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Multi-dimensional Comparative Study on Quanlity of Azithromycin Dry Suspension from Different Manufacturers

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Abstract

Objective: To compare the quality of azithromycin dry suspensions from different manufacturers. Methods: A comparative study was conducted on azithromycin dry suspensions produced by the original research manufacturer and two enterprises from China. The quality of each preparation was compared and evaluated by determining data such as appearance, content, palatability, redispersibility, and dissolution profile of azithromycin dry suspensions from different manufacturers. Results: The azithromycin content of products from all manufacturers ranged from 90% to 110%, meeting the requirements of the Chinese Pharmacopoeia. There were differences to varying degrees in indicators including appearance, palatability, and redispersibility. The dissolution profiles were similar in the pH 6.8 medium. In the pH 7.2 medium, the dissolution behavior of azithromycin dry suspension (Manufacturer W) was similar to that of the original research preparation, while the dissolution rate of azithromycin dry suspension (Manufacturer P) was excessively fast. Conclusion: The azithromycin content of the dry suspensions from the three manufacturers all meets the requirements of the Chinese Pharmacopoeia; however, there are differences in indicators such as appearance, palatability, redispersibility, and dissolution profile in the pH 7.2 medium.

Keywords

Azithromycin Dry Suspension; Quality; Comparative Study; Redispersibility; Dissolution Profile.

1. INTRODUCTION

Azithromycin is a semi-synthetic 15-membered macrolide antibiotic, modified from the structure of erythromycin [1]. It was successfully developed by Pliva in 1980 and launched globally. As a broad-spectrum antibiotic with relatively mild adverse reactions, it is mainly used clinically for the treatment of respiratory tract infections, skin and soft tissue infections, and genital infections [2]. Due to its high safety factor, azithromycin is listed by the World Health Organization (WHO) as one of the safest drugs and is widely used in pediatric clinical practice [3-4].

Azithromycin has no unpleasant odor but is bitter and almost insoluble in water. To improve the solubility and bioavailability of azithromycin and reduce toxic reactions, various oral formulations of azithromycin have been extensively studied. The dosage forms of the currently on the market include tablets, granules, sustained-release tablets, dispersible tablets and dry suspension. New technologies such as cyclodextrin inclusion, liposome technology and micronization technology have been applied. Among these, azithromycin dry suspension has uniform particle distribution, large distribution area in the gastrointestinal tract after oral

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administration, and rapid absorption. Compared with traditional capsules and tablets, it is more convenient to take, making it more suitable for children and the elderly [5-6].

Azithromycin dry suspension was first launched globally by Pfizer Inc. (USA) under the trade name "Zithromax" ("Xishumei" in Chinese). With clear efficacy and good safety, it quickly occupied an important position in the global macrolide antibiotic market, especially in the field of pediatric anti-infective drugs. After the patent expiration, many pharmaceutical companies worldwide have launched generic products. For example, Chinese companies such as CSPC Pharmaceutical Group and North China Pharmaceutical have obtained approval for related products [7].

To objectively evaluate the quality of marketed azithromycin dry suspension, this study collected the originator preparation and three generic products marketed in China. By studying and comparing quality-related indicators affecting the quality of dry suspension, including content, palatability, redispersibility and dissolution profile, this study provides a basis for clinical application.

2. INSTRUMENTS AND REAGENTS

2.1. Instruments

Waters ACQUITY UPLC H-Class PLUS Ultra Performance Liquid Chromatograph (Waters Corporation, USA); ZRS-8G Intelligent Dissolution Tester (Tianjin Tianda Tianfa Technology, China); SHIMADZU AUY220 Analytical Balance (Shimadzu Corporation, Japan); PB-10 pH Meter (Sartorius AG, Germany); Inverted Phase Contrast Microscope (Nikon Corporation, Japan); Stereomicroscope (Shanghai Optics, China).

