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Quality Assessment of Some Brands of Ciprofloxacin and Levofloxacin Tablets Circulating in Karu Local Government Area of Nasarawa state, Nigeria.

Pelumi O. Olawepo[1], Olubunmi J. Olayemi[1,2]*, John Alfa[1]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Bingham University, Karu, Nasarawa State, Nigeria

[2]Department of Pharmaceutical Technology and Raw Materials Development, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria

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* *Corresponding Author:*

olubunmibiala@yahoo.co.uk
+234 8033532299
https://orcid.org/0000-0001-5759-7176

ABSTRACT

Background: Circulation of poor-quality drugs has dire consequences on the health of consumers. Introduction of branded generics to ensure availability and affordability has shown potential for spread of poor-quality drugs. In this study, quality assessment of some commonly marketed ciprofloxacin (500 mg) and levofloxacin (500 mg) tablet brands in Karu Local Government Area (LGA) of Nasarawa State, Nigeria was evaluated.

Methods: Five tablet brands including an innovator, of either drug were sourced from 5 different Pharmacies in the LGA. Tablets were coded A1-A5 and B1-B5 for ciprofloxacin and levofloxacin brands respectively. Physical assessment of the tablets was done. Physico-mechanical properties, uniformity of weight, friability and disintegration time were also evaluated using pharmacopeia methods. *In vitro* dissolution was carried out and the profiles statistically analyzed using the similarity and difference factors in comparison with the innovator products.

Results: All the tablets had uniform weights within official specification, diameter was between 16.37 and 19.44 mm. Friability values were between 0.01 and 0.06 %; within specification. Disintegration time for ciprofloxacin and levofloxacin tablets was within 1.23 - 7.20 min and 3.19 - 12.90 min respectively; all met the specification. All (100 %) the ciprofloxacin brands met pharmacopeia requirement for drug release while only 60 % of the levofloxacin brands met this requirement. Comparatively A4 with f2 value of 41.62 % may not be interchangeable with the innovator brand while brands B2 and B4 with f2 values of 53.40 and 53.03 % respectively may be interchanged with the innovator brand or with each other.

Conclusion: All the tablet brands were found to have good mechanical properties but only 75 % of the ciprofloxacin and 50 % of the levofloxacin tablet brands were found to be interchangeable with the innovator drug brands. This calls for concern as it brings to question the possible interchangeability of these brands with the innovator.

1. Introduction

Poor-quality medicines are categorized as substandard or counterfeit drugs which are instigated by factors such as inaccuracies in content of active ingredients, dissolution profiles, others include misrepresentation of identity or deliberate/fraudulent mislabeling with respect to identity and/or source of the active medicament[1]. These ultimately have important consequences on the health of the population. Affordability and accessibility of quality medicines is a fundamental human right but is questionable in some climes, especially the developing countries. The World Health Organization estimated that 1 in every 10 medicines marketed or produced in developing countries are substandard or counterfeit[2]. The challenge of poor-quality drugs is highly perceptible in developing countries like Nigeria, due to high poverty rate, limited access to and affordability of good health care. Its prevalence appears to be rising and is not unconnected with low capacity in pharmacovigilance, weak drug regulatory systems, poor cooperation between drug manufacturing companies, government and international organizations involved in all matters of medicines quality[3]. However, poor quality drugs

are not only limited to poor or developing countries but have been reported in developed countries also; earlier reports show some of batches Avastin, circulating in some parts of United States of America (USA) contained no active medicament[4]. Another report revealed that 81 people died because of adulterated heparin legally imported into the USA[5]. In yet another report from USA, contaminated steroid injections was found to cause death and severe illness in users[6].

Therefore, circulation of poor quality drugs medicines is a global health issue however, the totality of these drugs also cause economic issues because monies are expended in purchase of these medicines which eventually do not cure the patients and sometimes leads to poisoning thereby incurring more expenses or could even lead to death. A study reported that the prevalence of poor-quality drugs in Africa is as high as 89 % while it is between 0.7 and 50 % in Asia[3]. A different report indicated that about 830 million US dollars of poor quality antimalarials are in circulation yearly in Nigeria which contributes to about 12,300 deaths annually[7].

