fr. J. Med. Med. Sci. (2021) **50,** 165-176

Chemical, biopharmaceutical and microbiological profiles of ciprofloxacin tablets in the Nigerian market

OE Adejumo[1], MB Awesu[1], AL Kolapo[2] and OA Bamiro[3]

Department of Pharmaceutical and Medicinal Chemistry[1], Olabisi Onabanjo University, Sagamu, Department of Biological Sciences[2], Augustine University, Ilara-Epe, Lagos State, and Department of Pharmaceutics and Pharmaceutical Technology[3], Olabisi Onabanjo University, Sagamu, Nigeria

Abstract

Background: The number of ciprofloxacin hydrochloride brands in the Nigerian market is continuously increasing; hence, there is need to establish their bioequivalence in the interest of public health. This study assessed the chemical, biopharmaceutical, and microbiological profile of thirty brands of ciprofloxacin (500 mg) tablets in Nigerian market.

Method: Quality parameters evaluated include weight uniformity, thickness and diameter, hardness, friability, disintegration, dissolution, identity, and antibacterial profile. Content of active ingredients was determined by a slightly modified and validated HPLC method.

Results: Results of thickness, diameter, and hardness tests of all the brands fell within acceptable limits. The percentage of brands within acceptable range for weight uniformity, friability, disintegration, dissolution, and active ingredient are 86.67, 96.67, 93.33, 26.67, and 93.33% respectively. About 87% of the tested generic version of ciprofloxacin demonstrated *in-vitro* antibacterial bioequivalence to the reference drug. The abysmal low dissolution rate of 26.67 % is a source of concern as it suggests a potential poor bioavailability of the active ingredient of these drugs.

Conclusion: The failure of a large portion of the tested brands may be due to deliberate counterfeiting, failure of current good manufacturing practices (cGMP) by manufacturers or poor handling by wholesalers/retailers. The study therefore recommends effective post marketing surveillance and enforcement of cGMP by the concerned regulatory agency in Nigeria.

Keywords: *Bioequivalence, ciprofloxacin, quality, GMP, drug faking, and infectious diseases*

Résumé

Contexte: Le nombre de marques de chlorhydrate de ciprofloxacine sur le marché nigérian ne cesse d'augmenter; par conséquent, il est nécessaire d'établir leur bioéquivalence dans l'intérêt de la santé publique. Cette étude a évalué le profil chimique, biopharmaceutique et microbiologique de trente marques de comprimés de ciprofloxacine (500 mg) sur le marché nigérian.

Méthode: Les paramètres de qualité évalués comprennent l'uniformité du poids, l'épaisseur et le diamètre, la dureté, la friabilité, la désintégration, la dissolution, l'identité et le profil antibactérien. La teneur en ingrédients actifs a été déterminée par une méthode HPLC légèrement modifiée et validée.

Résultats: Les résultats des tests d'épaisseur, de diamètre et de dureté de toutes les marques se situaient dans des limites acceptables. Le pourcentage de marques dans la plage acceptable pour l'uniformité du poids, la friabilité, la désintégration, la dissolution et l'ingrédient actif est de 86,67, 96,67, 93,33, 26,67 et 93,33% respectivement. Environ 87% de la version générique testée de la ciprofloxacine a démontré une bioéquivalence antibactérienne in vitro avec le médicament de référence. Le faible taux de dissolution abyssal de 26,67% est une source de préoccupation car il suggère une mauvaise biodisponibilité potentielle de l'ingrédient actif de ces médicaments.

Conclusion: L'échec d'une grande partie des marques testées peut être dû à une contrefaçon délibérée, à un échec des bonnes pratiques de fabrication actuelles (cGMP) par les fabricants ou à une mauvaise manipulation par les grossistes / détaillants. L'étude recommande donc une surveillance post-commercialisation efficace et l'application des BPF par l'organisme de réglementation concerné au Nigéria.

Mots clés: *Bioéquivalence, ciprofloxacine, qualité, BPF, contrefaçon de médicaments et maladies infectieuses*

Introduction

The Global Burden of Disease Study (GBDS), in the year 2000, estimated that infectious diseases (IDs)

Correspondence: Dr. Olufunmilayo E. Adejumo, Department of Pharmaceutical and Medicinal Chemistry, Olabisi Onabanjo University, Sagamu, Nigeria. E-mail: funmilayo@yahoo.co.uk.

were responsible for the 22% of all deaths and 27% of disability-adjusted life years (DALY) globally [1]. Since 2010, the pace of decline in global age-standardised DALY rates has accelerated in age groups younger than 50 years compared with the 1990–2010 period, with the greatest annualised rate of decline occurring in the 0–9-year age group. However, six infectious diseases (lower respiratory infections, diarrhoeal diseases, malaria, meningitis, whooping cough, and congenital syphilis) were among the top ten causes of DALYs in children younger than 10 years in 2019 [2]. Therapeutic agents that have been used against various infectious agents include antibiotics, antivirals, antifungals, antimalarials and antiprotozoal. Antibiotics are drugs of choice in the fight against bacterial infections. The different classes of antibiotics include β-lactam, quinolones, macrolides, tetracyclines, aminoglycosides, sulfonamides, phenicols, and others.

Fluoroquinolones (quinolones derivatives) have the largest market share of global antibiotics market after β-lactams [3]. The approved fluoroquinolones available in various brands and generic forms in the USA and Nigeria include ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, ofloxacin, and norfloxacin. Ciprofloxacin, a synthetic antibiotic is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid while Ciprofloxacin hydrochloride is the monohydrochloride monohydrate salt of ciprofloxacin [4-6].

Ciprofloxacin (CIP) (A) is a fluoroquinolone with fluorine at position 6 of naphthyridine ring. The broad spectrum of CIP against both gram-negative and gram-positive pathogens has been attributed to the presence of the fluorine atom [7-9]. CIP is indicated for bacterial infections like gonorrhea, gonococcal urethritis and the vaginal/urethral discharge syndrome, urinary tract infections (UTIs), acute uncomplicated cystitis in females, chronic bacterial prostatitis, lower respiratory tract infections, acute exacerbations of chronic bronchitis and complicated intra-abdominal infections [10-15].

The CIP innovator brand, Ciproxin, was introduced into the Nigerian health care system by the Bayer® group. However, due to the high cost of the drug, its continuous presence in the Nigerian pharmaceutical space was not sustainable [16, 17]. The quest to lower costs of health care has resulted in a tremendous increase in the use of generic drug products. This subsequently contributed to the rapid influx of multi-source ciprofloxacin hydrochloride tablets, mostly from Asian countries, into the Nigerian market [18]. Much as the health care cost was lowered sequel to the substitution of generic drugs for brand name products, it is sufficient to say that it was not unaccompanied with the incident of fake and substandard drug scenario.