2.2. Reagents

Azithromycin Dry Suspension X (originator product, Pfizer Pharmaceuticals Ltd., specification: 0.1g, batch numbers: 8189380, 8185617, 8188137); Azithromycin Dry Suspension W (Chinese W Pharmaceutical Enterprise, specification: 0.1g, batch numbers: 0632402116, 0632403066, 063212061); Azithromycin Dry Suspension P (Chinese P Pharmaceutical Enterprise, specification: 0.1g, batch numbers: 241122100, 240724400, 240726000); Azithromycin reference standard (Aladdin, 98%); Potassium dihydrogen phosphate, dipotassium hydrogen phosphate, phosphoric acid and hydrochloric acid were analytical grade; Acetonitrile was chromatographic grade.

3. METHODS AND RESULTS

3.1. Appearance (Particle Morphology)

One bag each of Azithromycin Dry Suspension X (originator product, batch number: 8189380), W (batch number: 0632402116) and P (batch number: 241122100) was taken, placed in appropriate containers, and their particle morphologies were observed with the naked eye, inverted phase contrast microscope and stereomicroscope. The specific results are shown in Figure 1.

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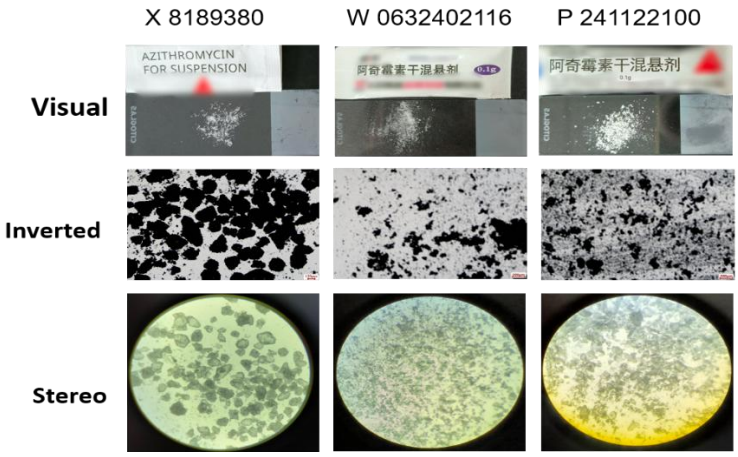

Figure 1. Appearance of Azithromycin Dry Suspensions from Different Manufacturers

The results showed that the particles of Azithromycin Dry Suspension X presented various irregular morphologies, some in irregular blocks and some in fragment-like shapes, with slight differences in size. The particle edges were clear, and the distribution was relatively uniform but scattered in the field of view, showing a natural dispersion state without obvious aggregation tendency, indicating ideal particle dispersion characteristics. For Azithromycin Dry Suspension W, the particle morphology was irregular with uneven edges and large differences in size. Most particles were in powder form, scattered sporadically in the field of view. Some particles showed a slight aggregation tendency. For Azithromycin Dry Suspension P, the particle morphology was significantly finer than that of the originator product, presenting a mixture of particles and powder. Most were small fragments or irregular small blocks, and some particles had visible broken edges.

3.2. Palatability Evaluation

3.2.1. Sample Preparation

Azithromycin dry suspension from different manufacturers was prepared into solutions with clinically commonly used concentration (20 mg/mL) according to the drug instructions. The sample solutions were transferred to uniform-specification transparent glass containers and labeled with unique random three-digit numbers to prevent subjects from identifying the drug source through packaging appearance or solution color.

3.2.2. Experimental Methods

Eight adult volunteers with normal taste were selected, who had no medication history in the past two weeks, no drinking or smoking habits, and no consumption of carbonated drinks, caffeinated drinks, or pungent-tasting fruits and foods within 1 hour before the test. Discussions were strictly prohibited during the evaluation.

The test solution combinations were randomly labeled. Before the test, volunteers rinsed their mouths with deionized water, then held the test solution in their mouths, fully felt the taste from the tip to the root of the tongue for 20 seconds, spit it out and rinsed their mouths 5 times. The next sample could be tested only after the bitter taste in the mouth completely disappeared for 1-2 minutes. After volunteers fully felt the taste of the sample, they evaluated it. The index scoring method [8] was adopted to evaluate taste, mouthfeel (whether there was a granular sensation) and swallowing difficulty, with a score range of 1-10 points. The specific scoring criteria are shown in Table 1.

