African Journal of Pharmaceutical Research & Development

Vol. 13 No.2; pp. 120-126 (2021)

QUALITY CONTROL ASSESSMENT OF DIFFERENT BRANDS OF OFLOXACIN TABLETS MARKETED IN NIGERIA

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ABSTRACT

Drug counterfeiting has caused the global health sector a lot of setbacks. Because antibiotics are the most used in Nigeria, it is expedient to regularly assess the authenticity of all antibiotics sold in the Nigerian market. This study evaluated the conformity to standard requirements, of five different brands of ofloxacin tablets marketed in Nigeria in terms of the quantity of the active ingredients and the quality of the products in general. Five branded ofloxacin tablets were compared with the standard specification in terms of their drug release pattern, the content of active ingredient and the integrity of the dosage form. Dissolution time and disintegration tests were performed in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) of pH 4.5 and 1.2 respectively without enzymes. An assay of the active ingredient was done to ascertain the conformity of the quantity of the active ingredient compared with the standard specification. Also, the friability test, hardness test, weight uniformity test was carried out. The result shows that all the tablet brands conformed to specifications except OFLO-A which failed both the weight uniformity (C.V 10.3 % and an assay of active ingredient (116 %) tests. The average percentage label claim of all the brands was found to be 102.98 ± 10.09. To a great extent, the assessed brands of ofloxacin tablets were found to conform to official standards.

KEYWORDS: **Ofloxacin; Quality assessment; Disintergration time.**

INTRODUCTION

The public health system globally is challenged by drug counterfeiting. This has posed great danger directly to individual health and welfare [1]. The world health organization (WHO) described fake drugs as drugs that have been purposely and fraudulently mislabeled with respect to identity and/or source [2]. The confidence of the public in the nation's health care delivery system has been badly affected by this monstrous problem of fake drugs with its attendant deleterious consequences. Poor or no response is seen as a result of resistance (antimicrobial resistance) due to the previous intake of fake drugs even when patients are treated with genuine drugs [1]. Counterfeit may be preparations without active ingredients, toxic preparations, relabeled expired drugs, drugs with no manufacturing information [3]. Quality control and assurance protocols become inevitable in ensuring the acceptable integrity of pharmaceutical products.

Ofloxacin is an oxazinoquinolone second-generation fluoroquinolones, bearing a methyl, a fluoro, 4-methylpiperazino and carboxy substituents (Figure 1). It is bactericidal and a DNA gyrase inhibitor widely prescribed in acute and chronic lower respiratory tract infections and infections of the ear and nose [4]. It inhibits the supercoiling activity of bacterial DNA gyrase, a type II topoisomerase and topoisomerase IV. It is available as tablets, oral solutions and injectable solutions as well as eye and ear drops. For a product to be of good quality and achieve the desired result it must be bounding to pre-set standard [5, 6].

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Drug products that are chemically and pharmaceutically equivalent must be identical in strength, quality, purity, active ingredient release profile in the same dosage form to the same route of administration [7]. Drug-producing industries need to examine the products during and after production and at various intervals during the shelf life of the product to ensure standard quality [7]. Worldwide, cases of treatment failures abound due to drug misuse and counterfeiting. These factors have resulted in antibiotic (ofloxacin) resistance [8-11]. It is, therefore, necessary to routinely subject these products to pharmacopeia and non-pharmacopeia tests to determine authenticity and conformity with the official requirements as contained in the label claims. To the best of our knowledge, quality control assessment of ofloxacin marketed in Nigeria was last reported over a decade ago [12]. However, quality control assessment of drug formulations with higher risk of abuse and misuse should be performed at regular intervals to track any deviation from official requirements; hence this study. We, therefore, report an investigation of the authenticity of the different brands of ofloxacin tablets marketed in Nigeria.

MATERIALS AND METHODS

Materials

UV/VIS spectrophotometer (Jeenway 6405, United Kingdom), tablet hardness tester (Monsanto, India), disintegration chamber (Erweka, Germany), magnetic stirrer (Life Assistance Scientific, United Kingdom), friability tester Erweka, Germany), pH meter (Hanna instruments, China), digital analytical balance (China), vernier caliper (China). Methanol (Sigma and Aldrich, USA).

Study design

Quantitative and qualitative evaluation of different brands of ofloxacin tablets marketed in Nigeria was carried out by the evaluation of weight uniformity, hardness, friability, disintegration, dissolution tests and an assay of active ingredients.

