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In vitro quality evaluation of brands of ciprofloxacin tablets marketed in Edo State, Nigeria

Adeniyi Akee M A[1], Nnorodim J I[2], Ahmad A A[2], Obarisiagbon J[3]
[1] Lecturer I, Department of Pharmaceutical Chemistry, Igbinedion University, Okada, Edo State, Nigeria
[2] Department of Pharmaceutical Chemistry, Igbinedion University, Okada, Edo State, Nigeria
[3] Associate Professor, Department of Pharmaceutics and Pharmaceutical Technology, Igbinedion University, Okada, Edo State, Nigeria

Abstract
Due to the rise in generic medicine products from various sources. People and prescribers now have to choose from a variety of items that appear to be pharmaceutically equivalent and this put regulating authorities under pressure, resulting in an influx of counterfeits and poor products. Ciprofloxacin is a second generation fluoroquinolones used in the case of typhoid fever, gonorrhea and urinary tract infection. The aim of this research was to evaluate the quality control parameters of ten brands of tablets ciprofloxacin hydrochloride marketed by drugstores around Edo State in Nigeria. Identification, hardness, disintegration, uniformity of weight, dissolution, friability and assay are the factors determined. The United State and the British Pharmacopoeia were used as standards for the evaluation of samples. Results obtained showed tablets weight ranging 0.634 ± 1.249 **%**, hardness from 7.4 ± 0.44 to 14.99 ± 0.03 kg/cm^2, friability values of less than (>) 1 % except CP-9 Brand, disintegration period of 1.43 ± 0.02 to 22.62 ± 0.19 min, assay of 91.3 to 110 %, and the brands released 70 % of their drug content within 45 min. The results indicated that overall quality of all tested ciprofloxacin hydrochloride tablets brands was satisfactory as they met the requirements of the official and unofficial quality control test.

Keywords: Ciprofloxacin, quality control, dissolution, pharmacopoeial specifications

Introduction
Concerns over healthcare costs have led to a massive surge in the usage of generic drugs. This aided the quick influx of multisource ciprofloxacin hydrochloride tablets into the Nigerian market, especially from Asian countries [1]. Bioequivalence and bioavailability of pharmaceuticals and their selection, have become main hardships in medicine and pharmacy over the last three decades, based on report from the United States Food and Drug Administration (FDA). Interchanging brand-name products and generic medications is contentious, and healthcare providers and patients are often skeptical [2]. Both substandard and fake medications are acknowledged as being of low quality. Analyses of the chemical composition and packaging are necessary to determine whether a medicine is genuine or a fake. However, this is challenging and hardly documented. [3]. Drug counterfeiting causes tremendous economic damage, which seems to be growing yearly. The WHO estimates that in 2004, the drug counterfeiting industry cost the world 32 billion US dollars [4].

Drug counterfeiting is not only against the law, but it also poses serious public health risks. Drugs that are counterfeit frequently have the right chemicals in the wrong amounts, but they may also have the wrong API—which could even be toxic or have no active ingredient at all [5]. Treatment using substandard medications, such as antibiotics, can result in the establishment of resistant organisms and may be harmful to a large portion of the population. In severe situations, counterfeit medications have the potential to be fatal in severe situations [6]. For instance, it has been reported that a fake vaccine in Nigeria that was administered to 60,000 – 80,000 children with lethal falciparum malaria included just chloramphenicol, an antibiotic that is typically given in conjunction with another drug, and may have caused more than 100 fatal infections [7]. Nigeria is fighting an uphill battle against the illegal and counterfeit drug trade because the majority of regulated drugs are expensive or need to be accessed through travel to a far-off medical facility. Most residents of isolated rural villages wait until the situation gets worst before making the medical trips. Drugs on the underground market are more frequently sought after, which can be even more harmful [8]. According to the World Health Organization (WHO), inferior and fraudulent medical products affect patients and are ineffective in treating the conditions for which they were designed. They cause people to lose faith in medical professionals and health care institutions. The Pharmaceutical Society of Nigeria claims that, in addition to other countries, counterfeit medications are mostly imported into Nigeria from China, Pakistan, and India [8]. Many reasons contribute to the rising incidence of counterfeit and inferior pharmaceuticals. Much of the counterfeit drug trade is most likely tied to organized crime, corruption, the narcotics trade, unethical politicians' commercial interests, and unregulated pharmaceutical businesses [9]. Because of the large profits that the manufacturers get from making these counterfeit goods, they have the ability to expand quickly, necessitating the need for action to combat this threat. The Center for Medicine in the Public reported approximately 10% of counterfeit drugs, indicating a $35 billion market [10]. Last but not least, drug dealers frequently show a lack of concern for expiration dates and storage conditions, especially in unsanitary environments and in the absence of national regulation, which contributes to the proliferation of inferior antibiotics [11].