Another in-road to the circulation of poor quality drugs could be linked to the introduction and encouragement of the use of generic brands of drugs[8,9]. This though seen as a means to make drugs easily available and accessible especially for low income developing countries, is controversial with some health care providers due to doubt of their quality, efficacy and safety[10,11]. The emergence of numerous tablet brands which are cheaper than the innovator brand poses a threat to patients as they may purchase cheap substandard drugs which could eventually cause harm their health. Therefore, routine quality assessment of marketed drug products is essential to safeguard the health of a country's citizens.

Ciprofloxacin and levofloxacin are fluoroquinolones antibiotics generally prescribed singly or sometimes in combination against bacterial infections[12]. Ciprofloxacin is one of the most essential antibiotics widely prescribed, it is available as an inexpensive generic medication as such in Nigeria alone, there are about 300 registered brands[13]. It is well absorbed from gastrointestinal tract after oral administration, its absolute bioavailability is about 70 % and is not affected by first pass metabolism. Levofloxacin on the other hand although also a fluoroquinolone antibiotic, has tremendously great activity against both gram-negative and gram-positive bacteria that are resistant to other antibacterials[14]. They are listed in the WHO Essential Drugs List[15] making them important, widely used drugs.

Some quality assessment of these marketed tablet products as revealed by literature shows that about 10 % of the ciprofloxacin tablets tested were substandard[16] while Joda *et al*.,[17] reported that 25 % of ciprofloxacin tablets tested were found to be substandard and others reported differently[18,19]. Assessment of levofloxacin tablets on the other hand revealed that two-thirds of tablet brands tested were substandard[12] while some other studies reported that all the brands passed the selected quality tests[20,21]. In yet other studies, the interchangeability of generic brands of these drugs for innovator brands have been refuted[22-27].

The population considered in this study is a dense, low socioeconomic area even though this area is close to a highly cosmopolitan city which creates a conducive environment for circulation of possible poor quality. Reported prevalence of substandard and/or counterfeit medicines in low-income areas is one of the prompting factors for this study. Therefore, the aim of this study is to evaluate the quality of brands of ciprofloxacin tablets (500 mg) and levofloxacin tablets (500 mg) marketed in some Pharmacies in Karu Local Government Area of Nasarawa State, Nigeria.

2. Materials and Method

2.1 Materials

Concentrated hydrochloric acid (Sigma-Aldrich Laborchemikalien GmbH, Germany), distilled water (produced in the National Institute for Pharmaceutical Research and Development; NIPRD, laboratory), Five (5) different brands each of ciprofloxacin tablets (500 mg) and levofloxacin tablets (500 mg) within their shelf-life were purchased from retail Pharmacies in Karu Local Government Area, Nasarawa State. All other reagents used were of analytical grade.

2.2 Method

2.2.1 Product information/Physical assessment of tablets

Visual inspection of the tablets was undertaken to detect any form of defect in the labelling, packaging or on the dosage form. The tablets brands were coded A1-A5 and B1-B5 for ciprofloxacin and levofloxacin tablets respectively. Information including National Agency for Food and Drug Administration and Control (NAFDAC) number, batch number, manufacturing date and expiry date were recorded. The tablets were also observed for shape, color and coating.

2.2.2 Determination of uniformity of weight

This was done using the weight variation method; ten (10) tablets were randomly selected from the different brands and weighed on an analytical balance (OHAUS, CP214, Switzerland); the average weight and standard deviation were determined.

2.2.3 Determination of tablet diameter

Diameter of ten (10) randomly selected tablets from the different brands was determined using the micrometer screw gauge (Mitutoyo IDC-1012EB, Japan) and the average was calculated.

2.2.4 Determination of friability test

Ten (10) tablets from the different brands were collectively weighed (w_1), placed into the friabilator (Erweka 66939 Friabilator, GmbH, Germany) and set to rotate at 25 rpm for 4 min. Afterwards, the tablets were de-dusted, re-weighed (w_2) and friability was calculated in percentage as in Equation 1.

$$F = {w1 - w2}/{w1}\, x100 \ldots\ldots\ldots \text{Equation 1}$$

2.2.5 Determination of disintegration time

The BJ-III Disintegration tester (Biobase, China) was cleaned, the tank was filled with water then the disintegration beakers were filled with the medium (distilled water) which was being maintained at 37 ± 0.5ºC. Six (6) tablets from the different brands were selected and one (1) tablet each was placed in each of the six (6) basket compartments. The apparatus was operated to run continuously by immersing and lifting of the compartments into the disintegration medium. The tablets in each tube were carefully observed, the time taken for the tablets to disintegrate, and all the particles of the tablets pass through the basket mesh was recorded. Disintegration time for each brand was calculated as the average disintegration time of the six (6) tablets assessed per time.

