SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 8.
Issue: 7
Page N. 187-194
Year: 2024

Original Article www.wjahr.com

QUALITY EVALUATION OF SOME AZITHROMYCIN TABLETS COMMONLY AVAILABLE IN THE SYRIAN MARKET

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Received date: 21 May 2024 **Revised date:** 11 June 2024 **Accepted date:** 02 July 2024

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ABSTRACT
This study aimed to assess the quality of some azithromycin tablets available in the Syrian market. Quality control tests (packaging, visual inspection, Weight Uniformity, Content Uniformity, Hardness, Friability, Disintegration, Dissolution test, and dissolution profiles comparison) were conducted on four different brands, one of them sourced from a foreign origin, with no license to import or local marketing. Tablets from local brands met the requirements for packaging and visual inspection. And all passed the weight uniformity test, with good hardness, acceptable disintegration time and friability. While the unlicensed brand failed to meet the requirements in two of these tests, packaging and visual inspection. All brands passed the assay and content uniformity tests except for one batch of the unlicensed brand that failed both tests. For the dissolution test, all brands met the requirements and released more than 80% in 30 minutes which was within the USP specification. Dissolution profiles comparison has confirmed that unlike the unlicensed brand, local brands showed batch to batch consistency and only two brands of the local were considered for interchangeability.

KEYWORDS: Azithromycin, Quality Control, HPLC, Dissolution Test.

1. INTRODUCTION

Azithromycin belongs to the Macrolide class of antibiotics and is the first in the subclass known as Azalides. It is a derivative of erythromycin with significantly enhanced activity against Gram-negative bacteria (including Enterobacteria) and provides coverage for many Gram-positive bacteria.[1] Its mechanism of action is similar to that of other macrolide antibiotics[2], but azithromycin's broad spectrum includes, in addition to Gram-positive and Gram-negative bacteria, atypical pathogens (such as malaria and viral agents).[3]

It was discovered in Croatia in 1980 by the pharmaceutical company Pliva and was approved for medical use in 1988.[4] The World Health Organization classifies it under "macrolides and ketolides" in the list of critically important antibiotics for human medicine (intended to help manage antibiotic resistance).[5] It is available as a generic drug and sold under many brand names worldwide.[6] In 2021, it was the 97th most prescribed medication in the United States, with over 7 million prescriptions.[7]

Azithromycin is stable in stomach pH and has an oral bioavailability of (37%). Although its blood concentrations are usually low, the drug accumulates highly in tissues and is mainly eliminated via biliary routes and feces; its half-life in blood is over 60 hours.[8] Several clinical trials have shown that using azithromycin once daily for 5 days is as effective as administering antibiotics orally for 7 to 14 days, given two to four times a day, for treating upper and lower respiratory tract infections and skin infections.[8]

Azithromycin was quickly adopted as a drug used to treat COVID-19 infection, despite the lack of evidence supporting this use at the beginning of the pandemic.[9] Surprisingly, all clinical trials concluded that its use is not recommended for mild to moderate cases, but it may be beneficial in severe cases where co-infection is a concern.[10] It is still widely and regularly prescribed for COVID-19 patients in some countries. This random and irrational use poses a potential threat to the development of resistance to this important antibiotic.[11]

With the spread of covid-19 pandemic, Syrian Market has witnessed a marked increase in using of various azithromycin foreign-brands, a considerable number of those products are not registered or licensed by the Syrian Ministry of Health, and are potential to be falsified or simply substandard products, as not subject to quality evaluation. This may affect public health and increase the risk of developing bacterial resistance. Therefore, this research studies some locally marketed azithromycin products from local and foreign origin.

2. MATERIALS AND METHODS

2.1. Chemicals and samples

Azithromycin dihydrate standard provided from Rama Pharma LTD (purity 99.7%), also used Sodium hydroxide (Eurolab – Belgium), Mono potassium phosphate (India), Acetonitrile (Honeywell – Germany.

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The study was conducted on samples belong to four pharmaceutical companies (A, B, C, D), three of which are local (B, C, D) and the fourth (A) is a foreign company, noting that this company does not have Ministry of Health approval for import or local marketing. All of them purchased from the local market during the research period. Samples were obtained from various local pharmacies, with two different batches (1 & 2) selected for each of the studied companies. Tests and quality control studies were carried out during the samples' validity period.

Table 1: Code, country of origin, manufacturing date, and expiry date of different brands of Azithromycin dehydrate.

