In-vitro Physicochemical Evaluation of Different Marketed Brands of Azithromycin Available in Aden-Yemen

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Abstract

The recent investigation is undertaken with an aim to compare quality evaluation and provide concise information on three different brands of film-coated Azithromycin tablets (500 mg). The evaluation of the physical characteristics of pharmaceutical products can ensure their identity as well as quality. These include criteria for FTIR spectra, weight variation, uniformity of diameter, thickness, hardness, and disintegration tests. The results showed the similarity among the studied brands.

Keywords: (Azithromycin drug, FTIR spectra, physical characteristics).

الملخص

تم إجراء الدراسة الحالية بهدف مقارنة وتقييم الجودة وتقديم معلومات موجزة عن ثلاث منتجات دوائية مختلفة من أقراص أزيثروميسين المغلفة بالفيلم (500 مجم). يمكن أن يضمن تقييم الخصائص الفيزيائية للمنتجات الصيدلانية هويتها وكذلك جودتها. وتشمل هذه معايير أطياف تحت الحمراء (FTIR)، واختلاف الوزن، وتوحيد القطر، والسُمك، والصلابة، واختبارات التفكك. أظهرت النتائج تشابهً بين العلامات التجارية المدروسة.

الكلمات المفتاحية: (عقار أزيثروميسين، وأطياف تحت الحمراء، والخصائص الفيزيائية).

1. Introduction

Azithromycin drugs are classified as macrolide antibiotics and are used to kill bacteria or inhibit their growth. It's a semi-synthetic antimicrobial compound derived from erythromycin, which falls into the macrolide class of drugs. Macrolide antibiotics such as erythromycin, clarithromycin, and roxithromycin were named after the presence of a macrocyclic lactone ring in their structure and were originally isolated from cultures of Streptomyces erythraea in 1952. The first synthesis of Azithromycin was in 1980 and was initially developed for the treatment of bacterial infections of the upper and lower respiratory tracts, skin infections, and treatment of uncomplicated Chlamydial infections [1,2].

Azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) consists of a 15 membered macrolide ring with 2 basic amine groups (Fig 1), and can also be described as an azalide antibiotic. Azithromycin generally is a white or almost white crystalline powder and the labeled water content of its anhydrate form must not exceed 2.0 % of water [3]. It differs structurally from the other macrolide antibiotics by methyl-substituted nitrogen in the macrolide ring, resulting in two basic amine groups, rather than the one in erythromycin [4]. The unique structure of this ring prevents degradation in acidic environments and improves the antibacterial spectrum and pharmacokinetics [5].

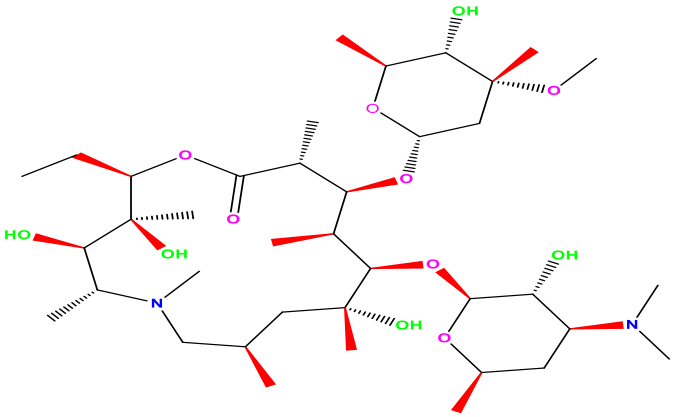


Figure (1)
Structure of Azithromycin

Azithromycin, like other macrolide antibiotics, prevents bacterial protein synthesis by binding to and interfering with the assembly of the 50S large ribosomal subunit and the growth of the nascent polypeptide chain [6-8]. In comparison to larger macrocyclic antibiotics, azithromycin drug binds at the polypeptide exit tunnel, near to the peptidyl transferase center (PTC) on the 23S rRNA, but does not inhibit PT activity. The high pH of Azithromycin leads to rapid penetration of the outer membranes and a more effective entrance into the bacteria, so improving activity against Gram-negative bacteria [9]. Binding sites on the bacterial ribosome for the structurally different macrolides, lincosamides, streptogramin B, and ketolides (MLSbK) overlap considerably so that modifications in a single ribosomal region concurrently alter susceptibility to many MLSbK antibiotics. Even though unsuccessful as a bactericidal agent against *Pseudomonas aeruginosa* at clinically appropriate concentrations, Azithromycin stops the generation of both growth-stimulating, quorum-sensing compounds, and alginate biofilm which protects the micro-organism from antibiotic actions [10-13].