Pharmaceutical equivalence refers to drug products with the same dosage forms and routes of administration that contain the same amounts of the same active ingredient, which is the

same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that need a reservoir or average, or such forms as prefilled syringes where the residual volume may vary, that deliver the same amount of the active drug ingredient over the same dosing period; don't always have to have the same inactive ingredients; and adhere to the same compendia or other relevant measures for quality, identity, purity and strength, including potency and also where applicable, dissolution, assay and disintegration. Other qualities that may differ are, packaging, scoring, shape, configuration, excipients (preservatives, colors and flavors), release mechanism, expiry date and labeling [12].

Ciprofloxacin is a second-generation fluorinated quinolone antibacterial medication with a broad spectrum of action that can be administered parenterally or ophthalmically [13]. In developing nations such as Nigeria, oral ciprofloxacin is an approved drug for treating gonococcal urethritis, gonorrhea and urethral/vaginal discharge disorder [14]. Ciprofloxacin is recommended for bacterial infections such as urinary tract infections (UTIs), acute uncomplicated cystitis in females, persistent bacterial prostatitis, lower respiratory tract infections, acute exacerbations of persistent bronchitis, and complicated intra-abdominal infections due to sensitive organisms [15, 16]. Ciprofloxacin hydrochloride works by preventing bacterial cell division by inhibiting DNA gyrase (a type II topoisomerase) and topoisomerase IV [17]. Ciprofloxacin creates a chelate complex with antacids and metallic cations, similar to other fluoroquinolones, resulting in decreased absorption and bioavailability [18].

Ciprofloxacin's chemical name is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It has the empirical formula $C_{17}H_{18}FN_3O_3$ and a molecular weight of 331.4 g/mol. It is a crystalline material that is slightly yellowish to light yellow in colour. Ciprofloxacin hydrochloride (USP) is the ciprofloxacin monohydrochloride monohydrate salt [19].

Ciprofloxacin is also effective against some gram-positive bacteria. Among the quinolones, ciprofloxacin is the most effective against Pseudomonas aeruginosa [20]. If the predominant pathogen is penicillin-susceptible Streptococcus pneumonia, ciprofloxacin should not be used as the first-line treatment. Ciprofloxacin is an acceptable therapeutic option for patients with mixed infections or gram-negative bacterial predisposing factors [21]. It can be used alone or in conjunction with other antibacterial medications to treat infections where the bacterial pathogen has not been identified, such as urinary tract infections and abdominal infections [22].

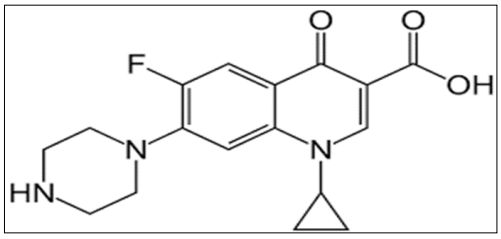

Fig 1: Structure of Ciprofloxacin

The objective of the study was to evaluate the quality control of ten brands of Ciprofloxacin Hydrochloride marketed and commonly prescribed in Edo State of Nigeria using monograph as contained in the British and United State pharmacopoeia.

