dx.doi.org/10.14227/DT170210P20

Comparative Assessment of the Quality Control Measurements of Multisource Ofloxacin Tablets Marketed in Nigeria

e-mail: jdjide@yahoo.com

Sunday O. Awofisayo[1,*], Oladoja A. Awofisayo[2], Nse Eyen[3], and Imo E. Udoh[1]

[1]*Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, University of Uyo, Nigeria*

[2]*Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Uyo, Nigeria*

[3]*Department of Laboratory Science, Akwa –Ibom State Polytechnic, Akwa Ibom, Nigeria*

ABSTRACT

This study aimed at evaluating some quality control parameters to compare the quality, safety, and efficacy of nine brands of ofloxacin tablets available in the Nigerian market. The physicochemical parameters and assay of the nine brands of ofloxacin tablets were assessed through the evaluation of uniformity of tablet weight, friability, hardness, disintegration, and assay of active ingredients according to established methods. The dissolution rate and disintegration time were determined in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) without enzymes. The concepts of dissolution efficiency (DE) and predicted availability equivalence (PAE) were used to estimate the likely in vivo bioavailability. All brands complied with the official specification for uniformity of weight, friability, and disintegration. The disintegration test revealed that the drugs had higher disintegration times in SGF (7.0 ± 0.95) relative to those in SIF (5.0 ± 2.55). The dissolution profiles in SGF showed that only one sample attained 70% dissolution in less than 45 min and the other 5 samples in 1 h, while in SIF, four samples attained 70% dissolution in 45 min and all samples in 1 h. The UV spectrophotometric assay of ofloxacin tablets revealed that three samples contained over 95% (w/w) of labeled chemical content. The PAE in SGF indicated over 90% release from five samples, while it revealed over 70% release in SIF from three samples out of the aforementioned. Only four of the brands considered in this study demonstrated comparable quality standards. The method is simple and rugged for both routine analysis and evaluation of the dissolution pattern of ofloxacin tablets as in vitro tests for batch-to-batch quality control assessment.

INTRODUCTION

The marketing of multisource drug products registered by national drug agencies in developing countries, with the view of improving health care delivery through competitive pricing, has its attendant problem of ascertaining their quality and interchangeability (*1*). Variable clinical responses to drugs presented as generics and batch-to-batch inconsistencies have been reported (*2*). Such unacceptable trends were exhibited in some drug products including metronidazole and metformin tablets (*3*).

Quality control procedures, which are useful tools for batch-to-batch consistency in manufacturing, should be performed for every drug product. Drugs having more than three generic products require analysis for their biopharmaceutical and chemical equivalency. These methods ensure that any of the generic products can be used interchangeably. The observation is that most of the generics have much lower shelf prices than the innovator products, which raises the issue of the likelihood of unequal product performance.

The prediction of the in vivo bioavailability of most oral drugs depends on the in vitro dissolution studies because in vitro disintegration tests do not always give good correlation (*4*, *5*). Dissolution testing of drug products plays an important role as a quality control tool to monitor batch-to-batch consistency of drug release from a dosage form and as an in vitro surrogate for in vivo performance (*6*). The therapeutic efficacy of a drug product intended to be administered by the oral route depends on its rate and extent of absorption by the gastrointestinal tract. A comprehensive evaluation, however, involves the determination of uniformity of weight, chemical content, friability, hardness, and disintegration tests along with dissolution rate. Drugs that are chemically and biopharmaceutically equivalent must be identical in strength, quality, and purity. The content uniformity, disintegration, and dissolution rates must be comparabe (*7*).

There is an increasing need to evaluate the performance of a number of the available fluoroquinolone antibacterial agents because of the unexplainable pattern of microbial sensitivity to the members of this class of drugs. Ciprofloxacin, the most commonly employed having about 50 brands in the market, now exhibits some characteristics in microbial culture and sensitivity that indicate an unreliable switch from one product to another (*8*). Ofloxacin now has about ten generic products in the market, and this number is likely to increase with time as manufacturers watch prescriptions for ofloxacin increase.