Ofloxacin samples

Five (5) different brands of ofloxacin marketed in Nigeria were procured from registered Pharmacies in Enugu State, Nigeria. Each brand contained a label claim of 200 mg of ofloxacin. The detailed descriptions of the brands are shown in Table 1. Pure ofloxacin was obtained from ofaxin brand by recrystallization in methanol at room temperature. Purity was confirmed by UV scan at 200-400 nm, analytical thin-layer chromatography [13] and melting point determination.

Preparation of dissolution media

Simulated gastric fluid (SGF), without enzyme, was prepared by adding 7 ml of HCl to 900 ml of water followed by the addition of 2.0 g NaCl. The solution was made up to 1 L with water and then the pH adjusted to 1.2. Simulated intestinal fluid (SIF), without enzyme, was constituted by dissolving 6.8 g of monobasic potassium phosphate in 250 ml of distilled water. A 77 ml of NaOH was added into the solution followed by the addition of 300 ml of distilled water. The pH was subsequently adjusted to 4.5- 4.6 at 25 ºC [14].

Standard calibration curve

A 10 mg of pure ofloxacin was dissolved in small methanol and the solution was made up to 100 ml. The resulting solution was diluted to get various aliquots of the solution as 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07 and 0.08 mg%. The absorbances of the various concentrations were taken at 265 nm and a graph of absorbance against concentration was plotted to get the calibration curve. The calibration obtained was subjected to both inter- and intraday validation at 0.001-0.008, 0.01-0.08 and 0.1-0.8 mg% ofloxacin.

Weight uniformity test

Twenty (20) tablets from each brand were weighed individually and then collectively. After which their mean weights were determined. The percentage deviation was determined for each brand. The percentage weight variation was calculated using the equation 1 [15].

$$\text{Weight variation } (\%) = \frac{\text{Average weight} - \text{individual weight}}{\text{individual weight}} \text{ x } 100 \text{ -} \qquad (1)$$

Hardness test

Ten (10) tablets from each brand were individually subjected to pressure using Monsanto hardness tester and the force at which the tablets cracked at the middle was noted [16].

Friability test

Five (5) tablets were selected at random from the various brands weighed and placed in a friabilator where the tablets were subjected to shock for 4 min at 25 rev/min. The tablets were then removed from the chamber, de-dusted and reweighed. The loss due to abrasion is a measure of tablets friability

which is expressed in percent. The abrasion resistance is calculated using the formula in equation 2 [15].

$$\text{Abrasion resistance} = \frac{\text{initial tablet weight} - \text{final tablet weight}}{\text{initial tablet weight}} \text{ x } 100 \quad \ldots \ (2)$$

Disintegration test

The disintegration times of the tablets were evaluated using SGF and SIF. Five tablets were randomly selected from various brands and placed into the disintegration chamber. The chamber was maintained at 37 ± 1 ºC. The rotating paddle was set at a speed of 500 rev/min [16]. The time taken for the tablets to break into small aggregate and fall through the screen was noted using a stop watch.

Dissolution rate test

One tablet from each brand was inserted into a membrane filter and was sealed properly. The sealed tablet was then immersed into a dissolution medium containing 900 ml of either SGF or SIF at a temperature of 37 ± 1 ºC. A 5 ml sample was removed from the dissolution chamber at periodic intervals of 5, 10, 20, 30, 40 and 60 min. The samples were filtered and analyzed for drug content using UV/Vis spectrophotometer [16].

Assay of active ingredients

Twenty tablets were randomly selected from each brand. The tablets were weighed collectively and crushed in a mortar. An amount equivalent to 200 mg of active ingredient was weighed out from each brand using an analytical balance. Each was dissolved in 50 ml absolute methanol in a well-labeled flask. Each was filtered and an aliquot of the filtrate was analyzed using UV/Vis spectrophotometer after appropriate dilutions. The same procedure was repeated for the standard. The concentrations of each sample were determined using the standard calibration plot and compared with the standard. The percentage of the assay was calculated using the formula in equation 3 [16].

$$\text{Assay (\%)} = \frac{\text{Conc of brand}}{\text{Conc of standard}} \text{ x } 100 \quad \ldots\ldots\ldots \ (3)$$