Azithromycin may work in synergy with antiviral drugs. Some works have found that this macrolide antibiotic can exert antiviral effects against rhinovirus, Ebola virus, and Zika virus [14-16].

Azithromycin perhaps acts alongside the word wild SARS-CoV-2 virus causes coronavirus disease-19 in different points of the viral cycle. Its immunomodulatory properties consist of the capability to downregulate cytokine production, retain epithelial cell integrity or stop lung fibrosis. Azithromycin usage was linked with a decrease in mortality and ventilation days in other viral infections. These properties might be beneficial throughout the COVID-19 [17-19].

On contrary to other Yemeni studies [20-22], the objective of the present work is to focus on the importance and some physical characteristics of Azithromycin and compare three brands available in Yemeni pharmacies.

2. Materials & Methods

Reagents: All materials used in this study had a high degree of purity. Azithromycin (99.5% purity) (Globella Pharma, India).

Instruments: Analytical balance (RADWAG, model AS 220.B, Poland), FTIR spectroscopy (PerkinElmer L1600400 Spectrum Two, UK). Pharma test tablet hardness, diameter, thickness (PTB511, Germany).

2.1 Samples collection

Three variably popular brands of Azithromycin were collected from selected community pharmacies (Aden, Yemen). Approximately 28 tablets of each brand were collected randomly for the analysis. The information of samples was properly checked (Table 1).

TABLE (1)
Detailed information on analyzed Azithromycin samples

Brand	Symbol	Manufacture	Strength	Mnf. date	Exp. date
Azicure	D1	Yemeni (Shaphaco Pharmaceutical Ind.)	500 mg film-coated tablets	2/2021	2/2024
Azicine	D2	Yemeni (RFA Pharmaceutical Ind.)	500 mg film-coated tablets	4/2021	4/2024
Zithrocin	D3	Indian (Unique Pharmaceutical Labs)	500 mg film-coated tablets	11/2020	11/2023

3. Results & Discussions

3.1 Weight variation

This experiment was used to measure the weight variation of the tablets. Based on the obtained results, the weight of the tablets (Table 2) for D1 had ranged between 707.4 mg and 745.5 mg with the deviation ranging between 0.45 and 2.64. D2 drug had minimum-maximum weight between 862.3 mg to 872.8 mg where the deviation rang found between 0- 0.70. Lastly, for the D3 drug the weight minimum was 957.7 mg and the maximum weight was 998.4 mg with a deviation of 0.29- 2.65. The result revealed that the tablets were uniform to each other and according to the results of the experiment. Not exceeding the accepted limit of weight variation ±5, the tablet is identical to each other [23]. The difference in the mean weights of all brands may be because of different excipients used in the different brands.

3.2 Thickness

Based on the obtained results (Table 3), the thickness of D1 tablets ranged between 5.75 mm to 5.93 mm whereas the deviation felt between 0.2 to 1.02. The tablets of the D2 sample (5.56-5.80 mm) had 0.58 to 2.78 deviation, while 0.10 to 1.20 variation for D3 drug with the thickness mean equals 5.306 mm. Thus, the thickness of the three brand tablets can be uninformed as they differ very little from each other and each tablet is indistinguishable. In relation to Indian Pharmacopoeia, general tablet thickness is controlled within 5% of a standard value where all the three brands of tablet Azithromycin were found to be within their permissible limit (±5%) [24].

3.3 Diameter

Based on the results obtained, the diameter of the tablets is shown in Table 4. Whereas The variation deviation ranges between 0.20-1.86 for D1, 0.10- 0.38 for D2, and 0- 0.34 for D3. The deviation of an individual unit from the diameter mean ensured to not exceed ± 5% for tablets with a diameter of less than 12.5 and ± 3% for a diameter of 12.5 mm or more where the results all the tablets have achieved

percentage difference below than 3% which means that each tablet had obeyed the theoretical value of standard diameter. By calculating the deviation of diameter, the uniformity of diameter of the tablets can be proven. The results we obtained showed that all the tablets have achieved a percentage difference below 3% which means that each tablet had obeyed the theoretical value of standard diameter. [24,25].

