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QUALITY ASSESSMENT OF SOME BRANDS OF CLARITHROMYCIN AND AZITHROMYCIN TABLETS USING THE CONCEPT OF DISSOLUTION EFFICIENCY AND SIMILARITY FACTOR

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Azithromycin, Clarithromycin, Bioequivalence, Interchangeability, *In-vitro* dissolution, Dissolution efficiency

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ABSTRACT: Counterfeit and substandard pharmaceutical products circulate widely in developing countries, yet adequate techniques to monitor quality is lacking. We report herein a quick and reliable approach to predict the *in-vitro* bioequivalence and interchangeability of common antibiotics using nine model drugs; four brands of azithromycin and five brands of clarithromycin tablets marketed in Nigeria. Pharmacopoeia guidelines (British and United States) were used to assess tablet quality such as friability, disintegration and dissolution times. All the brands tested passed the British Pharmacopoeia standard for disintegration time and their hardness and friability values were also considered adequate. There were no significant differences in the dissolution profiles of the brands, however, the azithromycin brands released >70% of the active drug within 30 min. The calculated similarity factor values for the azithromycin and clarithromycin brands were between 61 to 100 and 46 to 100 respectively. Based on the *in-vitro* tests, all the brands of azithromycin were considered bioequivalent with the innovator brand. However, only one brand had a similarity factor very close to that of the innovator brand and could be considered interchangeable. All the brands of clarithromycin were also considered bioequivalent, except one brand. Our results show that, the concept of dissolution efficiency could be a reliable method of predicting bioequivalence of antibiotics thereby serving as a tool to monitor and prevent the circulation of fake and counterfeited drug products.

INTRODUCTION: Increasing economic activities in many parts of the world and the low income per head in developing countries like Nigeria, has resulted in the proliferation of pharmaceutical manufacturing industries and the importation of different brands of the same drugs into Nigeria at cheaper prices [1].

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The sale of these drug products with extravagant claims and the 'get rich quick' syndrome associated with the society of today has ignited the corrupt practices of various unscrupulous manufacturers, importers and marketers giving rise to the tendency that expensive antibiotics like azithromycin and clarithromycin might easily be adulterated.

This can result in the development of bacterial resistance and therapeutic failures. The ability of microbes to resist antimicrobial therapy is a serious threat to health care as its rate of occurrence or prevalence and demands for prevention and/or treatment are on the increase [2, 3].

The upsurge of pharmaceutical industries with lower scrutiny or inspection of manufacturers whose existence has been encouraged by the affordability of generic brands, creating room for the manufacture and circulation of substandard products as well as administration of generic antibiotics at sub-therapeutic/sub-inhibitory doses has been implicated in antibiotic resistance [4, 5]. Some researchers [6, 7, 8, 9] opine that generic drugs may not be therapeutically equivalent to the innovator products and therefore may not be as effective. Also arising from poor drug quality is the administration of generics with poor drug release properties which is also likened to administering sub-therapeutic doses which may not only be ineffective but can have the capacity to increase bacterial resistance [3].

In addition to the inherent ability of bacteria to develop resistance [3], several studies have established that antibiotic therapy failure and bacterial resistance can also be related to the overuse or misuse of these drugs; the prominent factor here being self-medication following consideration of the cost of medical consultations, inadequate diagnosis, treatment and the ability of patients to purchase antibiotics without appropriate prescriptions [10, 11, 12]. Inadequate diagnosis, invariably leading to the prescription of broad-spectrum antibiotics rather than more organism specific antibiotics contributes largely to resistance and the administration of antibiotics without prescription or on recommendation following diagnosis is most frequently accompanied by sub-therapeutic dosing and duration of treatment which can modulate the bacterial virulence thereby resulting in resistance [13].

Azithromycin is a macrolide antibiotic used in the treatment of certain bacterial infections [14] such as *Mycobacterium avium* complex infection [15]. It is unique as anti-infective agent in that it appears to have potent anti-inflammatory properties [16]. Clarithromycin is also a macrolide antibiotic. It is very useful in the treatment of particularly respiratory infections, skin infections, lyme diseases and gastritis caused by *Helicobacter pylori* [17, 18, 19, 20]. As a result of uncontrolled competition, the corresponding price wars and claims of efficacy among different brands of the same antibiotic by manufacturers, distributors / marketers of antibiotics in Nigeria, heath care professionals and even the patients are often placed in a difficult situation as to the choice of an effective brand and the possibility of interchangeability among brands. In order to prove that two or more drugs of the same active ingredient is bioequivalent, a similarity in the rate and extent to which the drug in the dosage form becomes available for absorption needs to be demonstrated [21].

