Quality assessment of ten brands of ofloxacin tablets marketed in Lagos, Nigeria.

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ABSTRACT

Background: Ofloxacin is a synthetic chemotherapeutic agent used to treat severe and life threatening infections. It is a fluoroquinolone antibiotic with broad spectrum of activity.

Objectives: This study is aimed at evaluating some physicochemical parameters and assay of ten different brands of ofloxacin 200 mg tablets sourced from various pharmaceutical stores in Lagos.

Methods: The physicochemical tests carried out include uniformity of weight, hardness, friability, disintegration and dissolution tests according to the BP and USP established methods. The quantitative assay was carried out using the UV/visible spectrophotometry. Similarity factor (f_2) was used to assess the dissolution profile among the brands.

Results: The results indicated that all brands complied with the official specification for uniformity of weight, friability, and disintegration. However, the dissolution profiles in 0.1N HCl showed that only one brand (OFLO-6) failed to attain 80% dissolution in 30 min, although it passed quantitative assay test. The quantitative assay showed that two brands (OFLO-2 and OFLO-7) contained less than 90% of labeled ofloxacin content. OFLO-6, OFLO-7 and OFLO-10 brands showed dissimilarity in dissolution profile relative to the innovator brand (OFLO-1), thus may not be used interchangeably within clinical considerations.

Conclusion: The result shows that chemical equivalence does not indicate bioequivalence. Owing to the vast influx of pharmaceuticals into the Nigeria drug market, it is important that regulatory agencies engage in periodic post-marketing analytical quality assessment.

Keywords: Ofloxacin brands, post market quality assessment, similarity factor.

Évaluation de la qualité de dix marques de comprimés d'ofloxacine commercialisés à Lagos, au Nigeria.

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RESUME

Contexte: L'ofloxacine est un agent chimio-thérapeutique synthétique utilisé pour traiter les infections sévères et potentiellement mortelles. C'est un antibiotique fluoroquinolone à large spectre d'activité.

Objectifs de l'étude: Cette étude vise à évaluer certains paramètres physicochimiques et un dosage de dix différentes marques de comprimés de 200 mg d'ofloxacine provenant de divers pharmacies de Lagos.

Méthodes: Les tests physico-chimiques réalisés comprennent l'uniformité du poids, de la dureté, de la friabilité, de la désintégration et des tests de dissolution selon les méthodes établies par BP et USP. L'analyse quantitative a été effectuée à l'aide d'une spectrophotométrie UV/visible. Le facteur de similarité (f_2) a été utilisé pour évaluer le profil de dissolution parmi les marques.

Résultats: les résultats ont indiqué que toutes les marques étaient conformes aux spécifications officielles pour l'uniformité du poids, de la friabilité et de la désintégration. Cependant, les profils de dissolution dans le HCl 0,1N ont montré qu'une seule marque (OFLO-6) n'a pas réussi à atteindre une dissolution de 80% en 30 minutes, bien qu'elle ait réussi un test de dosage quantitatif. L'analyse quantitative montre que deux marques (OFLO-2 et OFLO-7) contiennent moins de 90% de la teneur en ofloxacine marquée. Les marques OFLO-6, OFLO-7 et OFLO-10 ont montré une divergence dans le profil de dissolution par rapport à la marque innovatrice (OFLO-1), ne pouvant donc pas être utilisée de manière interchangeable dans des considérations cliniques.

Conclusion: le résultat montre que l'équivalence chimique n'indique pas la bioéquivalence. En raison du vaste afflux de produits pharmaceutiques sur le marché des médicaments au Nigéria, il est important que les organismes de réglementation s'engagent dans une évaluation périodique de la qualité analytique post-commercialisation.

Mots clés: marques Ofloxacin, évaluation de la qualité post-marché, facteur de similarité.