In this study, in vitro dissolution techniques were used to ascertain the rate and extent of the active

*Corresponding author.

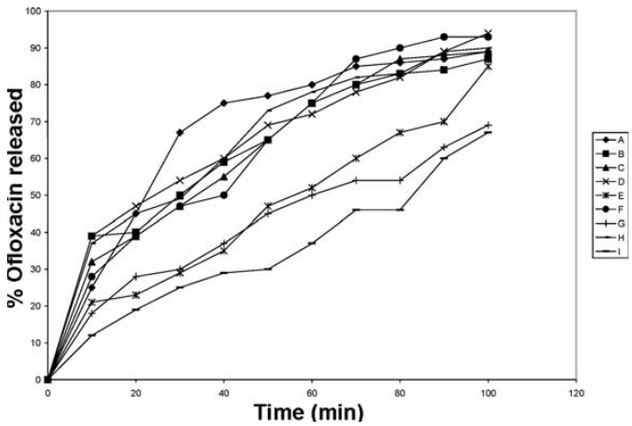

Figure 1. Dissolution profile of the nine different brands of ofloxacin in SGF.

pharmaceutical substance of the nine brands of ofloxacin tablets manufactured by nine different pharmaceutical companies imported and marketed in Nigeria. The basic purpose was to establish their quality prior to determining interchangeability with the innovator product.

MATERIALS AND METHODS

Materials and Reagents

Ofloxacin brands having a label strength of 200 mg (Table 1) were purchased from a retail pharmacy in Uyo, Akwa Ibom State, Nigeria. All tests were performed within product expiration dates. Ofloxacin powder was supplied by Walgreen Pharmaceuticals, Berkeley, California, USA.

The reagents used were methanol, chloroform, concentrated hydrochloric acid, acetic acid, ethyl alcohol, sodium hydroxide, and potassium phosphate (BDH Chemicals, UK). Freshly distilled water was used throughout the work.

Prepared Reagents

Simulated intestinal fluid was prepared by dissolving 40 g of sodium hydroxide and 34 g of potassium phosphate monobasic in 2 L of distilled water and then diluting to volume in a 5-L volumetric flask (*9*, *10*).

Simulated gastric fluid was prepared by adding 43 mL of concentrated hydrochloric acid to 2 L of distilled water in a 5-L volumetric flask; 500 mL of 2% sodium chloride solution was added, and the solution was diluted to volume (*9*, *10*).

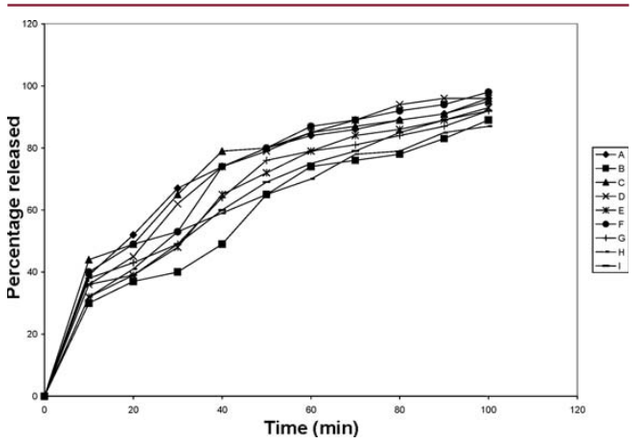

Figure 2. Dissolution profile of the nine different brands of ofloxacin in SIF.

Table 1. Ofloxacin Brands Used in the Study

Tablet	Brand	Manufacturer
A	Tarivid	Aventis, Midrand, South Africa
B	Oflomed	Evans, India
C	Gaxin	Grams, Nigeria
D	Asflovid	Suzhou Pharma, China
E	Floxavid	Jiangsu Pharm., China
F	Zanocin	Ranbaxy , India
G	Drovid	Tyonex, Milan, Italy
H	Floxan	Korea United Pharma, Korea
I	Traflox	Nigeria German Chemical, Nigeria

Visual Inspection

The shape, size, and color of the different brands of tablets were examined visually.