Dosage form	Brand	Code	Manufacturing country	Date of manufacturing	Expiry date
film coated tablets 500 mg	A	A1	FOREIGN	5/2021	4/2024
		A2		2/2022	1/2025
	B	B1	SYRIA	10/2020	10/2023
		B2		12/2022	12/2025
	C	C1	SYRIA	4/2021	4/2024
		C2		5/2023	5/2026
	D	D1	SYRIA	8/2022	8/2025
		D2		7/2023	7/2026

2.2. Equipment

Equipment used in this study included an HPLC (High Performance Liquid Chromatography) (SHIMADZU LC-2030CPLUS, JAPAN), electronic weighing balance (SARTORIUS ENTRIS4231-1S, GERMANY), a digital pH meter (Hach sensION+3, UNITED KINGDOM), a friability apparatus (Erweka TAR220, Germany), a disintegration test apparatus (Erweka ZT222, Germany), a dissolution test apparatus (Erweka DT126, Germany), Hardness apparatus (ERWEKA TYPZT222, GERMANY).

2.3. Preparation of the calibration curve of Azithromycin dihydrate in phosphate buffer (pH 7.5)

The standard stock solution (5 mg/mL) was prepared by taking a weight of azithromycin dihydrate standard equivalent to 500 mg Azithromycin, and dissolving it in a 100 mL volumetric flask using a small amount of the mobile phase. The flask was placed in an ultrasonic bath until complete dissolution, and then the volume was filled up to the calibration mark using the mobile phase.

The stock solution was then diluted with mobile phase to obtain solutions with concentrations ranging between (0.1 – 1.5 mg/mL). Linearity was evaluated by measuring the response at each concentration. A calibration curve representing the relationship between the average peak areas and the corresponding concentrations was plotted as shown in figure (1). The linearity equation and the coefficient of determination (R^2) were determined.

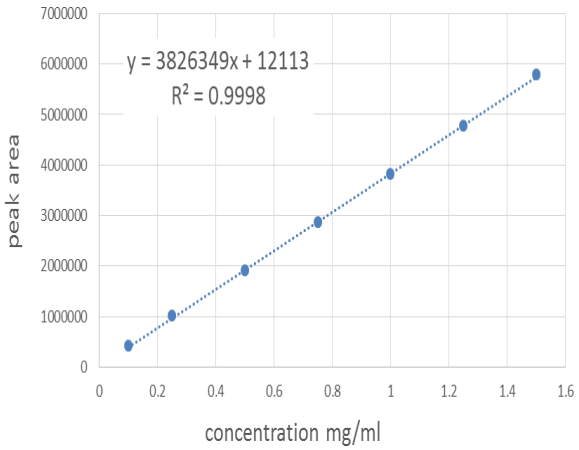

Figure 1: Calibration curve for Azithromycin dihydrate in phosphate buffer (pH 7.5).

2.4. Pharmaceutical Quality Tests

Several tests have been performed on Azithromycin dihydrate film coated tablets, including: Packaging, appearance, weight variation, content uniformity, hardness, friability, disintegration, dissolution test, and dissolution profiles comparison.

2.4.1. Physical Characteristics, Packaging and Labeling

Samples of azithromycin underwent an inspection of the outer packaging in accordance with GMP standards. This involved verifying the presence of the following information on the product's packaging: product name, active ingredient name and quantity, pharmaceutical form, number of dosage units per package, batch number, production and expiration dates, storage conditions, manufacturer's name and location, as well as an internal instruction leaflet containing drug information, usage instructions, and warnings.[12] The visual appearance inspection of the azithromycin tablet also was conducted according to GMP standards. Twenty tablets from each batch were visually inspected. The tablets should be smooth, intact, and of uniform color.[13]

2.4.2. Uniformity of Dosage Units

Uniformity of dosage units for solid pharmaceutical forms is achieved through the uniformity of their individually measured weights and the uniformity of their active ingredient content.[14] According to pharmacopeias, this is done by conducting two types of tests (Weight Uniformity, Content Uniformity):

2.4.2.1. Weight Uniformity

Weight Uniformity test for tablets is one of the essential tests required by pharmacopeias, as it is the primary indicator of content uniformity. This test was conducted based on the United States Pharmacopeia (USP), where 20 tablets were randomly selected from each batch, weighed individually, and deviations from the average weight was calculated.