The circulation of drugs with poor quality in terms of their being substandard, spurious, falsely labeled, falsified or counterfeit, has become an issue of public health concern as such drugs can jeopardize patient safety leading to treatment failure, development of drug resistance, increased morbidity and mortality, and a waste of financial resources [19]. Though, the incident of fake and substandard drugs had been known to be prevalent in the low and middle-income economy, however, recent data from WHO Global Surveillance and Monitoring System indicated that the problem is becoming global. For instance, between 2013 and 2017, it was documented that the percentage of reports for substandard and falsified medical products from African, European, Americas, West Pacific, Eastern Mediterranean, and South-East Asia WHO regions were 42, 21, 21, 8, 6 and 2 % respectively [20].

Given the cosmopolitan nature of fake and counterfeit drugs, Giri et al. [21] opined that routine laboratory testing of drug samples from the supply market is needed to protect public health, especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services. In this connection, various studies have reported on the quality assessment of Ciprofloxacin in Saudi Arabia [22], Kenya [23], Ethiopia [24] and Nigeria [25-29]. In all these studies the number of CIP brands assessed ranged between three and twenty. However, given that forty-six brands of CIP have been registered by NAFDAC-the Nigerian drug regulatory body, as at the year 2018 [30], not to talk of plethora of many unregulated brands which have flooded the Nigerian pharmaceutical market, it is important to assess a larger sample size of CIP across various locations to have a fair representation of the true status of CIP circulating in the Nigerian market. This study therefore, reports on the chemical, biopharmaceutical and microbiological profile of thirty brands of Ciprofloxacin tablets in the Nigerian market.

Materials and methods

Materials

Thirty different brands of ciprofloxacin tablets with label strength of 500 mg containing ciprofloxacin hydrochloride USP were purchased from registered pharmacies sale outlets in three southwestern states of Nigeria: Lagos, Ogun, and Oyo. Each brand was assigned a code number. The NAFDAC number, manufacturing, and expiry dates of all the products

were recorded as shown in table 1. Ciprofloxacin hydrochloride (99.4%) reference standard was kindly donated by Fidson Healthcare, Lagos, Nigeria. It was used without further purification. The study was performed within the expiration dates of all the drugs. *Staphylococcus aureus* ATCC 25923 was obtained from the Department of Medical Microbiology, University College Hospital, Ibadan. Clinical isolates of *Escherichia coli*, *Staphylococcus aureus, Pseudomonas aeruginosa, Listeria monocytogenes,* and *Salmonella typhi* were obtained from Olabisi Onabanjo Teaching Hospital, Sagamu, Nigeria. These microorganisms were highly prevalent pathogens in most communities in Nigeria.

The chemicals and reagents used in this study include: HPLC grade acetonitrile, methanol, methylene chloride, ammonia, and phosphoric acid (BDH, UK). Double distilled and deionized water (DDDW) obtained in-house from Pharmaceutics and Pharmaceutical Technology Laboratory of Olabisi Onabanjo University, Sagamu was used for the study. All solvents were filtered through membrane filter (Durapore, 0.2 μm, Ireland) and degassed before use.

The following instruments and equipment were used for this study: OHAUS Analytical Weighing Balance, Ketan Tablet Hardness Tester (Sumbim; India), Ketan Tablets Disintegration Test Apparatus (Sumbim; India), and DBK Friability Tester Apparatus (England). Others were, Agilent 1260 HPLC equipped with a C-18 (Shimpack-ODS; 250 x 4.6 mm; 5 μ particle size) column, coupled to UV-Vis detector (Linear) and Hewlett Packard desktop computer for easy data analysis. The mobile phase used was a mixture of water, acetonitrile, and phosphoric acid (800:200:2). Also, a UV/VIS spectrophotometer, T90+ (PG Instruments Limited, UK) and Copley Scientific Dissolution tester (DIS 6000, UK).

Methods

The various tests were carried out based on the Pharmacopoeial specifications: British Pharmacopoeia (BP) [31] and United States Pharmacopoeia (USP) [32].

Physical and Physicochemical Quality Tests

Uniformity of weight, diameter, and thickness, as well as hardness and friability tests were evaluated using British Pharmacopoeia methods [31].

Weight Uniformity test

Twenty (20) tablets of each brand were taken and weighed individually using Ohaus Analytical digital weighing balance and the average weight was determined. The deviation of individual tablet weights from the mean weight was determined by subtracting the mean weight from the individual weight and dividing by the mean weight.

Diameter and thickness test

Uniformity of diameter and thickness of ten tablets was determined with a micrometer screw gauge. In the process of the measurement, it was ensured that the tablet does not break or get chipped. The average diameter and standard deviations were determined.

Hardness test

Hardness test was done by placing one tablet between the fixed and a moveable jaw of a Ketan Hardness Tester machine. Pressure was then applied by turning the knurled knot just enough to hold the tablet in position. The pressure was increased afterwards as uniformly as possible until the tablet breaks. The pressure required to break the tablet was then read off the machine and recorded. Ten tablets of each brand were evaluated. The mean and standard deviation were subsequently determined.

Friability test

Friability test was done by weighing and placing ten tablets into automated DBK Friabillator (England). The drum was set in motion for 25 revolutions per minute for a total of 4 minutes and the tablets were removed, dusted, and reweighed to the nearest milligram. The friability of the tablets was calculated using the following expression:

% Friability = [(Initial Weight-Final Weight)/Initial Weight] x 100

Disintegration time test

The disintegration time test of randomly selected six tablets of each brand was carried out according to the specifications of British Pharmacopoeia [31]. The disintegration medium was 0.1 N HCI, maintained at 37 ± 0.5°C. Six tablets from each batch were used for the test using Ketan Tablet Disintegration test apparatus. The disintegration time was taken as the mean time needed for the tablets to break into particles small enough to pass through the screen into the disintegration medium.

Dissolution test

The dissolution study was carried out according to BP specifications using Erweka-D dissolution test apparatus (Erweka, U.K.) [31]. Vessels consisting of 900 mL of water as the dissolution medium were employed. The vessels were added to a circulating water bath maintained at 37 ± 0.5°C and allowed to

equilibrate. Once the desired temperature was attained, the tablets were added to the center bottom of the vessel and the paddle was rotated at 50 rpm. Ten milliliter (10 mL) samples of the dissolution medium were withdrawn from each vessel using a syringe after 5, 10, 20, 30, 45 and 60 minutes and an equivalent amount of the dissolution medium was immediately introduced as a replacement. The samples were filtered and suitably diluted with the dissolution medium. The concentrations were determined by measuring the absorbance at 276 nm using a UV/VIS spectrophotometer, T92+ PG Instruments (UK). The content of ciprofloxacin hydrochloride in each sample was determined based on the calibration curve generated at a wavelength of 276 nm. The regression equation for the calibration curve was. $y=14.34x + 0.412$, $r^2=0.980$.