The adult taste evaluation experiment in this paper is a research-oriented experiment, which has complied with the ethical requirements of Good Clinical Practice (GCP) and obtained informed consent from all volunteers.

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Table 1. Evaluation Criteria for Palatability of Azithromycin Dry Suspension

Taste index	describe specific feelings	Scoring Range
Taste, Mouthfeel and Swallowing Difficulty	Terrible taste, hard to accept	1-3
	Not very good taste, but bearable	4-6
	Acceptable taste	7-9
	Very good taste, quite satisfactory	10

3.2.3. Results

The palatability evaluation results of azithromycin dry suspension from different manufacturers are shown in Table 2. The determination results showed that Azithromycin Dry Suspension X had low sweetness, but the suspension was fine with almost no gritty granular sensation and smooth swallowing. After taking it, the volunteers' subjective feelings were mostly "slight and short-lived bitterness", with a fresh mouthfeel and almost no adhesion. Azithromycin Dry Suspension W had slightly higher sweetness than the originator product (X), but left a sour taste in the mouth after taking, with almost no granular sensation. Azithromycin Dry Suspension P had the highest sweetness, but during the experiment, it was found that some sample solutions had caking phenomenon, resulting in obvious viscosity during swallowing.

Table 2. Evaluation Results on Palatability of Azithromycin Dry Suspension from Different Manufacturers

Taste index	Scoring		
	Azithromycin Dry Suspension X	Azithromycin Dry Suspension W	Azithromycin Dry Suspension P
Taste	5.3	6.1	8.6
Mouthfeeland	7.9	8.2	6.6
Swallowing Difficulty	8.5	8.1	6.1
Total	21.7	22.4	21.3

3.3. Redispersibility

General Chapter <0123> of the Chinese Pharmacopoeia 2025 Edition stipulates that oral suspensions should be uniformly dispersed; if there is sediment after standing, it should be easily redispersed by shaking.

According to the requirements of the National Pharmacopoeia, the suspension placed in a stoppered measuring cylinder was inverted and placed on the test bench by hand. One inversion with a 5-second stay was counted as one shake until the suspended particles in the measuring cylinder were uniformly dispersed in the liquid, and the shaking time was recorded. The results are shown in Table 3. Some typical determination results are shown in Figure 2.

Table 3. Redispersibility of Azithromycin Dry Suspension

Manufacturer	Batch Number	Shaking Time (min)	Average Time (min)
Azithromycin Dry Suspension X	8189380	4	4.33
	8185617	4.5	
	8188137	4.5	
Azithromycin Dry Suspension W	0632402116	2.5	4.33
	0632412061	8.0	
	0632412061	2.5	
Azithromycin Dry Suspension P	241122100	11.5	9.83
	240724400	12.5	
	240726000	5.5	

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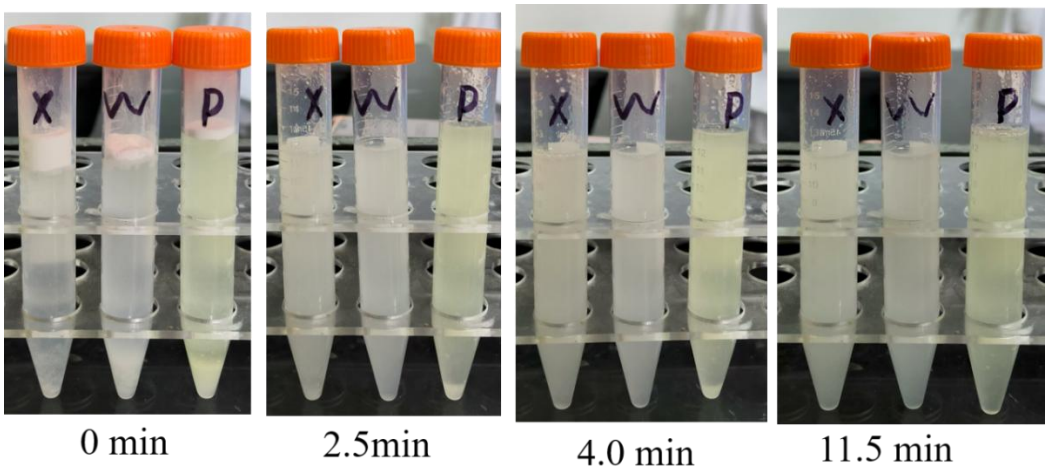