2.4.2.2. Content Uniformity

The purpose of the Content Uniformity test is to verify the uniform distribution of the active ingredient among the dosage units within a batch and to ensure that the content of each unit complies with the amount stated on the label. According to USP, tablets containing a large amount of the active ingredient (25 mg or more) or a large percentage of the active ingredient (25% or more of the tablet's weight), content uniformity is verified by conducting the Weight Variation test. Ten tablets were randomly selected from each batch, weighed individually, and the average weight was calculated. The ten tablets were then finely powdered, and a sample equivalent to the average weight (containing 500 mg) was transferred to a 100-ml volumetric flask and diluted to the required volume with mobile phase, then 5 ml of the previous solution was transferred to 25-ml volumetric flask and diluted to the required volume with mobile phase to obtain a solution having a concentration of 1 mg/ml of azithromycin, this solution was used to determine the amount of azithromycin using the analytical method employed in the research.

Azithromycin assay was conducted based on USP 41, using an HPLC device and applying the conditions listed in the table (2). This was done after validating the analytical method by evaluating its precision, linearity and determination of LOD and LOQ. Results were compared with the pharmacopeial acceptance range for azithromycin content, which is 90-110%.

Content uniformity of the tablets was evaluated by calculating the Acceptance Value (AV) using the following formula:

$$AV = |M - X| + k*$$

A batch is considered content uniform if ($AV \leq 15$). If ($AV > 15$), the test is repeated with 20 additional tablets, and the AV for the 30 tablets is calculated. In this case, two conditions must be met to accept the content uniformity: ($AV \leq 15$) and the individual content of each tablet (x) must be within ($0.75 * M < x < 1.25 * M$).

Table 2: HPLC Parameters for Azithromycin Assay (USP 41).[15]

Column	25 cm x 4.6 mm, 5 µm
Mobile Phase	Acetonitrile: buffer (65:35, v/v)
Injection Volume	100 µL
Detection	UV, 210 nm
Flow Rate	2 mL/min
Column Temp	50°C

2.4.3. Hardness Test

The hardness test assesses the tablets' resistance to pressure (or breaking and crushing resistance).[16] For the azithromycin tablets, ten tablets were randomly selected from each batch. A hardness tester was used to determine the hardness of each tablet individually (hardness units: kilopond; kp). The mean and standard deviation (Mean ± SD) of the hardness values were calculated.

2.4.4. Friability Test

The friability test measures the tablets' resistance to shock and motion that might cause loss of parts (chipping or dust).[17] The mass of the parts lost during the mechanical endurance test is determined and expressed as a percentage of the tablet's weight. For the azithromycin coated tablets, ten tablets were randomly selected (since the average weight of the study tablets exceeds 650 mg), dusted with a soft brush, weighed on a sensitive balance, and placed in a friability tester (100 rotations at 25 rpm). The tablets were reweighed after the test and dusting. Friability was calculated as a percentage of the initial weight.

Friability Percentage = (Initial weight- Final weight) *100 / Initial weight

2.4.5. Disintegration Test

The importance of this test comes from the fact that tablets disintegration is the first step in the releasing and dissolution of the active ingredient within the body.[18] This test was conducted on the studied azithromycin tablets by selecting six tablets from each batch randomly and measuring the disintegration time using water as the

medium at 37 ± 0.5°C (USP). The tablets should disintegrate within 30 minutes (as per the USP for film-coated tablets). The time taken for the tablets to disintegrate and pass through the mesh was measured in minutes and seconds.

2.4.6. In Vitro Dissolution Test

The dissolution test for the azithromycin coated tablets was conducted in accordance with USP standards using Apparatus 2. Six tablets from each batch were randomly selected and tested in 900 ml of dissolution medium (phosphate buffer pH 6) at 37 ± 0.5°C. Table (2) illustrates the dissolution test conditions.

At an appropriate time interval of 5, 10, 15, 20 and 30 minutes, 5 ml of sample solution were withdrawn using a syringe from the dissolution medium Then, was filtered through a 0.45m membrane filter. And transferred to a 25-ml volumetric flask and diluted to the required volume with mobile phase. Samples solutions were injected into HPLC and the released amount was then calculated by using the linearity equation and compared with the USP acceptance limit.

Table 3: Dissolution Test Parameters.

Medium	**900 ml of phosphate buffer, pH= 6**
Temperature	37
Apparatus 2	75 rpm
Time	30 min
Time intervals	5, 10, 15, 20, 30
Acceptance limit	NLT 80% of The labeled amount within 30 min

2.4.7. Dissolution profile comparison

The Microsoft Excel-2016 was used for statistical and graphical analysis of the results; it was used for drawing the calibration curve of the standard, in addition to plotting the graph of the time-dependent dissolution profiles of the drug.