Friability Test

Twenty tablets were weighed and subjected to abrasion using a Veego tablet friability tester at 25 rev/min.

Hardness Test

The crushing strength of the tablets was determined using a Mosanto tablet hardness tester (Mosanto, UK).

Uniformity of Weight

Tablets of each brand were weighed individually using a digital analytical balance (Adventure Ohaus, China). The percentage deviation of the individual tablets from the mean was determined.

Tablet Disintegration Test

Tablet disintegration was determined at 37 °C using a Veego model VTDH3 disintegration testing apparatus (Rutartek, India).

Dissolution Rate Determination

Dissolution rates in the simulated body fluids (i.e., SGF and SIF) were determined using a Veego dissolution rate testing apparatus using 900 mL of medium at 37 ± 0.5 °C. The basket was rotated at 100 rpm. Ten milliliters of sample was drawn at 10-min intervals for 1 h with 10 mL

Table 2. Disintegration Time, Hardness, Uniformity of Weight, Friability, and Chemical Content of Nine Brands of Ofloxacin Tablets

Brand	Disintegration Time in SGF (min)	Disintegration Time in SIF (min)	Hardness (crushing strength) (kg/cm²)	Uniformity of Weight (g)	Friability (%)	Chemical Content (%w/w)
A	5.0 ± 2.3	7.0 ±0.9	4.6 ± 0.2	232.30 ± 0.01	0.025	97.3 ± 1.2
B	5.0 ± 0.2	6.0 ± 0.9	6.8 ± 0.5	220.50 ± 0.01	0.035	92.5 ± 0.5
C	7.0 ± 0.5	10.0 ± 0.5	8.6 ± 0.5	245.70 ± 0.02	0.035	98.7 ± 0.3
D	6.0 ± 0.8	7.0 ± 0.5	10.5 ± 0.2	225.75 ± 0.02	0.055	90.3 ± 0.5
E	3.0 ± 0.3	9.0 ± 1.5	4.8 ± 0.6	245.80 ± 0.04	0.095	94.4 ± 3.3
F	5.0 ±0.4	7.0 ± 1.4	7.6 ± 0.5	235.65 ± 0.03	0.08	90.3 ± 0.2
G	7.0 ± 0.8	6.0 ± 2.1	7.0 ± 0.2	232.35 ± 0.02	0.075	90.4 ± 0.7
H	5.0 ± 2.5	6.0 ± 0.3	7.8 ± 0.7	222.55 ± 0.01	0.055	98.3 ± 1.3
I	5.0 ± 0.4	7.0 ± 0.9	6.8 ± 0.9	236.95 ± 0.03	0.072	92.2 ± 2.4

of fresh dissolution medium replaced after each withdrawal. The UV absorbance was measured at 315 nm using a UV/vis spectrophotometer (Unico-2120, USA). The amount of ofloxacin in the samples was determined based on the calibration curve generated at a wavelength of 315 nm. The regression equation for the calibration curve is

$$y = 643.54\,x + 0.013,\ r^2 = 0.9563$$

The dissolution profiles of the different brands of ofloxacin tablets were generated from the graph of the amount of ofloxacin released versus time. The T_{70} (average time for 70% of the active drug to be released) was determined.

Chemical Content Determination

Ofloxacin pure powder was weighed in amounts of 0.1, 0.2, 0.3, 0.4, and 0.5 mg. Each was dissolved separately in 100 mL of 1 M sodium hydroxide and shaken for 3 min, then further diluted to 200 mL with 1 M sodium hydroxide and allowed to stand for 15 min. A 2-mL aliquot of the final volume for each weight was taken and further diluted to 200 mL with water. The absorbances of the resulting solutions were determined at 315 nm, and the calculated value of A (1%) was 465 at 315nm. The procedure was applied to the nine brands of ofloxacin employed in the investigation.