Despite the considerable use of azithromycin and clarithromycin in Nigeria, there are no reports on the bioavailability and bioequivalence studies of the various brands of these tablets marketed in Nigeria. Prediction of *in-vivo* bioavailability in most oral drugs has been shown to depend on the in vitro dissolution studies [22, 23, 24, 25]. In the present study, we assessed the *in-vitro* bioequivalence and interchangeability of nine brands of azithromycin and clarithromycin tablet dosage forms marketed in Nigeria using parameters like T_{70}, T_{90}, dissolution efficiencies (DE) and similarity factor, f_2 [26] derived from the dissolution profiles of the brands.

Tablets are required to possess acceptable chemical and physical attributes which are assessed using the following parameters: weight uniformity, friability, resistance to crushing (hardness), disintegration and content uniformity. For dosage forms to be considered fit, they must comply with the Pharmacopoeia requirements for these tests. Although these tests are easy to perform, compute and analyze, they only give information on the properties or nature of the dosage form without depicting or predicting drug dissolution and release which is paramount to activity and in vitro bioequivalence to allow for interchangeability between products [27]. The similarity factor (f2) although more complicated to calculate and more time consuming to obtain data for, assesses the in vitro bioequivalence of innovator and generic or test drug products and estimates expected drug levels in humans (*in-vitro* - *in-vivo* correlation) using *in-vitro* dissolution profiles which is not obtainable with general physicochemical testing. The FDA considers *in-vitro* dissolution testing to be more discriminating than an *in-vivo* test [4, 26].

Other general quality assessment of the brands were also carried out. The result of the study will serve as a rationale for the bioequivalence and

interchangeability or otherwise of the selected brands with an innovator brand.

EXPERIMENTAL:

Materials: Four brands of azithromycin and five brands of clarithromycin tablets coded; AZ1, AZ2, AZ3, AZ4 and CL1, CL2, CL3, CL4 and CL5 respectively. Gifted pure samples of azithromycin and clarithromycin (M.J Biopharm Pvt ltd. Taloja, Navi-Mumbai, India). Clinical isolates of *Staphylococcus aureus* and *Escherichia coli* obtained from Bishop Shanahan hospital, Nsukka, Enugu state, Nigeria, nutrient broth (Fisher scientific, UK), Mueller Hinton Agar (Sigma-Aldrich, US), UV-Visible PC Spectrophotometer (Model Unico 2102, USA), Erweka disintegrating chamber, and Erweka DT-D dissolution tester (Erweka, UK). All other reagents and solvents were of analytical grade and were used as supplied with further purification.

Drug Sampling: The different brands of azithromycin and clarithromycin studied were selected based on frequency of prescription, use and availability in hospital and community pharmacies. The drugs were randomly purchased from pharmacies located in Eastern Nigeria. No particular sampling procedure was employed other than the researchers posing as a 'normal customer' to purchase the drugs from drug shops without prescription.

All the brands used were registered by the National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria, and were analyzed at least six months before their expiration date. After purchase, information on the manufacturer's address and country of origin of the brands, batch numbers, manufacturing dates, label strength, and registration status by NAFDAC were extracted from the product label where available.

