all drugs administered today exist in solid dosage forms. Most pharmaceutical companies prefer to introduce new molecules to the market as tablets or capsules due to considerations of cost, safety, and marketing. Consequently, tablets and hard gelatine capsules remain the most frequently used dosage forms. This widespread use underscores the importance of understanding the properties of powder systems for rational formulation and manufacturing procedures. Ensuring product quality in solid dosage forms involves multiple features: chemical and physical stability, suitable preservation against microbial contamination, uniformity of drug dosage, and acceptability to users, including prescribers and patients.

The quality of these products can be assessed through in vivo or in vitro testing methods [3]. The quality control assessment is carried out to control the quality of products which begins from starting materials, processing, packaging, labelling, and finished product testing as well as batch reviewing and stability monitoring. The control on all manoeuvres should be established in the structure of Standard Operating Procedures (SOPs) which noticeably explains to follow the in-process quality control tests (IPQCs) [4]. The majority of patients with hypertension require medication to maintain consistent blood pressure control. Common anti-hypertensive drugs include diuretics, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. Among these, calcium channel blockers and diuretics, such as (FSM), play important roles in managing hypertension and edema. (FSM) is widely prescribed for acute and chronic heart failure, severe hypertension, and various edematous conditions [5]. In resource limited countries like Libya, the circulation of substandard medicines remains a critical issue. Many imported drugs in these markets are often found to contain incorrect concentrations of active ingredients, indicating serious health risks. furosemide tablets are extensively prescribed for long-life use and are crucial for saving lives, and thus ongoing post market quality control assessments are essential [6]. Therefore, this study was conducted to assess the quality and physicochemical parameters of furosemide (FSM) tablets (40mg) from four different brands through in vitro tests, with the goal of reducing health risks and enhancing safety for residents.

METHODOLOGY

Sample Collection

Furosemide (FSM) samples were collected from various pharmacies in Misurata City, Libya. For the study, samples from four different brands were coded as brand X1, X2, X3, and X4. All of the brands of FSM were within their shelf lives and labeled to contain 40 mg of Furosemide; moreover, all necessary information about the samples was recorded in a standard analytical report form.

Chemicals , Reagents And Equipments

The chemical reagents used in this experiment included Sodium Hydroxide pellets, described under batch number V2D508072E, sourced from Carlo Erba Reactifs-SDS. Additionally, distilled water was prepared using a Purite Select Analyst HP water purification system. The equipment used in this study included an electronic balance (Mettler Toledo) for the weight variation test and a side calipers for measuring diameter and thickness. For the friability test, a digital friability test apparatus was used (Harrisons Pharma *Machinery PVT. LTD., Darya Ganj, New* Delhi). The tablet hardness test was conducted using a tablet hardness tester (Harrisons Pharma Machinery PVT. LTD.). The disintegration time was measured with a tablet disintegration tester (Harrisons Pharma Machinery PVT LTD.). A dissolution apparatus (paddle apparatus) from Pharma Test (D-63512 Hainburg PT-DT70) was used for the dissolution test. A UV-Vis spectrophotometer was employed for both the dissolution and assay tests.

PROCEDURES

Visual Inspection:

Visual inspection involves examining the tablets with the naked eye to identify any flaws. The inspection criteria include the shape (circular, oval, flat sides, etc.), uniformity of shape, and uniformity of color. The tablets should have no physical damage, such as cracks, breaks, abrasions, or stickiness. Additionally, the inspection checks for other observations, such as the absence of foreign contaminants and dirty marks. Packaging aspects like blister condition, manufacturer address, manufacturing date, batch number, country of origin, labeling, expiry date, and any cracks, capping, or chipping on the tablet surface are also assessed.

Weight Variation Test:

The weight variation test ensures that each tablet contains the correct amount of the drug by measuring its weight. This test is crucial for verifying that the tablets have the proper amount of the active ingredient as designated in the tablet formula. For Furosemide tablets, the weight variation test was conducted as follows: Twenty tablets from each brand were individually weighed as X1, X2, X3, ..., X20 using an analytical balance. Subsequently, the average weight, percentage deviation, and standard deviation (SD) were determined. Percentage deviation was computed using equation 1:

$$= \frac{(Individual\ tablet\ weight - Average\ weight\ of\ 20\ tablet]}{(Average\ weight\ of\ 20\ tablet]} \times 100$$

The tablets met the BP test as not more than 2 tablets were outside the percentage limit and no tablets deviate twice of the percentage limit [7].

