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Quality Evaluation of Azithromycin Oral Solid Dosage Forms in Nigeria: In Vivo-In Vitro Correlation Study

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ABSTRACT

Background: Azithromycin is used for bacterial infections, such as respiratory tract and genitourinary tract infections, and has also been effective for preventing maternal sepsis during vaginal birth in some settings. The availability of low-cost azithromycin products of the required pharmaceutical quality is crucial for a successful campaign against maternal sepsis-related death. This study aimed to evaluate the quality of the azithromycin oral solid dosage forms manufactured and marketed in Nigeria. **Methods:** Three locally manufactured generic products and the innovator product of azithromycin tablets/capsules were subjected to physicochemical tests in accordance with United States Pharmacopeia (USP) specifications. Dissolution profiles of the products in 0.1 N hydrochloric acid (HCl) and phosphate buffer (pH 6.0) were compared using model-dependent and model-independent approaches. The innovator and generic products with similar dissolution profiles were subjected to a 2-g single-dose randomized two-period crossover bioavailability and bioequivalence study. **Results:** All products met USP specifications for weight uniformity, disintegration (10–15 min), drug content (99.8–101.1%), and dissolution in phosphate buffer 6.0 (> 75% dissolution in 45 min); However, one product failed the test for friability. The kinetic model with the best fit for the products was the Korsmeyer–Pappas model (R^2 = 0.7137–0.9562). Only one product (AZI-E) had a comparable dissolution profile to the innovator brand (similarity and difference factors were 68 and 7, respectively), and bioavailability and bioequivalence studies showed it was bioequivalent to the innovator product. **Conclusion:** Product AZI-E was the most promising locally manufactured azithromycin formulation (AZI-E) that has potential to reduce maternal sepsis in Nigeria when compared with the innovator brand. Continuous pharmacovigilance is advocated to safeguard public health.

Keywords: Azithromycin, maternal sepsis, bioequivalence, drug quality, drug dissolution profile

INTRODUCTION

A drug is said to be of the required pharmaceutical quality if it is suitable for its intended use. This suitability includes attributes such as identity, strength, and purity (*1*). Cost-effective drug products and the required pharmaceutical quality are essential for patient care, particularly in low and middle-income countries such as Nigeria. There is increasing patronage of generic drug products due to their cheaper cost compared with innovator products (*2*). In addition, pharmaceutical expenditures of patients may increase owing to increased disease

prevalence and limited availability of cost-effective drug products. Considering the challenges associated with low-quality drugs, continuous drug monitoring is required to ensure the safety, efficacy, and quality of marketed drugs (*3*).

Pharmacovigilance and post-marketing surveillance are essential regulatory processes after a drug is authorized by the required regulatory agency. These processes are targeted at identifying drug-related problems, such as adverse events, and ensuring compliance with the required standards. In Nigeria, concerns have been raised regarding the quality of some drugs. For instance, Hassan et al. reported that only nine out of 22 products of artemether injection marketed in southwest Nigeria met the pharmacopeia standard for the percentage content of artemether (*4*). Charles-Okhe et al. reported that three out of five brands of co-trimoxazole suspensions (60%) marketed in Lagos, Nigeria failed the drug content test (*5*). The decision to substitute innovator products with generic ones is often a concern among clinicians because some generic products might not produce the same therapeutic effects as the innovator products (*6*).

Azithromycin, a macrolide antibiotic, is one of the most used antibiotics owing to its ease of dosing (once daily) and the availability of several generic forms. Azithromycin is used for bacterial infections, such as respiratory tract and genitourinary tract infections (*7*). Moreover, a single 2-g dose of azithromycin was found to be effective to prevent maternal sepsis when compared with a placebo in women undergoing vaginal birth (*8*, *9*).

The availability of cost-effective generic azithromycin products is essential for continuous campaigns against maternal sepsis and other infectious diseases that are treatable with azithromycin. Studies on the quality of generic azithromycin products in Nigeria and their bioequivalence with innovator products are limited. This study aimed to evaluate the quality of generic azithromycin products manufactured and marketed in Nigeria by establishing an in vitro-in vivo correlation (IVIVC) with the innovator brand.

