Nigerian Journal of Pharmaceutical and Applied Science Research, 8(3):15-22
September 2019 (ISSN 1485-8059 Available at www.nijophasr.com

Quantitative and qualitative analysis of some brands of ciprofloxacin tablets sold in Uyo metropolis, Akwa Ibom State, Nigeria

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ABSTRACT

The menace of counterfeit and fake drugs with its negative impact on the health of the people remains a problem in many developing nations including Nigeria. This study was conducted to assess the quality of ciprofloxacin tablets sold in Uyo metropolis, Akwa Ibom State, Nigeria. The analysis of fifteen brands of ciprofloxacin tablets was done using the following physical properties namely; the weight uniformity assessment, friability, hardness, disintegration and dissolution tests. Quantitative analysis was done using non-aqueous titration and UV spectrophotometry. All brands complied with the official specification for uniformity of weight (within 5 % limit). One of the brands failed friability test (above 1 % official standard). None of the brands failed disintegration test (within 30 minutes specification). The dissolution rate profile revealed that three of the brands did not comply with official specification (below 80 % at 30 minutes). The non-aqueous titrimetric analysis showed that ten brands complied with official specifications (BP 95 – 105; USP 90 – 110). Five brands did not comply with official specification by having lower strength (below 90 %). These few brands when used in therapy can cause therapeutic failure and hence leading to drug resistance. There is need for regulatory agencies to regularly undertake post marketing surveillance.

Key words: Ciprofloxacin, quantitative analysis, qualitative analysis, titrimetric method, spectrophotometric analysis

INTRODUCTION

There is hardly any drug product in the sub-Saharan countries nowadays that is not being faked. The types of counterfeit drugs most frequently found in poor countries with huge burden of infections are principally antibiotics. It is known that counterfeit antibiotics with low doses of active ingredients are quite dangerous and it has been one of the major contributing factors to the inability to eradicate or control dangerous infections such as those caused by bacteria in developing countries (Newton *et al.*, 2006; Perur, 2018). The safety of drug products can be guaranteed when their quality is reliable and reproducible. In order to ensure the quality of drugs, manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the drugs (Chow, 1997; USFAD, 2019). The need to select one product from several generic drug products of the same active ingredients is usually an issue of concern to health practitioners. Drug products that are chemically and biopharmaceutically equivalent must be identical in strength, quality, purity as well as content uniformity, disintegration and dissolution rate. These ensure that the pharmaceutical products are fit for their intended use and do not expose consumers to any form of risk (Shah, 1994). For solid dosage forms (for instance tablets), factors such as binder type or concentration, disintegrant type, lubricant type etc. have been shown to affect the bioavailability of various drugs from tablet dosage forms. Since excipients type usually varies from one pharmaceutical formulation to another, the possibility of different bioavailability of drugs from similar dosage forms produced by different companies cannot be ruled out (Dahlgren, 2018). It is observed that many developing countries do not have an effective means of monitoring the quality of generic products in the market, therefore there is distribution of substandard and counterfeit drug products and this poses a threat to public health (WHO, 2005; Cockburn *et al.*, 2005). The lack of poor quality control practices have allowed for the availability of poor quality drugs. There is also a decomposition of active ingredients due to high temperature and humidity of the storage condition and inadequate quality assurance systems during manufacturing (Khan, 2018). Quality control of drugs is a set of studies or experiments undertaken during production and occasionally by regulatory agencies and researchers. Quality control of product ought not to be a one off event but rather a continuous event throughout the shelf life of a drug product.

