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Quality Assessment of Fifteen Different Brands of Ciprofloxacin Hydrochloride Tablets Marketed in Anambra State, Nigeria

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ABSTRACT

This work is aimed at comparatively assessing the quality of 15 registered brands of ciprofloxacin tablets marketed in Anambra State, South eastern Nigeria. The physicochemical properties of fifteen brands of ciprofloxacin tablets marketed in the state were compared. The distinguishing features were noted and several parameters such as weight uniformity, crushing strength, friability, disintegration, assay of the content of active ingredients and dissolution were assessed using the methods described in the British Pharmacopoeia. The results showed that all the brands complied with Pharmacopoeial standards except tablets from one brand that could not release up to 75 % of its ciprofloxacin content within 45 minutes. This suggests good regulation of the pharmaceutical sector.

KEYWORDS: *Physicochemical Properties, Quality Assessment, Ciprofloxacin Hydrochloride, Tablets*

INTRODUCTION

The safety and efficacy of drug products can be guaranteed when their quality is reliable and reproducible from batch to batch. To ensure the requisite quality, drug manufacturers are required to test their products during and after manufacturing and at various intervals during the shelf life of the product [1]. Many developing countries do not have an effective means of monitoring the quality of generic drug products in the market. This results in widespread distribution of substandard and/or counterfeit drug products. It was in view of this fact that the World Health Organization (WHO) issued guidelines for global standard requirements for the registration, assessment, marketing, authorization and quality control of generic pharmaceutical products [2 – 3].

The combination of market forces, the low per capita spending on pharmaceuticals by most of the population and the lack of adequate resources for controlling and monitoring the quality of drugs in the market create an environment favorable for introducing low quality drugs in developing countries like Nigeria. Until very recently, developing country health advocates have been getting drugs into the supply chain at affordable prices. The quality of these drugs and the threat of counterfeit pharmaceuticals have been largely ignored. However, there is mounting evidence that counterfeit pharmaceuticals

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pose a serious threat to public health, especially in developing countries [3 – 4].

Concern about lowering health care costs has resulted in a tremendous increase in the use of generic drug products; about one half of all prescriptions written are for drugs that can be substituted with a generic product [5]. In 1975, approximately 9% of all prescription drugs dispensed were generic versions. This percentage rose to 20% in 1984, and 40% in 1991. Indeed substitution of generic drugs for brand name products is highly controversial and is often met with suspicion by health care providers and patients [6 – 7]. The FDA in the United States has mandated that all generic drugs meet the same standards as the brand name drugs in strength, safety, purity and performance. However, there are substandard and/or counterfeit generic drugs that do not satisfy the pharmacopoeial standards set for them.

In several developing countries, drug quality is a source of concern. There is a general feeling that there is a high incidence of drug preparations which are not of acceptable quality. There are many reports of the availability of counterfeit medicines, not only in developing countries but also in Europe and USA [8].

In 2003, WHO reported that fake drugs reported between 1999 and 2002 include analgesics and antipyretics (6%), antimalarial (7%), anti-asthma and anti-allergy (8%), antibiotics (28%), hormones and steroids (18%) and other therapeutic categories (33%). Thus, the aforementioned problems have resulted in a weak therapeutic efficiency, selection of resistant strains and poor quality of numerous drugs [9 – 11].

Lack of competent regulatory authorities and poor quality control practices in some countries, have allowed the availability of poor quality drugs. The widespread counterfeiting of medicines could be due to decomposition of the active ingredient in drug dosage form due to high temperature and humidity of the storage condition, and inadequate quality assurance systems during the manufacture of pharmaceutical products [12 – 13]. The present study evaluated the quality of different brands of ciprofloxacin tablets marketed in Anambra state, Nigeria. All the brands are registered with the National Agency for Foods, Drugs Administration and Control (NAFDAC) of Nigeria. Anambra State has the biggest open drug market in Nigeria and many health outfits source their drugs from there.