INTRODUCTION

Substandard medicines, produced by licensed manufacturers, pose a serious public health risk, especially in the developing world.[1] At their very best, these medicines are ineffective; at worst, they cause harm, creating drug-resistant pathogens or resulting in death.[1,2] These medicines are the product of poor manufacturing practices or improper storage or distribution practices, that result in deterioration in the quality of the medicines. [2] Substandard medicines run from products that contain correct ingredients in incorrect proportions to products without active ingredients or with harmful substitutes.[3]

Substandard antimalarials in Africa, for example, engender drug resistance by exposing parasites to sublethal concentrations of active ingredients.[4]

Caudron et al. (2008) identified ten categories of substandard medicines: overconcentration of active ingredient, under-concentration of active ingredient, irregular filling of vials, contamination, mislabeling (not counterfeit), problems with active ingredient, problems with excipients (inactive ingredients used as carriers for active ingredients in medicines), poor stability, packing problems, and unsatisfactory dissolution profiles.[5] These categories exemplify the diverse number of ways medicines may be rendered substandard.

Medicines may be rendered substandard at any point along the medical supply chain, from the point of manufacture through the point of distribution.[5,6] At manufacture, medicines may be produced with impure or improper proportions of active ingredients. Even if produced properly, it may be compromised during transportation, warehousing, distribution, and as a result of improper storage by the consumer.[4,6]

Regardless of where along the supply chain substandard medicines are compromised, they pose serious public health risks. Use of substandard medicines increases mortality and morbidity and may result in harmful side effects or allergies or engender drug-resistant pathogens that limit the therapeutic effectiveness of legitimate medicines.[4,6,7]

Substandard medicines also contribute to the spread of infectious diseases[7] and, if contaminated with pathogens (fungi, bacteria, viruses, or parasites) or other toxic elements, can cause further illness or poisoning.[7]

Also, variable clinical responses to drugs presented as generics and batch-to-batch inconsistencies have been reported.[8] Poor-quality medicines can reach the market through substandard production of legitimate drugs due to inadequate quality-control processes during manufacture.[5] In Nigeria, among other classes of drugs, anti-infectives (comprising antimicrobials and antimalarials) are the most patronized.

Ofloxacin (Figure 1), a synthetic chemotherapeutic agent of the fluoroquinolone drug class of antibiotics considered to be second generation, is a fluorinated carboxy-quinolone racemate nomenclatured as (±)-9-fluro-2, 3,-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido(1,2,3-de)-1,4-benzoxazine-6-carboxylic acid.[9,10] Generally, quinolone antibiotics inhibit DNA synthesis by targeting two essential type II topoisomerases: DNA gyrase and topoisomerase IV (Topo IV). In this wise, ofloxacin acts by inhibiting topoisomerase II (DNA gyrase and topoisomerase IV.[11,12]

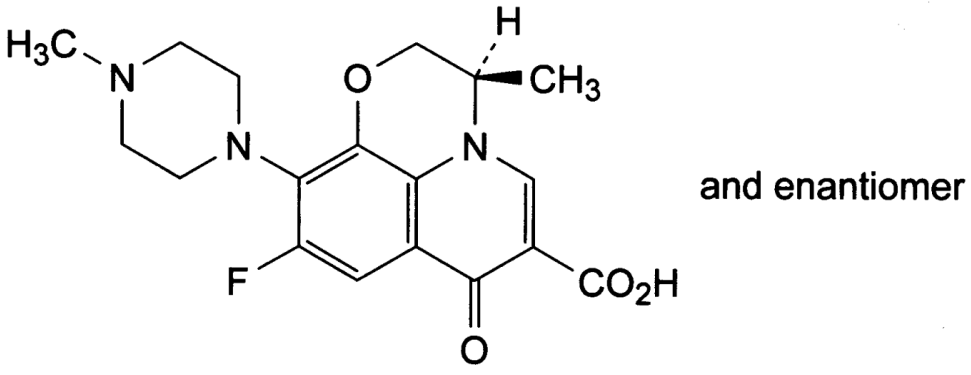

Figure 1: Structure of ofloxacin.[13]