The amounts of dissolved ciprofloxacin at 30 and 45 minutes were obtained for each brand using the standard curve as all the necessary corrections for dilution were made when calculating the amount of drug released.

Chemical quality tests

Identity test

Identity test was carried out using B.P. guidelines [31]. The identity of the drug was confirmed by high performance thin layer chromatography (HPTLC) with silica gel G60 F_{254} pre-coated (10 x 20) cm obtained from Merck (UK). The mobile phase was a mixture of methanol, methylene chloride, ammonia and acetonitrile (40:40:20:10). A test solution of 0.05 % w/v was prepared by mixing 750 mL of water with powdered tablets of ciprofloxacin equivalent to 2 g of ciprofloxacin in ultrasonic bath for 20 minutes and further diluted to 1000 mL.

A standard solution of ciprofloxacin hydrochloride was prepared by dissolving 58 mg with 100 ml of the mobile phase. A third solution, which was a 1:1 mixture of the reference and test solution, was prepared. A 10 µL of each of the solutions was applied separately as bands on pre-coated silica gel plate. The plates were placed in a suitable chromatographic chamber and the chromatogram was developed using the aforementioned solvent system. The plate was removed after the solvent has moved about three-fourth of the plate. The plate was dried in air for 15 minutes and examined under UV-light. The distance of each spot from the point of origin was marked with a pencil, measured, and recorded. The retention factor (R_f) value was calculated using the following expression.

R_f = Distance travelled by the substance from the origin/distance travelled by the solvent from the origin

Active content (ciprofloxacin hydrochloride) assay

HPLC Chromatographic conditions and preparation of mobile phase.

The HPLC system (Agilent Technologies 1260), equipped with a C-18 (Shimpack-ODS; 250 x 4.6 mm; 5 µ particle size) column was used for the chromatographic separations of the analytes. The analyte detection was performed using UV-Vis detector (Linear). All were coupled to a Hewlett Packard desktop computer to control the system and for easy data analysis. The mobile phase was a mixture of water, acetonitrile, and phosphoric acid (800:200:2). The HPLC system was operated in isocratic mode at a flow rate of 1.5 mL/min. During standard/sample run, column was kept at room temperature. Detection was made at the wavelength maximum of 278 nm. The injection volume was 20 µL.

Preparation of standards

Five milligrams (5 mg) of reference standard ciprofloxacin powder were accurately weighed and diluted with 5 mL of deionized water to obtain 1 mg/mL stock solution. Standard solutions of 5, 10, 25 and 50 µg/mL concentrations were prepared from this stock solution. All the solutions were filtered through 0.20 µm filter paper before injection into the HPLC column.

Preparation and assay of sample solutions

Twenty tablets of each brand of ciprofloxacin tablets to be used were ground to powder. A weight equivalent to 5 mg of ciprofloxacin for each brand, calculated based on the label claim, was taken and dissolved in 5 mL of deionized water to obtain 1 mg/mL stock solution. The solution was sonicated for 20 minutes and filtered. A working solution for each brand containing 100 µg/mL of ciprofloxacin was prepared from the filtrate and the peak area of the resulting solution determined at 276 nm using HPLC. The solutions were made ready in the sample vials which were injected to the system at intervals. The assays were repeated three times and the results presented were the mean of the three determinations. The active content of each sample was calculated from the peak areas of the chromatograms of the test and reference standard solutions. The regression equation for the calibration curve was. $y=104.8x + 225.0$, $r^2=0.999$

Microbiological assay

A ciprofloxacin tablet (500 mg) of respective brand was dissolved in 10 mL DDDW. This was suitably diluted to obtain a concentration of 50 µg/mL solution which was subsequently used for microbiological assay. Muller-Hinton agar medium was prepared and sterilized according to the manufacturer's

Table 1: Detailed information on thirty brands of ciprofloxacin hydrochloride tablets evaluated for quality.

Brand code	Country of manufacture	Prod. Date	Exp. Date	Batch no.	NAFDAC no.
CPX1	CHINA	03/14	03/17	140322	B4-1918
CPX2	INDIA	09/14	08/14	TP104	A4-8435
CPX3	INDIA	03/14	02/17	14ET05	B4-1287
CPX4	INDIA	03/16	02/19	360191	04-3202
CPX5	INDIA	12/15	11/18	T5L028	B4-5881
CPX6	INDIA	07/15	06/18	VG1508	04-0723
CPX7	INDIA	03/16	0219	ET- 058	B4-5060
CPX8	INDIA	06/14	05/17	EUR 404	A4-8224
CPX9	CHINA	07/14	07/17	1407103	B4-0029
CPX10	CHINA	01/15	12/17	111	04-9612
CPX11	INDIA	01/16	12/18	CR 602	B4- 5333
CPX12	NIGERIA	11/15	10/20	3721J	04-4699
CPX13	INDIA	12/14	11/17	4385	B4-3322
CPX14	CHINA	11/13	11/16	13112	04-5856
CPX15	CHINA	12/14	12/17	141220	B4-3485
CPX16	NIGERIA	10/15	09/19	15101102	A4-6601
CPX17	NIGERIA	12/15	11/18	SPS029B	04-2107
CPX18	CHINA	10/14	10/17	143121027	A3-7780
CPX19	INDIA	03/15	03/19	E-511	04-3221
CPX20	INDIA	01/14	12/16	16A14003	04-2307
CPX21	NIGERIA	04/14	03/17	5640556	04-2170
CPX22	NIGERIA	10/14	11/18	GH4001	B4-3148
CPX23	CHINA	04/14	04/17	14042001	04-4950
CPX24	INDIA	12/15	11/18	CNXT1502	04-3002
CPX25	CHINA	06/14	06/17	140615	A4-0482
CPX26	INDIA	07/14	06/18	ECFT-001	04-4061
CPX27	CHINA	12/13	10/16	18115118	04-6340
CPX28	NIGERIA	10/15	09/18	15029	04-567
CPX29	INDIA	06/15	05/18	1135010	B4-3835
CPX30	INDIA	O9/15	08/19	5258	04-5351

Prod. Date=Production Date; Exp. Date=Expiry Date; Batch no.= Batch number.
NAFDAC no.= National Agency for Food and Drug Administration and Control number.

specification and kept in molten form in 20 mL portions. Thereafter, the preparation of the seeded agar was done by transferring 0.1 mL of the microbial suspension of the test organism into sterile Petri-Plate before mixing it with molten agar at 45^{0}C. After thorough mixing, the plate was allowed to set. Cork-borer was then used to bore holes in 6 sectors of the plate and labeled accordingly. Into each cup, 100 µL of 50 µg/mL of ciprofloxacin HCL was added to its corresponding cup. Then a pre-diffusion time of thirty minutes was allowed before incubation at 37˚C for 24 h. The diameter of the zones of inhibition was measured in mm and interpreted as susceptible (≥ 21 mm), intermediate (16 - 20 mm) or resistant (d" 15 mm) according to CLSI [33] interpretative chart guidelines. The CLSI cut off for Salmonella typhi are susceptible (≥ 31 mm), intermediate (21 - 30 mm) or resistant (≤ 20 mm).