To compare the dissolution profiles of Azithromycin tablets included in the study, model-independent methods were considered by applying fit factors, the difference factor (f1) and similarity factor (f2) using equations (1) and (2).

This comparison was applied to assess batch-to-batch consistency of each brand (comparing batch 1 and 2 of each brand) and to ascertain the interchangeability of local brands (comparing Local Brands B, C and D with each other).

Two dissolution profiles were considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100.

$$f1 = \{[\sum_{t=1}^{n}|RT - Tt| / [\sum_{t=1}^{n} RT\ ]\}*100$$

$$f2 = 50 \log \{[1 + (\tfrac{1}{n}) \sum_{t=1}^{n}|RT - Tt|\ ]^2\}^{-0.5} *100$$

n = is the number of time points, RT = is the dissolution value of comparator product at time t,
Tt = is the dissolution value for the test product.

3. RESULTS AND DISCUSSION

3.1. Packaging

All the studied brands met the requirements of the pharmacopeia and GMP in terms of the external packaging, which includes the product name, the active ingredient name and quantity, the dosage form, the number of units per package, batch number, production and expiration dates, storage conditions, the name and location of the manufacturer.

All the studied brands included internal leaflet, except for brand a failed to include a leaflet with basic information such as usage instructions, contraindications, warnings, and side effects.

This was considered a preliminary indicator that the product might be falsified, which is further supported by the fact that company A's product lacks a Ministry of Health import or distribution license, thus making it classified by the World Health Organization as an unregistered and unlicensed product.[19]

3.2. Visual inspection

The visual inspection of the tablets from local companies B, C, and D showed uniform color and appearance with a continuous coating layer and no signs of deterioration as previously described in the practical section. However, tablets from company A showed defects such as non-uniform color and surface dark spots, as shown in figure (2). This defect in tablet appearance is referred to in studies as scuffing.[20] This defect may be caused by poor manufacturing standards or the low quality of raw materials.[21]

Figure 2: Brand (A) tablets scuffing.

3.3. Uniformity of Dosage Units

3.3.1. Weight Uniformity

Table (3) shows the average weight of each batch, the maximum and minimum deviations from the average and the number of tablets whose weights deviated beyond the limits. According to the United States Pharmacopeia, tablets with an average weight exceeding 250 mg are allowed a deviation range of ±5%, and two out of twenty tablets can exceed this range, but none should be deviated by more than ±10%. As shown in table (3), all batches from the studied brands meet the requirements for weight uniformity. For local brands B, C, and D, none of the tablets exceeded the allowed ±5% deviation, while tablets from company A exceeded this range (two tablets from batch A1 and one from batch A2), but none exceeded the ±10% deviation. These deviations in the weights may be due to an imbalance in machine adjustment during compression[22], or defects in tablets formulation.[23]

Table 4: Average weight, minimum & maximum deviation.

Brand	Code	Average Weight 20 Tablet (gram)	Minimum Deviation %	Maximum Deviation %	number of Samples Out of Range
A	**A1**	0.75263	0.341	6.594	2
	A2	0.71558	-0.004	6.188	1
B	**B1**	0.69337	-0.024	3.481	0
	B2	0.69109	0.059	3.662	0
C	**C1**	0.91493	0.019	-1.315	0
	C2	0.91405	-0.071	-1.219	0
D	**D1**	0.79267	-0.009	2.577	0
	D2	0.79076	0.044	1.953	0

3.3.2. Content Uniformity

Table (4) shows the assay results of azithromycin. All batches are considered acceptable except for batch (A1), as it falls outside the acceptable range (90-110%).

The content uniformity AV (Acceptance Value) was less than 15 for all studied batches except batch (A1) from company (A), making all acceptable for content uniformity except for batch (A1), where AV= 16.98 table (5). The pharmacopeia requires taking an additional 20 tablets and retesting to accept or reject the batch definitively. However, due to insufficient sample availability, only the first test results were presented.

It can be observed that, the most common type of substandard/falsified antimicrobial drugs have a reduced amount of the active ingredient.[24]

Table 5: API% and AV values.

