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Assessment of the quality control parameters of five brands of ciprofloxacin hydrochloride caplets in Nigeria

Tochukwu J. Okonkwo*, Eriarie O. Afieroho, Azubuike Odigwe and Patience O. Osadebe

Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka. Enugu State. Nigeria.

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Abstract

The hardness, friability, weight uniformity, disintegration time, content of active ingredient, and bactericidal characteristics of five brands of ciprofloxacin HCl caplets in Nigeria were evaluated using official methods. Brands: A, B and C, exhibited comparable bactericidal activity ($p<0.05$) against *Salmonella paratyphimurium* and could be used interchangeably; while A, and D exhibited comparable bactericidal activity ($p < 0.05$) against the Gram-positive *Staphylococcus aureus* and may be used interchangeably as well. All five brands passed the disintegration time test with disintegration time range of 105.00 - 482.00 sec; and the friability test with a range of percent weight loss on abrasion (B values) of 0.014 - 0.161 %. Only three brands; B, D, and E, passed the content of active ingredient test with percentage absolute drug contents of 94.08, 106.68 and 89.96 %, respectively. Brand B, however passed the weight uniformity test with percentage deviation value of 4.9277 %. None of the brands evaluated met fully the BP or USP requirements for caplets.

Keywords: Quality control; Bioactivity; Interchangeability; Ciprofloxacin caplets

Introduction

Clinically, the desired goal of any drug is to achieve a therapeutic effect on administration. It is therefore imperative that the quality of the drug or drug product must be assured. With the current trend of globalisation, regulation of the entry of drug products into a nation's market becomes a necessity. This will check the influx of fake, sub-standard, or adulterated drugs into the market and their attendant clinical problems especially in a third world society like Nigeria.

A drug is said to be fake if it does not contain what it purports to be in the label claim (WHO, 1998). Existence of fake or substandard brand of any drug or drug product impairs interchangeability among its different brands. Interchangeability is the process of dispensing a different brand of a drug product in place of the prescribed drug (Babalola, 2001). Interchangeable drugs must contain the same amount of the active principle, and must exhibit similar spectrum of biological activity and bioavailability profile on administration. However, because of variations in excipient type, concentration and method of incorporation in drug formulation by different pharmaceutical companies, the possibility of differential

* Corresponding author. *E-mail address*: aquafortisng@yahoo.com Tel: +234 (0) 805 7182279
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bioavailability of marketed brands of the same drug cannot be ruled out.

To determine the possibility of interchangeability of drug products, several quality control parameters like tablet's hardness, friability, weight uniformity, disintegration time, dissolution time, and content of active ingredient among others must be checked in order to assess its quality and efficacy (Olaniyi, 2001 and Swarbrick, 2002). Structurally, ciprofloxacin HCl is 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl) -1,4-dihydroquinoline-3-carboxylic acid hydrochloride. It is a quinolone antibiotic which has revolutionised the treatment of most fastidious bacterial infections like typhoid fever and septicemia (Olaniyi, 2000). Ciprofloxacin HCl like every other quinolone anti-bacterial agent acts by inhibiting the activities of DNAgyrase, and topoisomerase IV (Hardman *et al.*, 2001).

This study is aimed at assessing the quality control, and bactericidal status of five brands of ciprofloxacin HCl caplets (coded A - E) in Nigeria with the view of ascertaining their interchangeability.

Experimental

Sample collection and storage. Five brands of ciprofloxacin HCl caplets A *(E090 B)**; B *(DF – 4001)*; C *(FT -02)*; D *(A – 86)* and E *(E-613)* were randomly purchased from the Head Bridge Drug Market, Onitsha, South-Eastern Nigeria in October, 2005. All the drugs were stored in their packs under conditions specified by the manufacturers prior to assay, which was done before their expiry dates.

Content of active ingredient. Based on the label claim the equivalent mass of each brand of ciprofloxacin HCl containing 50.00 mg of the active ingredient was weighed from a pool of 20 crushed caplets using an analytical balance and dissolved in 500 ml volumetric flask with distilled water to mark. This is to obtain an equivalent active ingredient concentration of 100 ppm. After filtration, 1.5 ml of the stock solution was drawn into a 100 ml volumetric flash using a 5 ml capacity pipette and made up to mark with distilled water to obtain an equivalent active ingredient concentration of 1.5 ppm. This was used for the absorbance measurement at 276.0 nm (The British Pharmacopoeia, 2004; and United State Pharmacopoeia, 2004). The absorbance of five different concentrations (0.5, 1.0, 1.5, 2.0 and 2.5 ppm) of pure samples of ciprofloxacin HCl were used for the Beer-Lamberts plot. The content of active ingredient for each of the five brands of ciprofloxacin HCl caplets was extrapolated from the standard Beer-lamberts plot for the pure ciprofloxacin HCl sample.

Disintegration time test. The disintegration time of randomly chosen caplet of each of the five brands was determined in distilled water using a multi-unit disintegration time apparatus set at 50 rpm. The time taken for the last caplet to break up into small aggregates was noted as the disintegration time (The British Pharmacopoeia, 2004; and United State Pharmacopoeia, 2004).

Weight uniformity test

Ten caplets were selected randomly and weighed singly using an analytical balance (Mettler, UK) (The British Pharmacopoeia, 2004). Average tablet weight, standard deviation and percentage deviation for each of the five brands of ciprofloxacin HCl was calculated. Permitted percentage deviation of 5 % for caplet weight $\geq$ 250 mg was taken as the acceptable limit (Ofoefule, 2002).