Generic substitution is defined as dispensing of product that is generically equivalent to the prescribed innovator brand with the same active ingredients in the same dosage form, and identical in strength, concentration, and route of administration.[14] The indication for the use of generic names for drug purchasing as well as prescribing is precisely to facilitate drug substitution whenever appropriate. It has been stated that the use of generic names for drug purchasing and prescribing carries considerations of clarity, quality, and price.[14,15] All generic drug products must satisfy the same standards of quality, efficacy and safety as those applicable to the innovator products. Preliminary physicochemical assessment of the products is very important and *in-vitro* dissolution testing is a valuable predictor of the *in-vivo* bioavailability and bioequivalence of many oral solid dosage forms.[16] The hardness-disintegration ratio (HDR) and hardness friability ratio (HFR) can be used to estimate the hardness of a tablet. Increase in binder concentration was reported to increase the hardness and disintegration time. There is an inverse relationship exists between disintegration time and HDR.[17]

The objective of this study was to evaluate the physicochemical parameters of different brands of ofloxacin in the drug market within the Lagos metropolis using official methods and to establish data for a possible interchangeability of the brands by comparing the dissolution profile of the other brands with the innovator brand under biowaiver conditions.

MATERIALS AND METHODS

Instrumentation

Mettler Toledo Analytical Balance (China), Disintegration tester, Copley erewka-apparatebau, Germany); Copley scientific Dissolution Test Apparatus USP standard, Notingham, United kingdom (Paddle method), Friability tester (Erweka-apparatebau-GMBH, Heusenstamm, Germany); UV/Visible spectrophometer (T80+) PG Instrument Ltd., China; Hardness Tester, Mettler Toledo (Monsato type), China.

Test Drugs and Reference standard

Ten brands of ofloxacin labeled to contain 200 mg of the active ingredient were randomly purchased from registered pharmaceutical stores in the Lagos drug market. The innovator brand is Tarivid(R). Reference ofloxacin powder (USP reference standard) was graciously supplied by the Central Research Laboratory of the Faculty of Pharmacy, University of Lagos. Other reagents such as hydrochloric acid (BDH laboratory supplies, England), sodium hydroxide (Merck Germany) were of analytical grade. The water used to prepare the solutions was doubly distilled and stored at room temperature (courtesy, Department of Pharmaceutical chemistry, College of Medicine, University of Lagos).

Physical parameters

Uniformity of weight test

Twenty (20) tablets of each brand of ofloxacin were randomly selected. Each tablet was weighed, the average weight of the twenty tablets was determined and the percentage deviation of each tablet from the average was calculated.[18]

Friability test

Ten (10) tablets from each brand of ofloxacin were carefully dusted and accurately weighed before they were carefully placed in the friabilator and subjected to abrasion using ERWEKA Tablet Friability Tester at 25 rev/min for 4 minutes.[13]

Hardness test

Ten (10) tablets of each ofloxacin brand were individually placed in a vertical position between the jaws of the hardness tester with respect to the direction of application of the force. An initial reading was taken when each tablet was firmly held to the jaws of the tester. A final reading was then taken when tablet broke due to an applied force. Resistance to crushing of tablets (hardness), expressed in Kg/cm^2 was calculated by obtaining the difference between the final and initial readings.[8]

Disintegration test

This test was carried out using a disintegration tester containing 0.1N HCl as the disintegration medium. Six (6) tablets of each brand randomly selected from the pool of tablets were dropped into each of the cylindrical tubes (basket rack) and then immersed into the beaker containing the solution, maintained at 37±0.5°C. The tubes were oscillated up and down and the individual time it took for the entire tablet matrix to pass through the screen at the base of the tubes was recorded in minutes using a split timer.[13] The result for each brand was calculated and expressed as Mean ± SD.

Quantitative Assay for Active content

Ofloxacin standard preparation

The reference sample, 50 mg ofloxacin, was weighed into a 100 ml volumetric flask and dissolved in 70ml 1.0M NaOH and made up to volume (500 µg/ml stock solution). A 50 µg/ml working solution was prepared from the stock, which was further diluted to

concentrations of 2, 4, 6, 8, and 10µg/ml. The absorbance readings of these final concentrations were obtained at 294nm from the UV Spectrometer against a blank (1.0M NaOH) and the procedure was repeated.[19] The average absorbance was used for the calibration plot. The calibration plot of this standard gave a regression coefficient (R^2) of 0.9996.