Thickness Measurement:

The procedure involved taking ten Furosemide tablets from each brand, labeled as T1, T2, T3, ..., T20, and measuring their thickness using slide calipers. The thickness measurements were recorded in millimeters. The average thickness (T) was calculated using the formula: Average Thickness T = (T1+T2+T3+……T20)/20 Subsequently, standard deviations were calculated for the thickness measurements.

Friability Test:

The friability of the tablets was assessed using a Friabilator. This test measures the percentage weight loss of 20 tablets to determine their durability under mechanical stress. Initially, 20 tablets from each brand were individually weighed. They were then placed in the Friabilator and tumbled at 25 rpm for 4 minutes (100 revolutions). After tumbling, the tablets were re-weighed, and the percentage friability was calculated by comparing the initial and final weights using equation 2:

$$\%\ of\ friability = \frac{(Initial\ weight\ of\ 20\ tablets - final\ weight\ of\ 20\ tablets)}{Initial\ weight\ of\ 20\ tablets} \times 100$$

Friability results were evaluated against a specification that requires friability to be less than 1% (7].

Hardness Test:

The hardness test assesses a tablet's strength, a critical quality parameter affecting properties like disintegration, dissolution, and friability. It measures the load required to crush a tablet placed on its edges. For FSM tablets, the hardness test followed these steps: Tablets were positioned between two plates, with one *plate moving to exert pressure until the* tablet fractured. The load at which this occurred was recorded as the tablet's hardness. This procedure was repeated for 10 tablets, ensuring any fragments were removed between measurements, and an average hardness was calculated. Specifications dictate that oral tablets should have a hardness of 4 to 10 kg [7].

Disintegration time determination: Disintegration time determination is crucial in tablet quality control, reflecting product performance under specified conditions. Using a Tablet Disintegration Tester with discs in distilled water medium, six tablets from each brand were placed in separate tubes within a basket rack immersed in 900 ml of water at 37±0.5˚C. The disintegration time for each tablet was recorded using a stopwatch. According to BP specifications, uncoated tablets should disintegrate within 15 minutes. This criterion ensures that tablets meet the required standards for dissolution in clinical settings [7,8].

Dissolution Test:

The Dissolution Test evaluates how tablets break down in the stomach, aiding the release of active ingredients for absorption and metabolism. Tablets that fail disintegration tests often do not meet dissolution criteria, underscoring the role of disintegration tests in tablet quality control. In this study, the dissolution test used a Dissolution Tester (paddle apparatus) for each brand of tablets. Six

tablets from each brand were placed individually in vessels with 900 ml of distilled water at 37±0.5˚C and stirred at 50 rpm. After 45 minutes, 5 ml of dissolution sample was withdrawn, filtered, and 2.5 ml of the filtrate was taken by using pipette into a 10 ml conical flask and diluted. The absorbance of each sample was measured at 277 nm wavelength. The percent release of drug from the tablet should not be less than 80% in 45 min [9].

Uniformity Content Assay Method:

Weigh and powder 20 tablets. Shake a portion of the powder containing 0.2 g of Furosemide with 300 ml of 0.1 M sodium hydroxide for 10 minutes. Add enough 0.1 M sodium hydroxide to reach a total volume of 500 ml and filter the solution. Dilute 5 ml of the filtered solution to 250 ml with 0.1 M sodium hydroxide and measure the absorbance at its maximum at 271 nm. Finally, calculate the content of $C_{12}H_{11}ClN_2O_5S$ using 580 as the value of A (1%, 1 cm) at the maximum absorbance at 271 nm [8].

RESULTS AND DISCUSSION

All four brands of Furosemide (FMS) tablets included in this study were imported from foreign countries.