Figure 2. Partial Results of Redispersibility of Azithromycin Dry Suspension

The results showed that the dissolution time of the three batches of Azithromycin Dry Suspension X was 4.33 min on average, with small differences between batches, indicating that its production process or formula had good consistency and stable suspension performance. Although the average dissolution time of Azithromycin Dry Suspension W was the same as that of the originator product, the dissolution time fluctuated greatly between batches. This significant difference may be due to differences in raw material batches, insufficient control of production processes (such as granulation process parameters) or stability defects in the formulation. Azithromycin Dry Suspension P had an average dissolution time of 9.83 min, and the dissolution time fluctuated from 5.5 min to 12.5 min between batches. Both the overall suspension speed and batch stability were significantly weaker than those of the originator preparation, which may be related to raw material solubility, particle size distribution, excipient selection or preparation process.

3.4. Content and Batch Variation Analysis

3.4.1. Chromatographic Conditions

Chromatographic column: Waters (2.1×100 mm, 1.7 μm); Mobile phase: phosphate buffer (0.05 mol/L dipotassium hydrogen phosphate solution, adjusted to pH 8.2 with phosphoric acid) and acetonitrile (volume ratio 30:70); Flow rate: 0.2 mL/min; Column temperature: 40 °C; Detection wavelength: 210 nm; Injection volume: 10 μL.

3.4.2. Solution Preparation

An appropriate amount of azithromycin reference standard was accurately weighed, dissolved in acetonitrile, and quantitatively diluted with mobile phase to prepare a solution with a concentration of 1.0 mg/mL. In addition, an appropriate amount of Azithromycin Dry Suspension sample was accurately weighed, dissolved in acetonitrile with ultrasonic treatment for 5 minutes, and quantitatively diluted with mobile phase to prepare a sample solution containing 1.0 mg/mL of azithromycin. After filtering through a 0.22 μm microporous membrane, the subsequent filtrate was reserved for use.

3.4.3. Method Validation

An appropriate amount of azithromycin reference standard was taken, dissolved in acetonitrile and diluted to prepare a reference standard stock solution with a concentration of 10 mg/mL for method validation. The validation results showed that the blank solvent had no interference with azithromycin detection, and the typical chromatogram is shown in Figure 3. The relative standard deviation (RSD) of the reference standard solution for 6 consecutive injections was 0.40%. Azithromycin showed good linearity in the concentration range of 0.010-1.519 mg/mL, with the standard curve equation y= (R=0.9997). The limit of detection was 0.003