Preparation of sample solution

For each brand, 20 ofloxacin tablets were weighed and powdered. A powdered portion equivalent to 50 mg of ofloxacin was weighed, dissolved in 70 ml of 1.0M NaOH and made up to 100 ml. A 50 µg/ml working solution was prepared from the stock, which was further diluted to 6µg/ml. The solution was analysed using UV/Visible spectrophotometer against the blank (1.0M NaOH) at 294nm.[19] The procedure was repeated and the average absorbance was calculated. The concentration of this test sample was obtained from the regression equation. The result was compared with the official range in USP.[18]

Dissolution Test

In-vitro dissolution tests were carried out using a dissolution apparatus USP (paddle method) set at a speed of 100 rpm. According to United State Pharmacopoeia[18], the dissolution medium for ofloxacin dissolution test was freshly prepared 900 ml 0.1N HCl, regulated to 37 ± 0.5°C. At intervals of 5, 10, 15, 30, 45 and 60 minutes, aliquots (5ml) of the dissolution medium were withdrawn and replaced with equal volume of fresh 0.1N HCl to maintain constant volume in the dissolution vessel. On withdrawal, the medium was filtered through a 0.45µm Millipore filter and transferred into sample bottles. This procedure was repeated using six tablets from each brand and the concentrations of the released ofloxacin per time were determined using a UV/Visible spectrophotometer at 294nm wavelength against the blank (0.1M HCl).[18]

Comparison of Dissolution profile

The *in vitro* dissolution profile for each brand relative to the reference was assessed using the model-independent approach based on the similarity factor statistics[20] and conclusions were drawn using a sufficient number of time points for these calculation. Time points of 10mins, 15mins and 30minutes were considered, and the dissolution similarity was determined using the formula as shown:

$$f_2 = 50 * \log\{[1 + (1/n)\Sigma t=1n (Rt - Tt)\ 2] - 0.5 * 100\}$$

Where f_2 is the similarity factor; n is the number of time points, R(t) is the mean percent of the reference drug (OFLO-1, Tarivid(R)) dissolved at time t after initiation of the study; T(t) is the mean percent of the test drug dissolved at time t after initiation of the study. A similarity factor (f_2) value between 50 and 100 suggests that the dissolution curve is similar to that of the reference drug; hence their dissolution profile is similar.[16]

RESULTS

The physicochemical assessments of ofloxacin tablets include the determination of uniformity of weight, hardness, friability, disintegration time, active content assay and dissolution test. The uniformity of weight results are shown in Table 1. The average weight per tablet ranged from 272.12 mg (Oflo 10), to 985.57mg (Oflo 5). The friability test result ranged from 0.01 to 0.31.The disintegration time ranged from 1.18± 0.18 for Oflo 4 to 17.42±1.94 minutes for Oflo 7. The hardness test result obtained for the brands ranged from 1.6±0.34 to 9.65±0.44 kg/cm^2. The hardness-friability ratio (HFR) and hardness-disintegration ratio (HDR) were calculated and shown in Tables 1.

The dissolution test result and the similarity factor, f_2, are shown in Figure 2 and Table 2. The active content result ranged from 72.44± 1.72 (Oflo 2) to 100.56±6.01 (Oflo 8, Table 2).

Table 1: Physical parameters of the brands of Ofloxacin tablets

Product code	Mean weight (mg)	Hardness (kg/cm2)	Friability (%)	HFR	Disintegration	HDR
OFLO-1 (Tarivid®)	402.23 ± 2.84	6.2 ± 0.40	0.01	620	8.45 ± 0.37	0.73
OFLO-2	627.28 ± 5.99	3.14 ± 0.78	0.01	314	7.55 ± 1.26	0.42
OFLO-3	382.45 ± 7.96	2.63 ± 0.30	0.31	8.48	3.81 ± 0.88	0.69
OFLO-4	543.32 ± 7.43	1.6 ± 0.34	0.07	22.86	1.18 ± 0.18	1.36
OFLO-5	985.57 ± 10.17	8.15 ± 0.00	0.01	815	9.91 ± 0.49	0.82
OFLO-6	575.99 ± 7.00	8.53 ± 0.79	0.01	853	6.99 ± 1.94	1.22
OFLO-7	410.22 ± 10.73	7.18 ± 1.16	0.01	718	17.42 ± 1.94	0.41
OFLO-8	391.53 ± 7.43	9.65 ± 0.44	0.05	193	5.01 ± 0.34	1.93
OFLO-9	324.75 ± 6.22	5.28 ± 1.20	0.01	528	5.55 ± 0.39	0.95
OFLO-10	272.14 ± 3.19	5.45 ± 0.93	0.01	545	4.95 ± 2.49	1.10