Experiments

Chemicals: Ciprofloxacin hydrochloride was obtained from Gemini Pharmaceutical Nigeria limited. TEN commercially available top brands of ciprofloxacin hydrochloride tablets, each with a label claim of 500 mg, were obtained from various pharmacies in Edo State. They were then checked for their manufactured and expiry dates, NAFDAC registration numbers and batch numbers. CP1 to CP10 were used to designate the samples. Other chemicals like methanol, sodium hydroxide, distilled water, and hydrochloric acid were of analytical grade.

Instruments utilized: They include an electronic analytical weighing balance (KERN ABS-N analytical balance), a Roche friabilator (model: 902 intech REV), a Monsanto hardness tester, a disintegration apparatus (Single Basket Disintegration Test Apparatus), a dissolution apparatus (Single Tablet Dissolution Apparatus), and UV-Visible spectrophotometer. The study also made use of Whatman filter paper, general-purpose glassware, and a mortar and pestle.

Identification Test

The solid samples were dissolved in 0.5 mL 0.1N HCL and allowed to stand for 2 min. The supernatant was decanted and neutralized with 0.1N NaOH added in installments of 25µL till precipitation commenced. The precipitate obtained was washed 2-3 times with distilled water to remove any traces of excess acid or alkali. Finally, the precipitate was suspended in 0.5 mL water. 2-3 drops of 0.1% Bromothymol blue (50% alc.) and 0.1% methyl red (50% alc.) were added and after few minutes colour of supernatant liquid was observed to be yellow. This was done to all the brands of Ciprofloxacin hydrochloride.

Weight uniformity

Twenty (20) tablets from each brand were chosen at random and weighed using an electronic analytical weighing balance. The average weight was calculated, and the weight of each individual tablet was subtracted from the mean tablet weight to calculate the percentage deviation of each tablet from the mean.

$$\% \text{ deviation} = \frac{(\text{weight of tablet} - \text{Mean tablet weight}) \times 100}{\text{Mean tablet weight}}$$

Hardness Test

The Monsanto hardness tester was utilised for this test. Ten (10) tablets of ciprofloxacin hydrochloride were chosen at random from each of the ten brands and tested. The pressure required to break diametrically arranged tablets was measured using a coiled spring, and the results were reported.

Friability Testing

Ten tablets were selected randomly from each brand and weighed combined to obtain weight W_1 (initial weight). Each brand was friability tested in the friabilator at twenty-five rotations per minute for four minutes before being reweighed to determine weight W_2 (final weight).

The weight loss (W_1-W_2) was calculated and the following formula was used to evaluate the percentage friability:

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} x\ 100$$

Disintegration Time Test
Six tablets of each brand were chosen at random and separately placed in each of the six cylinder-shaped tubes of the basket rack of the disintegration device, using distilled water as a disintegration medium at 37°C. The disintegration time was then evaluated.

Preparation of Calibration Curve for Assay
A 100 mg pure ciprofloxacin sample was dissolved in 0.01M NaOH to yield a stock solution of 1 mg/ml. From the stock solution, 5 µg/ml, 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, and 50 µg/ml working solutions were made, and their absorbance was measured at 276 nm. The standard calibration curve was obtained by plotting the absorbance versus concentration graph.

Assay of the Ciprofloxacin tablets
Twenty ciprofloxacin tablets of each brand were pulverized, and a portion equivalent to 100 mg of drug was extracted with 100 mL of 0.01M NaOH to yield a stock solution of 1 mg/ml of each brand. Aliquots of 10 µg/ml of each stock solution were measured for absorbance at 276 nm. These were then extrapolated on the standard curve to get the extrapolated concentration. By comparing the extrapolated concentration to the expected concentration, the percentage recoveries were calculated.