METHODS

Three generic azithromycin tablet/capsule formulations manufactured in Nigeria were purchased from accredited wholesalers and distributors. The products were visually inspected for cracks, discoloration, and other physical anomalies. The National Agency for Food and Drug Administration and Control (NAFDAC) registration number, batch number, manufacturing date, and expiry date of the tablets/ capsules were recorded and assigned code names, as follows. AZI-T (film-coated tablet; batch 01 K, NAFDAC B4-1591, manufactured Nov 2021, expiration Oct 2024); AZI-E (hard gelatin capsule; batch S00563SC, NAFDAC A4-8316, manufactured Mar 2023, expiration Mar 2026); and AZI-M (uncoated tablet; batch A 018, NAFDAC A11-0331, manufactured Nov 2023, expiration Mar 2026). The innovator product was purchased from Pfizer-accredited distributors in Nigeria and code-named AZI-Z (hard gelatin capsule; batch D13501, NAFDAC 04-1388, manufactured Mar 2023, expiration Feb 2027).

Azithromycin standard was purchased from Aladdin Industrial Corp. (Qigang RD, Fengxia, Shanghai, CAS: 83905-01-5). Analytical grade chemicals such as potassium hydrogen phosphate (Molychem, Mumbai, India), sodium hydroxide pellets (Scharlab, Spain), diethyl ether, and concentrated hydrochloric acid (HCl) were purchased. High-performance liquid chromatography

(HPLC) grade acetonitrile and methanol (Scharlab, Spain) and Milli-Q distilled water were used.

Weight Uniformity Test

Twenty tablets/capsules of each product were randomly selected and weighed. The mean weight for each product was calculated. The number of tablets/capsules weighing more than ± 5% of the mean weight was determined.

Thickness Evaluation

Five tablets per sample were randomly selected, and their thickness was measured using a micrometer screw gauge.

Hardness Test

The hardness of five tablets per product was measured using a Monsanto-type hardness tester (Model VMT 6804337162, Vinsyst Technologies). The force required to fracture the tablet diametrically was recorded.

Friability Test

Twenty tablets were randomly selected, dusted, and weighed. The tablets were carefully placed in a CS-3 tablet friability tester (Sinopharm) and rotated at 100 revolutions (25 rpm for 4 min). The tablets were collected from the friability tester and weighed to determine the percentage of weight loss.

Disintegration Test

The disintegration test was performed using a basket-disk rack disintegration apparatus (Model DTT-K1, Infitek) and six tablets/capsules, with pH 6.0 phosphate buffer as the immersion medium. The temperature of the medium was maintained at 37 ± 2 °C. The time taken for each tablet/capsule to disintegrate completely was determined.

Drug Content Assay

Drug content assay was performed using HPLC (1260 Infinity Quaternary Pump, Agilent Technologies) according to the United States Pharmacopeia (*USP*) (*10*). Twenty tablets/capsules were weighed and powdered. The amount of the powder drug equal to 100 mg of azithromycin (based on the label claim) was weighed and dissolved in the HPLC mobile phase (mixture of acetonitrile and phosphate buffer, 65:35, pH 7.5), sonicated (JP Selecta, Spain), and shaken as needed to dissolve to produce 1 mg/mL of sample solution. Azithromycin standard was equally dissolved in the HPLC mobile phase at a concentration of 1 mg/mL. An equal amount of the sample and standard solutions (50 uL) was injected into the HPLC with UV, and the output was recorded. The percentage of the drug that was released was calculated.

In Vitro Dissolution Study

Performance Verification Test

The suitability of the dissolution test was validated using USP Prednisone tablets. Six tablets were subjected to a dissolution test with deionized water as the medium, as specified in the *USP* (i.e., paddle apparatus at 50 rpm for 30 mins; spectrophotometric analysis at 246 nm) (*10*). Samples (5 mL) from the dissolution medium were obtained and analyzed to determine the concentration

of Prednisone in the samples. The results obtained were compared with acceptance criteria in the USP certificate.

Validation of the Analytical Finish

The HPLC analysis procedure was tested for linearity following the method of Vyas et al (*11*). The analytical method was calibrated by preparing known concentrations of azithromycin standard in the two selected media separately. The calibrated concentrations were injected into the HPLC. In each medium, a calibration curve of the concentrations against the respective peak areas obtained from the HPLC chromatograms was plotted. For 0.1-N HCl and phosphate buffer (pH 6.0), the linear correlation coefficient (R^2) for the calibration curve was estimated to be 0.9998 and 0.9996, respectively.