Table 2: Results of the dissolution test, similarity factor, f_2 and the active content assay of the different brands of ofloxacin

Product code	10 (min)	15 (min)	30 (min)	f_2	Active content assay (%)
OFLO-1 (Tarivid$^{(R)}$)	75.43	91.1	84.8	100*	95.14 ± 0.79
OFLO-2	88.24	92.63	93.43	62	72.44 ± 1.72
OFLO-3	91.11	92.52	92.88	65.4	91.78 ± 8.07
OFLO-4	88.58	87.88	90.38	67.9	97.03 ± 4.56
OFLO-5	83.44	86	90.08	68	95.57 ± 11.93
OFLO-6	73.5	82.06	83.9	41.7	91.19 ± 6.33
OFLO-7	76.6	76.9	78.28	49.2	81.04 ± 16.71
OFLO-8	94.1	95.4	97.7	54.8	100.56 ± 6.01
OFLO-9	93.28	95.34	96.4	55.6	95.40 ± 5.03
OFLO-10	78.5	80.5	92.4	42.7	95.14 ± 3.65

* chosen reference for calculating f_2

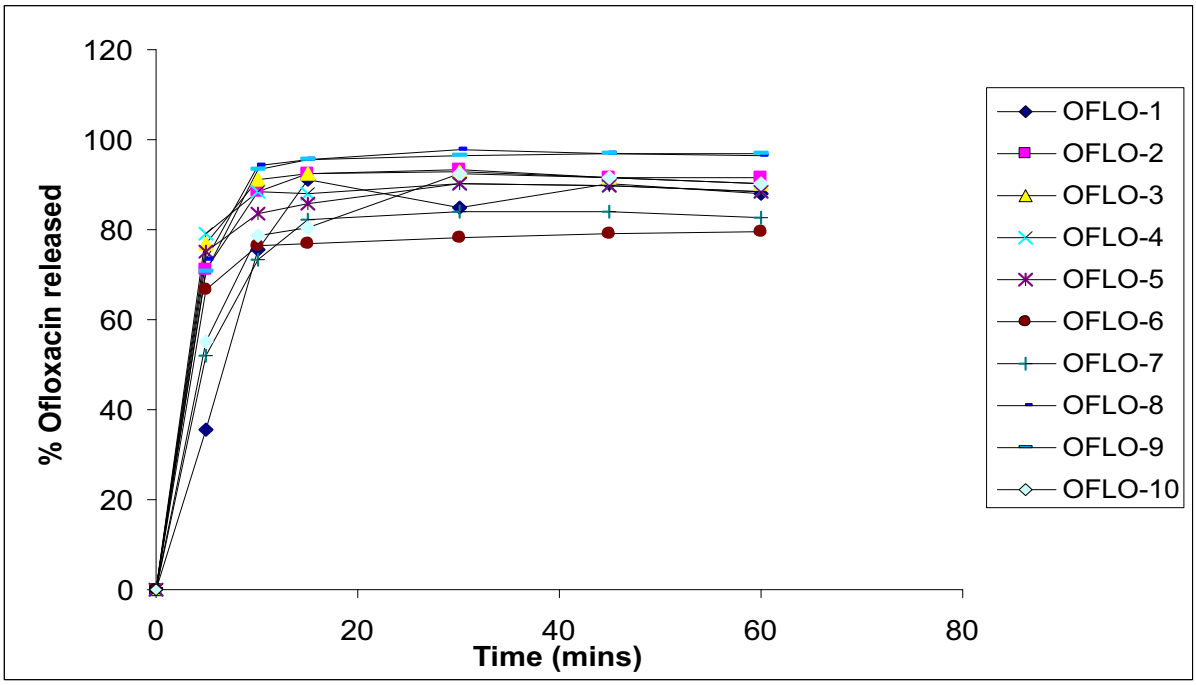

Figure 2: Plot showing the dissolution profiles of ofloxacin released from different tablet brands