TABLE 1: SOME LABEL INFORMATION ON THE BRANDS OF AZITHROMYCIN AND CLARITHROMYCIN EVALUATED

Brand code	Batch no.	Labelled strength (mg)	NAFDAC number	Manufacturer's country of origin
Zithromax (AZ1)*	0011k07A	250	Yes	USA
AZ2	BFK001128	250	Yes	India
AZ3	812	250	Yes	India
AZ4	171207	250	Yes	Portland
Klabax (CL1)*	1834824	500	Yes	India
CL2	T-7005	500	Yes	India
CL3	EX08177	500	Yes	India
CL4	01B07007	500	Yes	India
CL5	CLWH0043	500	Yes	India

*Innovator brand, NAFDAC (National Agency for Food and Drug Administration and Control)

Microbiological Assessment: The one point microbiological assay method was used to measure the inhibition zone diameters (IZDs) of the standards (azithromycin and clarithromycin) and compare with the test brands. The method employed for the assay was the microbroth diffusion method and the test microorganisms used were turbidimetrically standardized *S. aureus* and *E. coli*. A 0.1 mL of the standardized test microorganism was seeded with 20 mL of sterile molten nutrient agar. The culture plates were divided into five equal segments using a wax pencil. Using a standard cork borer, six holes (8 mm in diameter) coded; S1, S2, S3, S4, T1and T2 representing different concentrations of both the standard and test sample were bored into each segment with one hole in the middle of the plate. A drop of each drug concentration was introduced into each hole, allowed to stand for 15 min and incubated at 37 ºC for 48 h. The IZDs were then measured and a plot of IZD in mm against the log concentration was obtained for the standard. The IZDs of the test samples were then extrapolated from the graph to get the concentrations of the drug.

Physical and Mechanical Properties of the Tablets: *In-vitro* properties of the tablet brands such as weight uniformity, crushing strength, friability, disintegration time and dissolution profile studies were evaluated using standard methods [16, 17, 18].

Assay: A simple analytical procedure based on UV spectrophotometry was adopted for quantitation of the drug in solution.

Calibration Curve: Serially diluted solutions of 0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/mL were prepared from a stock solution of 100 mg% in sodium phosphate buffer (pH 6.0) for azithromycin and 0.1M sodium acetate buffer for clarithromycin respectively. Absorbance readings were taken at 215 and 205 nm for azithromycin and clarithromycin respectively in a spectrophotometer. A plot each of absorbance against concentration for azithromycin and clindamycin was made from which the regression equation was calculated.

Dissolution Studies: The dissolution profile of each brand of azithromycin and clarithromycin was assessed using the paddle method according to the United States Pharmacopoeia (USP) guidelines [28]. The Erweka DT dissolution apparatus fitted with a paddle that rotated at 50 rpm was used. The dissolution media consisted of 900 mL of freshly prepared sodium phosphate buffer (pH 6.0) maintained at 37 ± 1 ºC. One of the tablets chosen randomly from each of the azithromycin tablet brands was placed in a basket (mesh size 325 mm) immersed half way into the dissolution media so that a distance of 2.0 ± 0.2 mm existed between the basket and the bottom of the dissolution vessel. A 5 mL volume sample was withdrawn at predetermined time intervals and this was followed by the addition of fresh and equivalent volume replacement maintained at the same temperature. Each withdrawn sample was filtered, diluted and analyzed spectrophotometrically against the blank, sodium phosphate buffer (pH 6.0) at 215 nm in a UV spectrophotometer. This procedure was repeated for the clarithromycin brands using sodium acetate buffer as the dissolution medium. Each withdrawn sample was filtered, diluted and analyzed spectrophotometrically at 205 nm.

The concentrations were thereafter determined from the calibration curves of pure azithromycin and clarithromycin respectively. The percentages of azithromycin and clarithromycin released were plotted against time and the dissolution efficiencies [DE] [29] of each was calculated at 60 min using the trapezoid rule. The data were expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time.

$$DE = \left\{\frac{AUC_{0-T}}{\%D_{max} \times T}\right\} \times 100$$

Where: % D_{max} is the maximum dissolved at the final time T; AUC_{0-T} is the area under the curve from zero to T.

$$AUC_{0-T} = \sum_{i=1}^{i=n} \frac{(t_{1-} t_{i-1})(y_{i-1} + y_i)}{(2)}$$

Where: t_i = the i^{th} time point; y_i = percentage of dissolved product at time t_i

In-vitro bioequivalence was demonstrated by comparing the dissolution profiles after fitting them into the f_2, similarity factor equation.

$$f_2 = 50.log\left\{\left(1 + \frac{1}{n}\sum_{i=1}^{n}(Rt - Tt)^2\right)^{-0.5}\right\} \times 100$$

Where: Rt = Average percentage of reference drug dissolved at time (n); Tt = Average percentage of test drug dissolved at time (n)

The difference factor (f_1) was also determined using standard methods [27].