MATERIALS AND METHODS

Reagents and Tablet Samples

Ciprofloxacin hydrochloride powder was a gift from Pauco Pharmaceutical Industries, Awka, Nigeria and complied with the British Pharmacopoeial standards. All other reagents were of analytical grade. Fifteen different brands of ciprofloxacin tablets were sourced mainly from private retail pharmacies and drug stores in Awka, Anambra state, Nigeria and were stored in their original packages as supplied by the manufacturers, away from light. The State has one of the largest medicines open markets in Africa and many retail outlets source from the open market.

Tablet Identification

The different brands of ciprofloxacin tablets were checked for nominal strength, batch number, date of manufacture, date of expiration and NAFDAC number [14].

Determination of Uniformity of Weight

Twenty tablets from each of the brands were weighed individually using an analytical weighing balance (Adventurer, Ohaus, England). The average weight for each tablet batch as well as percentage deviation was calculated [15].

Determination of Crushing Strength (Hardness)

The crushing strengths of the tablets were determined using Monsanto hardness tester. Ten tablets were selected randomly from each batch. The pressure at which each tablet crushed was recorded and the means and standard deviations were calculated [13].

Friability Test

The friability test was conducted using a friabilator (DBK 5020/7, India). Ten tablets selected from each brand were dedusted, weighed (W_1) and rotated in the friabilator at 25 revolutions per minute for 4 minutes. The agitated tablets were reweighed (W_2) and compared with their initial weights. The percentage friability (%F) was determined using the formula below [13].

$$\% F = [(W_1-W_2) / W_1] \times 100\%.$$

Assay of Drug Content

The ferric chloride complex method as reported by Ngwuluka et al (2009) was adopted. A solution of 1% w/v ferric chloride was freshly prepared. Five tablets from each batch were crushed and a sample equivalent to 100 mg of the drug was taken from each powdered sample. This was dissolved in 100 ml of 0.1N hydrochloric acid (HCl). A drop of ferric chloride was added to 5 ml of each drug solution and the volume made up to 50 ml with 0.1N HCl solution. The absorbance of each sample was taken at a wavelength of 438 nm in an ultraviolet spectrophotometer (UV-1700, Shimadzu, Japan). The drug content was calculated for each brand [16].

Tablet Disintegration Test

The British Pharmacopoeia disintegration apparatus (DBK 5029/8, India) was employed using six tablets from each brand in a freshly prepared 0.1N HCl at 37 ^{o}C. The disintegration time was recorded as the time no particle remained on the basket of the disintegration unit [16].

Dissolution

The dissolution test (basket method) was done according to USP specification using dissolution apparatus (DBK 5036/3, India) in 6 replicates for each batch. The dissolution medium was 900 ml of 0.1N HCl maintained at 37±0.5 °C. During the dissolution process, 5 ml volume of the dissolution sample was withdrawn at 5 minutes intervals and replaced with equal volume of blank dissolution medium to maintain sink condition. The sampling times were selected in due consideration to the short disintegration times. The samples were filtered and assayed by ultraviolet spectrophotometry (model uv-1700, Shimadzu) at a wavelength of λmax = 277 nm. The concentration of each sample was determined from a predetermined calibration curve for ciprofloxacin hydrochloride [17 – 18].

Beer's Plot of Ciprofloxacin Hydrochloride

Different concentrations of ciprofloxacin hydrochloride (0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.11, 0.12, 0.13 and 0.14 mg/ml) were prepared in 0.1 N hydrochloric acid solution. Their absorbances were determined at an absorption wavelength of 277 nm and a calibration curve (Beer's plot) of absorbance verses concentration was plotted [17-18].

RESULTS AND DISCUSION

Tablet Identification Properties

Table1 below shows the information on ciprofloxacin tablet formulations included in the study.