DISCUSSION

The globalization of the pharmaceutical industry has the potential to rapidly spread medicines of different qualities worldwide before adequate detection and intervention are possible. The rapidly expanding population tendency of Lagos positions the metropolitan city as a viable hub for all forms of drug manufacture, merchandising, distribution and consumption. This outlook necessitated the need for the study as a means to assess the quality of one of the most prescribed and patronized fluoroquinolones in Nigeria. Different brands of ofloxacin were sourced from major drug outlets in urban and peri-urban parts of Lagos. Eighty percent of the ofloxacin brands studied were manufactured in Asia while the remaining 20% were manufactured in Africa (with only one manufacturer being indigenous). This suggestive influx of Asian-manufactured drugs into the drug market should inform the need for post-marketing surveillance (PMS).

Table 1 represents the variation in weight of the tablets of ofloxacin studied. The percentage deviation for each tablet per brand from the mean showed that all the brands of ofloxacin tablets complied with the USP[18] specifications for uncoated tablet matrices greater than 250mg, that is, not more than two tablets of ofloxacin brands deviated by ±5%. The friability test is closely related to the tablet hardness which evaluates the ability of the tablet to withstand stress or abrasion during handling, packaging, and transportation. The results showed that all brands passed the friability test based on the specification which states that no compressed tablet should have a friability value greater than 1.0%w/w.[13] The values obtained ranged from 0.00 to 0.31% w/w, which suggests an impressive and acceptable friability.

The resistance of a tablet to chipping, abrasion or breakage under conditions of storage, handling and transportation, prior to usage by the consumer depends on the hardness of the tablet.[8] The hardness of the studied ofloxacin tablets ranged from (1.6 ± 0.34) kg/cm^2 to (9.65 ± 0.44) kg/cm^2 corresponding to OFLO-4 and OFLO-8 respectively (Table 1). The brands OFLO-1, OFLO-9 and OFLO-10 are the only brands of ofloxacin that passed the hardness test since the crushing strengths lie within the limit range of 4 to 8kg/cm^2. While three of the brands (OFLO-2, OFLO-3 and OFLO-4) are lower than the lower limit of 4kg/cm^2, four of the brands (OFLO-5, OFLO-6, OFLO-7 and OFLO-8) had higher crushing strengths than the acceptable upper limit of 8kg/cm^2. The hardness-friability ratio (HFR) also serves as a parameter for measuring tablet strength according to Odeku et al.[17] Generally, the higher the HFR value, the stronger is the tablet.[21] Based on the HFR, OFLO-6, OFLO-5 and OFLO-7 were the hardest tablets (Table 1) and bearing the length of expiry, storage and handling, these brands are likely to withstand chipping and abrasion.

Disintegration is important to break up tablet matrices

into particulate forms that can enhance dissolution and absorption of the drug into the target physiological milieu. All tablets of the different brands of ofloxacin disintegrated within 1.18 to 17.42 minutes (Table 2). The time for disintegration of tablets should not be greater than 30 min.[13] Though all the brands passed the disintegration test based on the BP specifications, OFLO-4 had the least disintegration time of (1.18 ± 0.18) minutes while OFLO-7 had the highest of (17.42 ± 1.94) minutes. An ideal tablet should be hard enough to withstand abrasion, stress and handling, yet loose enough to disintegrate at acceptable time in a physiological fluid. The low crushing strength of OFLO-4 is consistent with the disintegration time in the simulated gastric fluid. The opposite is true of OFLO-8, despite a high hardness value, the tablets disintegrated within BP acceptable limits of (5.01 ± 0.34) minutes. This could be due to appreciable use of disintegrants as excipients during formulation and compression to improve the breakdown of the tablet matrix. The addition of disintegrants (e.g., starch, methyl cellulose) in the right proportion can yield tablets free of disintegration problems.[22] The hardness-disintegration ratio (HDR) can also be used to estimate hardness of a tablet. An inverse relationship exists between disintegration time and HDR.