The results of crushing strength and disintegration time tests were analyzed using Student's *t*- test (SPSS15) and expressed as mean ± SD. Differences between the means of the brands were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION:

TABLE 2: SOME *IN-VITRO* AND *IN-VIVO* PROPERTIES OF THE AZITHROMYCIN AND CLARITHROMYCIN TABLETS

Brand code	Hardness (kgf) ± SD	Friability (%)	Disintegration Time (min) ± SD	Assay (%)	Microbiological assay	
					S. aureus (%)	*E. coli* (%)
AZ1	11.58 ± 0.58	0.05	3.75 ± 0.50	100.83	95.0 ± 0.34	98.0 ± 0.39
AZ2	7.80 ± 0.22	0.12	3.25 ± 0.50	98.42	93.0 ± 0.34	94.0 ± 0.39
AZ3	5.83 ± 0.52	0.92	11.50 ± 1.29	98.05	82.0 ± 0.34	117.0 ± 0.39
AZ4	6.0 ± 0.38	0.15	5.75 ± 0.32	98.32	85.0 ± 0.34	92.0 ± 0.39
CL1	9.90 ± 0.58	0.03	4.50 ± 1.29	98.24	90.0 ± 0.20	91.0 ± 0.56
CL2	7.75 ± 0.28	0.07	2.25 ± 0.95	96.61	98.0 ± 0.20	95.0 ± 0.56
CL3	9.41 ± 0.38	0.06	7.50 ± 1.00	99.94	100.8 ± 0.20	100.3 ± 0.56
CL4	7.67 ± 0.82	0.06	4.25 ± 0.96	97.23	116.0 ± 0.20	96.0 ± 0.56
CL5	7.18 ± 0.32	0.10	16.50 ± 0.58	96.42	103.0 ± 0.20	98.0 ± 0.56

The values represent some *in-vitro* and *in-vivo* properties of the azithromycin and clarithromycin tablet brands. Each value represents the mean ± Standard deviation (SD) for 10 tablets per batch. Statistically significant differences between the brands were analyzed using the Student's t-test with SPSS version 15.

From the results presented in **Table 2**, azithromycin tablets had crushing strength values in the range of 5.83 ± 0.52 kgf to 11.58 ± 0.58 kgf while the clarithromycin brands had crushing strength values in the range of 7.67 ± 0.82 kgf to 12.10 ± 0.6 kgf. Tablet friability between 0.05 to 0.92 and 0.03 to 0.05% were obtained for azithromycin and clarithromycin respectively. All the tablets except CL5 disintegrated within 15 min. The *in-vitro* assay results ranged from 98.05 to 100.83% and 96.42 to 99.4% for the azithromycin and clarithromycin tablet brands respectively. Similarly, the results of the one point microbiological assay for the azithromycin brands ranged from 82.0 to 95.0% and 92.0 to 117.0% for *S. aureus* and *E.coli* respectively while that of clarithromycin brands ranged from 90.0 to 116.0% and 91.0 to 100.3 for *S. aureus* and *E. coli* respectively.