Determination of chemical content

Standard solution preparation: A 10 mg of ofloxacin reference standard was weighed and was transferred to a 10 mL volumetric flask. Then, 5 mL of MeOH was added and shaken for 5 min, diluted with a phosphate-buffered saline (PBS) to volume, to obtain a 1 mg/mL of ofloxacin. Sample solution preparation: 20 tablets from each brand were weighed and powdered. An accurately weighed portion of the powder, 105.9 mg (OFLO A), 164.5 mg (OFLO B), 121.8 mg (OFLO C), 141.2 mg (OFLO D), 133.6 mg (OFLO E) and 142.4 mg (innovator), equivalent to 50 mg of ofloxacin was transferred to a 50 mL volumetric flask; 30 mL NaOH solution was added and sonicated for 10 min. Then, a PBS solution was added to volume; mixed and filtered to obtain a 1 mg/ml solution of ofloxacin. Equal volumes (3 mL) of the standard preparation and sample preparation were separately assayed spectrophotometrically. The percentage content of ofloxacin in the portion of tablets was calculated using the following formula:

$$\text{Drug content (\%)} = \left[\frac{\text{C x A1 x 100}}{\text{A2}}\right] \text{x purity of ofloxacin standard} \quad (4)$$

Where, C = concentration (mg/mL) of ofloxacin reference standard in the standard preparation, and A1 and *A2* are the absorbances of the assay preparation and the standard preparation, respectively. To determine the in-vitro bioequivalence the mean drug content was used to calculate the difference (f1) and similarity (f2) factors of the brands following standard approach [17].

Statistical analysis of data

The experimental results were analyzed using the GraphPad Prism v.6.01 software. Results were expressed as mean±SD (n=3). Weight uniformity results were also presented as mean ± coefficient of variation (%). Results of all the parameters were calculated from the standard equations as shown in the various experimental sections. A model independent mathematical approach was also used to compare the dissolution profiles of the samples and the reference product using difference factor (f1) and similarity factor (f2).

RESULTS

Calibration curve

The results indicate that the plot of absorbance versus concentration gave a linear graph within the concentration of 0.01 – 0.08 mg%. A high correlation coefficient (0.998) was obtained for the plot showing the linearity and accuracy of the determinations. The linear regression equation defining the plot is given in equation; A = 6.895C + 0.011.

Weight uniformity test
The results of weight uniformity test results are shown in Table 2. OFLO-A has the highest % C.V of 10.3 while OFLO-D showed 0.20 %.

Friability test
The results of the friability test showed that OFLO-B and OFLO-D resulted in abrasion resistance of 1.02 and 0.13 % respectively (Table 2). However, OFLO-A, OFLO-C and OFLO-E did not show any visible friability.

Hardness test
The results of the hardness test (Table 2) showed that the tablet hardness of all the brands tested range from 5.40-6.41 Kgf with OFLO-C and OFLO-E at the extreme values respectively.

Disintegration test
The disintegration test of the brands showed that ofloxacin disintegrates faster in SGF than in SIF. Pairwise comparison of each brand in SGF and SIF showed that OFLO-A disintegrated fastest and OFLO-D disintegrated slowest. The disintegration times of various brands of ofloxacin in SGF and SIF are shown in Table 2.

Assay of active ingredients
The results of the assay of active ingredients (Table 2) showed that the brands tested contained 93 to 116 % of ofloxacin in each tablet. OFLO-C showed 93 % content of ofloxacin while OFLO-A contained 116 % ofloxacin.

Dissolution time test
The dissolution profiles of different brands of ofloxacin tablets in SGF and SIF are shown in Figure 2. OFLO-A showed sharp dissolution in SGF and SIF in 0-30 and 0-10 min respectively. The dissolution, however, declined with increasing time reaching peaks of 88 % and 108 % in SGF and SIF respectively. The dissolution of OFLO-B in SGF was the lowest while OFLO-E showed the least dissolution in SIF.

Comparison of dissolution profiles
A model independent approach was used to compare the dissolution profiles of the samples and the innovator product using difference factor (f1) and similarity factor (f2). The results (Table 3) showed difference factor (f1) values were less than 15 and similarity factor (f2) values were greater than 50 for the brands of ofloxacin tablets.