The method described was used to limit the available brands of ofloxacin to the four products comparable in quality to the innovator product. As manufacturers' interest in ofloxacin manufacture and marketing increases, more brands are likely to be introduced into the market, and this method can be used to assess the quality and drug-release pattern in the gastrointestinal tract.

The objective of this work was to examine the dissolution rate and obtain the PAE to summarily identify the products of ofloxacin that can be used interchangeably with respect to the amount of chemical content released in vivo prior to the determination of bioequivalence.

Statistical Analysis

Statistically significant differences among the brands were analyzed using the *F*-test with $P < 0.2$ considered significant.

RESULTS AND DISCUSSION

Dissolution of drug from oral solid dosage forms is a necessary criterion for drug bioavailability (i.e., the drug must be solubilized in the aqueous environment of the gastrointestinal tract to be absorbed). For this reason, dissolution testing of solid oral drug products has emerged as one of the most important control tests for assuring product uniformity and batch-to-batch equivalence (*11*, *12*). The uniformity-of-weight determination for the nine brands of ofloxacin tablets gave values that comply with the USP specification for uncoated tablets with a deviation less than 5% from the mean value (i.e., maximum deviation value 0.045) (Table 2). The strict adherence to good manufacturing practice (GMP) during the granulation and compression stages ensures tablet uniformity of weight. This is the point at which large intrabatch variations in tablet weight occur. A variation beyond the pharmacopoeial limits indicates unacceptable products. All the brands also passed the friability test; none had a weight loss of up to 1% (w/w), with the maximum value being 0.095 (Table 2). Drug products chip at the edges during transportation as a result of abrasion; this is evidence of poor production. All the brands, however, had good compression characteristics except samples G, F, H and D; these brands did not meet the requirements for crushing strength. The mean crushing strength observed for samples G, F, H, and D was 7.0 kg /cm².

Table 3. Dissolution Profiles for Nine Brands of Ofloxacin Tablets in SGF and SIF

	Dissolution Parameters in SGF		Dissolution Parameters in SIF	
Sample	T_{70} (min)	C_{45} (%)	T_{70} (min)	C_{45} (%)
A	38	75	36	76
B	58	60	58	55
C	56	58	32	78
D	65	62	38	78
E	-	39	50	68
F	56	58	36	75
G	-	39	45	70
H	53	65	55	62
I	-	25	-	58

The observed disintegration times for all the brands of ofloxacin investigated were less than the 15-min limit prescribed by the official compendium (Table 2). All tablets of the different generic brands passed the disintegration test. The various brands could have employed disintegrants to improve the penetration of aqueous liquids. The addition of disintegrants (e.g., starch, methyl cellulose) in the right proportion yields tablet products free of disintegration problems (*9*). The relative solubility characteristics of ofloxacin at room temperature as defined by USP nomenclature indicate that ofloxacin is soluble in aqueous solutions at a pH between 2 and 5. It is sparingly to slightly soluble in aqueous solutions at a pH of 7 and freely soluble in aqueous solutions at a pH > 9. This solubility profile allows the use of pH 1.15 (SGF) and pH 7.23 (SIF) as dissolution media for the in vitro testing of ofloxacin 200-mg tablets. There was a wide variation in the dissolution of the various brands of ofloxacin tablets in pH 1.15 (SGF), whereas dissolution was comparable in pH 7.23 (SIF). In both cases (SGF and SIF), however, the release after 30 min was lower than the acceptance criterion in the USP and the requirement for an immediate-release dosage form. This is an indication that all the brands fell short of pharmacopoeial standards in this regard. The dissolution rate profile showed that only brand A attained >70% dissolution in 45 min in SGF (PH 1.15) and in SIF (PH 7.23). However, the dissolution profiles of the drug in the simulated fluids gave a clear distinction among the products (Table 3). Four brands (i.e., B, E, H, and I) did not achieve 70% dissolution in 45 min in simulated gastric fluid and simulated intestinal fluid, which presumes that these brands have different absorption rates. Brands A, C, D, F, and G, however, had ≥70% release in SIF, therefore a greater amount of drug absorption is expected to occur in the intestine (*13*, *14*). The predicted availability equivalence of brand H in SIF and SGF was 69.5% and 88.6%, respectively, and that of product I was 54.3% and 86.2%, which clearly indicates that these products are not of comparable quality with the others. The dissolution efficiency (DE) and the predicted availability equivalence were calculated using the equations below (*15*, *16*).