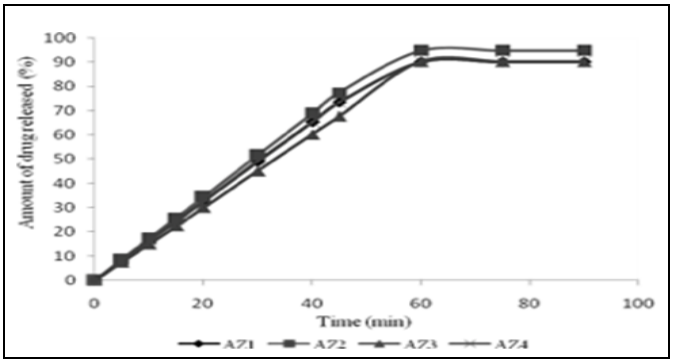

FIG. 1: RELEASE PROFILE OF AZITHROMYCIN FROM FOUR BRANDS AZITHROMYCIN TABLETS

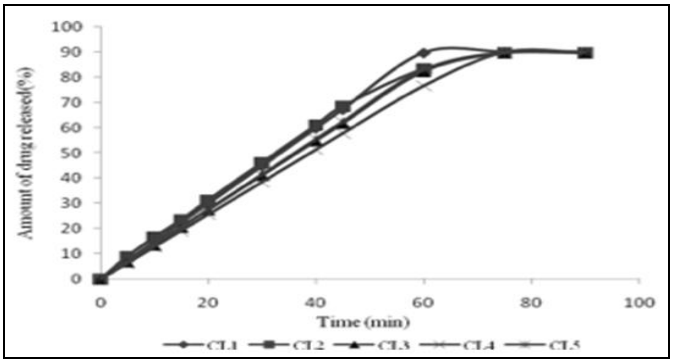

FIG. 2: RELEASE PROFILE OF CLARITHROMYCIN FROM FIVE BRANDS OF CLARITHROMYCIN TABLETS

A graphical representation of the dissolution profile of azithromycin and clarithromycin brands over 90 min is shown in **Fig. 1** and **2**. The time required to obtain 70 and 90% drug release (T_{70} andT_{90} respectively), dissolution efficiencies (DE) and similarity factor (f_2) were used as parameters to predict bioequivalence.

The dissolution profile of the azithromycin brands **Fig. 1** indicates that at least 70% of the active ingredient was released within 45 min for all the brands assessed. On the other hand, clarithromycin tablets released between 54.91 and 61.14% of the active ingredient within the same period **Fig. 2**.

TABLE 3: SOME RELEASE PARAMETERS FROM THE DISSOUTION PROFILE OF THE AZITHROMYCIN AND CLARITHROMYCIN TABLETS

Brand code	T_{70} (min)	T_{90} (min)	DE (%)	Difference factor, F_1	Similarity factor, F_2
AZ1	> 40	60	47.97	15	100
AZ2	>45	60	45.10	5	61
AZ3	>40	60	48.00	4	63
AZ4	>40	<60	50.20	0	99
CL1	> 45	>90	45.27	15	100
CL2	>45	>90	38.42	3	68
CL3	>45	75	44.86	6	59
CL4	>45	>90	41.16	10	46
CL5	>45	>90	41.50	5	61

The cumulative amount of azithromycin released in phosphate buffer (pH 6.0) was highest in brand AZ2 and least in AZ4. Similarly, the cumulative amount of clarithromycin released in 0.1M sodium acetate buffer was highest in the brand labeled CL1 and least in CL5. The dissolution efficiencies (DE) of the tablet brands at 60 min is presented in **Table 3**. The azithromycin brand, AZ4 exhibited the highest DE (50.20%) while AZ2 had the least DE (47.97%) within the same period. For clarithromycin tablets, brand CL1 had the highest DE (45.27%) while CL2 had the least DE (38.42%) within 60 min. The calculated similarity factors, f_2, for all the brands of azithromycin and clarithromycin are shown in **Table 3**. Apart from batch CL4, all the other brands fell within the acceptable range of 50-100 [19]. An f_2 value between 50 and 100 suggests that the two dissolution

profiles are similar [14, 15, 19]. Various methods to employ in comparing drug dissolution profiles and several criteria to be met before products can be termed similar have been suggested [30, 31, 32, 33]. According to FDA, comparison of dissolution profiles is one of the three dissolution test specifications made for immediate release products [34]. The other specifications (single-point and two-point) also termed 'point estimate' approaches are mostly only suitable for formulations containing BCS class 1 substances. The applicability of single-point specification is limited to quality assessment of unmodified products and evaluation of only minor post approval and scale-up and modifications including changes in manufacturing site, formulation process, equipment and composition, scale-up, *etc.* [35] The point estimate approach also lacks precision as drugs with inherently varying dissolution profile may be considered similar as results obtained may comply with the standard for point estimates in the pharmacopeia. Dissolution profile comparison is therefore a more suitable and precise technique in evaluating the effect of major scale-up and post approval changes on drug dissolution rates. The use of Moore and Flanner's similarity factor (f2) in dissolution profile comparison [26] was recommended by the FDA as a preferred method [26, 29, 36, 37, 38].