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Activities of post market monitoring of a drug have been identified to include: review of drug products condition, inspection of manufacturer's processes, evaluation and investigation of reported drug complaints. Others include procedures for production and complementary handling, market surveys of technical and clinical documentation, review of product claims and labeling, public access to information taken and reported to regulatory agency(ies) and *in-vitro* testing of products for compliance to standards (Garcia, 2006; Uddin, 2017). Ascertaining the quality of drug products involves the use of various procedures that includes both biopharmaceutical and chemical assay techniques. Various methods have been reported for the chemical assay of ciprofloxacin tablets. The United States Pharmacopeia (USP) and British Pharmacopeia (BP) standards are usually used to assess content purity and the non-aqueous titrimetry helps to determine the end point in drug samples assessment (Talan *et al.*, 2000). Although World Health Organization issued guidelines for global standardization and requirements for the registration, assessment, marketing, authorization and quality control of generic drug products, many developing countries do not have technical, financial or human resources required to monitor the quality of generic drug products being distributed within their regions (WHO, 1996). Preliminary physicochemical assessment of drug products has a paramount importance in ensuring the quality of drug products. Generic drug products must satisfy the same standard of quality, efficacy and safety as those applicable to the innovator products (Aganwal, 2018). This preliminary study was carried out to evaluate the physicochemical quality and equivalence of fifteen (15) brands of ciprofloxacin tablets purchased from different pharmacy outlets in Uyo metropolis in Akwa Ibom State of Nigeria.

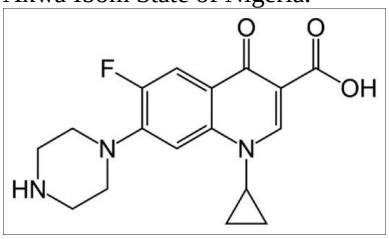

Figure 1. Structure of ciprofloxacin

MATERIALS AND METHODS

Chemical Collection and Sample Labeling

Hydrochloric acid and glacial acetic acid were analytical grade, obtained from Merck. Perchloric acid, potassium hydrogen pthalate and acetic anhydride were obtained from Sigma-Aldrich. Crystal violet indicator was analytical grade and distilled water was prepared using the Milli-Q50 water purification System (Millipore, Bedford, MA, USA). Analytical standard of ciprofloxacin (100 %) was a kind gift from the SKG-Pharma Ltd., Lagos, Nigeria. Fifteen (15) brands of ciprofloxacin tablets evaluated in this study were purchased from different Pharmacy shops in Uyo metropolis. They were coded $D_1 - D_{15}$ (Table 1).

Reagents preparation and standardization

Preparation of 0.1N HCl: Concentrated hydrochloric acid (2.08 mL) was accurately measured into 200 mL of distilled water in a volumetric flask and the volume made up to 250 mL mark with more distilled water. This was prepared fresh and used as solvent in the dissolution test and assay of ciprofloxacin.

Preparation and Standardization of 0.1 N Perchloric Acid: Exactly 4.2 mL of a 70 % perchloric acid was diluted in about 200 mL of glacial acetic acid in a 500 mL volumetric flask. Exactly 15 mL of acetic anhydride was added to the mixture and glacial acetic acid was used to make up the volume to 500 mL mark. The mixture was well covered with aluminium foil and kept for 24 hours. To standardize the acid, potassium hydrogen phthalate (0.5 g) was weighed and dissolved in 50 mL of glacial acetic acid in a 250 mL conical flask. The mixture was warmed in a water bath to enhance dissolution of the salt and it was allowed to reflux. Two drops of crystal violate was added and the mixture was titrated against 0.1 N perchloric acid solution until the violet colour changed to blue-green and a factor was obtain.

Tablet Description: One tablet of each of ciprofloxacin was observed and the tablets were looking good and non-sticky. The color and shape of each tablet was analyzed with ordinary eye (O'Neil, 2006).

Hardness Test: The crushing strength was determined with a Monsant type (Make: Singhla) hardness tester. Twenty (20) tablets were randomly selected from each brand and placed between two anvils. Appropriate force was applied to the anvils, and the crushing strength that just caused the tablet to break was recorded. The pressure at which each tablet crushed was recorded, averaged and the result is shown in Table 2.

Friability Test: Twenty (20) tablets of each formulation of the test drugs were weighed and subjected to abrasion at 25 rev/min for 4 minutes using Digital Friability test apparatus, Veego

Instrument (VFT-DV, India). The tablets were dusted, re-weighed and compared with their initial weights. From the result (Table 2), percentage friability was obtained (BP, 2003).