Preparation of Calibration Curve for dissolution test
An analytical balance was used to weigh out 10mg of pure Ciprofloxacin standard (primary standard), which was then diluted to give a working concentration of 100 ug/ml of stock solution. A suitable volume of the stock solution was used to create concentrations of 2.5, 5.0, 7.5, and 10 **µ**g/ml. The equation of regression was derived by scanning the above doses for their absorbance in the UV-Visible machine, at 276nm wavelength and then using the values obtained to plot the calibration curve. This equation was finally used to calculate the concentrations of different brands of ciprofloxacin used for dissolution,

Dissolution test for Ciprofloxacin tablets
Dissolution test (with 6 replicates of each brand) was done using the BP method. Deionised water was used as the medium and.to clean the dissolution chamber as recommended by the BP. The water bath had a suspended beaker in which 900ml of water was introduced and the set up was maintained at 37 degrees centigrade by the thermostat. With 50 revolutions per minute agitation, dissolution medium (5 ml) was taken for each tablet of each brand of Ciprofloxacin at 0, 5, 10, 15, 30, 45, and 60 minute intervals and same volume of the medium was added to sustain sink condition. filter and made up to 50 mL for perfect readings, before assay at 276nm with a UV/vis spectrophotometer. The absorbance reading for each brand was used in calculating the amount released in percentage, by mean of the calibration curve obtained from standard samples of ciprofloxacin.

Results and Discussion
Sample tablets description
The sample obtained on the chosen brands of Ciprofloxacin hydrochloride tablets was checked to ensure that the tablets from the 10 brands are authentic and have the correct batch documentation, they were examined for a few regulatory identity requirements. All of the investigated Ciprofloxacin brands had a two to three-year shelf life and were properly batch coded by the National Agency for Food and Drug Administration and Control (NAFDAC). Samples observe for their colour, shape and coating. They were then coded with name CP-1 to CP-10. All tablets colour were white except for CP-2 that was orange in colour. They were all film coated while CP-1, CP-5, CP-6, CP-8, and CP-10 were the scored samples. Table 1: indicates the information on the ten brands of ciprofloxacin tablets.

Weight Uniformity
A weight uniformity test is necessary to ensure that the medication content in each unit dose is dispersed within a small range around the label strength. If the drug component makes up the majority of an oral solid dose form, any weight variation clearly reflects changes in the active ingredient's quantity. The British Pharmacopoeia (2014) specifies that a ± 5% deviation from the average is required to pass the first uniformity of weight test for tablets with a strength greater than 250 mg (uncoated or firm coated tablets). The tablets met the requirements of the BP standard, which states that no tablet (out of ten tablets tested) should differ from the average by more than 10% and no more than two tablets should deviate by ± 5%. Consequently, the findings show that the 10 brands of Ciprofloxacin tablets examined have appropriate weight uniformity in accordance with pharmacopoeia standards.

Identification Test
A crucial preliminary test that must be carried out before a product is assessed is an identification test. It is crucial to determine the contents of both the reference sample and the sample being tested before conducting any experimental work on them. The brands and that of pure ciprofloxacin gave a yellow colouration which indicates the presence of ciprofloxacin.

Friability testing
The tablets' resistance to scratch is normally evaluated using the friability test, which is typically related to handling, packing, and transportation. According to the USP (2013), a tablet batch should have less than 1% friability. Except for CP-9, which had a percentage loss of 1.3%, the friability value for other brands was less than 1%. The use of insufficient binder, the wrong compression force, and making the tablets friable could all be contributing factors to CP-9's failure. All of the brands that passed the test may have been the inverse.

Hardness test
The crushing strength test, often known as the hardness test, evaluates a tablet's capacity to tolerate handling without breaking or chipping. Friability, disintegration, and dissolution may also be affected. The tablet becomes less friable and takes longer to dissolve the harder it is. CP-5 tablets have the highest average hardness value of 14.99±0.03 kg/cm^2, while CP-7 tablets have the lowest

value at 7.40±0.436 kg/cm^2. According to the British Pharmacopoeia (2014), a force of at least 4 kg/cm3 is considered to be sufficient for hardness of a tablet. As a result, every brand passed the examination.