2.2.6 *In vitro* dissolution test

The United State Pharmacopeia (USP) Type II apparatus (RC-1 Dissolution tester, India) was used. One ciprofloxacin tablet was immersed in 900 mL of dissolution media (0.1N HCl) maintained at 37 ± 0.5ºC, the apparatus was set to rotate at 50 rpm. Aliquots of 5 mL were withdrawn at intervals of 5 min for 30 min and replaced immediately with equal volume of fresh medium maintained at the recommended temperature to ensure sink conditions. Withdrawn samples were diluted appropriately and absorbance determined at 275 nm using the UV-Visible Spectrophotometer (Agilent Cary 60, USA). Similar procedure was repeated for levofloxacin tablets; one (1) tablet was placed in the dissolution medium, and the apparatus was set to rotate at 75 rpm. Samples were withdrawn as done for ciprofloxacin tablets, but absorbance of the samples was determined at 290 nm in the UV-Visible Spectrophotometer. The concentration of each drug was determined from predetermined calibration curves for both drugs.

2.2.7 Model-dependent drug release fitting

The kinetics of drug release was determined by fitting the data obtained from *in vitro* dissolution studies into the Zero order, First order, Higuchi and Hixson-Crowell kinetic models while the mechanism of release was determined by the Korsmeyer-Peppas model[27]. The highest coefficient correlation was used to ascertain the best fit for modelling drug release.

2.2.8 Data analysis

All data from this study were expressed as percentage (%) and mean ± standard deviation as appropriate. Statistical considerations for *in vitro* dissolution profiles were analyzed using the similarity fit factors and calculated using the equation given in Equation 2 and 3

$$f1 = \{[\textstyle\sum_{t=1}^{n}(R_t - T_t)]/[\sum_{t=1}^{n}R_t]\}x\ 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Equation\ 2$$

$$f2 = 50xlog\{\left[1 + \left(\frac{1}{n}\right)\sum(Rt - Tt)^2\right]^{-0.5} x100 \ldots\ldots\ldots\ldots\ldots\ldots Equation\ 3$$

Where f1= difference factor, f2= similarity factor, Rt =cumulative percentage of reference product dissolved at time t, Tt = cumulative percentage of test product dissolved at time t, n = number of time points.

3. Results

3.1 Product information/Physical properties

Upon visual inspection, there was no indication of defects on the labelling, packaging or dosage form itself. All the brands of ciprofloxacin tablets were white in color except for the innovator brand (A1) which was white on one side and yellow on the other side. Three of the levofloxacin tablet brands were red in color, one (B2) was white while the innovator was reddish white. All the tablets were oblong in shape and film-coated except A1 which was gelatin-coated. All the products had NAFDAC registration numbers, batch numbers and were within their shelf-life during the period of investigation (Table 1).

Table 1: Label Information and Organoleptic Properties of Tablets

Code	NAFDAC No.	Batch No.	MFD	Country of origin	EXPD	Color	Shape	Coat
				Ciprofloxacin				
A1*	04-0723	C011026	06/2021	Nigeria	05/2024	White &yellow	Oblong	Gelatin
A2	04-5495	200501	06/2020	Nigeria	04/2023	White	Oblong	Film
A3	B4-5832	HB200102	01/2020	India	01/2023	White	Oblong	Film
A4	04-4061	ECPT017	10/2020	Nigeria	09/2024	White	Oblong	Film
A5	04-6340	PL21008	01/2021	India	12/2023	White	Oblong	Film
				Levofloxacin				
B1#	04-3143	1RR3C	11/2021	Nigeria	10/2024	Reddish-white	Oblong	Film
B2	B4-6520	210204	02/2021	India	02/2024	White	Oblong	Film
B3	A4-9867	TE2107230	07/2021	Nigeria	06/2024	Red	Oblong	Film
B4	A4-0530	N-2471	01/2021	India	01/2024	Red	Oblong	Film
B5	A4-2984	210305	03/2021	Nigeria	03/2024	Red	Oblong	Film