Brand	Code	API %	AV	Result
A	A1	88.88	16.98	Rejected
	A2	90.03	13.94	Accepted
B	B1	94.32	8.68	Accepted
	B2	95.64	7.18	Accepted
C	C1	91.45	7.69	Accepted
	C2	92.65	6.53	Accepted
D	D1	93.74	6.50	Accepted
	D2	94.21	5.63	Accepted

3.4. Hardness Test

All companies showed acceptable values for tablet hardness, with all values exceeding 4 kp, which is a good indicator of the tablets' ability to withstand transportation and shipping. High hardness is considered beneficial as long as it does not affect disintegration time. While the hardness values for companies A, B, and C were similar (around 16.5 kp), company D had relatively lower values compared to the other companies (around 9 kp) (table 6). Low hardness values can be explained by the use of large sized granules[25], low pressure force[16], or the addition of excessive amounts of lubricating agents.[26]

Table 5: Average Hardness values in Kilopond.

Brand	Code	Hardness average (kp) ± STDD
A	A1	15.4±1.33
	A2	16.83±1.0
B	B1	16.92±0.77
	B2	16.82±0.60
C	C1	16.15±0.22
	C2	16.22±0.33
D	D1	9.21±0.37
	D2	10.19±0.72

3.5. Friability Test

With all values ranging between 0.026% and 0.132%, all results are within the limit for tablet friability, as weight loss was less than 1%. This result refers to the good adhesion of the film on the tablets surface.

3.6. Disintegration Test

All companies showed acceptable values for disintegration time, with all values not exceeding 30 min in water, which meet the requirements of USP. Some differences in the speed of disintegration can be observed between brands depending on the excipients used in the formulation. Where it accelerates due to using a combination of super disintegrant agents[27], and it becomes longer using a large amount of lubricating agents or other hydrophobic materials.[26]

Table 6: Shows disintegration time for each brand.

Brand	Code	Disintegration time	Result
A	A1	6.03	Accepted
	A2	7.54	Accepted
B	B1	3.50	Accepted
	B2	4.03	Accepted
C	C1	2.58	Accepted
	C2	2.30	Accepted
D	D1	5.20	Accepted
	D2	4.49	Accepted

3.7. Dissolution Test and dissolution profile comparison

The assay of the samples withdrawn from dissolution test was performed using the HPLC method as listed in table (2). The amount of azithromycin released (%) from each tablet and the corresponding concentration (mg/mL) at each time interval were calculated.

All studied batches met the pharmacopeial acceptance limit minutes (single time point test), releasing more than 80% within 30 minutes, as shown in table (8).

Table 8: Dissolution test results for all brands.

Brand	Code	Released amount after 30 min	Time required for releasing 80%	Result
A	A1	90.35	25.00	Accepted
	A2	86.22	20.00	Accepted
B	B1	84.59	25.00	Accepted
	B2	84.43	25.00	Accepted
C	C1	87.95	20.00	Accepted
	C2	88.17	15.00	Accepted
D	D1	87.99	20.00	Accepted
	D2	86.56	20.00	Accepted

The time dependent dissolution profile (percentage of drug released over time) of the studied brands were evaluated, to provide more information about similarity and batch-to-batch consistency. The results were represented as shown in figure (3).