Procedures

In vitro release characteristics of azithromycin oral formulations were determined in 900 mL of two media separately (0.1 N HCL and phosphate buffer at pH 6.0) at 37 °C. Three tablets/capsules of each product were tested. An Electrolab (India) USP dissolution paddle apparatus (75 rpm) was used for the tablets, and a basket (100 rpm) was used for the capsule. At 5, 10, 15, 30, 45, and 60 minutes, 5 mL of the resulting solution was withdrawn and replaced with an equal volume of dissolution medium. Each sample was filtered using a 0.22-mm Millipore filter and assayed using HPLC with a UV detector at a wavelength of 210 nm to determine the amount of the drugs released into the dissolution medium at each time point.

Model-Dependent and Model-Independent Comparison of In Vitro Dissolution Profiles

The in vitro dissolution profiles of the locally manufactured products were compared with the innovator product using kinetic models (model-dependent) and similarity (f_2) and difference (f_1) factors (model-independent) (*3*).

In Vivo Bioavailability and Bioequivalence Studies

A single-dose, randomized, two-period crossover study was designed to evaluate bioavailability and bioequivalence in healthy volunteers. from the study protocol was approved by the College of Medicine University of Lagos Health Research Ethics Committee (CMULHREC Number: CMUL/HREC/02/24/1372), and all participants provided written informed consent.

The method for the crossover study was used as previously described with slight modifications (*12*). Briefly, the study was performed at two time points, the initial phase and crossover phase. The volunteers were randomly assigned into two groups: test (AZI-E [generic]) and comparator (AZI-Z [innovator]). The interval between the two phases was 15 days (washout period). In each phase, the volunteers were switched so that those in the test group in the initial phase were assigned to the comparator group in the crossover phase and vice versa.

At each time point, the volunteers were required to fast overnight for at least 10 hours before the study day. A pre-test blood sample (5 mL) was collected from each participant and recorded as 0 h. Thereafter, the participants were required to swallow a 2 g capsule of AZI-E or AZI-Z whole without chewing or crushing with 250 mL of water and remain in a supine position for the first 4 hours. The volunteers continued the fast for the first 4 hours of the study, after which a standard meal was provided. The volunteers were required not to participate in any strenuous activity. At

0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 120 hours, 5 mL of blood was collected from each participant into heparinized tubes. The blood samples were subjected to centrifugation (Cencom II, JP Selecta) for plasma separation. The separated plasma samples were stored frozen at a temperature of less than 20 ˚C. The concentrations of azithromycin in the plasma samples (1 mL) were determined using HPLC.

Various concentrations of azithromycin in plasma (0.25, 0.5, 1, 4, 10, and 20 ug/mL) were prepared. To the 1 mL of calibrated concentrations of azithromycin and plasma samples obtained from participants, 2 mL of methanol was added for deproteination, followed by centrifugation for 10 mins at 4000 g. I precipitates were decanted into 10-mL plain sample bottles. To the precipitates, 1 mL of 1-M sodium hydroxide was added and vortex mixed (Scientific Industries, Inc.). To the resulting mixtures, 6 mL of diethyl ether was added and vortex mixed, followed by centrifugation for 10 mins at 3500 g. The organic layers were removed, filtered, and evaporated to dryness over a water bath (B-Bran Scientific & Instrument Co. Ltd.) at 80 ˚C. The resulting extracts were reconstituted in 100 µL of a mixture of acetonitrile and phosphate buffer at pH 7.7 (65:35). The resulting solutions were then subjected to HPLC analysis.

A linear correlation graph of concentration against peak area for known concentrations of azithromycin in plasma was plotted and the equation of the graph was obtained. The equation was used to determine the concentration of azithromycin in each plasma sample obtained from the participants. Non-compartmental linear-trapezoidal modeling was used to estimate pharmacokinetic parameters from plasma concentrations.

In Vivo-In Vitro Correlation (IVIVC)

The fraction of drug absorbed in vivo and the fraction dissolved in vitro were calculated for the first hour from the respectively data. A level-A IVIVC correlation plot was used to assess the correlation between the in vivo and in vitro drug release profiles (*10*).

Statistical Analysis

All data were analyzed using Microsoft Excel 2016. The data were presented as means with standard deviation. Statistical differences between means were measured using the student t-tests for two means and a one-way analysis of the variance of more than two means. Statistical difference was set at $p < 0.05$. The 90% confidence intervals at a 5% level of significance for the geometric mean ratio of the log-transformed pharmacokinetic parameters of the test to the innovator products were calculated.