3.4 Hardness

The results obtained in Table 5 proved that one tablet will have its hardness which is it might be the same or different from other tablets. The coated tablets were generally more difficult to pulverize. Commonly, the hardness of the individual tablet will be slightly different compared to others. Tablets that have hardness more than 50 Newton (N) are generally considered acceptable. The hardness average of D1, D2, and D3 was 152.9, 304.9, and 251.3 N, respectively which means this force is needed to break a tablet. The hardness of studied brands is considered difficult to crush and it is not fragile. [26-28].

TABLE (2)
Weight variation (n=10)

Brand	Weight, (mg)										
	Tablet No.	1	2	3	4	5	6	7	8	9	10
D1	W (mg)	742.4	721.1	722.6	729.6	707.4	745.5	720.4	713.1	730.4	730.2
	Mean ± SD = 726.3 ± 12.5										
	Mean ± Deviation	726.3± 2.2	726.3± 0.70	726.3± 0.50	726.3± 0.45	726.3± 2.60	726.3± 2.64	726.3± 0.81	726.3± 1.81	726.3± 0.56	726.3 ±0.53
D2	W (mg)	862.3	871.7	866	866.5	872.8	870.7	867.5	868.4	871.1	867.0
	Mean ± SD = 868.4 ± 3.203										
	Mean ± Deviation	868.4 ± 0.70	868.4± 0.38	868.4± 0.27	868.4± 0.27	868.4± 0.50	868.4± 0.20	868.4± 0.10	868.4± 0	868.4± 0.20	868.4 ± 0.16
D3	W (mg)	961.2	980.0	969.7	964.5	957.7	965.1	963.2	985.5	998.4	980.4
	Mean ± SD = 972.6 ± 12.98										
	Mean ± Deviation	972.6± 1.17	972.6± 0.76	972.6± 0.29	972.6± 0.83	972.6± 1.50	972.6± 0.77	972.6± 0.96	972.6± 1.32	972.6± 2.65	972.6 ±0.80

TABLE (3)

The thickness of drug samples (n=6)

Brand	Thickness, (mm)						
	Tablet No.	1	2	3	4	5	6
D1	T (mm)	5.90	5.83	5.75	5.90	5.93	5.91
	Mean ± SD = 5.87 ± 0.067						
	Mean ± Deviation	5.87±0.51	5.87±0.68	5.87±0.20	5.87±0.51	5.87±1.02	5.87±0.68
D2	T (mm)	5.80	5.75	5.58	5.56	5.56	5.61
	Mean ± SD = 5.64 ± 0.104						
	Mean ± Deviation	5.64±2.78	5.64±1.89	5.64±1.11	5.64±1.47	5.64±1.47	5.64±0.58
D3	T (mm)	5.31	5.27	5.30	5.37	5.26	5.33
	Mean ± SD = 5.306± 0.040						
	Mean ± Deviation	5.31±0.75	5.31±0.67	5.31±0.10	5.31±1.20	5.31±0.86	5.306±0.45

TABLE (4)

Diameter values (n=6)

Brand	Diameter, (mm)						
	Tablet No.	1	2	3	4	5	6
D1	D (mm)	9.45	9.39	9.24	9.48	9.43	9.46
	Mean ± SD = 9.408 ± 0.0879						
	Mean ± Deviation	9.408±0.46	9.408±0.20	9.408±1.86	9.408±0.79	9.408±0.24	9.408±0.57
D2	D (mm)	8.20	8.18	8.15	8.16	8.18	8.14
	Mean ± SD = 8.168 ± 0.022						
	Mean ± Deviation	8.168±0.38	8.16±0.14	8.168±0.22	8.168±0.10	8.168±0.14	8.168±0.34
D3	D (mm)	20.27	20.18	20.26	20.28	20.25	20.28
	Mean ± SD = 20.25 ± 0.0014						
	Mean ± Deviation	20.25±0.098	20.25±0.34	20.25±0.049	20.25±0.14	20.25±0	20.25±0.14

TABLE (5)

Results of hardness test (n=6)

Brand	Hardness, (N)						
	Tablet No.	1	2	3	4	5	6
D1	H (N)	122.3	120.5	292.0	115.6	143.8	123.0
	Mean ± SD = 152.86 ± 68.85						
	Mean ± Deviation	152.86±19.9	152.86±21.3	152.86±91	152.86±24.3	152.86±6.45	152.86±19.5
D2	H (N)	304.8	304.8	304.9	304.7	304.9	304.9
	Mean ± SD = 304.89 ± 0.081						
	Mean ± Deviation	304.8±0.03	304.9±0.03	304.9±0.0	304.9±0.065	304.9±0.0	304.8±0.0
D3	H (N)	251.0	290.1	226.1	238.4	266.6	235.8
	Mean ± SD = 251.33± 23.58						
	Mean ± Deviation	251.33±0.13	251.3±15.4	251.3±10	251.3±5.14	251.3±6.07	251.3±6.17

3.5 Disintegration test

Table 6 implied that D2 and D3 brands have good values disintegration according to USP [29] where the allowed range for film-coated tablets is between 5-30 min. On the other hand, Azithromycin tablets labeled D1 brand did not have a standard disintegration value.