Table 1: Weight variation of four brands of Furosemide tablets

No. of tab	Weight of individual tablets (g)				% of Deviation			
	X1	X2	X3	X4	X1	X2	X3	X4
1	0.1672	0.1652	0.1571	0.1631	2.09128	0.60595	-0.5035	-0.26905
2	0.1631	0.1683	0.1562	0.1629	-0.41215	2.49383	-1.0984	-0.40474
3	0.1603	0.1617	0.1564	0.1653	-0.02122	-1.49569	-1.02898	1.04107
4	0.1619	0.1629	0.1574	0.1612	-1.14486	-0.63262	-0.45308	-1.40807
5	0.1695	0.1651	0.156	0.1609	3.49565	0.63306	-1.36479	-1.67299
6	0.1649	0.1681	0.1588	0.1613	0.686918	2.41899	0.320015	-1.53151
7	0.1641	0.1659	0.1548	0.1642	0.198443	1.11595	-2.18607	0.136605
8	0.1628	0.1678	0.155	0.1658	-0.59533	2.44179	-2.21239	1.122225
9	0.1638	0.1628	0.1576	0.1679	0.015265	-0.51962	-0.741	2.491501
10	0.1641	0.1661	0.1597	0.1715	0.198443	1.69523	0.51954	4.906868
11	0.1628	0.1652	0.1554	0.1619	-0.59533	1.11680	-2.14078	-0.52172
12	0.1641	0.1584	0.1598	0.1651	0.198443	-2.89818	0.415045	1.391601
13	0.1632	0.1681	0.1602	0.1624	-0.35109	3.17915	0.712841	-0.11208
14	0.1649	0.1665	0.1620	0.1653	0.686918	1.88298	1.935276	1.657391
15	0.1659	0.1546	0.1566	0.1601	1.297512	-5.05909	-1.18939	-1.30687
16	0.1632	0.1600	0.1553	0.1644	-0.35109	-1.42624	-2.20352	1.123596
17	0.1632	0.1661	0.1622	0.1677	-0.35109	1.52760	1.693428	3.385776
18	0.1605	0.1652	0.1601	0.1629	-1.99969	0.53492	0.803564	1.283925
19	0.1625	0.1646	0.1581	0.1580	-0.77851	0.441644	-0.18834	-1.34044
20	0.1635	0.1615	0.1592	0.1589	-0.16791	-1.18396	0.411549	-1.43903
Mean	0.1637	0.1642	0.1578	0.1635				

Furthermore, all FMS brands were subjected to various quality control tests to assess their dissolution profile, as well as other quality parameters such as weight variation, friability, hardness, and assay.

Visual Inspection:

All brands of FSM tablets exhibited uniform color, size, and shape, with no visible cracks or breaks. Additionally, there were no defects in the packaging and labeling of any brand.

Weight Variation Test:

The weight variations of four different brands of FSM tablets were determined. For each brand, 20 tablets were weighed, and the observed results are shown in Table 1. The test for uniformity of weight is carried out on tablets to ensure accurate and consistent dosage forms for patients. As shown in Table 1, the average weight obtained for 20 tablets from each brand was as follows: 0.163775 g, 0.16421 g, 0.157895 g, and 0.16354 g. According to the BP and USP specified criteria, for tablets weighing between 80 mg and 250 mg, a minimum of 18 tablets should not deviate from their average weight by more than 7.5%. The uniformity of weight for the tablets is acceptable, as all 20 tablets per each brand did not deviate by more than 7.5% as shown in the Figure (1).

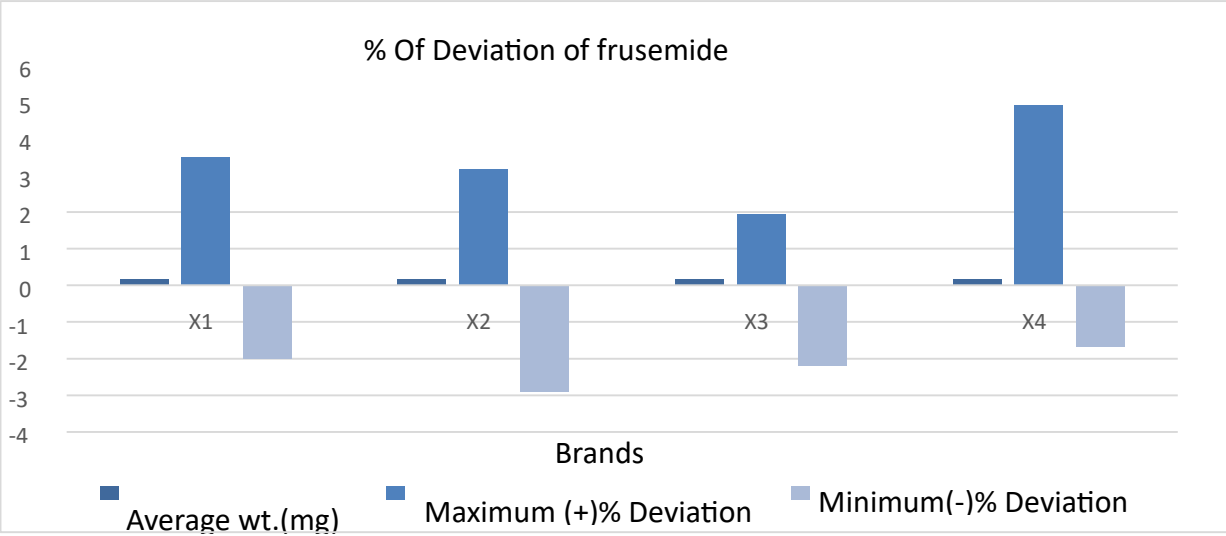

Figure 1: % Deviation of four brands of furosemide tablets

Thickness Measurements:

The thickness and diameter of the FSM tablets were measured using a slide caliper. According to the results obtained, as shown in Table 2, the average thickness of the tablets for each brand was as follows: X1 = 2.841 mm, X2 = 2.922 mm, X3 = 3.156 mm, and X4 = 2.255 mm. The average diameter of the tablets for each brand was: X1 = 8.192 mm, X2 = 8.188 mm, X3 = 8.061 mm, and X4 = 8.171 mm. The diameter and thickness measurements are uniform, with slight variations between brands. The thickness and diameter results of the FSM brand samples, as mentioned in Table 2, show that all test samples comply with BP and USP standards [8].

Table 2: Thickness Measurements of four brands of Furosemide tablets.

No. of tab	Thickness				Diameter			
	X1	X2	X3	X4	X1	X2	X3	X4
1	2.89	2.90	3.14	2.25	8.17	8.47	8.04	8.20
2	2.86	2.93	3.17	2.25	8.18	8.00	8.00	8.11
3	2.85	2.92	3.18	2.26	8.25	8.00	8.05	8.17
4	2.83	2.94	3.20	2.28	8.18	8.01	8.10	8.18
5	2.81	2.93	3.18	2.24	8.18	8.47	8.05	8.21
6	2.84	2.91	3.11	2.23	8.17	8.02	8.04	8.16
7	2.80	2.94	3.13	2.25	8.20	8.04	8.20	8.19
8	2.88	2.93	3.16	2.27	8.19	8.41	8.03	8.17
9	2.82	2.90	3.15	2.28	8.23	8.03	8.04	8.11
10	2.83	2.92	3.14	2.24	8.17	8.43	8.06	8.21
Mean ± SD	2.84 ± 0.029	2.92 ± 0.0147	3.15 ± 0.027	2.25 ± 0.017	8.19	8.18	8.06	8.17

Hardness Test:

The hardness of four FSM tablet brands was assessed, and the results are summarized in Table 3. The test involved placing tablets between two plates, one of which was moved to apply increasing pressure until the tablet fractured. The load at which the fracture occurred was recorded as the tablet's hardness. Measurements were taken from 10 tablets for each brand.

Table 3: Results of Friability, Hardness, Disintegration Time and Assay of Five Brands of Furosemide Tablets.

Brands	Average Weight (mg) ± SD	Mean Hardness ± SD	Friability (%)	Disintegration Time (DT) second	% of drug release (45 min) ± SD	Assay (%)
X1	0.1637	5.46 ±1.199	0.2081%	27	202.45% ± 0.031	100.06%
X2	0.1642	8.035 ± 1.137	0.6982%	48	311.24% ± 0.060	102.66%
X3	0.1578	4.89 ± 0.834	0.2129%	48	164.55% ± 0.203	99.42%
X4	0.1635	9.22 ± 0.925	0.2157%	134	269.42% ± 0.040	102.12%

As shown in Table 3, the average hardness for each brand was as follows: X1 = 5.46±1.199 kg, X2 = 8.035±1.137 kg, X3 = 4.89±0.834 kg, and X4 = 9.22±0.925 kg. These values represent the force needed to break a tablet. The hardness of the tablets is considered acceptable, as none of the tablets were very fragile. All brands of furosemide (FSM) tablets in this study met the hardness test limits, indicating they have sufficient strength to withstand handling, packaging, storage, and transportation conditions. Hardness is a crucial parameter for ensuring tablet quality and durability [10].

Disintegration Test:

Disintegration is the process of breaking up of a tablet. It's important for a drug to be in solution form for it to be absorbed from a solid dosage after oral

administration. As shown in Table 3, the mean disintegration time results of furosemide tablets were between 27sec. and 134sec. Uncoated tablets should disintegrate within 15min's. Hence, all the brands of furosemide tablets were within acceptable limits [7,8].