RESULTS

Physicochemical Characterization

The mean (± SD) weights for the generic (AZI-T, AZI-M, AZI-E) and innovator (AZI-Z) azithromycin products were 0.67 ± 0.02, 0.65 ± 0.01, 0.65 ± 0.01, and 0.56 ± 0.01 g, respectively ($p = 9.58 \times 10^{-36}$). None of the brands had more than two tablets/capsules exceeding 5% of the mean weight.

Mean thickness measurements for AZI-T, AZI-M, AZI-E, and AZI-Z were 8.03 ± 0.01, 6.36 ± 0.28, 7.27 ± 0.29, and 7.12 ± 0.05 cm, respectively ($p = 2.12 \times 10^{-9}$).

Friability results for AZI-T and AZI-M (tablets) were 9.15% and 0.97%, respectively. Mean (±SD) hardness values for AZI-T and AZI-M were 8.30 ± 2.48 and 7.80 ± 1.64 kg/cm^2, respectively (p = 0.77).

Mean disintegration times for AZI-T, AZI-M, AZI-E, and AZI-Z were 15.04 ± 0.56, 10.04 ± 0.70, 11.44 ± 2.42, and 14.14 ± 0.57 mins, respectively ($p = 8.98 \times 10^{-5}$).

Results of the drug content assay for AZI-T, AZI-M, AZI-E, and AZI-Z were 99.92% ± 0.19%, 99.81% ± 1.53%, 100.39% ± 0.63%, and 101.14% ± 0.69%, respectively (p = 0.518).

In Vitro Dissolution Profile

The dissolution profiles of the products in each medium are shown in Figures 1 and 2. For all products, at least 75% dissolution was achieved within 45 min in phosphate buffer (pH 6.0), and less than 75% dissolution occurred in 0.1 N HCL.

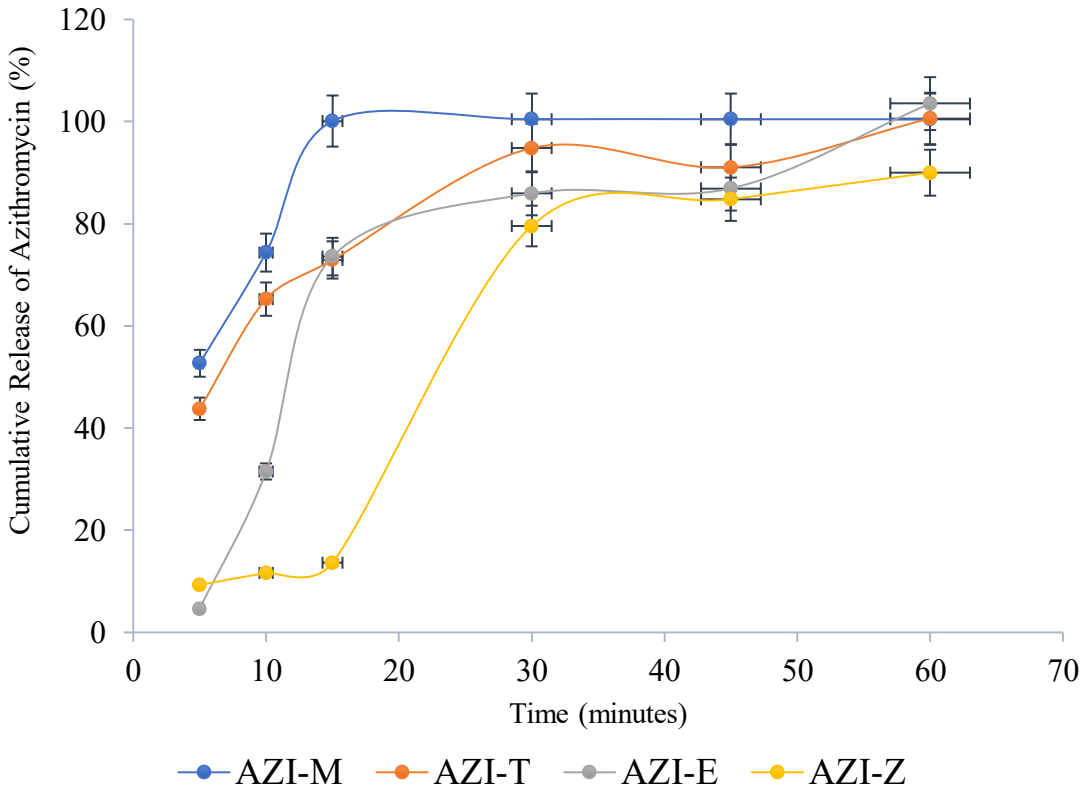

Figure 1. Dissolution profiles of generic (AZI-M, AZI-T, AZI-E) and innovator (AZI-Z) azithromycin products in phosphate buffer (pH 6.0). Data are presented as mean (dot) ± SD (vertical whiskers) ± range (horizontal whiskers).