*Key: MFD = manufacturing date, EXPD = expiry date, * = innovator brand for ciprofloxacin tablets being a lead market product which is also among the first group of ciprofloxacin brands marketed in Nigeria, # = innovator brand for levofloxacin tablets from the first company to manufacture the drug which was approved by FDA*

3.2 Uniformity of weight

Table 2 shows that the average weight for brands of ciprofloxacin tablets varied widely between 542.30 and 784.64 mg and between 518.80 and 718.08 mg (Table 3) for levofloxacin tablets. The deviation of tablet weights was calculated to be between 0.50 and 2.90 % for ciprofloxacin tablets and 0.85 and 1.80% for levofloxacin tablets.

Table 2: Physico-mechanical Properties of Ciprofloxacin Tablets

Sample code	Tablet weight (mg)	% weight deviation	Diameter (mm)	Friability (%)	Disintegration time (min)
A1	542.30 ± 2.10	0.50	18.35 ± 0.02	0.02	4.20
A2	567.15 ± 4.70	1.10	17.20 ± 0.04	0.02	1.46
A3	765.43 ± 3.90	0.80	19.19 ± 0.03	0.01	7.20
A4	580.10 ± 4.63	0.90	19.44 ± 0.02	0.03	1.23
A5	784.64 ± 6.20	2.90	16.66 ± 0.03	0.02	2.13

3.3 Tablet diameter

The results presented in Tables 2 and 3 show diameter of ciprofloxacin tablets were between 16.66 and 19.44 mm while those of levofloxacin were between 16.37 and 19.33 mm. Our finding shows that deviation from the average tablet diameter was minimal; between 0.02 and 0.21.

3.4 Friability

Table 2 shows percentage friability of ciprofloxacin tablet brands to be between 0.01 and 0.03 % while Table 3 shows values of levofloxacin tablets brands were between 0.01 and 0.06 %.

3.5 Tablet disintegration

Our findings show that brands of ciprofloxacin tablets disintegrated within 1.23 and 4.20 min while disintegration time of levofloxacin tablets was between 3.19 and 12.90 min (Tables 3 and 4)

Table 3: Physico-mechanical Properties of Levofloxacin Tablets

Sample code	Tablet weight (mg)	% weight deviation	Diameter (mm)	Friability (%)	Disintegration time (min)
B1	518.89 ± 4.83	1.30	19.00 ± 0.32	0.01	6.27
B2	589.30 ± 3.73	0.75	16.37 ± 0.58	0.01	12.9
B3	718.80 ± 3.89	0.81	18.20 ± 2.01	0.05	5.13
B4	592.60 ± 4.70	1.10	18.35 ± 0.22	0.06	3.19
B5	626.10 ± 5.60	1.80	19.33 ± 1.52	0.02	9.38

3.6 *In vitro* Dissolution

The dissolution profile of the different brands of ciprofloxacin tablets is displayed in Figure 1. At the end of the dissolution time (30 min), all the brands had drug release ranging from 88 to 102 %. Brands A3, A5 and A2 released 102, 99 and 98 % respectively, brand A4 on the other hand, had lowest release (84.46 %) at the end of the dissolution process.