DISCUSSION
Quality control of ofloxacin formulations is significant not only for regulatory purposes but also considering its spectrum of activity, possibility of ofloxacin and potential of abuse [9, 11]. We identified ofloxacin misuse and counterfeit as the major causes of treatment failures and hence this study. To ensure authenticity and conformity with the official requirements, ofloxacin tablets were subjected to pharmacopeia and non-pharmacopeia tests which included weight uniformity, friability, hardness, disintegration time, dissolution time and assay of active ingredient tests.

The weight uniformity tests showed that all the tablet brands showed an acceptable variation in the test except OFLO-A which has a percentage variation of 10.3 %. In general, tablets of weight 130 -324 mg should have a limit of acceptance of ±7.5 % in weight uniformity. In quality control, evaluation of weight uniformity represents an important process. Tablets meet the specification if not more than two tablets are outside the percentage limit and if no tablets differ by more than twice the percentage limit [15]. The tablet weight and its uniformity can be altered by the die filling process before compression, thus making this test significant in the quality control process [16]. Tablets of good quality should be able to resist abrasion. This is due to tablets collisions, sliding over a hard surfaces and one another during the time of manufacturing and handling. Friability test is carried out to ascertain the ability of tablets to resist disintegration after manufacturing, packing, and handling and even after transportation [16]. This test is important since it affects the final weight of the tablets. According to standard specifications, an upper limit of 0.5 - 1 % is considered acceptable in practice for the tablet dosage form. From the results, all the brands showed the impressive results in the test except OFLO-B that deviated from the specified range with 0.02 %. This implied that all the tablets within the range are mechanically stable. A hardness test is used to evaluate the ability of tablets to resist mechanical shocks during all the processes before consumption of the tablets. Tablet hardness affects tablet density, porosity and friability. It also affects disintegration and dissolution time which also affects the bioavailability of the drug. The hardness test result is shown in Table 2. A hardness value within the range of 4 to 7 Kgf is considered acceptable [16, 17]. According to the results, all tablet brands passed the test as they all have their hardness values within the range, an indication that their disintegration and dissolution characteristics might not hinder bioavailability. The USP (2015) specified that the

Table 1: Description of tablet brands

Brands	BGVID	TINOVID	LABVID	OFAXIN	AGOFLOXIN
Manufacturer	Stallion PVT, India	Scott-Edil Pharmacia Ltd, India	Zim Lab Ltd, India	MeCure Ltd, Lagos	Mart Pharma, India
Distributors	BGS Pharma Ltd	Simpec Ltd, Nigeria	Krismediks Ltd, Nigeria	MeCure Ltd, Lagos	Agog Pharma, Nigeria
Description	Red, oblong film-coated	White film-coated	White, film-coated	White, film-coated	White, film-coated
Batch No.	N-1393	S797154	H 148	DX 09	Q 3108
Expiry date	03/2019	08/2020	07/2020	12/2020	07/2020
NAFDAC No.	A4-2783	B4-2196	B4-1648	A4-0040	B4-2204
Codes	OFLO-A	OFLO-B	OFLO-C	OFLO-D	OFLO-E

Table 2: Assay parameters of ofloxacin tablets

Parameters/brands	OFLO-A	OFLO-B	OFLO-C	OFLO-D	OFLO-E
Weight uniformity (g)	409.5±42.5^a	420.5±5.0^a	602.7±2.0^b	415.9±0.8^a	659.0±9.8^b
Coefficient of variation (%)	10.3	1.2	0.3	0.2	1.5
Friability (%)	0.0±0.0	1.02±0.1^a	0.0±0.0	0.13±0.1^b	0.0±0.0
Hardness (KgF)	5.56±0.34^a	5.91±0.11^a	5.40±0.09^a	6.46±0.18^b	6.41±0.92^b
Disintegration time, SGF, min	0.72±0.08^a	7.49±0.15^b	3.17±0.08^c	7.67±0.72^b	7.34±0.24^b
Disintegration time, SIF, min	1.60±0.01^a	7.75±0.16^b	4.61±0.44^c	9.74±0.91^b	8.80±0.52^b
Active ingredient (%)	96.03±2.6^a	94.27±1.1^a	93.55±2.1^a	100.07±0.9^a	110.95±0.14^b

Data expressed as mean±SD (n=3). Values across the row with the same superscript are not statistically different (p>0.05).