Disintegration test

Tablet disintegration is primarily influenced by a number of variables, including the kind and concentration of the disintegrant, the compression force, the medium temperature in the disintegration equipment, and the type and quantity of binder utilized. The British Pharmacopoeia [23] suggests that the disintegration time required for coated tablets falls within 30 minutes and 15 minutes for uncoated tablets when it comes to the disintegration test. According to the data in Table 2, all of the selected Ciprofloxacin brands passed the test. Since the 10 brands were coated tablets, disintegration should occur within 30 minutes [23]. With average disintegration times of 1.43 ± 0.022 and 1.468 ± 0.024, respectively, CP-1 and CP-5 had the lowest average disintegration times, while CP-6 had the highest average disintegration time of 22.62 ± 0.188.

Dissolution test

The dissolution process is critical in releasing a medication from its dosage and making it available for subsequent gastrointestinal absorption. As a result, dissolution analysis of pharmaceutical solid dosage forms is a critical test of product quality and can be employed as a sensitive tool for distinguishing distinct formulations of the same medicinal agent [24]. Drugs with a poor dissolution profile will not be available in the body's system to have therapeutic action [25]. The British Pharmacopoeia monograph states that the amount of active drug component in the solution for each of the tablets tested for dissolution should not be less than 70% of the declared or prescribed dosage within 45 minutes [23]. According to the study results (Figure 2), all ten brands passed the dissolution rate test for conventional instant-release tablets. The pass of these ten brands may be attributed to a suitable amount of binder, compression force, and disintegrants as a result of rigorous adherence to good manufacturing practice during the manufacturing process of these tablets.

Assay

Based on quantitative assay results, only six out of ten brands (60%) met the British Pharmacopoeia (BP) 2015 criteria (95-105%) [26]. Four out of ten brands were rejected by the British Pharmacopoeia. This is due to the fact that they evaluated their results using United States Pharmacopoeia (USP) specifications, which allowed for a broader range of recovery (90 - 110 percent) [27]. Harmonization of specifications (BP and USP) is required so that producers and researchers are properly guided. The BP range of 95-105 percent, which is actually 100 % ± 5.0, is suggested since it will encourage manufacturers to use finer aspects of quality assurance to ensure better products that would achieve targeted treatment objectives.

Table 1: Ciprofloxacin brands information

Code	Producer	Shape	Colour	Scoring	Coating	Nafdac Number	Manufac. Date	Expiry Date	Batch Number
CP-1	Hale wood lab.	Oblong	White	Scored	Coated	B4-6819	01/2021	12/2023	Hv1003
CP-2	Emcure Pharma. Ltd	Ova	Orange	Not Scored	Coated	O4-2307	03/2020	02/2023	Ei6qp20047
CP-3	Saga Vitaceuticals	Oblong	White	Nor scored	Coated	04-2170	04/2021	04/2024	Cf210408
CP-4	Elbe pharma.	Oblong	White	Not scored	Coated	04-3002	08/2020	07/2023	M0120
CP-5	May and Baker	Oblong	White	Scored	Coated	A4-4306	09/2021	08/2024	CP5Ac21062
CP-6	Jiangsu Rulinian Quanjin Pharma.	Oblong	White	Scored	Coated	B4-5850	03/2021	03/2024	210304
CP-7	Surmount	Oblong	White	Not scored	Coated	C4-0594	02/2021	01/2024	K0102
CP-8	Pharmatex	Oblong	White	Scored	Coated	B4-2270	09/2021	08/2024	T1105
CP-9	Embassy	Oblong	White	Not scored	Coated	O4-4061	02/2021	01/2024	Ecqt-006
CP-10	Jiangsu Pengynes	Oblong	White	Scored	Coated	B4-5947	03/2021	03/2024	210358