Table 1: Detailed information on different brands of ciprofloxacin 500 mg tablet evaluated for quality

Code Name	Strength	Batch No	NAFDAC Reg. No	Mfg. Date	Expiry Date
CP1	500 mg	120703	04-5495	07/2012	07/2015
CP2	500 mg	Wc3001	04-5635	02/2013	01/2016
CP3	500 mg	Cnxt1303	04-3002	03/2013	02/2016
CP4	500 mg	111229	A4-7046	12/2011	12/2014
CP5	500 mg	130322	04-7405	03/2013	03/2016
CP6	500 mg	Cf207c5	04-2170	07/2012	06/2015
CP7	500 mg	0078	04-5734	09/2013	08/2016
CP8	500 mg	B-301	04-1363	02/2013	01/2016
CP9	500 mg	U11003	04-3458	01/2012	12/2014
CP10	500 mg	47	A4-5360	09/2013	08/2017
CP11	500 mg	Kp1320	B4-0293	12/2013	11/2016
CP12	500 mg	14011104	A4-6601	01/2014	12/2017
CP13	500 mg	12cz16	04-4061	06/2012	05/2016
CP14	500 mg	130455	04-4950	07/2013	07/2016
CP15	500 mg	Dx1206	A4-0932	05/2012	04/2015

NAFDAC – National Agency for Food and Drugs Administration and Control
Reg. No - Registration number, **Mfg. date-**Date of manufacture

The tablets from the fifteen different brands were checked for some regulatory identity requirements in order to make sure that they are genuine with proper batch documentation. All the brands of ciprofloxacin studied were duly registered with National Agency for Food and Drug Administration and Control (NAFDAC) and well batch coded with shelf life of 2-4years. The shelf lives were determined from the records of dates of manufacture and expiration. The data generated in Table 1 show that the quality of brands of ciprofloxacin tablets used in this study is adequately controlled and assured by Nigerian drug regulatory authorities [14].

Weight Uniformity of Tablets

Table 2 below shows the weight uniformity results of the different brands of Ciprofloxacin employed in this study. Table 2 shows the mean tablet weight and the number of tablets within and outside the BP specification limit for the different ciprofloxacin tablet brands included in the study. Weight uniformity test is required to assure that the drug content in each unit dose is distributed in a narrow range around the label strength. If the drug substance forms the greater part of the oral solid dosage form, any weight variation obviously reflects variation in the content of active ingredient. According to the specification outlined in the British Pharmacopoeia (2014), the test for uniformity of weight for tablets where the strength is above 250 mg (uncoated or film coated tablets), a ± 5 % deviation from the average pass the test for uniformity of weight. The tablets complied with the BP standard which stipulates that no tablet (out of ten tablets tested) should deviate by more than ±10 % from the average and not more than two tablets should deviate from the average by ± 5 %. The results, thus, indicate that the fifteen brands of ciprofloxacin tablets tested possess acceptable weight uniformity as per the pharmacopoeia standards. Moreover, the relative standard deviation of the tablets is less than 6 and the number of tablets outside the BP range is within the limit stipulated in the pharmacopoeia [15].

Crushing Strength, Friability, Assay and Disintegration Time of Tablets

The Table 3 below shows the hardness, percentage friability, disintegration time and content of active ingredient of the various brands of immediate release ciprofloxacin tablets.

Crushing strength (hardness) test assesses the ability of tablets to withstand handling without fracturing or chipping [19]. It can also influence friability, disintegration and dissolution. The harder a tablet, the less friable and the more time it takes to disintegrate [20]. Table 3 above shows that CP6 tablets had the highest hardness value (with average of 6.10 kgf) while CP9 and CP13 tablets had the lowest values (3.00 kgf). The British Pharmacopoeia (2014) states that a force of not less than 4 kgf is accepted as satisfactory for hardness [21]. Therefore, all the brands passed the test except for CP9 and CP13 tablets which had hardness values less than 4 kgf.

Friability test is used to evaluate the tablets resistance to abrasion. The USP (2013) specified that a tablet batch should not be more than 1% friable. Friability value for all the brands was below 1 % as shown in table 3 above. This means that all the brands complied with the compendia specification. But, it should be noted that the brand most likely to lose particles during handling is CP9 tablets. CP13 tablets may have had low crushing strength but it is one of the least friable brands, this could be attributed to the physicochemical properties of the excipients employed in the manufacture of this brand [20].