The similarity factor (f2) is a relatively simple and widely accepted model-independent approach for comparing drug data. It is a mathematical method described by Moore and Flanner [27] which has been adopted by many regulatory authorities including the Food and Drugs Administration (FDA) [40, 41] as a suitable and preferred method for dissolution profile comparison. It is easier to compute and does not consider statistical or modeling details, neither does it require or take advantage of any theoretical model of profile shape [39]. It depicts the closeness or equivalence of two comparable formulations. Its value ranges between 0-100. Values tending towards 100 indicate increasing similarity. Usually, similarity factor within 50 and 100 is stipulated by FDA. This value reflects the similarity of two dissolution profiles implying that the products will have similar *in-vivo* drug release characteristics as it moves closer to 100.

Literature survey shows that, several studies [39-48] have successfully used the similarity factor (f2) to compare dissolution profiles of drug samples. For example, Emami [41] compared the in vitro and in vivo performances of amiodarone generics using the similarity factor and concluded that the products were not equivalent as f2 values obtained were not within the acceptable range. In a similar study, Tanni *et al*., [42] compared the dissolution profiles of etericoxib generic tablets using the fit factors (f1 and f2). The authors reported that, 9 of the 10 brands assayed were similar and could be used interchangeably.

In a different study, Costa and his team [39] employed both the model dependent and model-independent techniques to assess the difference between dissolution profile of coated and uncoated ibuprofen pellets. They observed that the similarity factor f is more sensitive in finding dissimilarity between dissolution curves than the difference factor. Other reports which has utilized the similarity factor include; Hossain *et al*., [43] who compared the dissolution profile of sustained release indapamide matrix tablets with the innovator brand and recorded a similarity factor of 90.95 which indicated compliance of quality of the test formulation with the innovator product, Kassaye *et al.,* [44] who used the fit factors (f1 & f2) and dissolution efficiency to compare the dissolution profiles of 8 amoxicillin brands with the innovator brand with a conclusion that, about 62.5 % of the brands assayed were not substitutable with the innovator brand.

Papneja *et al.,* [45] used the fit factors to compare the dissolution of optimized ketoconazole solid dispersion tablet with the conventional immediate release tablets and found them to possess similar dissolution profiles. On their part, Lourenço *et al.,* [46] compared the rate of drug release from prolonged release formulations using the similarity factor and the two one-sided equivalence test. The authors concluded that the two one-sided equivalence test was a simpler approach.

When Júnior *et al.,* [47] compared the *in-vitro* dissolution profiles of coated ranitidine tablets using the fit factors, they concluded that, there was significant variation in the dissolution profiles of the tablets [51]. In a more elaborate study, Patel *et al.,* [48] compared the various methods for dissolution profile comparison using the dissolution profiles of

different oxcarbazepine brands. Results show that the model-independent methods were easier to apply and interpret while the model-dependent and ANOVA-based methods were more complicated and selective. Though limited in scope, the closest study to ours found in literature was that of Manani *et al.*, [49]. The authors assayed the pharmaceutical equivalence of clarithromycin tablets using the specifications for similarity factor and concluded that only 25% of the tested products passed indicating non-equivalence of a significant percentage of clarithromycin generics to the innovator brand. This study was limited to generic clarithromycin tablets unlike our report which looks at the interchangeability between clarithromycin and azithromycin tablets.

With the increasing incidence of drug counterfeiting and the use of different grades and quality of excipients in solid dosage formulations, efficacy and bioavailability have become a major concern. In a case where affordability of certain brands of the same drug is a major consideration, interchangeability of available brands is usually an alternative. Interchangeability of the brands of the same drug can only be undertaken by pharmacists and clinicians when a reliable *in-vitro* or *in-vivo* study establishes bioequivalence of the brands of the same drug. In our study, parameters like T_{70}, T_{90}, f_2 [24] and DE derived from the dissolution profiles of the brands of azithromycin and clarithromycin tablets were used as estimates of the bioavailability of azithromycin and clarithromycin tablet brands and hence their bioequivalence.

All the brands of azithromycin and clarithromycin evaluated did not show any significant variation in weight according to the USP weight variation limit. Previous studies suggest that, uncoated tablets with hardness of $\geq$ 4 kgf are considered adequate for handling and transportation [23, 24, 25]. All the brands of azithromycin and clarithromycin were therefore considered adequate in terms of their hardness. The friability of the azithromycin and clarithromycin tablets were within the acceptable limit of $\leq$ 1 % [23, 24, 25]. All tablet brands disintegrated within 30 min **Table 2**.