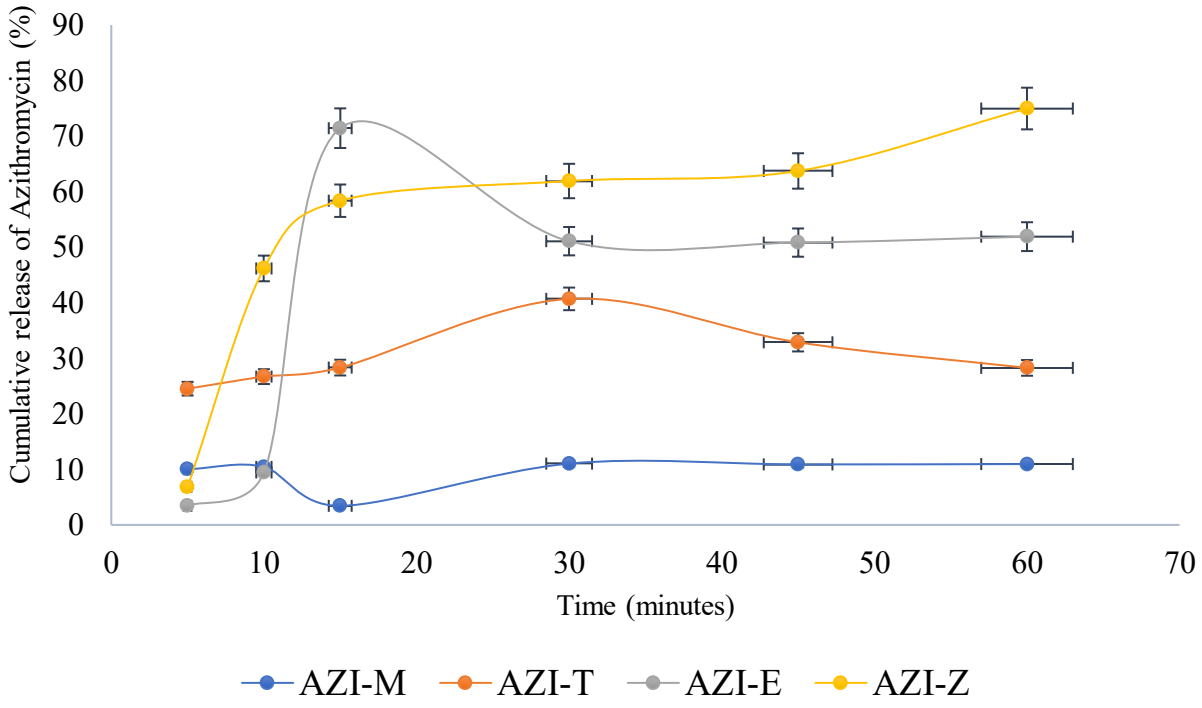

Figure 2. Dissolution profile of generic (AZI-M, AZI-T, AZI-E) and innovator (AZI-Z) azithromycin products in 0.1 N HCL. Data are presented as mean (dot) ± SD (vertical whiskers) ± range (horizontal whiskers).

Model-dependent and model-independent comparisons of the products are shown in Table 1. Using similarity factor analysis, only AZI-E had a similar dissolution profile as AZI-Z in phosphate buffer (ph 6.0). The dissolution profiles best fit the Korsmeyer–Peppas kinetic model for all products.