Weight Uniformity Determination: Twenty tablets each of the different brands of ciprofloxacin previously selected randomly were weighed and there after the total weight averaged. The percentage mean deviation of each tablet was also calculated and presented in Table 3.

Disintegration Test: Six (6) tablets from each brand were used for the test in distilled water at 37 ± 0.5°C using Digital tablet disintegration apparatus (Model 011021, USA). The disintegration time was taken to be the time no particle remained on the basket and the result is shown in Table 3.

Dissolution Test: This test was preceded by the preparation of stock and working solution of pure ciprofloxacin. In summary, pure ciprofloxacin (20.0 mg) was weighed and dissolved in 20 mL of 0.1N HCl to obtain a stock solution of 1 mg/mL. From the stock solution, calibration concentrations of 0.2 mg/mL, 0.4 mg/mL, 0.6 mg/mL and 0.8 mg/mL were prepared. The absorbance readings of the aliquots were measured in triplicate at 272 nm using Spectro UV-VIS, UVS-2700 spectrophotometer. The standard graph was obtained by plotting absorbance against concentration and was used in extrapolation of the concentration of the test samples. The dissolution test was undertaken using USP apparatus I (basket method) for each brand. The dissolution medium was 900 mL 0.1N HCl which was maintained at 37 ± 0.5°C. Throughout the test, 5 mL of dissolution sample was withdrawn using a pipette at 0, 10, 20, 30, 40, 50 and 60 minutes into separate labeled clean beakers and replaced with equal volume to maintain sink condition. Samples were filtered into separate labeled clean test tubes and assayed spectrophotometrically at 272 nm. The concentration of each sample was extrapolated from the calibration curve of pure ciprofloxacin and the result is presented in Table 3 and the profile shown in Figure 1.

Assay of ciprofloxacin by titrimetric method: Each brand of ciprofloxacin (0.3 g) was weighed and dissolved in 80 mL of glacial acetic acid in a conical flask. The mixture was filtered into a clean conical flask. Two drops of crystal violet indicator in glacial acetic acid was added to the solution. This was titrated against the perchloric acid and the end point was determined by a colour change of sample to bluish green. The titration was carried out in triplicate for each brand and the average calculated and presented in Table 4.

Assay of ciprofloxacin by Uv-Vis Spectrophotometric Analysis: A powder containing 10 mg of each brand of ciprofloxacin was weighed and dissolved in a freshly prepared 10 mL 0.1 N HCl to obtain stock solutions of 1 mg/mL, respectively. A 0.04 mg/mL aliquot of each solution was prepared in clean and labeled test tubes. The absorbance of each sample was determined at 272 nm against a 0.1N HCl as blank and the result in presented in Table 5.

RESULTS AND DISCUSSION

Results

Table 1: Label information and visual description of the ciprofloxacin tablets evaluated

S/N	Samples	Strength	NAFDAC Number	Manufacturing Date	Expiry Date	Color	Shape	Form	Coated/Uncoated
	D_1	500 mg	Yes	02/15	01/20	White	Spherical	Solid	Coated
	D_2	500 mg	Yes	03/13	02/16	White	Spherical	Solid	Coated
	D_3	500 mg	Yes	03/15	02/20	White	Spherical	Solid	Coated
	D_4	500 mg	Yes	04/14	03/04	White	Spherical	Solid	Uncoated
	D_5	500 mg	Yes	03/14	03/17	White	Spherical	Solid	Uncoated
	D_6	500 mg	Yes	09/12	05/16	White	Spherical	Solid	Coated
	D_7	500 mg	Yes	06/12	05/16	White	Spherical	Solid	Uncoated
	D_8	500 mg	Yes	07/14	06/17	White	Spherical	Solid	Uncoated
	D_9	500 mg	Yes	06/14	06/17	White	Spherical	Solid	Uncoated
	D_{10}	500 mg	Yes	07/13	07/17	White	Spherical	Solid	Uncoated
	D_{11}	500 mg	Yes	10/13	09/16	White & Yellow	Spherical	Solid	Coated
	D_{12}	500 mg	Yes	10/14	09/17	White	Spherical	Solid	Uncoated
	D_{13}	500 mg	Yes	11/14	10/17	White	Spherical	Solid	Uncoated
	D_{14}	500 mg	Yes	12/13	11/16	White	Spherical	Solid	Uncoated
	D_{15}	500 mg	Yes	12/13	11/16	White	Circular	Solid	Uncoated