NAFDAC: National Agency for Food and Drug Administration and Control

Table 2: Brands quality control test summary

Brands code	Average weight	Standard Deviation for the average weight	Mean Hardness Test ± SD (kg/cm^2)	Percentage Friability	Disintegration Time ± SD (min)	Assay ± SD % [n=3]
CP-1	0.7498	±1.8868	13.85±2.029	0.01	1.43±0.022	97.5±0.0008
CP-2	0.6338	±1.2489	9.74±0.449	0.03	5.05±0.023	97.5±0.002
CP-3	0.9224	±1.4966	9.2±1.229	0.02	17.18±0.069	103.8±0.001
CP-4	0.7632	±1.7493	14.65±0.229	0.08	2.395±0.059	97.5±0.0033
CP-5	0.7343	±1.7284	14.99±0.03	0.07	1.468±0.024	91.3±0.001
CP-6	0.7156	±1.7457	14.9±0.2	0.11	22.62±0.188	110±0.002
CP-7	0.7329	±1.6093	7.4±0.436	0.83	2.102±0.053	103.8±0.0033
CP-8	0.6506	±1.3592	14.83±0.419	0.85	7.365±0.067	97.5±0.002
CP-9	0.9991	±6.6851	11.35±1.566	1.30	10.472±0.039	110±0.001
CP-10	0.7701	±1.2835	14.58±0.225	0.08	15.198±0.058	91.3±0.002

Calibration curve equation: y=0.0016x + 0.5944, R^2 = 0.9987

Note: Weight uniformity test acceptable limit of deviation is ±5%of the mean percentage deviation. Disintegration time acceptable limit for coated tablets is less than 30 minutes. The acceptable limit for hardness of tablet is greater than 4kg/cm^2.

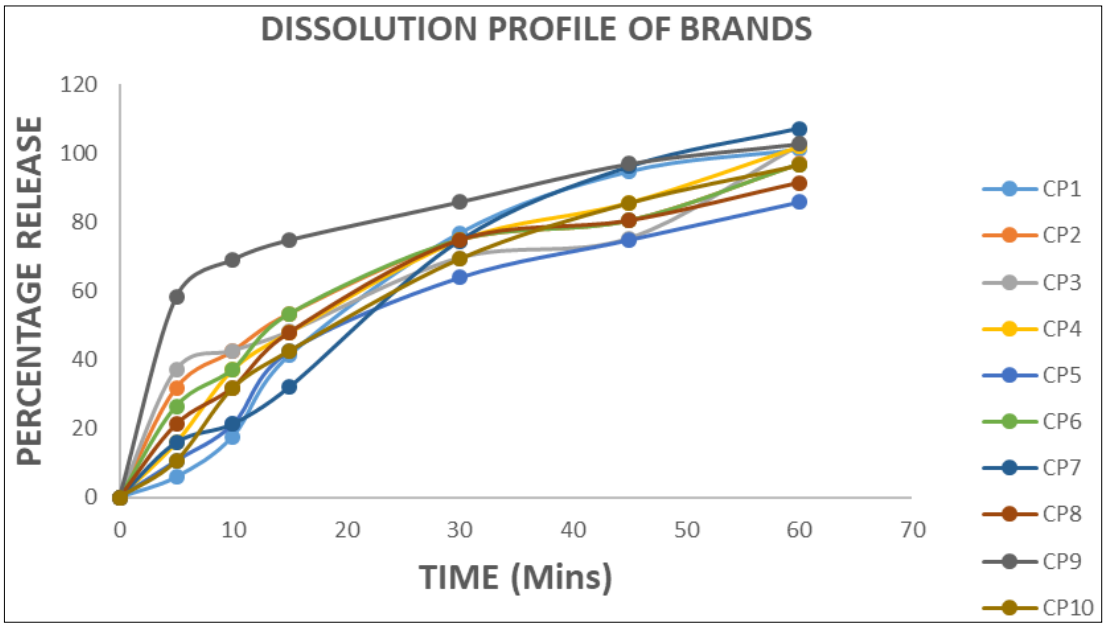

Fig 2: Dissolution rate profile of brands of ciprofloxacin hydrochloride tablets

Conclusion

The quality of ten brands of ciprofloxacin tablets marketed in Edo State were evaluated in this study. The physicochemical study revealed that all ciprofloxacin tablet brands examined for uniformity of weight, hardness, disintegration, assay, and drug release met the pharmacopoeia requirements outlined in the British Pharmacopoeia and United State Pharmacopoeia.

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