$$DE_X = AUC_t\,X \,/\, AUC_T\,X \quad (1)$$

where DE_X is the dissolution efficiency of brand *X*, $AUC_t\,X$ is the area under the dissolution time curve for brand *X* at time *t*, And $AUC_T\,X$ is the total area under the dissolution time curve for brand *X*.

$$DE_P = AUC_t\,P \,/\, AUC_T\,P \quad (2)$$

where DE_P is the dissolution efficiency of the innovator product, $AUC_t\,P$ is the area under the dissolution time curve of innovator product at time *t*, and $AUC_T\,P$ is the total area under the dissolution time curve of innovator product.

$$PAE = DE_X/DE_P = (AUC_T\,X/AUC_T P) * 100$$

The implication of the PAE is to express the relative ease of release and predictive release pattern of the drugs in vivo (*17*). Products B, C, and D with PAE values in SGF and SIF of 81.23%, 102.1%, 95.48% and 74.8%, 73.3%, 75.2%, respectively, are evidently interchangeable with the innovator product A. However, the dissolution profiles of the drug in the simulated fluids gave a clear distinction among the products. Brands E, G, and I had ≤70% dissolution in one hour in simulated gastric fluid, which presumes that these brands have a different absorption rate. Brands B, C, D, E, F, G, and H had ≤65% release in SGF. The effect of acidic dissolution media on the disintegration and dissolution of the drug is reflected in the poor dissolution profile. Only

Table 4. Content of Ofloxacin in Pure Powder and the Innovator Brand Using UV Spectrophotometry

Weight of sample (g) (Pure powder or equivalent of generic)	**Chemical Content of Pure Ofloxacin Powder (%)** (mean ± SD)	**Chemical Content of Powdered Ofloxacin Tablet (%)** (innovator product) (mean ± SD)
0.1	99.31 ± 1.4	96.13 ± 1.1
0.2	97.46 ± 2.1	95.41 ± 2.1
0.3	99.11 ± 1.7	97.16 ± 1.4

Table 5. AUC and Concentration of Drug Released in SGF and SIF

Brand	SGF AUC	SGF AUC_{40}	SGF DE*	SGF PAE	SGF T_{70} (%)	SIF AUC	SIF AUC_{40}	SIF DE*	SIF PAE	SIF T_{70} (%)
A	8409.5	3420.0	0.41	100	38	6882.3	3208.0	0.47	100	36
B	6939.0	2292.5	0.33	81.23	58	7171.5	2501.5	0.36	74.80	58
C	8489.5	3526.5	0.42	102.1	56	7211.0	2461.0	0.34	73.20	32
D	8425.0	3271.5	0.39	95.48	65	7853.5	2752.5	0.35	75.20	38
E	7703.5	2763.0	0.36	88.20	-	5588.0	1467.0	0.26	56.30	50
F	8255.0	3054.5	0.37	91.00	56	7536.0	2395.5	0.32	68.20	36
G	7643.5	2916.5	0.38	93.80	-	4745.5	1441.0	0.30	65.20	45
H	7149.3	2576.0	0.36	88.60	52	6999.5	2267.5	0.32	69.50	55
I	7496.0	2628.0	0.35	86.20	-	4007.0	1013.5	0.25	54.30	-

brand A satisfactorily met the dissolution requirement for uncoated tablets. Sample H also barely achieved 70% dissolution in SIF. The UV spectrophotometric determination of ofloxacin content in the nine brands gave values of 90.27–98.65% (w/w) (Table 4).

The PAE calculated for the nine brands of ofloxacin were in the range of 54.3–100% in SGF and 86.20–102.1% in SIF (Table 5).