Statistical analysis

Data obtained were expressed as means ± standard deviation. Analysis of variance was carried out on the data obtained to determine the significance of differences. A two-tailed P value of less than 0.01 was considered to be statistically significant. Values that were significantly differ-ent were separated using the Duncan Multiple Range test using SPSS for Windows Version 17.0 statistical package.

Results and discussion

The physical parameters such as weight uniformity, thickness, diameter, hardness, and friability of thirty brands of the selected thirty brands of ciprofloxacin hydrochloride are shown in Table 2. Results for weight uniformity test showed that twenty-six (86.7%) out of the thirty evaluated brands were

Table 2: Weight uniformity, thickness, diameter, hardness, and friability of thirty brands of ciprofloxacin hydrochloride tablets evaluated for quality.

Brand code	Weight Uniformity (mg) (n=20)	Thickness (mm) (n=10)	Diameter (mm) (n=10)	Hardness (Kg/cm^2) (n=10)	Friability (%) (n=10)
CPX1	0.8923 ± 4.8000^{b}	4.09 ± 0.02^{b}	8.03 ± 0.02^{b}	13.8 ± 0.10^{a}	0.0593 ± 0.0044^{e}
CPX2	1.0079 ± 7.7000^{a}	6.55 ± 0.01^{a}	9.34 ± 0.03^{a}	4.2 ± 0.10^{e}	0.1312 ± 0.0045^{d}
CPX3	0.7739 ± 7.7900^{b}	5.72 ± 0.01^{a}	9.35 ± 0.02^{a}	9.8 ± 0.30^{c}	0.5367 ± 0.0091^{b}
CPX4	1.0217 ± 0.0100^{a}	6.52 ± 0.02^{a}	10.41 ± 0.04^{a}	13.0 ± 0.00^{a}	0.0242 ± 0.0010^{f}
CPX5	0.6776 ± 0.0700^{bc}	5.37 ± 0.02^{a}	8.69 ± 0.02^{b}	13.8 ± 0.20^{a}	0.0124 ± 0.0009^{f}
CPX6	0.8002 ± 0.0600^{b}	5.51 ± 0.03^{a}	6.37 ± 0.01^{c}	15.0 ± 0.00^{a}	0.0271 ± 0.0012^{f}
CPX7	0.7713 ± 0.0300^{b}	6.48 ± 0.04^{a}	8.52 ± 0.02^{b}	14.4 ± 0.10^{a}	0.1254 ± 0.0011^{d}
CPX8	0.7774 ± 0.1000^{b}	4.49 ± 0.01^{b}	7.38 ± 0.01^{b}	13.0 ± 0.20^{a}	0.0040 ± 0.0002^{g}
CPX9	0.7338 ± 2.2300^{b}	4.58 ± 0.01^{b}	8.65 ± 0.02^{b}	8.2 ± 0.10^{c}	0.0965 ± 0.0031^{e}
CPX11	0.6781 ± 0.0900^{bc}	4.77 ± 0.02^{b}	8.61 ± 0.03^{b}	8.4 ± 0.20^{c}	0.0815 ± 0.0042^{e}
CPX10	0.6618 ± 12.5700^{bc}	5.64 ± 0.02^{a}	7.07 ± 0.01^{b}	15.0 ± 0.00^{a}	0.0929 ± 0.0061^{e}
CPX12	0.7600 ± 0.0900^{b}	4.32 ± 0.01^{b}	7.51 ± 0.01^{b}	9.0 ± 0.20^{c}	1.5615 ± 0.0117^{a}
CPX13	0.7026 ± 0.1100^{b}	3.28 ± 0.02^{c}	7.75 ± 0.02^{b}	10.2 ± 0.30^{b}	0.0047 ± 0.0005^{f}
CPX14	0.6743 ± 0.1200^{bc}	4.53 ± 0.01^{b}	7.56 ± 0.02^{b}	12.2 ± 0.20^{b}	0.0419 ± 0.0016^{f}
CPX15	0.8249 ± 5.4000^{b}	5.01 ± 0.03^{a}	8.95 ± 0.02^{b}	14.0 ± 0.00^{a}	0.0565 ± 0.0021^{e}
CPX16	0.8061 ± 0.0900^{b}	3.39 ± 0.01^{c}	7.53 ± 0.01^{b}	13.6 ± 0.10^{a}	0.0244 ± 0.0015^{f}
CPX17	0.6127 ± 0.0200^{bc}	3.34 ± 0.01^{c}	6.35 ± 0.01^{c}	14.2 ± 0.10^{a}	0.2715 ± 0.0081^{c}
CPX18	0.8000 ± 0.2400^{b}	4.20 ± 0.01^{b}	8.90 ± 0.02^{b}	11.6 ± 0.20^{b}	0.0801 ± 0.0013^{e}
CPX19	0.6392 ± 0.0500^{bc}	4.89 ± 0.02^{b}	6.25 ± 0.02^{c}	10.8 ± 0.10^{b}	0.0237 ± 0.0009^{f}
CPX20	0.6451 ± 0.0300^{bc}	2.55 ± 0.01^{d}	10.52 ± 0.04^{a}	8.2 ± 0.10^{c}	0.0493 ± 0.0041^{f}
CPX21	0.9311 ± 0.0200^{a}	4.39 ± 0.02^{b}	8.31 ± 0.02^{b}	14.0 ± 0.00^{a}	0.1695 ± 0.0013^{d}
CPX22	0.6636 ± 0.0800^{bc}	3.53 ± 0.01^{c}	7.26 ± 0.01^{b}	11.6 ± 0.20^{b}	0.0999 ± 0.0031^{e}
CPX23	0.8098 ± 0.0400^{b}	4.21 ± 0.02^{b}	8.79 ± 0.02^{b}	12.2 ± 0.20^{b}	0.0393 ± 0.0033^{f}
CPX24	0.8023 ± 2.9500^{b}	5.03 ± 0.02^{a}	7.70 ± 0.01^{b}	14.2 ± 0.10^{a}	0.0267 ± 0.0004^{f}
CPX25	0.8725 ± 0.0900^{b}	4.42 ± 0.01^{b}	8.72 ± 0.02^{b}	12.8 ± 0.10^{b}	0.0408 ± 0.0018^{f}
CPX26	0.9653 ± 0.0500^{a}	5.28 ± 0.01^{a}	7.49 ± 0.02^{b}	7.6 ± 0.10^{d}	0.1127 ± 0.0061^{d}
CPX27	0.7478 ± 0.0500^{b}	4.86 ± 0.02^{b}	7.53 ± 0.01^{b}	10.4 ± 0.10^{b}	0.0423 ± 0.0021^{f}
CPX28	0.5759 ± 0.3300^{c}	5.36 ± 0.03^{a}	10.89 ± 0.02^{a}	4.0 ± 0.00^{e}	0.2868 ± 0.0201^{c}
CPX29	0.7375 ± 0.0800^{b}	5.30 ± 0.02^{a}	10.50 ± 0.03^{a}	15.0 ± 0.00^{a}	0.1095 ± 0.0068^{d}
CPX30	0.6814 ± 0.1000^{bc}	5.25 ± 0.02^{a}	10.61 ± 0.01^{a}	$12.0 \pm 0.20^{b.}$	0.0328 ± 0.0022^{f}