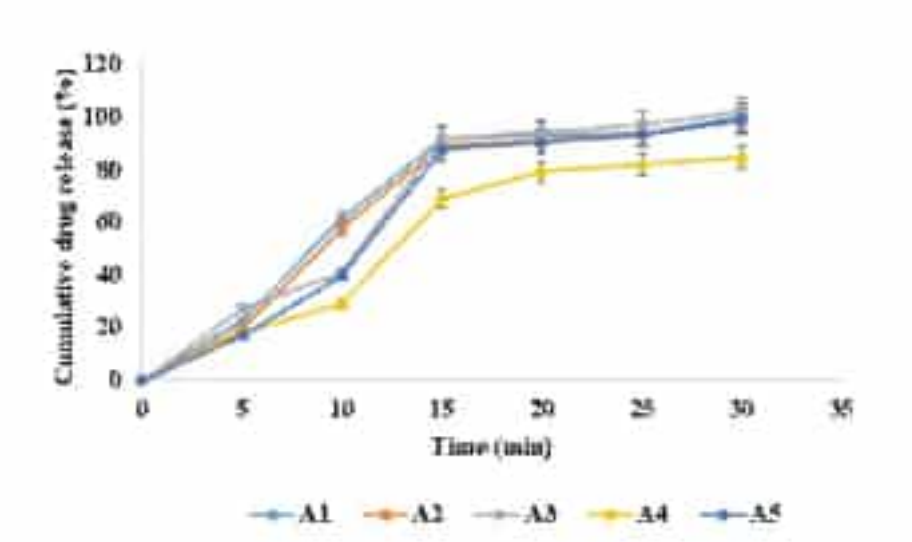

Figure 1: Cumulative drug release of ciprofloxacin tablet brands

The amount of levofloxacin released at the end of 30 min was in the range of 43 and 100 % (Figure 2). The innovator levofloxacin brand (B1), B2 and B4 released 96.38, 100.52 and 85.23 % respectively at the end of the dissolution process while the other brands; B3 and B5, had lower values; 72.80 and 43.86 % respectively.

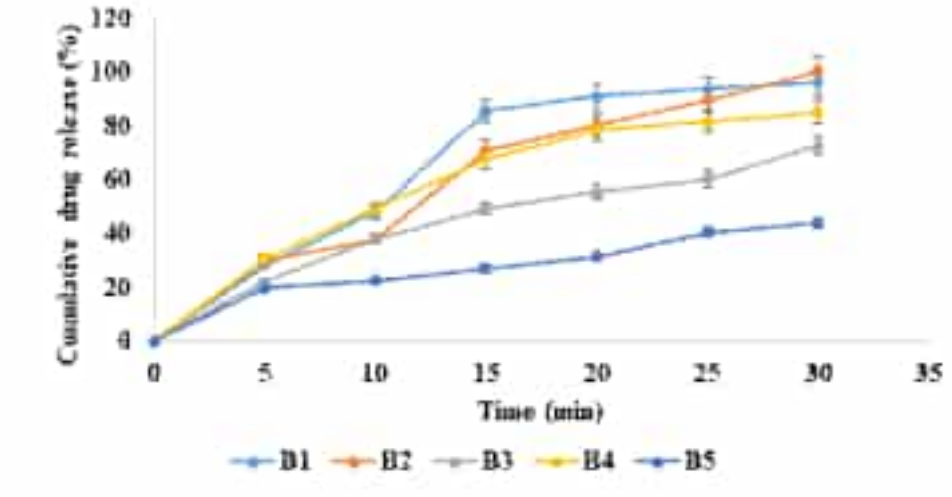

Figure 2: Cumulative drug release of levofloxacin tablet brands

Release kinetics of the formulated tablets was determined by the Zero order, First order, Higuchi, Hixson-Crowell models while the mechanism of release was determined by the Korsmeyer-Peppas model. The corresponding regression values (r^2) of the various models and the diffusion coefficient (n) are shown in Tables 4 and 5.

For ciprofloxacin tablet brands, the best linearity for dissolution data plots of brands A1, A2, A3 and A5 was the First order model with r^2 between 0.9191 and 0.9524 while that of brand A4 was Korsmeyer-Peppas model with r^2 of 0.9215 (Table 4). The result also shows that the kinetics of release of only brands A2, A3 and A5 were the same as that of the innovator brand (A1). On the other hand, the best-fit release model for levofloxacin tablet brands differed greatly. The innovator brand (B1) and B4 release data favored First order, brands B2 and B3 were found to follow the Higuchi model while B5 had Hixson-Crowell model as the predominant model of release (Table 5).