Table 2: Results of non-compendial tests

Samples	Hardness test (kg/cm)	Friability test		
		Initial Weight of 10 tablets (g)	Weight After Friabilation (g)	Percentage Loss (%)
D_1	12.40±0.42	7.97	7.96	0.12±0.0013
D_2	9.50±0.35	6.68	6.66	0.29±0.0053
D_3	6.00±0.35	7.52	7.51	0.12±0.011
D_4	6.62±0.41	6.66	6.64	0.29±0.012
D_5	6.88±0.54	7.03	7.01	0.29±0.017
D_6	5.38±0.51	10.40	10.30	0.12±0.008
D_7	6.50±0.35	6.88	6.80	1.16±0.007
D_8	9.13±0.22	9.55	9.53	0.29±0.015
D_9	9.50±0.35	7.07	7.04	0.42±0.008
D_{10}	11.62±0.373	8.13	8.11	0.29±0.010
D_{11}	11.88±0.308	7.73	7.68	0.65±0.0084
D_{12}	5.88±0.545	7.50	7.40	0.12±0.011
D_{13}	10.75±0.433	9.53	9.51	0.29±0.050
D_{14}	10.25±0.433	6.50	6.49	0.12±0.0079
D_{15}	5.88±0.414	7.76	7.73	0.42±0.0048

Result given as average ± standard deviation except in friability test in which the standard deviation is shown in percentage loss.

Table 3: Results of compendial tests

Samples	Weight Uniformity test (g)	Disintegration test (Mins)	Dissolution test: Percentage drug release (%)					
			10 Mins	20 Mins	30 Mins	40 Mins	50 Mins	60 Mins
D_1	0.800±0.008	10.86±0.47	39	45	72	93	87	87
D_2	0.667±0.020	13.40±0.95	18	30	75	87	87	87
D_3	0.750±0.010	4.61±0.70	45	63	84	87	87	95
D_4	0.665±0.009	6.15±1.07	30	60	84	93	93	93
D_5	0.710±0.020	3.61±0.41	57	72	81	90	90	90
D_6	1.038±0.019	2.91±0.98	60	66	75	81	81	75
D_7	0.682±0.017	4.70±1.05	54	66	84	90	90	90
D_8	0.946±0.016	3.76±0.64	48	60	81	87	87	87
D_9	0.777±0.044	1.62±0.31	72	78	90	96	96	96
D_{10}	0.811±0.066	5.45±1.81	69	72	84	90	90	90
D_{11}	0.773±0.008	13.43±1.26	51	69	87	96	93	87
D_{12}	0.749±0.011	6.19±1.12	54	72	81	93	93	93
D_{13}	0.953±0.030	2.52±0.38	78	84	90	96	96	96
D_{14}	0.649±0.007	2.60±0.63	60	69	87	90	90	87
D_{15}	0.774±0.005	2.55±0.25	51	81	87	93	93	96

Result of weight uniformity and disintegration tests given as average ± standard deviation

Formula for dissolution test:

Amount of Drug Released = Concentration × Bath Volume (900ml)

$$\text{Concentration} = \frac{\text{Absorbance}}{\text{Slope of Calibration Curve}}$$

$$\%\text{ of Drug released} = \frac{\text{Amount of Drug Released}}{\text{Labelled Claim}} \times 100$$