Values are mean ± standard deviation. Within a column, values with different superscripts are significantly different ($p < 0.01$).

within the acceptable limit as none of them deviated by up to 5% from the mean value as stipulated by the B.P. [31]. On the contrary, products with brand codes CPX 2, CPX 3, CPX 11, and CPX 15 failed the weight uniformity test. The uniformity of weight is a good indicator of good manufacturing practice (GMP), as weight variation aside other components obviously reflects variation in the content of active ingredient, which in turn varies the therapeutic activity of the drug. The significance of this test is to verify that the tablets in each batch falls within the appropriate size range. Hence, 86.7% conformity was observed in this study for weight uniformity. This value is lower than the 100% conformity reported by two previous Nigerian studies: who evaluated seven and ten brands of CIP respectively [24, 27]. It has been suggested that non-uniformity in weight of pharmaceutical products could be attributed to uneven feeding of granules into the die or irregular movement of the lower punch producing a die space of varying capacity [34]. This may have been responsible for the failure of the four brands which failed the weight uniformity test. It was documented that by the end of the year 2018, NAFDAC, the Nigerian food and drug regulatory body, had approved about forty-six brands of CIP. The result of the present study underscores the need to test larger population size of these approved brands in the course of post market surveillance testing for the interest of public health.

Table 2 shows that the range of diameter and thickness of the evaluated thirty brands were 6.25 – 10.89 mm and 2.55 – 6.55 mm, respectively.

Table 3: Drug release profiles of thirty brands of ciprofloxacin hydrochloride tablets evaluated for quality.

Brand code	Drug released (%) @ 30 minutes	@ 45 minutes
CPX1	82.46[a]	89.99[a]
CPX2	18.03[g]	23.03[f]
CPX3	81.20[a]	93.87[a]
CPX4	28.94[e]	39.65[d]
CPX5	16.12[g]	16.20[f]
CPX6	61.06[b]	64.15[b]
CPX7	26.55[f]	30.85[e]
CPX8	42.18[d]	42.32[d]
CPX9	29.30[e]	29.45[e]
CPX10	25.70[f]	28.38[e]
CPX11	68.45[b]	80.98[a]
CPX12	35.92[e]	35.92[e]
CPX13	36.97[e]	38.59[e]
CPX14	52.68[c]	76.13[b]
CPX15	48.24[d]	65.63[b]
CPX16	60.77[b]	70.56[b]
CPX17	77.11[a]	93.52[a]
CPX18	48.03[d]	56.69[c]
CPX19	61.90[b]	63.24[b]
CPX20	26.13[f]	30.14[e]
CPX21	60.14[b]	70.99[b]
CPX22	24.15[f]	28.80[e]
CPX23	43.73[d]	50.14[c]
CPX24	36.83[e]	55.70[c]
CPX25	33.59[e]	35.99[e]
CPX26	41.27[d]	45.70[d]
CPX27	51.34[c]	53.59[c]
CPX28	64.15[b]	75.21[b]
CPX29	24.65[f]	32.04[e]
CPX30	41.97[d]	46.20[d]

Values are mean ± standard deviation. Within a column, values with different superscripts are significantly different ($p < 0.01$).

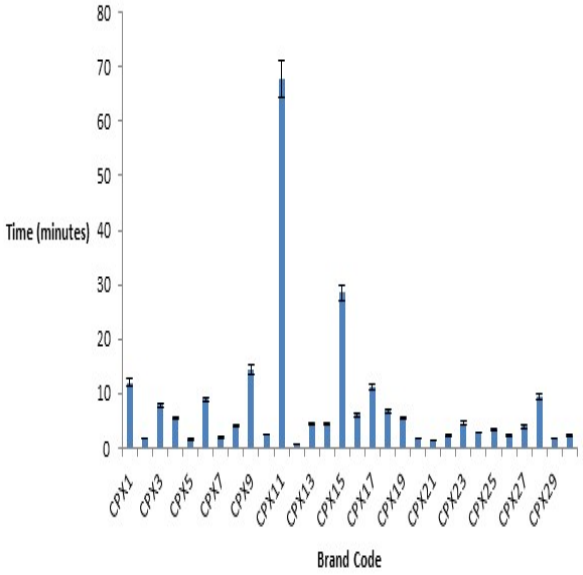

Fig. 1: Bar chart showing Disintegration time of the different brands of ciprofloxacin hydrochloride tablets.

It is interesting to note that for all the brands assessed, the average diameter and thickness varied within 5% of the mean values which is in accordance with the USP requirement [32]. Similarly, none of the brand possessed hardness value of less than 4 Kg/cm^2, as the hardness values of the thirty brands ranged between 4.0 and 15.0 Kg/cm^2. Osadebe and Akabuogu opined that variations in hardness could be due to differences in formulation's excipients, techniques and compressional forces employed by different manufacturers [35]. The wide variation in the hardness values of the brands evaluated in this study may be a reflection of these factors among the different manufacturers of the evaluated products. The USP and BP recommend 4-6 Kg/cm^2 as ideal force required to break pharmaceutical tablets. Hardness/crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. It has the potential of influencing other parameters like friability and disintegration. The one hundred percent conformity recorded for hardness testing in the present study is comparable to those documented by Adegbolagun *et al*. and Ahmad *et al*. [26, 22]. However, a conformity rate of about 60% was observed by Okonkwo *et al*. and Mu'az *et al*. [25, 27].

Results for friability (%) of the evaluated thirty brands of CIP tablets are as shown in Table 2. All the tested brands, except CPX12, gave friability test results much less than 1% specified by the BP [31]. Friability test is an indicator of pharmaceutical tablets to resist abrasion, breakage and chipping under conditions of storage, transportation and handling. Virtually, all the tested brands had impressive friability values, with the exception of CPX12. The % friability range obtained in the present study was 0.0047 -1.56 and this compares favourably with 0.014 - 0.160 , (n=5); 0.000 - 0.710, (n=10); 0.170 - 0.710, (n=7) and 0.110 - 0.310, (n=3) reported by Okonkwo *et al.*, Adegbolagun *et al.*, Mu'az *et al.* and Ahmed *et al*. respectively [25-27, 22].