Table 1. Model-Independent and Model-Dependent Comparison of Generic (AZI-M, AZI-T, AZI-E) and Innovator (AZI-Z) Azithromycin Products in Phosphate Buffer pH 6.0

	AZI-M	AZI-T	AZI-E	AZI-Z
Model-independent				
Difference factor, f_1	38	23	7	Reference
Similarity factor, f_2	32	39	68	Reference
Model-dependent (R^2 values)				
Zero-order	0.4150	0.6731	0.6765	0.8678
First order	0.2752	0.3544	0.4637	0.7396
Higuchi	0.6996	0.8944	0.8413	0.8371
Korsmeyer–Pappas	0.7137	0.7864	0.8853	0.9562
Hixon–Crowell	0.3648	0.7119	0.5056	0.08266

In Vitro Bioavailability and Bioequivalent Study

Six healthy participants (three men and three women) with a mean age of 26.5 years (range: 22–30 years), mean weight of 69.8 kg, and mean body mass index (BMI) of 23.61 kg/m^2 were enrolled in the study.

No significant adverse event was reported. The only reported adverse effect was a mild gastrointestinal disturbance, which resolved without any intervention.

The plasma release profiles of the products (AZI-E and AZI-Z) are shown in Figure 3. Table 2 shows the statistical comparison between the pharmacokinetic parameters of the two products in vivo.

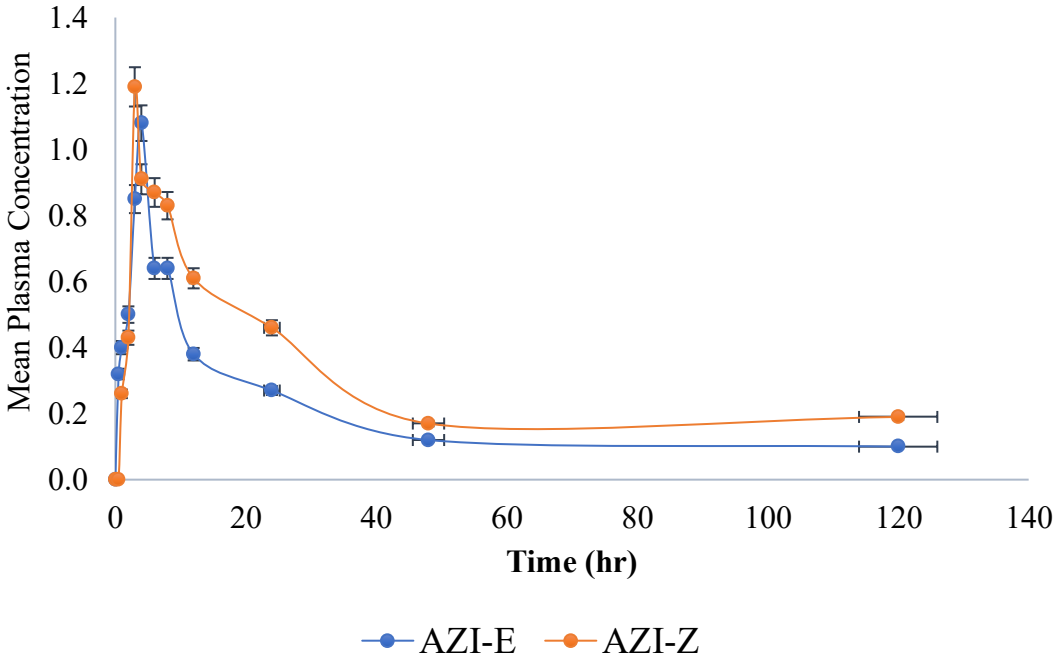

Figure 3. Plasma concentration-time curve for the test (AZI-E) and innovator (AZI-Z) azithromycin products. Data are presented as mean (dot) ± SD (vertical whiskers) ± range (horizontal whiskers).

Table 2. Statistical Comparison of Pharmacokinetic Profiles of Generic (AZI-E) and Innovator (AZI-Z) Azithromycin Products

	AZI-E	AZI-Z	p-value	Mean ratio	90% CI
T_{max} (h)	5.00	5.00	0.73	1.06	0.84–1.26
C_{max} (µg/mL)	1.22	1.37	0.70	0.88	0.51–1.21
AUC_{0-120}	13.46	34.99	0.08	0.79	0.38–1.14
$AUC_{0-\infty}$	23.66	39.24	0.13	0.79	0.23–1.26
Volume of distribution (L)	5618.42	2123.68	0.15	2.10	1.26–3.07
Clearance	144,077.43	75,285.65	0.36	2.99	0.79–4.36
Mean residence time $_{0-\infty}$	95.50	87.16	0.85	1.28	0.20–2.12
Elimination constant	0.15	0.31	0.61	1.78	0.38–2.34
Half-life	57.64	50.48	0.82	1.50	0.43–2.63

IVIVC

The IVIVC plot is shown in Figure 4. The correlation of in vitro dissolution and in vivo absorption of products AZI-E and AZI-Z was good (R^2 = 0.9187).