The various brands were chemically equivalent because all had chemical content not less than 90% and not more than 100% (w/w) (*8*).

SUMMARY

The presented quality control method is useful in monitoring the production consistency of batch-to-batch product release of each brand of ofloxacin and in comparing the quality characteristics of different brands marketed. The therapeutic equivalence of the drugs must also be investigated by challenging susceptible microorganisms.

ACKNOWLEDGMENT

The authors are grateful to JDJIDE pharmaceuticals, Ikot Ekpene, Nigeria for financial support.

REFERENCES

1. Olaniyi, A. A.; Babalola, C. P.; Oladehinde, F. O.; Adegoke, A. O. Towards Better Quality Assurance of Drugs. Proceedings of 4th National Workshop, Department of Pharmaceutical Chemistry, University of Ibadan, Ibadan, Nigeria, 2001; pp 59–60.
2. *Remington : the Science and Practice of Pharmacy*, 20th ed.; Troy, D. B., Ed.; Lippincott Williams & Wilkins: Philadelphia, 2001; pp 473–474.
3. Okeke, I.; Lamikanra, A. Quality and bioavailability of Tetracycline capsules in Nigeria semi urban community. *Int. J. Antimicrob. Ag*. **1995**, *5*, 245–252.
4. Babalola, C. P. Bioavailability and Bioequivalence (BA/BE) Assessment. In *Towards Better Quality Assurance of Drugs in the 3rd Millennium. Biopharmaceutical Methods in Drug Quality Assurance,* 1st ed.; Olaniyi, A. A., Babalola, C. P., Oladehinde, F. O., Adegoke, A. O., Eds.; Omoadade Printing Press: Ibadan, Nigeria, 2004**;** p 79.
5. Olaniyi, A. A. Principles of Pharmacokinetics. In *Essential Medicinal Chemistry,* 3rd ed.; Hope Publications: Ibadan, Nigeria, 2005; pp 59–79.
6. Dressman, J. B., Amidon, G. L., Reppas, C.; Shah, V. P. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm. Res.***1998**, *15* (1), 11–22.
7. *United States Pharmacopeia and National Formulary USP 24–NF 19*; The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2000; pp 1882–1883.
8. Andriole, V. T. Clinical overview of the newer quinolone antibacterial agents. In *The Quinolones,* 1st ed.; Andriole, V. T., Ed.; Academic Press Ltd.: London, UK, 1988; pp 155–200.
9. Jantratid, E.; Janssen, N.; Reppas, C.; Dressman, J. B. Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. *Pharm. Res*. **2008**, *25* (7), 1663–1676.
10. Osadebe, P. O.; Akabogu, A. Assessment of quality control parameters and interchangeability of multi-sourced metformin hydrochloride tablets marketed in Nigeria. *Boll. Chim. Farm.* **2004,** *143* (4) , 170–173.
11. Voegele, D. Drug release in vitro: An aid in clinical trials? *Met. Find. Exp. Clin. Pharmacol*. **1992**, *21* (1), 55–62.
12. Moore, J. W.; Flanner, H. H. Mathematical comparison of dissolution profiles. *Pharm. Technol*. **1996**, *20*, 64–74.
13. Welling, P. G. Effects of food on drug absorption. *Annu. Rev. Nutr*. **1996**, *16*, 383–415.

14. Nwodo, N.; Uzochukwu, I.; Omeje, E. O. Quality control assessment and the possibility of interchangeability between multisourced norfloxacin tablets marketed in Nigeria. *Sci. Res. Essays* **2007**, *2* (8), 348–352.
15. *British Pharmacopoeia 2004*; The Stationary Office: London, 2004; pp 247–254.
16. WHO Expert Committee on Specifications for Pharmaceutical Preparations: 34th Report. WHO Technical Report Series; Geneva, Switzerland, 1996; No. 863; pp 115–116.
17. *Martindale*: *The Complete Drug Reference*, 33rd ed.; Sweetman, S.C., Ed.; Pharmaceutical Press: London, 2002.