The results of the disintegration test are shown in a bar chart in Figure 1. The values ranged between 0.77 and 67.88 minutes. Twenty-eight out of thirty brands met the BP [31] requirement of maximum of fifteen minutes stipulated for disintegration of uncoated pharmaceutical tablets. In this regard, brands CPX11 and CPX15 failed the test.

Table 4: Retention factor (R_f) values and active ingredient contents of thirty brands of ciprofloxacin hydrochloride tablets evaluated for quality.

Brand code	Retention factor	Active ingredient (Ciprofloxacin hydrochloride)			
		Label claim (mg)	Drug content (mg)	Percentage label claim	Percentage content deviation
CPX1	0.80[a]	500[a]	524.68[b]	104.94[b]	+4.94[b]
CPX2	0.80[a]	500[a]	480.65[e]	96.13[c]	-3.87[c]
CPX3	0.80[a]	500[a]	498.75[d]	99.75[c]	-0.25[c]
CPX4	0.80[a]	500[a]	493.30[d]	98.66[c]	-1.34[c]
CPX5	0.79[a]	500[a]	497.72[d]	99.54[c]	-0.46[c]
CPX6	0.78[ab]	500[a]	524.40[b]	104.88[b]	+4.88[b]
CPX7	0.78[ab]	500[a]	524.87[b]	104.97[b]	+4.97[b]
CPX8	0.78[ab]	500[a]	514.62[c]	102.92[b]	+2.92[b]
CPX9	0.78[ab]	500[a]	501.21[c]	100.24[b]	+0.24[b]
CPX10	0.78[ab]	500[a]	494.11[d]	98.82[c]	-1.18[c]
CPX11	0.78[ab]	500[a]	509.68[c]	101.94[b]	+1.94[b]
CPX12	0.77[b]	500[a]	511.23[c]	102.25[b]	+2.25[b]
CPX13	0.78[ab]	500[a]	510.43[c]	102.09[b]	+2.09[b]
CPX14	0.77[b]	500[a]	506.30[c]	101.26[b]	+1.26[b]
CPX15	0.77[b]	500[a]	515.60[c]	103.12[b]	+3.12[b]
CPX16	0.78[ab]	500[a]	478.43[e]	95.69[c]	-4.31[c]
CPX17	0.77[b]	500[a]	485.15[e]	97.03[c]	-2.97[c]
CPX18	0.76[b]	500[a]	513.34[c]	102.67[b]	+2.67[b]
CPX19	0.76[b]	500[a]	522.55[b]	104.51[b]	+4.51[b]
CPX20	0.76[b]	500[a]	505.89[c]	101.18[b]	+1.18[b]
CPX21	0.76[b]	500[a]	515.37[c]	103.07[b]	+3.07[b]
CPX22	0.76[b]	500[a]	513.54[c]	102.71[b]	+2.71[b]
CPX23	0.76[b]	500[a]	499.98[d]	99.99[c]	-0.01[c]
CPX24	0.76[b]	500[a]	431.19[b]	86.24[d]	-13.76[d]
CPX25	0.74[c]	500[a]	504.00[c]	100.80[b]	+0.80[b]
CPX26	0.77[b]	500[a]	524.13[b]	104.83[b]	+4.83[b]
CPX27	0.76[b]	500[a]	510.72[c]	102.14[b]	+2.14[b]
CPX28	0.76[b]	500[a]	495.93[d]	99.19[c]	-0.81[c]
CPX29	0.77[b]	500[a]	512.46[c]	102.49[b]	+2.49[b]
CPX30	0.80[a]	500[a]	568.95[a]	113.79[a]	+13.79[a]

R_f value of the reference standard =0.81
Values are mean ± standard deviation. Within a column, values with different superscripts are significantly different ($p < 0.01$).

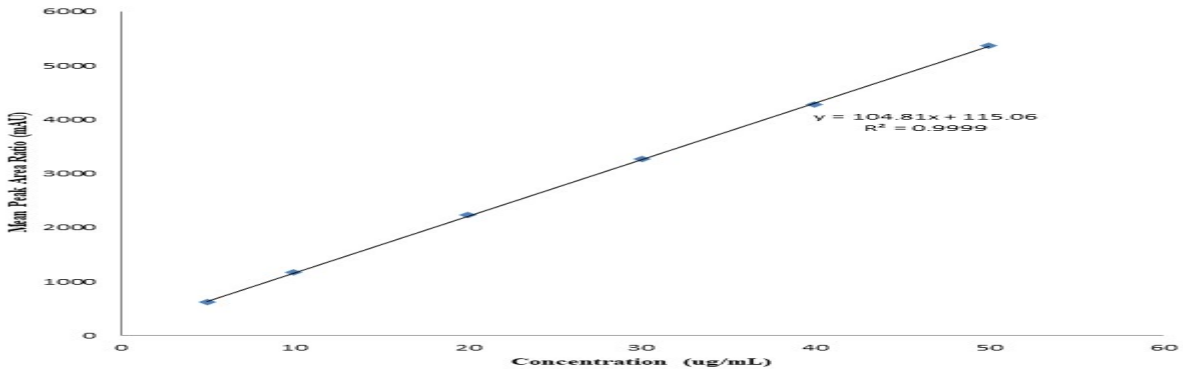

Fig. 2: Graph showing the calibration curve of Ciprofloxacin standard.

Table 5: Antibacterial activity profiles of thirty brands of ciprofloxacin hydrochloride tablets evaluated for quality.

Brand code	Test Microorganisms					
	A	B	C	D	E	F
Reference standard	S	S	S	S	S	S
CPX1	S	S	S	S	S	S
CPX2	S	S	S	S	S	S
CPX3	S	S	S	S	S	S
CPX4	S	S	S	S	S	S
CPX5	S	S	S	S	S	S
CPX6	S	S	S	S	S	S
CPX7	S	S	S	S	S	S
CPX8	S	S	S	S	S	S
CPX9	S	S	I	I	I	S
CPX10	S	S	S	S	S	S
CPX11	S	S	S	S	S	S
CPX12	S	S	S	S	S	S
CPX13	S	S	S	S	S	S
CPX14	S	S	S	S	S	S
CPX15	S	S	S	S	S	S
CPX16	S	S	S	S	S	S
CPX17	S	S	S	S	S	S
CPX18	S	S	S	S	S	S
CPX19	S	S	S	S	S	S
CPX20	S	S	S	S	S	S
CPX21	S	S	S	S	S	S
CPX22	S	S	S	S	S	S
CPX23	S	I	S	S	S	S
CPX24	S	S	S	S	S	S
CPX25	S	S	S	S	S	S
CPX26	S	S	S	S	S	S
CPX27	S	S	S	S	S	S
CPX28	S	S	S	S	S	S
CPX29	S	I	S	S	S	S
CPX30	S	S	S	S	S	I