Table 4: Kinetics and Mechanism of Release from Ciprofloxacin Tablet Brands

Models/ Tablet brands	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas		Mechanism of drug release
	r^2	r^2	r^2	r^2	r^2	n	
A1	0.7540	0.9234*	0.8475	0.6914	0.8647	1.0639	Case II
A2	0.7680	0.9517*	0.8597	0.6984	0.8673	0.9788	Case II
A3	0.7973	0.9524*	0.8579	0.7778	0.8978	1.1120	Case II
A4	0.8446	0.9191	0.8972	0.8135	0.9215*	0.9639	Case II
A5	0.8069	0.9191*	0.7651	0.7651	0.9105	0.8861	Case II

** = model with the highest regression value*

The mechanism of drug release as determined by Korsmeyer-Peppas model shows the release coefficient (n) values from ciprofloxacin tablet brands to be between 0.8861 and 1.1120 (Table 4) while values for levofloxacin brands were between 1.2743 and 1.9973 (Table 5). The release mechanism of the tablet brands was observed be the same as that of the innovator brands for both drugs.

Table 5: Kinetics and Mechanism of Release from Levofloxacin Tablet Brands

Models/ Tablet brands	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas		Mechanism of drug release
	r^2	r^2	r^2	r^2	r^2	n	
B1	0.8171	0.9588*	0.8875	0.7861	0.9238	1.2743	Case II
B2	0.9457	0.8484	0.9596*	0.9123	0.9474	1.3051	Case II
B3	0.9676	0.8920	0.9861*	0.9237	0.9873	1.5689	Case II
B4	0.8999	0.9730*	0.9573	0.8574	0.9695	1.6527	Case II
B5	0.9719	0.9600	0.9281*	0.9847	0.9124	1.9973	Case II

* = *model with the highest regression value*

Data from dissolution profile was subjected to the similarity assessment tool (Table 6) and results reveal f1 comparison between ciprofloxacin brands A1 and A4 to be 21.88 % while comparison of A1 with A2, A3 and A5 gave values of 2.80, 6.76 and 7.71 % respectively. Correspondingly, similarity value (f2) between A1 and A4 was 41.62 %. The other brands on the other hand had f2 values between 53.31 and 83.94 %.

Only levofloxacin tablet brands B2 and B4 had similar f2 value with that of the innovator brand (53.40 and 53.03 % respectively) while the other brands, B3 and B5 had values below 50 % (33.92 and 21.91 % respectively).

Table 6: Similarity fit for brands of Ciprofloxacin and Levofloxacin tablets with innovator brands

Ciprofloxacin tablet brands	A1 vs A2	A1 vs A3	A1 vs A4	A1 vs A5
Fit factor				
f1	2.80	6.76	21.88	7.71
f2	83.94	53.31	41.62	57.13
Levofloxacin tablet brands	B1 vs B2	B1 vs B3	B1 vs B4	B1 vs B5
Fit factor				
f1	10.07	36.67	12.94	58.19
f2	53.40	33.92	53.03	21.91

4. Discussion

Visual assessment of all the tablets assessed showed they are aesthetically appealing, have been duly registered by the appropriate drug regulatory body and had proper information correctly printed on the outer package.

Uniformity of tablet weight is an important process evaluation parameter; it establishes that all ingredients in the tablet are evenly distributed thus, preventing issues of inconsistencies in tablet doses and possible problems in bioavailability of the active medicament. It also ensures that there is intra and inter batch uniformity within tablet batches. Tablet weight is generally influenced by factors such as compression machine, compression pressure, compression speed and flow characteristics of the material being compressed all of which should be optimized before tablet production. Results presented in Tables 2 and 3 show the tablet brands had different weights, the variations could be attributed to the different excipients and techniques used by different manufacturers in production of the tablets. The deviation of tablet weights was calculated to be between 0.50 and 2.90 % for ciprofloxacin tablets and 0.85 and 1.80 % for levofloxacin tablets which are within the acceptable deviation limit of 5 % for the range of tablet weight as specified by the United States Pharmacopeia[28]. Therefore, all the brands of ciprofloxacin and levofloxacin tablets evaluated can be said to have acceptable uniform weights.

Tablet diameter is an essential parameter for packaging purposes; tablets with wide diameter variations could affect the quantities required to be packaged into the primary packaging container[29]. In addition, non-uniform diameter and sizes of tablets could make patients assume the tablets contain different amounts of the active ingredient; this could make the patient lose confidence in that formulation which is ascribed to the size of punch and die set used for compression. Our findings show that deviation from the average tablet diameter for each brand was minimal; between 0.02 and 0.21 showing that tablets in the batch did not differ greatly from each other.