The quantitative assay of the different brands was determined by UV/visible spectrophotometric analysis as evidenced by the presence of a chromophoric system in the molecular structure of the compound (Figure 1). The quantitative assay result of ofloxacin in the brands is given on Table 2. According to the United States Pharmacopeia, 2014, the acceptable limit of ofloxacin in ofloxacin tablet should range between 90-110%.[18] All the brands passed the quantitative assay test except OFLO-2 and OFLO-7 with values of 72.43 % and 81.04 % respectively.

The dissolution of a drug from oral solid dosage forms is a necessary criterion for drug bioavailability (i.e., the drug must be soluble 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.[23] *In vitro* dissolution testing is an important tool used for development and approval of generic dosage forms. According to the FDA (2000)[20], a drug product is considered to be very rapidly released if $\geq$ 85% of the drug is dissolved in 15 min, which corresponds to gastric emptying half life in fasting conditions.[20] The brands OFLO-1, OFLO-2, OFLO-3, OFLO-4, OFLO-5, OFLO-8 and OFLO-9 may be considered as very rapidly dissolving tablets as more than 85% of the labeled amount of ofloxacin dissolved within 15minutes. Furthermore, the USP (2007) specified an 80% release at 30 minutes of dissolution time[18], thus only OFLO-6 with a 78.28% release at 30min can be said to have failed the dissolution requirement for film coated tablets. Bearing these two official specifications, OFLO-6 may be said to show a poor dissolution profile.

The similarity factors determined using the percentage of ofloxacin released at timed interval (Table 2) can be an important index used to predict similarity in dissolution profiles of different brands (Figure 2) and consequently inform a prescriber's choice on generic substitution. This parameter may also be insensitive to the type of excipient used in the formulation. The similarity factor (f_2) is a simple and viable comparison approach to assess dissolution similarity between different brands of a formulation with same active ingredient. The similarity factor has been adopted by the Center for drug Evaluation and Research (FDA) and the Human Medicines Evaluation Unit of the European Agency for the Evaluation of Medicinal Products as a criterion for assessment of similarity between two *in-vivo* dissolution profiles.[16] The similarity factor as defined by these two agencies is a logarithmic reciprocal square root transformation of one plus the mean squared differences in percent dissolved between the test and reference products.[24] A f_2 value between 50 and 100 is indicative of the similarity in the dissolution profiles between two drugs of the same API.[16] Relative to the innovator brand, only six (6) brands showed a similarity factor that lies within limits of 50 to 100, suggesting that the brands had a similar dissolution profile like the innovator brand. It therefore follows that all the brands are interchangeable with the innovator brand except OFLO-6, OFLO-7, and OFLO-10. The indigenous brand, OFLO-3, though had a low HFR, compared well with the innovator brand. The indigenous companies in Nigeria are closer to the regulating agencies such as NAFDAC and are more compliant to the rules. It would be of interest if the quantification of some toxic metals can be included in future work. It was difficult to get deionized water for the study. Despite this limitation encountered sample size could be increased.

CONCLUSION

All the brands of ofloxacin passed the uniformity of weight, friability and disintegration tests. OFLO-2 and OFLO-7 failed the test for specified limit for percentage purity of ofloxacin in tablet. Generic substitution can be

effected among six of the brands except OFLO-6, OFLO-7 and OFLO-10. A brand substituted on assumption of chemical equivalence with another brand may not give the desired onset of action and subsequent therapeutic effectiveness.