Key *A=Staphylococcus aureus* ATCC 25923, B=*Escherichia coli*, C=*Staphylococcus aureus, D=Pseudomonas aeruginosa, E= Listeria monocytogenes,* F= *Salmonella typhi*
Zone of inhibition for all the test organisms except *Salmonella typhi*: S=Susceptible (e" 21 mm) I= Intermediate (16 – 20 mm). Zone of inhibition for *Salmonella typhi* S=Susceptible (e" 31 mm) I= Intermediate (21 – 30 mm)

Except for these two brands, data from the present study compares favourably with 1.77 - 8.03, (n=5); 1.25 - 21.75, (n=10); 2.40 - 14.70, (n=7) and 2.00 - 4.00, (n=6) reported by Okonkwo *et al.,* Adegbolagun *et al*., Mu'az *et al*. and Kahsay and G/ Egziabher respectively [25 - 27, 24]. The disintegration test measures the time required for a tablet to disintegrate into particles when in contact with gastrointestinal fluids. This is a necessary condition and could be the rate-determining step in the process of drug absorption. The type and amount of excipients used in tablet formulation as well as the manufacturing process affect both the disintegration and dissolution parameters.

The percentage release of CIP at 30 minutes of dissolution (C_{30}) and 45 minutes of dissolution (C_{45}) are shown in Table 3. Eight brands (CPX1, CPX3, CPX11, CPX14, CPX16, CPX17, CPX21, and CPX28) passed the dissolution tests according to British Pharmacopoeia [30] specifications which stipulate that at least 70% of the content must have been released by 45 minutes, thus resulting in 26.67 % success rate. The C_{45} values for the tested thirty CIP brands ranged from 16.20 to 93.87 %. This is comparable to the range of 3.64 – 99.82 % reported by Adegbolagun *et al*. [26]. However, higher success rate of 50, 93.75 and 100 % have been reported by Adegbolagun *et al*., Joda *et al*. and Kahsay and G/

Egziabher respectively [26, 29, 24]. Dissolution rates have direct bearing on bioavailability profile of tablet dosage forms as it can be used to predict the drug release pattern *in vivo*. Kahsay and G/Egziabher [24] opined that products with different formulations, different inactive ingredients, and different formulation design may have different dissolution profiles or release characteristics and therefore may have different bioavailability. In the present study, the abysmal low dissolution success rate of 26.67 % compared with high disintegration success rate of 93.33% is a source of concern. This could suggest that the tested tablet dosage form disintegration characteristic did not have a direct correlation with bioavailability of the active ingredient. While dissolution tests under proper operating conditions provide valuable *in vitro* data for the development of pharmaceutical products, an indication of relative potential *in vivo* performance and means for quality control; it is clear that tablet disintegration time is in most cases, a poor guide to the biological availability of the drug [36, 37].

The results for the identity test of the drug samples are shown in Table 4. The retention factor (R_f) of the tested brands ranged from 0.74 to 0.80 while the value for the reference standard was 0.81. The results revealed that out of the tested thirty brands, twenty brands have R_f values that are within 5% deviation from the BP reference standard.

The HPLC method [32] used with slight modification to analyse the thirty samples of Ciprofloxacin tablets was validated and found to be linear, accurate and precise without interference from excipients. The retention time for ciprofloxacin elution in this study is 4.5-4.6 while an earlier study [23] reported 5.1 – 5.2 minutes using a mobile phase of 0.025 M phosphoric acid adjusted with triethylamine to a pH of 3.0 ± 0.1) and acetonitrile HPLC grade (87:13). The calibration curve for standard is shown in Figure 2.

Results for the mean percentage label claim of the different tested brands of ciprofloxacin 500 mg tablets included in the study are depicted in Table 4. The values ranged between 86.24 and 113.79 %. Based on the B.P. requirement which stipulates that the percentage drug content of the label claim must be between 95 and 105 % [30], twenty-eight (93.33 %) out of the tested thirty brands passed this test. In this regard, brands CPX24 and CPX30 failed the test and thus could be considered under dosage and over dosage respectively on administration. Based on [31], the percentage active ingredient data of 86.24-113.79 % obtained from the present study; compares favourably with 78.08 - 106.68, (n=5); 98.71 - 105.78, (n=6); 95.50 - 99.50, (n=3); 75 - 104, (n=16) reported by Okonkwo *et al*. [25], Kahsay and G/Egziabher [24], Ahmed *et al*. [22] and Joda *et al*. [29] respectively. An abysmal low dissolution rate of 26.67 % observed suggests a potential poor bioavailability of the active ingredient of these drugs.

The antibacterial activities of the tested CIP brands and the reference standard are shown in Table 5. At the tested concentration of 50 µg/mL solution, all the tested bacterial pathogens were susceptible to all the drugs apart from CPX9, CPX23, CPX29, and CPX30. Brand CPX9 demonstrated intermediate activity against both gram positive (*Staphylococcus aureus, Listeria monocytogenes*) and gram negative (*Pseudomonas aeruginosa*) bacteria. Also, the activities of CPX23 and CPX29 against *Escherichia coli* and CPX30 against *Salmonella typhi* were intermediate. Out of the tested drug samples, twenty-six (Š87%) generic versions demonstrated *in-vitro* antibacterial bioequivalence to the reference drug.

Conclusion

The observations in failed brands may be due to deliberate counterfeiting, failure of current good manufacturing practices (cGMP) by manufacturers or poor handling by wholesalers/retailers. Consequently, the authors recommend effective post marketing surveillance and enforcement of cGMP by the concerned regulatory agencies in Nigeria to guarantee the drugs' quality, efficacy and safety.