Adequate tablet friability is a necessary requirement for consumer aesthetic acceptance, while also being important for drug efficiency because any tablet weight loss could potentially cause loss of active medicament[30]. Tables 3 and 4 show friability values are within the limit of $\leq$ 1% specified by the Unites States Pharmacopeia[28]. This implies that the tablets have good mechanical strength which can withstand weight loss due to the processes of handling, transportation, and storage.

Tablet disintegration is the first visible transformation seen after the tablet encounters the medium. It is the process of the tablet breaking down into smaller particles or granules. The time it takes for a tablet to disintegrate corresponds to the time taken for the tablet to dissolve and for the active medicament to be available for therapeutic action[31]. Although an optimum disintegration time ensures requisite bioavailability, this may be influenced by the presence/absence of disintegrant, the type and concentration of disintegrant incorporated in the tablet formulation. According to the USP[28], conventional oral solid dosage formulations like tablets, with film or gelatin coatings are required to disintegrate within 30 min. Our findings show that the disintegration time within the drug brands were different and can be attributable to the physicochemical properties of the drugs, the type/extent of excipients and the different manufacturing process employed in tablet formulation. However, all the tablets disintegrated within the stipulated time thus, all the brands evaluated passed the disintegration time test.

Dissolution is a precursor to drug bioavailability and its desired therapeutic response. It is crucial for tablet formulations to release the required amount of drug within the stipulated period to avoid therapeutic failure. According to official specification, not less than 80 % of ciprofloxacin or levofloxacin is required to be released from a tablet formulation in 30 min[28]. Although these are single point dissolution test recommendations, a range of testing times were evaluated because dissolution profiling of drugs is seen as a more appropriate means of characterizing drug release of a product than a single point dissolution test. It also helps to assure similarity in product performance and possible bioequivalence which may lead to product interchangeability as in the case of branded generics and innovator brands.

The dissolution profile of the different brands of ciprofloxacin tablets is displayed in Figure 1. Brands A3, A5 and A2 showed similar release which was not significantly different ($p<0.05$) from that of the innovator ciprofloxacin brand; A1 (100 %) while brand A4 had lowest release. Nevertheless, all the tablet brands met the official specification for the amount of ciprofloxacin released after 30 min, although their release profile was found to differ per time.

Only the innovator levofloxacin brand (B1), B2 and B4 met the drug release specification at the end of the dissolution process which is not less than 80 %. The other brands; B3 and B5, had values lower that that specified limit. Figure 2 shows that brands B1, B2 and B4 passed the test while B3 and B5 failed the test. As was observed with the ciprofloxacin tablet brands, the dissolution profile was also

found to differ per time for the brands of levofloxacin tablet.

Model-dependent fitting for drug release enables the quantitative interpretation of dissolution data and predict the overall release pattern of drugs from dosage forms[32]. The coefficient of correlation (r^2) from the plots was used to indicate the degree of curve fitting and values approaching 1 indicates the predominant dissolution profile fitting to the mathematical equation. Kinetics of drug release of four (4) of the ciprofloxacin tablet brands including the innovator brand favored the First order model which indicates that the rate of drug release directly dependent on concentration; implying that the velocity of dissolution of the tablet in the medium is a function of the concentration at the tablet surface[33]. However, brand A4 which also had the least cumulative drug release (Figure 1) was observed to fit the Korsmeyer-Peppas model. Levofloxacin brands B2 and B3 which followed the Higuchi model indicates that drug release was by diffusion from a porous matrix system. On the other hand, release from brand B5 followed the Hixson-Crowell model which assumes that the rate of drug release is based on the change in surface area and diameter of the particles in the tablets and suggests that drug release is not by diffusion but by dissolution of tablet particles[34]. Only brand B4 was found to follow the same kinetics of release (First order) with that of the innovator brand (B1) which suggests that the rate of drug release is directly proportional to the concentration of drug in the tablet surface.