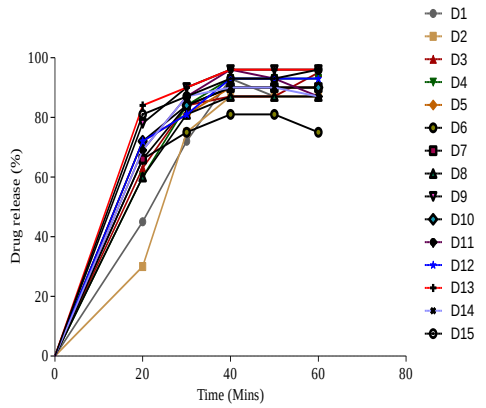

Figure 1: Dissolution profile of ciprofloxacin tablets evaluated

Table 4: Result of titrimetric analysis of ciprofloxacin tablets

Samples	Average titre (mL)	Percentage Composition (%)	Composition by weight (mg)	Label claim (mg)
D_1	8.90	90.00	450.00	500.00
D_2	8.55	86.00	430.00	500.00
D_3	8.40	85.00	425.00	500.00
D_4	7.00	71.00	355.00	500.00
D_5	7.80	79.00	395.00	500.00
D_6	9.50	96.50	482.50	500.00
D_7	9.10	92.50	462.50	500.00
D_8	8.20	83.00	415.00	500.00
D_9	9.10	92.50	462.50	500.00
D_{10}	9.95	101.00	505.00	500.00
D_{11}	9.55	97.00	465.00	500.00
D_{12}	9.00	91.00	455.00	500.00
D_{13}	9.80	99.60	498.00	500.00
D_{14}	10.00	102.00	510.00	500.00
D_{15}	9.90	100.60	503.00	500.00

Formula

$$\text{Percentage composition} = \frac{\text{Titre value} \times \text{Factor} \times \text{Milliequivalent}}{\text{Weight}} \times 100\%$$

Result for UV Spectroscopy

Table 5: Result of UV-Vis spectrophotometric assay of different brands of ciprofloxacin to determine their concentration

Samples	**Absorbance (272 nm)**	**Concentration (mg/mL)**	**Percentage composition (%)**
D_1	0.065	0.451	90.20
D_2	0.066	0.458	91.62
D_3	0.060	0.417	83.30
D_4	0.055	0.381	76.30
D_5	0.057	0.395	79.20
D_6	0.070	0.486	97.20
D_7	0.068	0.472	94.40
D_8	0.058	0.402	80.50
D_9	0.072	0.500	100.00
D_{10}	0.067	0.465	93.10
D_{11}	0.069	0.479	95.80
D_{12}	0.065	0.451	90.20
D_{13}	0.074	0.513	102.00
D_{14}	0.073	0.507	101.30
D_{15}	0.071	0.493	98.61

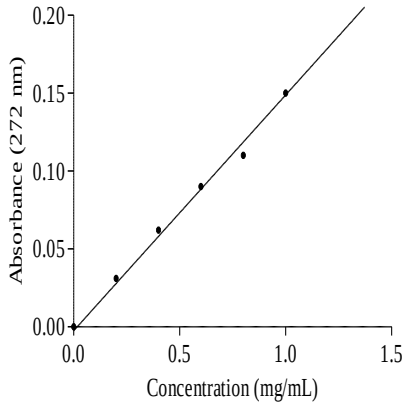

Figure 3: Standard curve of pure ciprofloxacin used in UV-spectrophotometric assay

DISCUSSION

Table 1 shows the different brands of ciprofloxacin analysed in the study, their coding and visual description of the tablets. The visual description was done by inspecting the physical appearance of the formulation. All brands were solid and white as described in USP except D_{11} that was white and yellow. Only D_{15} was circular as compared to all others that were spherical. Ten brands were uncoated while 5 were coated. Among the coated brands, D_{11} had the thickest coating. All brands of ciprofloxacin tested in the study were satisfactory for hardness with a hardness value > 50 N thus fulfilling the requirement for hardness test (BP, 2003). A force of about 4 kg/cm is the minimum requirement for a satisfactory hardness of a tablet (Shah *et al*., 2012).