References

1. WHO in World Health Report, World Health Organization, Geneva. 2002.
2. Vos T, Lim SS, Abbafati C, Abass M, Abbasifard M *et al*. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019, The Lancet 2020; 396: 1204-1222.
3. Research and Markets. Antibiotics: Global markets to 2023. Available from*:* https://www.research andmarkets.com/research/k9z38f/global. Accessed 07/07/2020
4. Drusano GL, Standiford HC, Plaisance K, *et al*. Absolute oral bioavailability of ciprofloxacin. Antimicrob Agents Chemother 1986; 30: 444–446.
5. The Merck Index. 14th ed. Whitehouse station, NJ. Merck & Co., INC. 2006; pp.386, 1624,
6. "Ciprofloxacin Hydrochloride". The American Society of Health-System Pharmacists. Bethesda MD. Ciprofloxacin hydrochloride Drug

Information Available from: https://www.ncbi.nlm.nih.gov/mesh/68002939. Accessed 27/09/2020

7. Bertino J. The safety profile of the fluoroquinolones. Clin Ther 2000; 22:798-817
8. Samanidou V, Demetriou C and Papadoyannis I. Direct determination of four fluoroquinolones, enoxacin, norfloxacin, ofloxacin and ciprofloxacin, in Pharmaceuticals and blood serum by HPLC. Anal Bioanal Chem 2003; 375: 623-629.
9. Shi LW, Han S, Zhao YL and Guan XD. Safety Profile of Fluoroquinolones: analysis of Adverse Drug Reactions in Relation to Consumption data Using Pharmacovigilance Database in Hebei, China. Value in Health 2015; 18: A1–A307
10. Cipro (Ciprofloxacin): Uses, dosage, side effects, drug interactions, warning and precautions, overdosage and contraindications, clinical pharmacology, medication guide. Available from: https://www.rxlist.com/cipro-drug.htm Accessed 25/05/2021. Fasugba O, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired Escherichia coli urinary tract infections: a systematic review and meta-analysis of observational studies. BMC Infect Dis. 2015;15:545.
11. Kaplan YC and Koren G. Use of ciprofloxacin during breastfeeding. Can Fam Physician. 2015; 61(4):343-344. .
12. Kaguelidou F, Turner MA, Choonara I and Jacqz-Aigrain E. Ciprofloxacin use in neonates: a systematic review of the literature. Pediatr Infect Dis J. 2011; 30(2):e29-37.
13. Cozzani E, Chinazzo C, Burlando M, Romagnoli M and Parodi A. Ciprofloxacin as a Trigger for Bullous Pemphigoid: The Second Case in the Literature. Am J Ther. 2016; 23(5):e1202-1204.
14. Thai T, Salisbury BH and Zito PM. Ciprofloxacin. StatPearls Publishing LLC, 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535454/ Accessed 25/05/2021
15. Adepoju-Bello AA, Coker HAB and Abioye AO. Quinolones: A review. Nig J Pharm 2007; 40: 58-63.
16. Ngwuluka NC, Lawal K, Olorunfemi PO and Ochekpe NA. Post-market in vitro bioequivalence study of six brands of ciprofloxacin tablets/caplets in Jos, Nigeria. Scientific Research and Essay 2009; 4: 298-305.
17. Ilupeju TO, Oladeinde EO, Olaniyi AA and Amosu M. Bioequivalence study of multi-sourced (generic) co-trimoxazole tablets in human urine. In: Olaniyi AA, Babalola CP, Oladeinde EO, Adegoke AO Eds. Towards better quality assurance of Drugs in the 3rd Millennium-Biopharmaceutical methods in drug quality assurance. 1st ed. Ibadan, Nigeria: Omoade Printing Press, 2001.
19. Almuzaini T, Choonara I and Sammons H. Substandard and counterfeit medicines: A systematic review of the literature. BMJ 2013; 3: e002923. Available from: https://www.researchgate.net/publication/255975639_ [cited: 27th September 2020].
20. World Health Organization. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Geneva: World Health Organization, 2017.
21. Giri TK, Parveen N, Thakur D, *et al.* In vitro evaluation of commercially available enteric coated tablet containing diclofenac sodium. Int J Res Pharmaceut and Biomed Sci 2012; 3: 875-881.
22. Ahmed MM, Farhat F, Ansari MJ, *et al*. Equivalent assessment of Ciprofloxacin tablets Available in KSA: A post market surveillance study for cost effective treatment. J Pharm Sci Res 2016; 8: 13-18.
23. Minyeto D. *In Vitro* Comparative evaluation of the quality and pharmaceutical equivalence of selected generic ciprofloxacin hydrochloride tablet brands marketed in Kenya. M.Sc. Thesis. Kenya: University of Nairobi, 2014.
24. Kahsay G,G. and Egziabher AG. Quality assessment of the commonly prescribed antimicrobial drug, ciprofloxacin tablets, marketed in Tigray, Ethiopia. Momona Ethiopian J Sci 2010; 2: 93-107.
25. Okonkwo TJ, Afieroho EO, Odigwe A and Osadebe PO. Assessment of the quality control parameters of five brands of ciprofloxacin hydrochloride caplets in Nigeria. J Pharm Biores 2006; 3: 83-88
26. Adegbolagun OA, Olalade OA and Osumah SE. Comparative evaluation of the biopharmaceutical and chemical equivalence of some commercially available brands of ciprofloxacin hydrochloride tablets. Trop J Pharm Res 2007; 6: 737-745.
27. Mu'az J, Gazali LK, Sadiq GU and Tom GM. Comparative *in vitro* evaluation of the pharmaceutical and chemical equivalence of multi-source generic ciprofloxacin hydrochloride tablets around Maiduguri metropolitan area. Nig J Pharm Sci 2009; 8: 102-106.

28. Osonwa UE, Agboke AA, Amadi RC, Okorie O and Opurum CC. Bioequivalence studies on some selected brands of ciprofloxacin hydrochloride tablets in the Nigerian market with ciproflox® as innovator brand. J Appl Pharmaceut Sci 2011; 1: 80-84.
29. Joda AE, Tayo F and Aina BA. Quality Assessment of Ciprofloxacin Tablets Obtained From Community Pharmacies In Lagos, Nigeria. Ife J Sci 2018; 20: 155-168.
30. NAFDAC [homepage on the internet]. List of registered Imported Drugs. National Agency for Food, Drug, Administration and Control, Lagos. [Updated] Available from: https://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Directorate_Resources/R_and_R/List-of-Registered-Imported-Drugs.pdf. Last accessed 07/07/2020.
31. British Pharmacopoeia, Vol. II and IV. Her Majesty's Stationery Office, London. 2005.
32. United States Pharmacopoeia and National Formulary, United States Pharmacopoeia XXIII: Rockville U.S.P Convention Inc. 2007.
33. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; 16th Information supplement. Clinical and laboratory Standards Institute. Wayne. PA. 2007.
34. Staniforth JN and Aulton ME. Aulton's Pharmaceutics The design and manufacture of medicines. In: Aulton ME Ed. Powder flow. 3rd Ed. New York. Churchill Livingstone 2007.
35. Osadebe PO and Akabuogu IC. Assessment of quality control parameters and interchangeability of multisourced metformin HCl tablets marketed in Nigeria. Boll. Chim Farma 2004; 143: 170-173.
36. Levi G. Comparison of dissolution and absorption rates of different commercial aspirin tablets. J Pharm Sci 1961; 50: 388-392.
37. Rawlins EA Eds, Bentley's textbook of pharmaceutics. Eight Edition. ELBS and Baillière Tindall Book published by Cassell Ltd, London. 1977; 657

Received = 23rd December 2020
Accepted = 26th May 2021