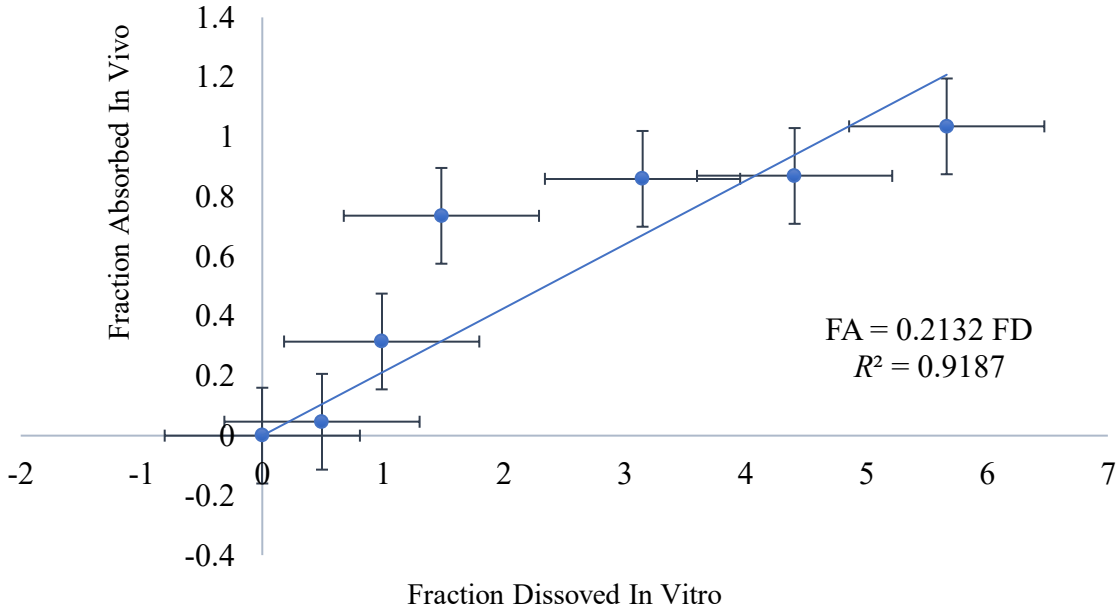

Figure 4. Level A in vivo-in vitro correlation plot for the tested azithromycin product. Data are presented as mean (dot) ± SD (vertical whiskers) ± range (horizontal whiskers). FA: fraction absorbed; FD: fraction dissolved.

DISCUSSION

In this study, the obtained data for azithromycin oral formulations were compared with compendia standards for disintegration time, friability, weight variation, and drug content to ascertain the quality. The *British Pharmacopeia* (*BP*) and *USP* specify that for tablets/capsules weighing more than 324 mg, no more than two of 20 tablets should have a weight difference of ± 5% from the mean weight. Only one generic product (AZI-T) had two tablets with a weight that did not meet this limit, which could be due to a manufacturing error (*13*).

The amount of active pharmaceutical ingredients in a drug formulation must meet the approved amount that provides the desired therapeutic effect (*3*). According to *BP* and *USP*, the drug content should be 95–105% and 90–110% of the label claim, respectively. The assay results showed that the active ingredients in all the products were within the range of 99.81–101.14% of the label claim. These results are consistent with studies of azithromycin dihydrate tablets/capsules conducted by Ukwueze et al. on azithromycin dihydrate tablets and capsules in Nigeria and that reported by Mekasha et al. for five azithromycin products in Ethiopia (*3*, *14*).

Attrition during packaging might cause partial powdering or fragmentation of tablets (*3*, *15*). The acceptable compendia limit is 1%. AZI-M and AZI-T, the two products formulated as tablets, had friability of 0.9% and 9.1%, respectively, indicating that AZI-T is highly friable.