Friability Test:

As shown in Table 3, the friability of four brands of FMS tablets were in the range of 0.2081% (X1) to 0.6982% (X2). In this study, friability is defined as the percentage of weight loss by tablets due to mechanical action during the test. Tablets were weighed before and after testing, and friability was expressed as the percentage loss. Friability refers to the ability of a compressed tablet to resist fracture and breaking during transport. The results showed that the percentage weight loss for each brand (X1, X2, X3, X4) was 0.2081%, 0.6982%, 0.2129%, and 0.2157%, respectively. According to standards, a compressed tablet should not lose more than 1%. Therefore, all the tested brands met the specification of friability (7,11].

Standard Curve Preparation:

The standard curve of the standard solution of FSM tablets was obtained by plotting concentration against absorbance. Table 4. shows the absorbance values of FSM against their respective concentration. The standard curve is shown in figure 2.

Table 4: Absorbance and Concentration of Standard Solution of Furosemide

Concentration (µg/ml)	Absorbance
0	0
2	0.09
4	0.17
6	0.26
8	0.36
10	0.44

Dissolution Test:

The dissolution study of furosemide tablets was carried out in neutral media (H2O) and the absorbance was obtained (Table 5). From the straight-line equation y = 0.0443 x -0.0014, we calculate the percentage of release of each one of the brands by use the following formula.

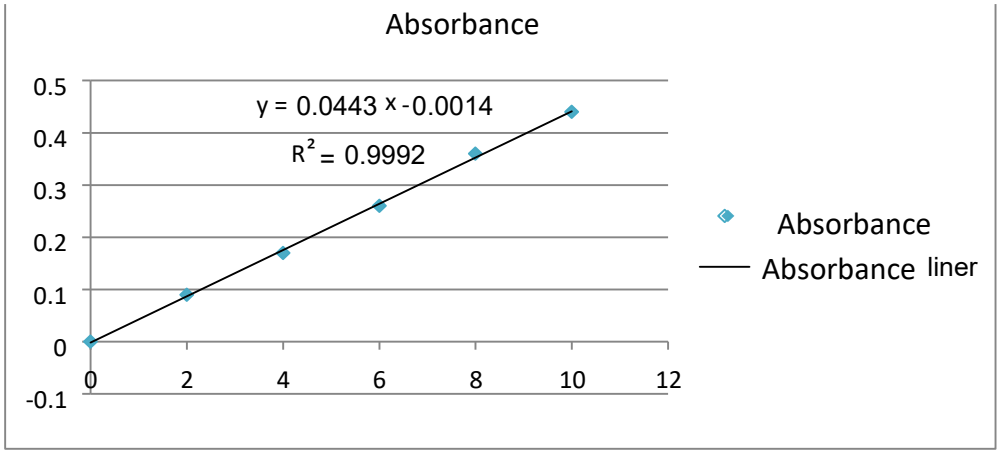

Figure 2: Standard calibration curve of Furosemide.

$$Conceentration\ of\ drug\ release = \frac{Absorbance - Intercept}{slope}$$

$$Amount\ of\ release = \frac{Concentration\ * Volume\ of\ dissolution\ media}{1000}$$

$$\%\ drug\ release = \frac{Amount\ of\ drug\ release\ * Dilution\ factor}{Drug\ dose}$$

Table 5: Results of Absorbance, Concentration of drug release and Amount of drug release of Furosemide

No.	Abs. X_1	Abs. X_2	Abs. X_3	Abs. X_4
1	0.37608	0.69942	0.20297	0.57682
2	0.40286	0.58635	0.10840	0.56196
3	0.44507	0.59846	0.55733	0.56364
4	0.38252	0.57248	0.48046	0.488392
5	0.42746	0.67739	0.48220	0.49050
6	0.36605	0.55110	0.12104	0.50992
Average	0.400007	0.6142	0.3254	0.531872
±SD	0.031	0.060	0.203	0.040
CDR (µg/ml)	8.997893	13.83296	7.31377	11.97454
ADR (mg)	8.098104	12.44966	6.582393	10.77708

CDR, Concentration of drug release; ADR, amount of drug release; ± SD, Standard deviation; Abs, Absorbance.

As shown in Table 5, the mean percentage of FSM API released was found in the range of 164.55 ± 0.203 (X_3) to 311.24 ± 0.06 (X_2) at 45 min. According to USP, the percentage amount of furosemide dissolved within 45min. should not be less than 80% (Q). The dissolution test results revealed that all the brands met USP dissolution limits [11].