The British Pharmacopoeia (2014) stated that ciprofloxacin tablets should contain not less than 95.0 % and not more than 105.0 % of the label claim. All the brands of ciprofloxacin tablets passed assay test except CP15 and CP12 tablets whose contents of ciprofloxacin are not within the Pharmacopoeia specification.

According to the British Pharmacopoeia (2014), the time limit for disintegration of film coated tablets is < 30 minutes. All the brands of ciprofloxacin tablets used in this study complied with the pharmacopoeia standard [13 – 16].

Dissolution Profile: Figure 2 and figure 3 below are the diagrammatic representations of the release of ciprofloxacin from the tablets studied.

Table 2: Uniformity of weight for the different brands of ciprofloxacin tablets (n=20)

Code Name	Mean weight (mg) ± Standard Deviation	No. of tablets within the BP range	No. of tablets outside the BP range
CP1	741±0.97	20	0
CP2	753±0.86	20	0
CP3	777±1.21	20	0
CP4	871±0.65	20	0
CP5	923±0.80	20	0
CP6	950±0.32	20	0
CP7	734±0.73	20	0
CP8	859±0.56	20	0
CP9	768±3.40	19	1
CP10	754±0.32	20	0
CP11	830±1.26	20	0
CP12	820±0.46	20	0
CP13	946±4.18	18	2
CP14	744±1.21	20	0
CP15	914±0.92	20	0

Table 3: Crushing Strength, Friability, Assay and Disintegration Time of Ciprofloxacin Tablets

Code Name	Crushing Strength (kgf)	Friability (%)	Mean percentage label claim / Assay (%)	Disintegration Time (min)
CP1	4.50 ± 0.05	0.01	99.77	6.00 ± 0.12
CP2	4.48 ± 0.02	0.17	97.75	5.00 ± 0.18
CP3	4.50 ± 0.07	0.08	95.12	10.00 ± 0.22
CP4	4.20 ± 0.12	0.19	101.90	10.00 ± 0.60
CP5	4.50 ± 0.14	0.13	97.70	9.00 ± 0.21
CP6	6.10 ± 0.37	0.23	105.90	14.00 ± 1.00
CP7	4.10 ± 0.18	0.18	102.92	9.00 ± 0.01
CP8	4.50 ± 0.26	0.02	101.21	11.00 ± 0.30
CP9	3.00 ± 0.33	0.27	102.80	1.00 ± 0.02
CP10	4.50 ± 0.05	0.06	97.52	5.00 ± 0.11
CP11	4.50 ± 0.22	0.01	99.63	5.00 ± 0.00
CP12	4.57 ± 0.29	0.23	89.20	6.00 ± 0.92
CP13	3.00 ± 0.41	0.06	98.70	2.00 ± 0.20
CP14	5.00 ± 0.28	0.07	103.53	10.00 ± 0.73
CP15	4.50 ± 0.30	0.14	106.04	10.00 ± 0.40