Disintegration and dissolution rates are directly related, as disintegration is one of the first steps in drug dissolution. Moreover, drug absorption and efficacy rely on disintegration and dissolution rates (*13*). Azithromycin is a BCS class II drug, meaning that it has low solubility and high permeability; hence, prompt disintegration might facilitate its dissolution, thereby reducing the time until onset of action (*16–19*). Film-coated tablets and hard gelatin capsules should disintegrate within 30 minutes, and uncoated tablets should disintegrate within15 minutes. In phosphate buffer pH 6.8, which mimics the pH of the duodenum, all products disintegrated completely within 15 minutes, complying with compendial specifications.

The *BP* and *USP* both specify that 75% of tablets should dissolve in the specified medium within 45 min, and 80% of capsules should dissolve within 30 min. However, in the current study, the dissolution profiles of the products were evaluated in two media (0.1 N HCL and phosphate buffer pH 6.0) at different time points to provide the necessary information to compare release behaviors of the azithromycin products. At 30 and 45 minutes, all the products had less than 75% mean dissolution in 0.1 N HCL; however, dissolution exceeded 75% in phosphate buffer (pH 6.0). This indicates that the products dissolve more in the intestine, where the drug residency time is higher, thereby aiding absorption rather than in the stomach. Notably, phosphate buffer (pH 6.0) is the *USP*-specified dissolution medium (*10*). This result is consistent with the result obtained by Mekasha et al. (*3*).

Several approaches have been proposed for comparing the release profile of drugs. There are statistical, model-independent, and model-dependent approaches (*18*). The model-independent approach includes the use of similarity and difference factors (f_2 and f_1, respectively) to compare the in vitro drug release profiles of drug products. Values of 0–15 for f_1 and 50–100 for f_2 are indicative of the equivalence of two dissolution profiles (*15*). When the generic products were compared with the innovator (AZI-Z) using similarity factor analysis, AZI-E was the only product with a similar dissolution profile as AZI-Z in phosphate buffer (ph 6.0). Dissimilarities in the dissolution profiles of azithromycin tablets using f_1 and f_2 have been reported in Ethiopia and Nigeria (*3*, *14*). Using model-dependent approaches, the dissolution profiles of the products were characterized using zero order, first order, Higuchi, Korsmeyer–Peppas, and Hixon–Crowell kinetic models (*18*). Based on the highest R^2 values, the dissolution profiles best fit the Korsmeyer-Peppas kinetic model for all products, which is consistent with the study conducted in Ethiopia (*3*).

The results of the bioequivalence study showed that generic AZI-E is bioequivalent to the innovator (AZI-Z). There were no statistically significant differences in the estimated pharmacokinetic parameters of the two products (all $p > 0.05$). According to regulatory guidance, the 90% confidence interval should be between 80% and 125% (*19–22*). In addition to this general approach, the 1992 guidance provided specific recommendations for logarithmic transformation of pharmacokinetic data, methods to evaluate sequence effects, and methods to evaluate outlier data, as seen in Table 2 (*22*). In the currently study, only the time taken to reach the maximum concentration (Tmax) has a 90% confidence interval between the stipulated range (0.84–1.26). Other pharmacokinetic parameters, such as maximum concentration (Cmax) and area under the concentration-time curve (AUC) had lower confidence limits that were lower than the specified value but the stated upper confidence limit was not exceeded (0.51-1.21; 0.38-1.14; and 0.23-1.26, respectively). However, these findings are consistent with those of other similar studies (*23*).

Considering the paucity of data on the bioequivalence of azithromycin products in Nigeria, this study provides insight into the quality of locally manufactured products, highlighting the efforts of relevant pharmaceutical companies and regulatory agencies to ensure that medicines of the required quality are available for patient use.

The results of the IVIVC analysis showed a good correlation (R^2 = 0.9187), indicating that in vivo absorption of azithromycin correlates with its in vitro dissolution profile.

This study has some limitations. The available locally manufactured products at the time of the study were limited, resulting in the use of only three products for the study; however, not many azithromycin products are locally manufactured.

CONCLUSION

This study showed that, in general, the locally manufactured azithromycin products met the required physicochemical specifications for drug content, disintegration, dissolution, and weight uniformity. Only one out of three generic azithromycin products (AZI-E) had a similar dissolution profile as the innovator product in phosphate buffer at pH 6.0. AZI-E was bioequivalent to the innovator product and had a good IVIVC. AZI-E has the required quality for the potential treatment of maternal sepsis and is a cost-effective alternative to the innovator product in the Nigerian market. Continuous post-marketing surveys are crucial to ensure that generic antibiotics retain their quality throughout the shelf life of the product.

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DISCLOSURES

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SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author

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