The release diffusion coefficient (n) characterizes the drug transport mechanism and for cylindric systems like tablets, "n" value of 0.45 indicates the release is diffusion - controlled which is known as Fickian diffusion. Values ≥ 0.89 indicate swelling-controlled release (Case II or Super-case II transport) while "n" values between 0.45 and 0.89 indicate Non-Fickian or Anomalous diffusion which is a super-imposition of the other two mechanisms[35]. Drug release from all the tablets (ciprofloxacin and levofloxacin brands) was observed to be by the Case II transport which implies that erosion and not diffusion is the mechanism of drug release from these tablets. The results also indicate that mechanism of drug release from the all the tablet brands is the same with those of the innovator brands of both drugs.

The availability of multiple brands of drugs often poses a challenge on selection of the appropriate brand for clinicians and pharmacists. Therefore, in order to validate possible bioequivalence and interchangeability of brands with the innovator brand, further analysis by similarity fit factor is usually employed. Similarity factor is an assessment tool that can be used to compare the dissolution profiles of the innovator brands and the individual generic brands. When similarity values (f2) are less than 50 %, the tablet formulations are said to differ in the dissolution profiles while f2 values equal to 100 % indicates that the brands have identical dissolution profiles and are bioequivalent. In addition, f2 values between 50 and 100 % indicate that the dissolution profiles are similar and also bioequivalent. On the other hand, f1 values between 0 and 15 % are used to predict the difference or dissimilarity in the dissolution profiles between the innovator and the generic brands[36-38].

Fitting into the similarity factor tool shows that only dissolution profile of ciprofloxacin brands of A4 differs from that of the innovator brand (A1) and the other brands. This shows that ciprofloxacin brand A4 is not interchangeable with the innovator brand. The other brands had f2 values between 53.31 and 83.94 % which indicates that the dissolution profiles are similar and can be interchanged with the innovator brand or with each other.

Variations or similarity in dissolution profiles of innovator brand and generic brands of levofloxacin tablets presented in Table 4 shows only brands B2 and B4 was found to be similar to the innovator brand while the other brands, B3 and B5 were not. This corresponds with results deduced from Figure 2; showing that brands B3 and B5 had low drug release indicating that their dissolution profiles differ significantly from that of B1. Brands B2 and B4 can therefore be interchanged with the levofloxacin innovator brand and with each other.

Our results from *in vitro* dissolution studies show the existence of variations in the dissolution profiles of the tablet brands of the two drugs. The brands were found to have different kinetics of drug release from those of the innovator brands although all tablet brands exhibited a similar release mechanism as the innovator brands. Differences in the rate of drug release might be attributed to different composition of excipients and different manufacturing processes employed during tablet formulation. It could also be related to possible adulteration in the composition of the tablet formulations.

Generic brands of drugs are known to be readily available and relatively cheaper than innovator brands which are positive indicators for their use. However, if these brands have very dissimilar/non-comparable dissolution profiles with the innovator brands or have drug release rates outside the limit/range specified by official standards, their use would ultimately lead to therapeutic failure. Some studies in literature have revealed similar findings[12,22,24] while others have reported that tablets brands of these drugs tested were

of good quality and may be interchanged with the innovator brands[39-41].

Although the legal framework for regulation of drugs in Nigeria is in place, inadequate enforcement or non-enforcement of these laws in addition to lack of routine monitoring creates loopholes for proliferation of substandard drugs. This study lends its voice to need for regular post-marketing quality assessment of these drug formulations in a bid to detect fake, substandard or non-interchangeable tablet formulations with the overarching goal of safe guarding the health of Nigerian populace.

5. Conclusion

Physico-mechanical quality parameters (uniformity of weight, friability and disintegration time) of all brands of ciprofloxacin and levofloxacin tablets assessed met the United States Pharmacopeia (USP) standards. Kinetic analysis of the dissolution data showed that all the brands exhibited similar mechanism of release. All five brands of ciprofloxacin tablets met the USP specifications for drug release however, all but one brand (75 %) may be interchangeable with each other and the innovator brand. Only two of the levofloxacin tablet brands passed the USP specification for drug release and only these two brands (50 %) were found to be interchangeable with the innovator brand or with each other. This shows that not all generic brands met the required specifications and points out the relevance of conducting post-market quality assessments. It also gives an insight into the brands of these drugs that may be substituted for the innovator brands.

Competing interests:

The authors declare that they have no competing interests

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