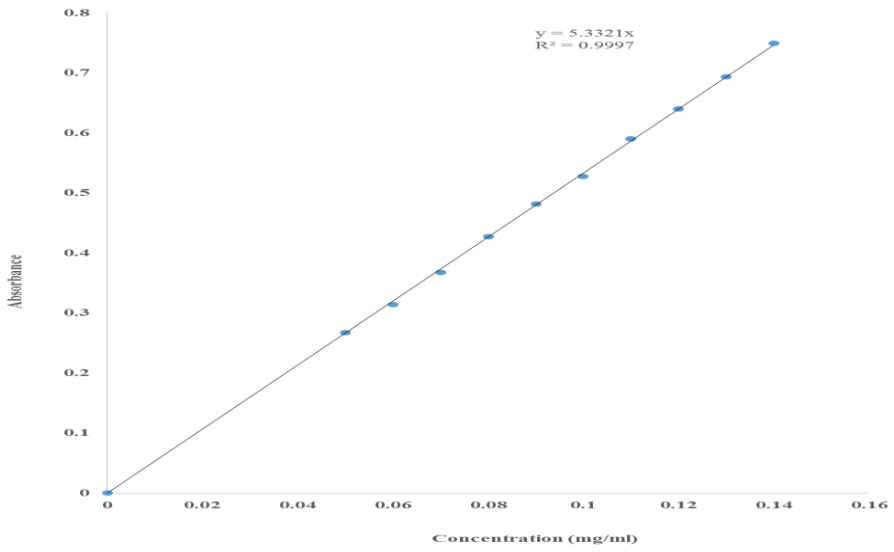

Figure 1:Beer's Plot of Ciptofloxacin hydrochloride

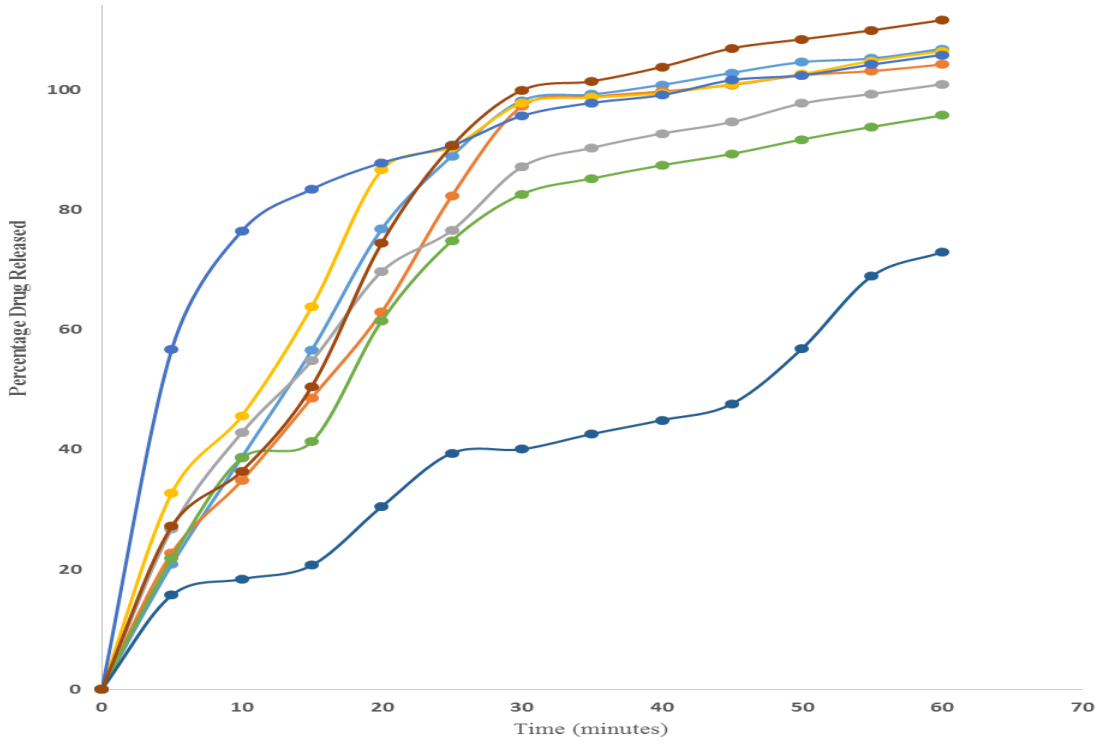

Figure 2: Dissolution profiles of ciprofloxacin from CP1 to CP8 Tablets

Figure 2: Dissolution profile of ciprofloxacin from CP1 to CP8 tablets

The general dissolution requirement of the USP is that 75 % of drug content must be dissolved within 45 minutes. Thus, from the dissolution profile, all the different brands of ciprofloxacin tablets released up to 75 % of their ciprofloxacin content before 45minutes, except for CP11 tablets which released only 47.6 % of its drug content at 45 minutes. Therefore, all brands studied complied to the compendial specification on dissolution/ drug release except CP11 which failed the test [**17 – 18].** This is an indication of good regulation.