The hardness or crushing strength assesses the ability of tablets to withstand handling without fracturing or chipping. It can also influence friability and disintegration as can be seen from the results in Table 2. The harder a tablet, the less friable and the more time it takes to disintegrate. However, the result reveals a wide range of variation in average hardness of the evaluated products. The reason for this variability between brands may have been related to the manufacturer's formulation conditions such as granulation methods, variation in machine speed, and quantity of lubricants added at the time of manufacturing of the products (Birhanu, 2014: Okoye and Ndiwe, 2016). The result in Table 2 also shows that the friability of all brands of the tested drug was below 1% except D_7 which was 1.16%. The compendial specification for friability is 1%. Friability test is used to evaluate the tablets resistance to abrasion. Tablet friability is a method to determine the physical strength of uncoated tablets upon exposure to mechanical shock or attrition (Osei-Yeboah and Sun, 2015). The result in Table 3 shows that all brands of ciprofloxacin used in the study complied with the compendial specification for uniformity of weight which states that for tablets weighing more than 324 mg, weights of not more than 2 tablets should not differ from the average weight by more than 5 % (BP, 2015). Uniformity of weight serves as a pointer to good manufacturing practices (GMP) as well as amount of the active pharmaceutical ingredient (API) contained in the formulation. This result is in agreement with some documented reports on weight uniformity assessment of ciprofloxacin (Jaman *et al*., 2015; Uddin *et al*., 2017). The result in Table 3 also reveals that all brands of ciprofloxacin analysed complied with the compendial specifications for disintegration indicating the good quality (oral absorption) of tablets in terms of disintegration time. The disintegration result of this study is in line with a similar study done by Jaman *et al*. (2015). The BP specification for disintegration is within 15 minutes for uncoated tablets and 30 minutes for film coated tablets; while USP specifies that uncoated and film coated tablets should disintegrate within 30 minutes. Disintegration could be directly related to dissolution and subsequent bioavailability of a drug. A drug incorporated in a tablet is released rapidly as the tablet disintegrates. It is a crucial step for immediate release dosage forms because the rate of disintegration affects the dissolution and subsequently the therapeutic efficacy of the medicine (Irfan *et al*., 2016). Table 3 shows the result of dissolution test of ciprofloxacin used in the study. All brands complied with both USP and BP specifications except brands D_1, D_2 and D_6 with percentage dissolution below 80 % at 30 minutes (Figure 1). According to the USFDA guidelines for pharmaceutical industries, the dissolution rate of immediate release solid oral dosage forms for class I and in some cases class III drugs like ciprofloxacin (Wu and Benet, 2005; Kasim *et al*., 2004), should be 85 % in 0.1 N HCl in 15 minutes. This is to ensure that the bioavailability of the drug is not limited by dissolution (Onyekweli *et al*., 2013). The dissolution test result of this work, based on the USP standard, is similar to the earlier report of Fahmy and Abu-Gharbieh, (2014). The result of Table 4 shows that brands $D_2 - D_8$ did not comply with the United States Pharmacopeia (USP) specification for titrimetric assay while brands D_1, D_7, D_9 and D_{12} did not meet British pharmacopoeia (BP) standard. The USP specification states that the content of ciprofloxacin should not be less than 90 % and not more than 110 %; while BP specifies that the content should not be less than 95 % and not more than 105 %. However, the titrimetry assay result ascertains the presence and quantity of ciprofloxacin counterfeits without APIs. This study is in line with the earlier discovery of remarkable variation in the pharmaceutical qualities of some drugs marketed in Nigeria (Eichie *et al*., 2009). Table 5 shows that apart from D_3, D_4, D_5 and D_8 which deviated from the standard according to the pharmacopeial reference books, all other brands complied with the USP standard while only D_6, D_9, D_{13}, D_{14} and D_{15} complied with the BP standard. The USP specification states that the content of ciprofloxacin should not be less than 90 % and not more than 110 % while BP specifies that the content should not be less than 95% and not more than 105 %. Just like in the case of titrimetric analysis, the result ascertains the presence and compendial quantity of ciprofloxacin counterfeits without APIs.

CONCLUSION

Post-market monitoring is very crucial for effective clinical outcome and this study has shown that chemical equivalence does not indicate bioequivalence. The differences in quality control parameters observed in this study with respect to ciprofloxacin tablets have implications in terms of product and standards of multisource products available within the source area. Healthcare providers should take this into account.

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