This is considered adequate for film coated tablets [32]. The hardness, disintegration time and dissolution rate of tablet dosage forms are known to be affected by such factors as type and concentration of binders used, type and concentration of other excipients used such as type and concentration of diluents, disintegrants and lubricants, compressional pressure and the type of granulation technique employed. Variations in these parameters may occur as a result of variations in the polymer films employed in the coating of the dosage form.

In the pharmaceutical industry, it is common practice to utilize excipients with economic advantage and convenient manufacturing technique based on experience [33] and the resultant effect of such technological decisions may lead to differences in the hardness and disintegration times of the different brands of azithromycin and clarithromycin. Such differences however are not a problem as long as the standard specifications for the interrogated parameters are met as is clearly seen in this report.

Furthermore, the type and thickness of the polymer film employed in the coating of the tablets may contribute to the variation in these parameters. The spectrophotometric and microbiological assays indicate that there was a very good correlation between the results obtained with all the brands of azithromycin and clarithromycin. Further statistical analysis of the results obtained from the two assay methods indicated that there was no significant difference ($p>0.05$) in the results obtained from the two assay methods and that the methods employed were independent. *In-vitro* dissolution study shows that there was no significant variation among the different brands of azithromycin tablets, implying that, there may be no appreciable variations in their bioavailability too.

A similar result was observed among the clarithromycin tablets. Four of the azithromycin brands AZ1, AZ2, AZ3 and AZ4 exhibited >90% dissolution in 60 min **Table 2** and **Fig. 1**. Although this high release might imply that there may be little or no bioavailability problems resulting from drug dissolution and thus justifies inter-changeability among the four brands, earlier studies have however, shown that in cases where > 85% of the drug is dissolved within 15 min, dissolution profiles are usually accepted as similar without further mathematical evaluations [34].

The brands therefore did not meet this criterion and they were subjected to further mathematical evaluations (Dissolution efficiency) to demonstrate bio-equivalence. Dissolution efficiency (DE) is a comparative parameter that offers the advantage of allowing comparisons to be made between a large numbers of formulations. In addition, it can be theoretically related to *in-vivo* data based on the assumption that that the degree of absorption of a drug *in-vivo* is proportional to the solution in contact with a suitable region of the gastrointestinal tract (GIT) [31, 32]. Statistical analysis of dissolution efficiencies of the brands shows that there was no significant difference ($p > 0.05$) in the DE of all the brands of azithromycin and clarithromycin tablets. They are thus considered interchangeable with their innovator brands, AZ1 and CL1.

It has been established that, comparison of the therapeutic performance of two or more medicinal products containing the same active substance is a critical means of assessing the possibility of alternative use between the innovator and any essentially similar medicinal product [32]. Based on our findings and the statistical analysis of the azithromycin brands using similarity factor f_2, all the brands are considered bioequivalent with the innovator brand, AZ1 with f_2-values in the range of 61 and 99. The brand, AZ4 with an f_2 value of 99 and an f_1 value of 0 shows a significantly higher ($p < 0.05$) bioequivalence when compared with the innovator drug (AZ1), therefore it can be can be considered to be a better alternative to the innovator drug when compared to the other brands. Similarly, statistical comparison of the clarithromycin brands show high level similarity or equivalence of all the brands with the innovator drug (CL1) except for CL4 which had an f2 value of 46 which lies outside the FDA acceptable range of 50 - 100 [27].

CONCLUSION: The overall results indicate that all the brands of azithromycin and clarithromycin tablets evaluated in this study possess acceptable physical and mechanical properties expected of a good pharmaceutical tablet. We applied the principle of dissolution efficiency and similarity factor to conclude that, AZ4 is a better brand for interchangeability with the innovator drug, while CL4 could be substituted for one another in treatment of certain bacterial infections particularly respiratory infections. We opine that, there is need for constant monitoring of new products that are being introduced into our drug market with a view to ascertain their bioequivalence and conformity with pharmacopoeia standards.

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