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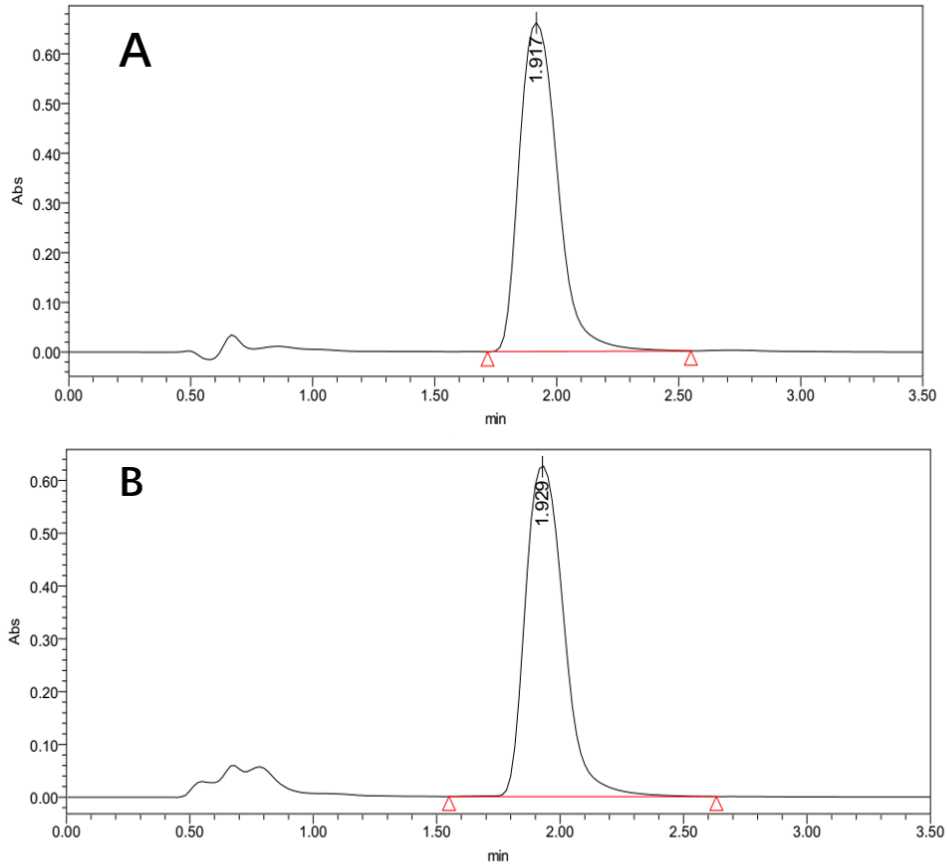
mg/mL, and the repeatability RSD was 0.59%. The validation results showed that this chromatographic method was accurate and reliable, and suitable for the content determination of azithromycin.



A: Azithromycin Reference Standard B: Sample of Azithromycin dry suspension

Figure 3. Typical Chromatogram for Content Determination of Azithromycin Dry Suspension

3.4.4. Content Determination Results

The content determination results are shown in Table 4. The results showed that the content of azithromycin dry suspension from different manufacturers was within 90%-110% of the labeled amount, which met the requirements. The RSD values of azithromycin dry suspension from different manufacturers were 0.77%, 1.22% and 1.76% respectively, indicating that their inter-batch precision met the requirements.

Table 4. Content of Azithromycin Dry Suspension from Different Manufacturers

Manufacturer	Batch Number	Content (%)	Average Content (%)	RSD (%)
Azithromycin Dry Suspension X	8189380	97.83	97.12	0.77
	8185617	96.34		
	8188137	97.19		
Azithromycin Dry Suspension W	632402116	103.3	101.9	1.22
	632412061	101.47		
	632412061	100.92		
Azithromycin Dry Suspension P	241122100	103.28	101.4	1.76
	240724400	99.76		
	240726000	101.05		

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3.5. Dissolution Profile Comparison

The dissolution profile was determined with reference to the second method (paddle method) in Appendix 2 of Volume II of the Chinese Pharmacopoeia 2025 Edition. Using 900 mL of pH 6.8 phosphate buffer and pH 7.2 phosphate buffer as dissolution media [9], with a rotation speed of 50 rpm, 2 mL of dissolution solution was taken at 5 min, 10 min, 20 min, 30 min, 45 min, 60 min and 90 min respectively. After filtering through a 0.22 μm microporous membrane, it was used as the test solution. An appropriate amount of azithromycin reference standard was taken, dissolved in acetonitrile and diluted with dissolution medium to prepare a reference standard solution with a concentration of 0.11 mg/mL. The detection was carried out under the chromatographic conditions specified in 2.4.1, and the chromatogram was recorded. The cumulative dissolution rate was calculated by the external standard method using peak area. The specific results are shown in Figure 4.