Uniformity content assay method:

The assay test was conducted according to the specified monograph of BP [8]. And the absorbance of Furosemide brands was recorded at Tablet 6. The percentage content of FSM ($C_{12}H_{11}ClN_2O_5S$) in the portion of tablets was calculated using the following formula:

$$\%\ content\ of\ the\ drug\ = \left\{\frac{Actual\ concentration}{Theoretical\ concentration}\right\} * 100\%$$

Were the actual concentration obtained from the equation:

$$Actual\ concentration\ = \frac{Absorbance\ of\ sample}{Absorbance\ of\ standard} * conc.\ of\ standard$$

Where the theoretical conc. as the monograph confirmed

$$Theoretical\ concentration\ = \frac{200mg\ * 5ml}{500ml\ * 250ml} = 0.008mg/ml$$

Table 6: % Content of the drug for Furosemide brands.

Brand	Weight of 20 tablets(gm)	Quantity of powder containing 0.2gm of furosemide	Absorbance of sample (at 271nm)	Actual conc. (mg/ml)	Theoretical conc. (mg/ml)	% content of the drug
X_1	3.2802	0.8200	0.4643	0.0080	0.008	100.06%
X_2	3.3131	0.8282	0.47672	0.0082	0.008	102.66%
X3	3.1670	0.7917	0.46135	0.0079	0.008	99.42%
X4	3.2660	0.8165	0.4738	0.0081	0.008	102.12%

The assay process involves analyzing a substance to determine the concentration of a drug compared to its labeled amount. According to the BP monograph, FSM tablets should have a drug content between 95.0% and 105.0% of the stated amount. As shown in Table 6, the results for all brands (X1=100.06%, X2=102.66%, X3=99.42%, X4=102.12%) are within the acceptable range [8].

CONCLUSION

This study aimed to assess the quality and physicochemical bioequivalence of 4 different brands of furosemide tablets marketed in Misurata city. All tested brands passed the minimum standards for major quality attributes, including visual inspection, weight variation, thickness, diameter, hardness, friability, disintegration, dissolution tests, and uniformity content assay , in accordance with BP and USP quality requirements. Therefore, these generic brands of furosemide tablets are of good quality and can be used interchangeably in clinical practice. Physicians can confidently recommend these four products to patients, as they all demonstrated reliable results and are expected to achieve the desired therapeutic effect.

REFERENCES

1-W.Brown., “Development of a compendial Taxonomy and Glossary FOR Pharmaceutical Dosage form;,” *USP-NF,* vol. 35(5), p. 1151, 2009.

2-S. A. P. S. C. B. a. D. S. Ghimire P, “Pharmaceutical Comparsion of in-process and finished product quality control test for pharmaceutical tablets,” *GSC Biological and Pharmaceutical Sciences ,* vol. 11(3), pp. 155-165, 2020.

3-S.B.a.K.KH., “Floating drug delivery systems an approuch to oral controlled drug delivery via gastric retention,” journal of control Released, pp. 63(4): 235259, 2000.

4-K. Fung and K. Ng, “Product-centered processing: pharmaceutical tablets and capsules.,” AIChE J, vol. 49, pp. 1193-1215, 2003.

5-G. M. Sandeep N, “Immediate drug release dosage form: a review article.,” Journal of Drug Delivery & Therapeutics, pp. 3(2), 155-161, 2013.

6-G. Plæhn., T .Fuglsang., P. Hindersson and T. Breindahl,"Adverse effects from counterfeit and mislabeled medicine containing tapentadol and carisoprodol." Clinical Case Reports 12.8, 2024.

7-G. M. Sandeep N, “Immediate drug release dosage form: a review article.,” Journal of Drug Delivery & Therapeutics, pp. 3(2), 155-161, 2013;.

8-“British Pharmacopoeia Commission.,” British Pharmacopeia 2009, vol. I&II, no. London:TSO, pp. 3952-3955, 2009.
9-B. J. A. R. McCallum A, “Comparsion and correlation of the strong cobb and the monsanto tablet hardness testers.,” Journal of the American Pharmaceutical Association. , pp. 44(2): 83-85, 1955.
10-R. K Khar, “Lachman/liebermans: the theory and practice of industrial pharmacy.,” Cbs Publishers & Distribu, 2013.
11-“US Pharmacopoeia National Formulary.,” USP 38/NF 33, United States Pharmacopoeial Convention. Rockville, MD, USA; 2015.