TABLE (6)
Disintegration values

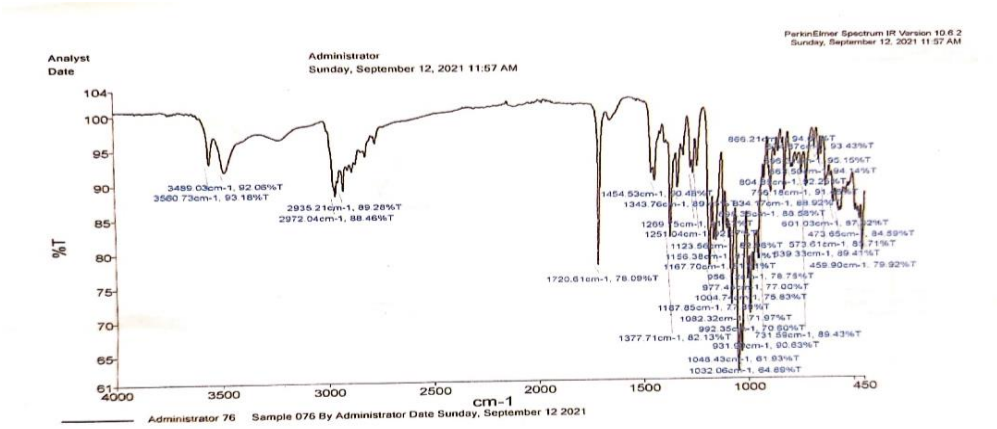
Brand	Final time
D1	1.30 min
D2	9.59 min
D3	20.9 min

3.6 FTIR peak of Azithromycin

The IR spectra for Azithromycin (Figures 2-5 and Table7) showed bands at 3560-3561 cm^{-1} represented -OH group. Wavenumbers 2972 -2971 cm^{-1} and 1376.89 cm^{-1} related to the axial

stretching and bending of C-H of the methyl groups. The axial stretching of the C=O was observed at 1720 cm^{-1}.

The value ~ 1188 cm^{-1} was appeared due to the absorption associated with the axial stretching of C-O as R-O-R. Another important band in the spectrum was at 1081 cm^{-1} related to the axial stretching and bending of C-N [30]. The spectra showed the three brands are pure and identical.



(2) Figure

FTIR spectrum of Azithromycin – (Pure)