Table 3: Difference factor and similarity values of the ofloxacin tablets

Brands	F1	F2
Innovator	-	-
OFLO-A	3.4	90.3
OFLO-B	6.1	88.2
OFLO-C	2.8	98.5
OFLO-D	7.3	78.3
OFLO-E	10.2	82.7

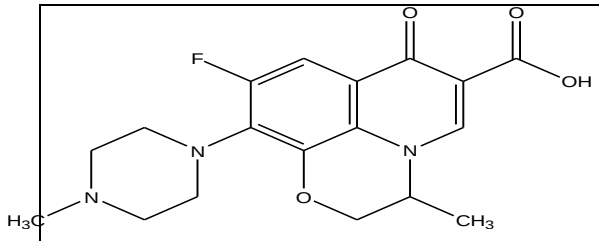

Figure 1: Chemical structure of ofloxacin

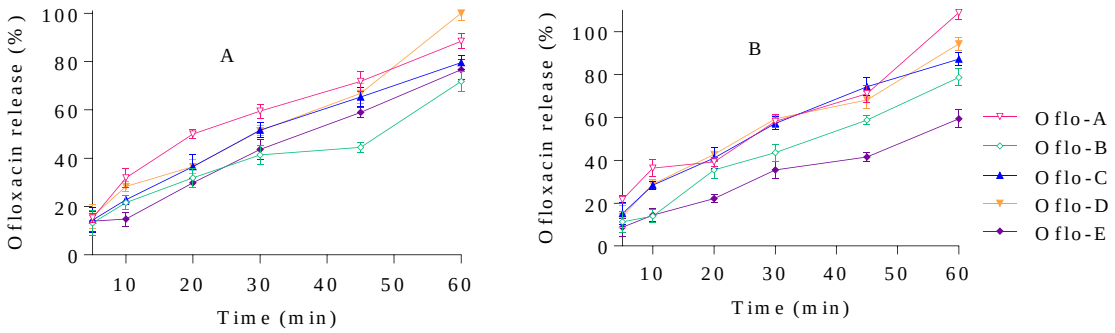

Figure 2: The dissolution profile of ofloxacin in (A) SGF and (B) SIF. Data are expressed as mean±SD (n=3).

disintegration time of uncoated tablets should not be more than 15 min [15]. The results showed that all the tablet brands passed the test as their disintegration times fall below 15 min in both the SGF and SIF. The first step of absorption for the solid dosage form of a drug after oral administration is disintegration. Disintegration is the breaking up of drugs into smaller particles in solution. The disintegration test is used to measure the time required for a tablet to break up into smaller particles under specified conditions [17]. This test is a vital quality assurance tool since drug absorption and therapeutic effectiveness is dependent on it. According to USP (2015) [15], the acceptable limit of ofloxacin in ofloxacin tablet should be in the range of 90-110%, an indication that all the brands passed the test except OFLO-A. This assay was significant because it helped to determine the quantity of ofloxacin present in the tablet brands sold in Nigeria and to find out if they are of the quality standard as specified in the official compendium. The BP (2001) stated that in dissolution testing the active ingredient should not be less than 70 % of the specified amount after the test [19]. All the tablet brands passed the test since they all have percentage release above 70 % after 60 minutes of testing. A dissolution time test is an important tool in drug development and quality control. It allows the determination and indicates the time needed for the release of active pharmaceutical ingredients from its dosage form. It has a significant effect on the bioavailability and therapeutic efficacy [17, 20]. Being acid in nature, ofloxacin release in SIF was more predominant compared with SIF. The difference in the dissolution rates of ofloxacin in SIF and SGF means that the brands have absorption rate, with higher intestinal absorption [14, 21]. To assess in vitro bioequivalence, a model independent approach showed that the difference factor (f1) values were less than 15 and similarity factor (f2) values were greater than 50 for the brands of ofloxacin tablets This indicates that release of the drug from all the ofloxacin tablets is similar to the innovator product. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100 [18]. Hence based on this requirement, all the brands of ofloxacin tablets could be used interchangeably with a comparator drug in clinical practice.

CONCLUSION

This study assessed the level of compliance of the various brands of the ofloxacin tablets marketed in Nigeria with the specified standards. All the tablet brands passed the various test carried out on them except OFLO-A which failed in both the weight uniformity and assay of active ingredient tests. To a great extent, ofloxacin tablet brands marketed in Nigeria are of good quality and are also recommended for the recommended therapeutic use.

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