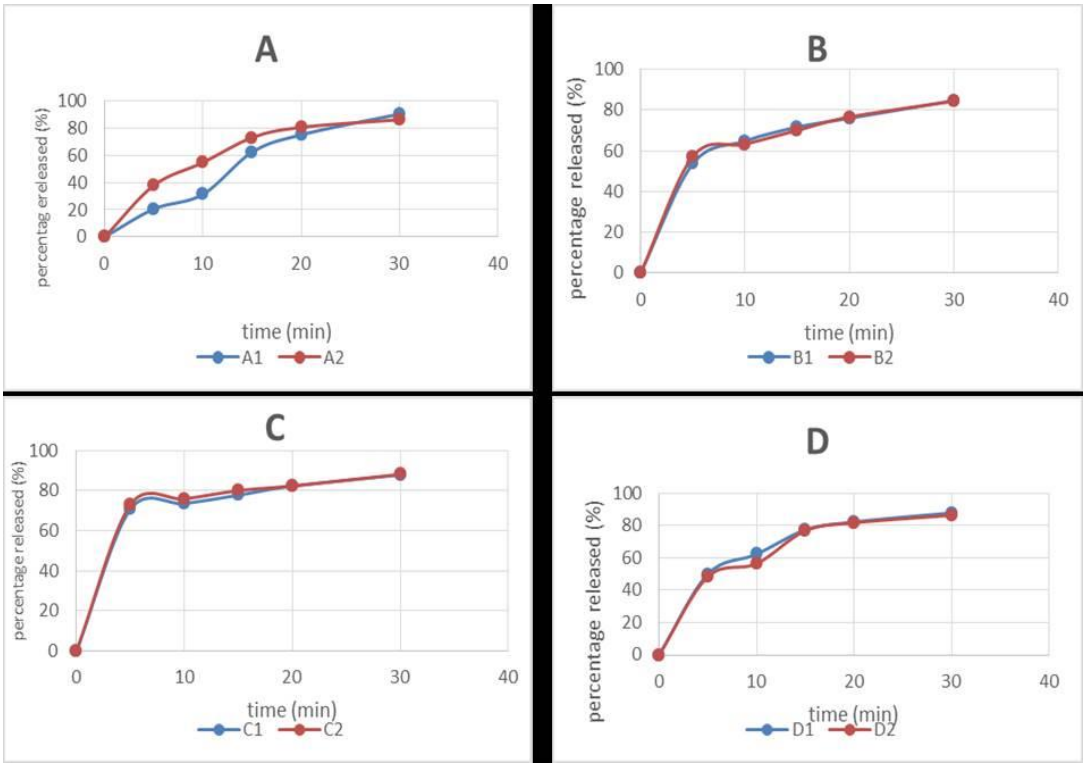

Figure 1: Dissolution profiles for brands A, B, C and D.

By observing the dissolution profile in figure (3), some differences are noted in the release behavior during the first ten minutes. Brand (C) released the largest amount of azithromycin, reaching approximately 75% within 10 minutes, while other companies reached that percentage after around 15 to 20 minutes as shown in Table (9). These differences in dissolution rates can be attributed to differences in the formulation of each company, which align with the previously mentioned hardness and disintegration results.

Table 7: Differences in dissolution rates.

Time (min)	A		B		C		D	
	A1	A2	B1	B2	C1	C2	D1	D2
	Average released amount%	Average released amount%	Average released amount%	Average released amount%	Average released amount%	Average released amount%	Average released amount%	Average released amount%
5	20.58	37.87	53.63	57.18	70.75	73.06	50.08	48.44
10	31.33	54.71	64.75	63.18	73.56	75.93	62.36	56.51
15	62.29	73.00	71.61	70.03	77.79	80.05	77.44	76.90
20	75.11	80.59	75.99	76.58	82.27	82.45	82.38	81.86
30	90.35	86.22	84.59	84.43	87.95	88.17	87.99	86.56

In order to assess batch-to-batch consistency, f1 and f2 factors were calculated comparing batch 1 and 2 of each brand (considering the first batch of each as the reference). Results shown in table (10) illustrate the similarity between batches of the local brands, unlike brand A which showed differences in the dissolution profiles comparing its batches.

Table 8: fit factors studied batch-to-batch.

Ref	Test	f1	f2	Result
A1	**A2**	18.86	42.34	No similarity
B1	**B2**	0.24	83.47	similarity
C1	**C2**	1.87	84.35	similarity
D1	**D2**	2.77	76.26	similarity

To ascertain the interchangeability of local brands, f1 and f2 factors were calculated comparing Local Brands B, C and D with each other (considering one of them as the reference). As shown in table (11), brand D and B are interchangeable.

Table 9: Fit factors studied brand-to-brand.

Ref	Test	f1	f2	Result
B	**C**	12.82	49.82	No similarity
C	**D**	10.29	45.51	No similarity
B	**D**	1.21	63.42	similarity

4. CONCLUSION

The quality of azithromycin products marketed locally by four different companies (A, B, C, D) was monitored. Three of the studied brands (B, C, D) are from local origin and A is a foreign unsilenced brand.

Tablets from local companies (B, C, and D) met the requirements for the external inspection and visual examination. In contrast, company A's batches A1 and A2 failed the external inspection for not including an internal instruction leaflet and the visual examination for color inconsistency in the coating layer and the appearance of dark spots (scuffing). All companies (A, B, C, D) passed the weight uniformity test, although significant deviations were observed in the weights of company A's batches. All tablets had good hardness with acceptable disintegration time and friability.

All companies passed assay and content uniformity, except for batch (A1) from company (A), In contrast all companies (A, B, C, D) met dissolution test requirements, and released (more than 80%) API within 30 minutes.

By comparing dissolution profiles, all local brands showed batch to batch consistency unlike the unlicensed brand (A), and two of the local brands (B, D) considered interchangeable.

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