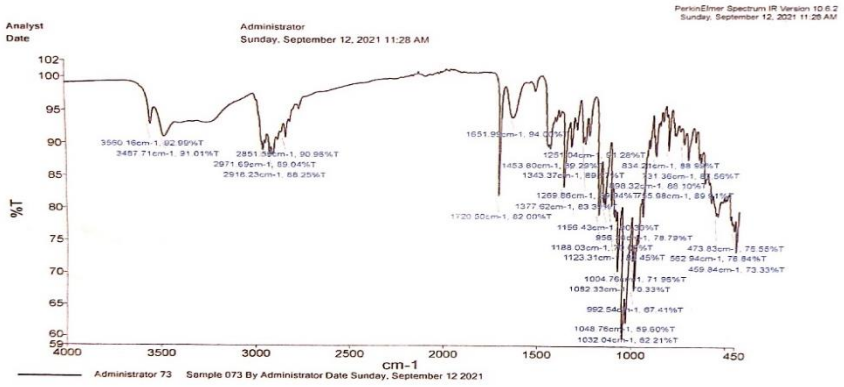


Figure (3)
FTIR spectrum of Azithromycin - D1

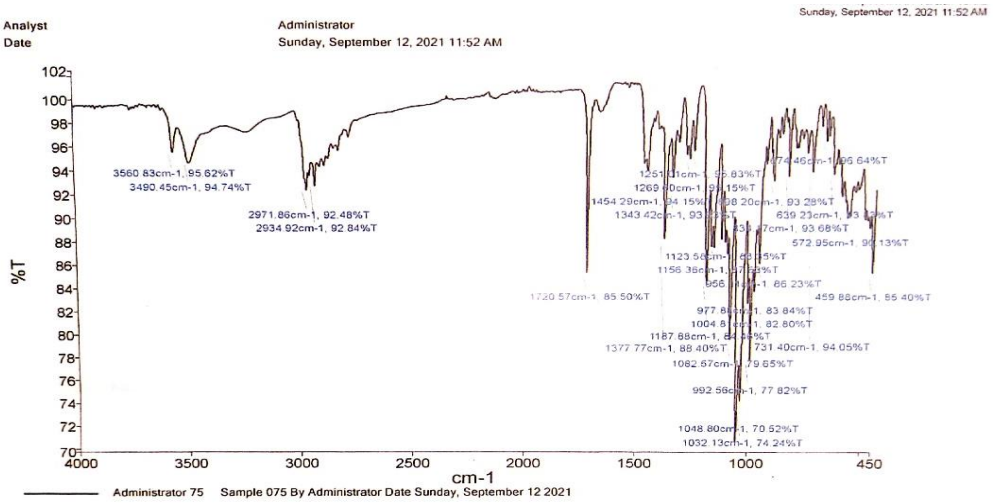


Figure (4)

FTIR spectrum of Azithromycin – D2

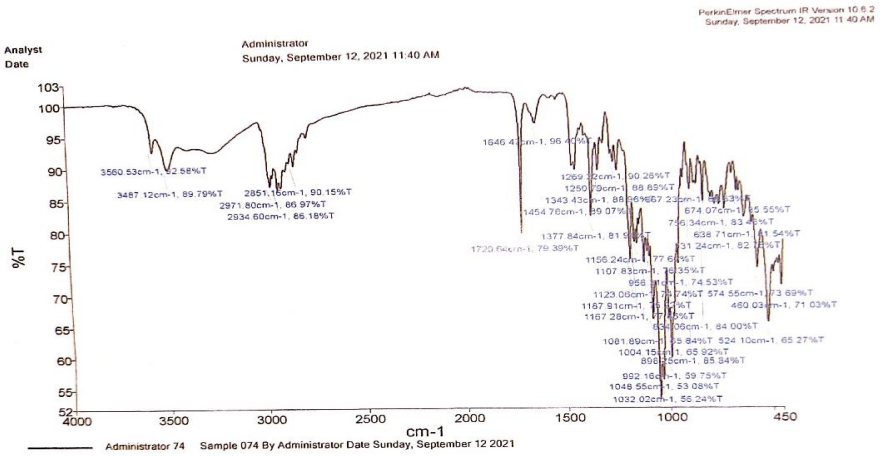


Figure (5)
FTIR spectrum of Azithromycin – D3

TABLE (7)
A comparison of FTIR peaks of Azithromycin

Pure-Observed peak in drug (cm^{-1})	D1-Observed peak in drug (cm^{-1})	D2-Observed peak in drug (cm^{-1})	D3- Observed peak in drug (cm^{-1})	Reported peak(cm^{-1})	Functional group
3560.73	3560.16	3560.83	3560.53	3500-3700	-OH
2972.04	2971.69	2971.86	2971.80	2800-3200	$-CH_3$
1720.61	1720.50	1720.57	1720.64	1705-1725	-C=O
1187.85	1188.03	1187.88	1187.91	1000-1300	R-O-R
1082.32	1082.33	1082.57	1081.89	1000-1350	-C-N

4. Conclusions

This research objected to characterizing three drug brands (i.e. Azicure, Azicine, and Zithrocin). This research has provided quantitative evidence of the quality in recognized Yemeni markets of the

randomly selected Azithromycin tablets (500mg). The drugs and excipients compatibility was carried out by FT-IR studies. Whereas weight variation of tablets is important in process control evaluation of tablets which is a valid indication of the corresponding variation in the drug content. The specification of this weight variation test is given in pharmacopeias. All three brands of Azithromycin tablets passed the weight variation uniformity, thickness, and diameter tests as specified in the pharmacopeia according to which the acceptable limit for the deviation of weight for tablets averages does not exceed 5%. Regarding the results, average hardness for each brand was considered acceptable but the standard deviation for D1 and D3 were largely supposed to be a little deviation. The standard disintegration time for a film-coated tablet usually varies to 30 minutes. Results indicate that all three brands comply with this limit where the time of Disintegration for D1, D2, and D3 brands was found to be within their permissible limit. However, the D1 has a disintegration time lower than them and it has been assumed that the D1 brand has uncoated tablets.

Conflict of Interest:

The authors declare that there are no conflicts of interest.

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