CONCLUSION

All the ciprofloxacin tablets tested conformed to compendial standards on weight uniformity, friability, disintegration time, content of active ingredient and drug release except CP11 tablets that failed the dissolution test plus CP9 and CP13 tablets that did not comply with pharmacopoeial specifications on crushing strength.

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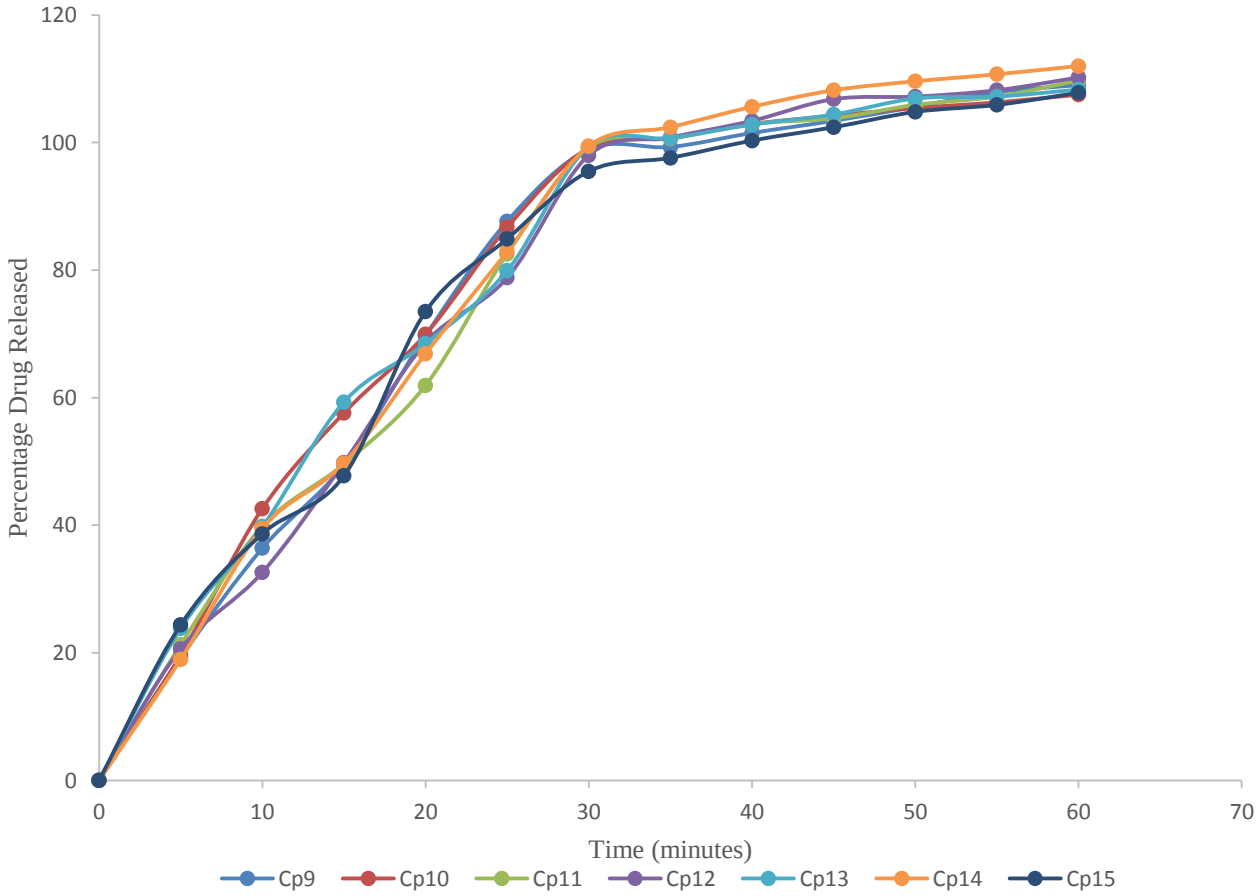

Figure 3: Dissolution profiles of ciprofloxacin from CP9 to CP15 tablets

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