The determination results showed that the dissolution rate of azithromycin dry suspension from different manufacturers in pH 6.8 medium was more than 85% at 5 min and reached 100% at 10 min. Therefore, it is considered that the dissolution profiles of azithromycin dry suspension from the three manufacturers are similar in pH 6.8 dissolution medium. In pH 7.2 medium, the dissolution profile of Azithromycin Dry Suspension W (batch number: 0632402116) was basically consistent with that of the originator preparation (batch number: 8189380); the dissolution rate of Azithromycin Dry Suspension P (batch number: 241122100) was significantly faster than that of the originator preparation, indicating that there was a difference between this product and the originator preparation, which may be caused by differences in preparation process or excipient selection.

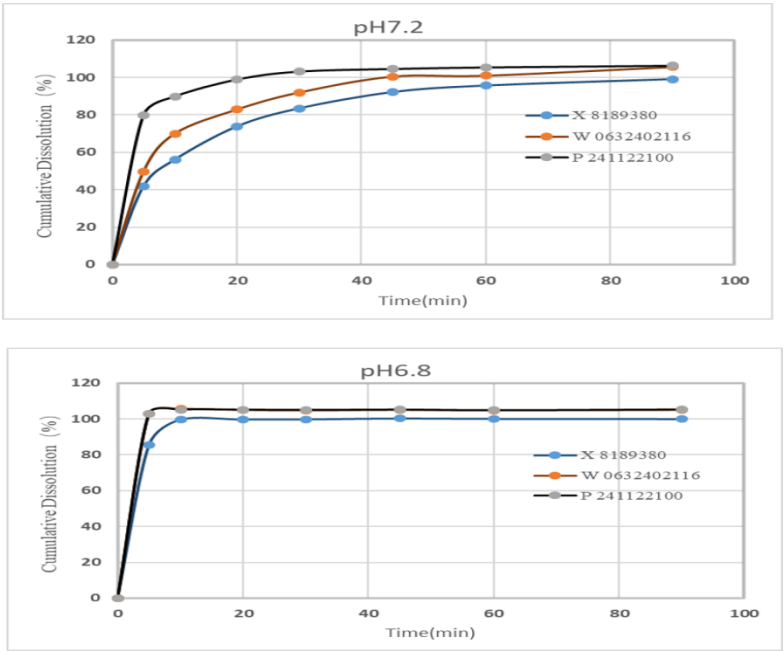

Figure 4. Dissolution Profile of Azithromycin Dry Suspension in Media with pH 6.8 and pH 7.2

4. CONCLUSION

This study conducted a systematic analysis on the quality of the originator azithromycin dry suspension (S) and two domestic generic products (W, P). The results showed that the content (90%-110% of the labeled amount) and appearance of the three preparations all met the requirements of the Chinese Pharmacopoeia and had the basic quality conditions for clinical medication, but there were significant differences in core quality attributes.

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In terms of physical properties and administration experience, the originator product S had uniformly dispersed particles without aggregation, a fine suspension, smooth swallowing, and stable batch-to-batch redispersibility (average 4.33 min); although the average redispersion time of generic product W was consistent with that of the originator product, there was a large batch-to-batch fluctuation (2.5 min-8 min), and a sour taste remained after administration; generic product P had fine particles, easy caking of the suspension, the worst redispersibility (average 9.83 min, batch variation 5.5 min-12.5 min), and obvious viscosity during swallowing.

In terms of dissolution consistency, the three products had similar dissolution profiles in pH 6.8 medium (dissolution rate >85% at 5 min); however, in pH 7.2 medium, only generic product W had consistent dissolution with the originator product, while generic product P had a significantly faster dissolution rate, which is inferred to be related to differences in process or excipients.

In conclusion, although domestic generic products meet the basic standards of the Pharmacopoeia, there are still gaps with the originator product in terms of stability, administration experience and dissolution characteristics, which can provide references for clinical medication selection and enterprise process optimization. In the future, it is necessary to combine bioequivalence and clinical effect studies to establish a more comprehensive quality evaluation system and promote the quality improvement of generic products.

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