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REFERENCES

1. Ham TM (2003). Health Risks of Counterfeit Pharmaceuticals. *Drug Safety* 26 (14): 991-997.
2. World Health Organisation (WHO) (2008). International Products Anti-Counterfeiting Task Force.
3. World Health Organization. (2010b). Medicines: spurious/falsely-labelled/alsified/counterfeit (SFFC) medicines. http://www.who.int/mediacentre/factsheets/fs275/en/. Updated 2016.
4. Newton PN, Green MD, Mildenhall DC, Plançon A, Nettey H, Nyadong L, Hostetler DM, Swamidoss I, Harris GA, Kristen P, Timmermans AE, Amin AA, Opuni SK, Barbereau S, Faurant C, Soong RCW, Faure K, Thevanayagam J, Fernandes P, Kaur H, Angus B, Stepniewska K, Guerin PJ, and Fernández FM (2011). Poor Quality Vital Antimalarials in Africa - An Urgent Neglected Public Health Priority. *Malaria Journal* 10: 352-374. http://www.malariajournal.com/content/10/1/352.
5. Caudron JM, Ford N, Henkens M, Mace C, Kiddle-Monroe R, Pinel J(2008). Substandard medicines in resource-poor settings: a problem that can no longer be ignored. *Tropical Medicine and International Health* 13:1062–1072.
6. Newton PN, Green MD, Fernandez FM (2010). Impact of poor-quality medicines in the developing world. *Trends in Pharmacological Sciences* 3(3):99-101.
7. Nsimba S (2008). Problems Associated with Substandard and Counterfeit Drugs in Developing Countries: A Review Article on Global Implications 68 of Counterfeit Drugs in the Era of Antiretroviral (ARVs) Drugs in a Free Market Economy. *East African Journal of Public Health*; 5:205-210. http://www.ncbi.nlm.nih.gov/pubmed/19374325.
8. Remington TDB (2001). The Science and Practice of Pharmacy, 20th edition; Lippincott Williams & Wilkins, Philadelphia; pp. 473–474.
9. Nelson JM, Chiller TM, Powers JH, Angulo FJ (2007). Fluoroquinolone-resistant Campylobacter species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. *Clinical Infectious Diseases* 44(7):977.
10. Budavari S (2001) In. The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, 13th Edition; Merck & co., Inc; Whitehouse Station, NJ, USA: pp. 1213 - 1229.
11. Anderson MI and MacGowan AP (2003). Development of the quinolones. *Journal of Antimicrobial chemotherapy* 51(suppl. 1):1-11.
12. O' Donnel JA, Gelone SP (2000). Fluoroquinolones. *Infectious Disease Clinics of North America* 14:489-513.
13. British Pharmacopoeia (2013). Ofloxacin. British Pharmacopoeia commission. The stationery office limited, London; volume 1 and 2. CD.
14. Management Sciences for Health and World Health Organisation (1997). Managing Drug Supply: The selection, procurement, distribution, and use of pharmaceuticals. Kumarian Press, Inc. West Hartford, CT, USA: pp. 428.
15. World Health Organisation (1993). How to Investigate Drug Use in Health Facilities. Selected Drug Use Indicators. World Health Organisation, Department of Essential Drug and Medicine Policy: Geneva; pp. 10.pdf. http://apps.who.int/medicinedocs/en/d/Js2289e/6.html
16. European Medicines Agency (2010). Guideline on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98. London: European Medicines Agency Rev.1, Jan. 2010. *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf*
17. Odeku OA, Itiola OA (2003). Evaluation of the effects of khaya gum on the mechanical and release properties of paracetamol tablet formulation. *Drug Development and Industrial Pharmacy* 29(3):311-320.
18. United States Pharmacopeia. (2014). Ofloxacin. The United States Pharmacopeia, USP 39/ The National Formulary, NF 34; Rockville, MD; U.S. Pharmacopeial Convention, Inc. 3:1046-1048.
19. Samreen K, Shahnaz G, Rabia R, Sakina F (2012).

Post market surveillance of different brands of ofloxacin 200mg Tablets available in local market of Karachi (Pakistan). *International Journal of Pharmacy and Pharmaceutical Sciences* 4(4):668-672.

20. US Food and Drug Administration (2000). Center for Drug Evaluation and Research Guidance for Industry - Waiver of InVivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry *pdf*.
21. Adetunji OA, Odeniyi, MA, Itiola OA (2006). Compression, mechanical and release properties of chloroquine phosphate tablets containing corn and trifoliate yam starches as binders. *Tropical Journal of Pharmaceutical Research* 5(2):589-596.
22. Jantratid E, Janssen N, Reppas C, Dressman JB (*2008)*. Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. *Pharmaceutical research 25*(7):1663–1676.
23. Moore JW, Flanner HH (1996). Mathematical comparison of dissolution profiles. *Pharmaceutical Technology* 20:64–74.
24. Costa P, Sousa JM (2001). Modeling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences* 13(2):123–133.