Hardness test. Five caplets of each brand were randomly chosen. The hardness of each caplet was determined using the Mosanto Stokes hardness tester and the average hardness of 5 – 7 kgf was considered acceptable for coated tablets (Ofoefule, 2002; and Osadebe and Akabuogu, 2004).

Friability test. Friability is a measure of the resistance of tablet and granules formulations of pharmaceutical products to abrasion (Ofoefule, 2002).Caplets were dedusted,

weighed and agitated in a Roche friabilator. After a time interval of 5 minutes at 25 rpm, they were then dedusted, and re-weighed. The measure of abrasion B calculated as the percentage loss in weight was done using the expression:

$$B = (W_o - W) / W_o \times 100$$

Where B = measure of abrasion (% loss in weight).
W_o = original weight before agitation.
W = weight after agitation and dedusting.

Values of B not exceeding the upper limit of 0.8 – 1 % were considered to be acceptable[9]

Bactericidal assay. The bactericidal activities of each of the five brands against the gram-positive bacteria. *Staphylococcus aureus* (at 5 µg/ml) and the gram-negative bacteria, *Salmonella paratyphimurium* (at 250 µg/ml) measured as inhibition zone diameter (IZD) were determined using the agar diffusion method (Howard et al., 1987). Their minimum inhibitory concentrations (MIC) were also determined from the antilog of the y- intercept of a plot of natural log. Drug concentration against d^2.The mean of the IZD for the five brands at specified concentrations were statistically compared using the student t-test ($p \leq 0.05$) to ascertain their bio-equivalence.

Results and Discussion

The hardness test results in Table 1 showed that whereas three brands: B, C and D were within the acceptable limit of 5 – 7 Kgf (Ofoefule, 2002; and Osadebe and Akabuogu, 2004), two brands: A and E were well above the acceptable limit. Generally, the observed order for the degree of hardness as: E>A>C>B>D.

The observed variations in hardness could be adduced to differences in formulations' excipients, techniques and compressional forces employed by different manufacturers (Osadebe and Akabuogu 2004).

The result of the weight uniformity test in Table 2 revealed that only one brand, B, could be considered acceptable. This fell within the allowed percentage deviation limit of 5 %. A, was slightly higher; while the remaining three brands could be considered to have failed the test. For pharmaceutical products, non-uniformity in weight may be adduced to uneven feeding of granules into the die or irregular movement of the lower punch producing a die space of varying capacity (Aulton, 1990).

Considering the friability test results in Table 3, all the five brands have an abrasion resistance value (B) with a range of 0.014 - 0.16 %. These were considered acceptable based on the acceptable abrasion resistance (B) upper limit of 0.8–1 % for pharmaceutical products (Ofoefule, 2002). The observed trend in abrasion resistance (B) for the five brands were D > C > E > B > A

The result of the Disintegration time test in Table 4, showed that all the five brands have a disintegration time ranging from 105.00 - 482.00 sec. compared to the acceptable upper limit of 900 sec. for film coated tablets/caplets (The British Pharmacopoeia, 2004) they could therefore be considered as satisfactory. Disintegration time determination is one of the two pharmacopoeia tests for measuring in vitro, the ability of the incorporated active ingredient to be released from the tablet.

The results of the content of active ingredient (absolute drug content) assay in Table 5 revealed that three brands, B, D and E, falls within the USP (2004) acceptable limit of 90 - 110 % absolute drug content for ciprofloxacin HCl caplets/tablets (United State Pharmacopoeia, 2004). Two of these, B and E, were considered safe based on the acceptable BP (2004) limit of 95 – 105 % active ciprofloxacin HCl (The British Pharmacopoeia, 2004). Brands, A and C, were below the acceptable BP (2004) and USP (2004) limits for percentage active ciprofloxacin HCl in ciprofloxacin caplets; and could be considered as under dosage on administration as purported in their label claim.

The mean growth inhibitory activities of each brand against *Staphylococcus aureus* and *Salmonella paratyphmurium* at 5 µg/ml and 250 µg/ml respectively, were compared statistically using the student t-test. The results indicated that the bioactivity of A and D against Staphylococcus aureus at 5.00 µg/ml were not significantly different at $p < 0.05$. Against *Salmonella paratyphmurium*, the spectrum of activity of the following pairs: B and C; B, A and C; at 250 µg/ml, were not significantly different at $p < 0.05$. Thus, in the management of infections due to Staphylococcus aureus and by extension other gram-positive bacteria, brands A, and D can be used interchangeably, since both expressed identical spectrum of anti-staphylococcus activity. On the other hand, brands B, A and C can be used interchangeably in the treatment of enteric typhoid fever, and other clinical conditions associated with gram-negative bacteria. Brands E and C could also be used interchangeably against infections due to *Salmonella paratyphmurium*, since both have identical spectrum of anti-salmonella activity at $p < 0.05$.

Table 1: Caplets hardness characteristics of the sampled brands of Ciprofloxacin HCl caplets

Brands	Mean hardness (kgf) ± S.E.M.	Standard deviation	Coefficient of variation (%)	Remark
A *(E090 B)*	11.70 ± 0.42	0.95	8.12	Failed
B *(DF – 4001)*	7.30 ± 1.32	2.95	40.41	Passed
C *(FT -02)*	7.70 ± 0.76	1.70	22.08	Passed
D *(A – 86)*	6.60 ± 0.41	0.93	14.09	Passed
E *(E-613)*	14.20 ± 0.09	0.20	1.41	Failed

Table 2: Weight uniformity characteristics of the sampled brands of Ciprofloxacin HCl caplets

Brands	Mean weight (mg) ± S.E.M.	Standard deviation	Percentage deviation	Remark
A *(E090 B)*	993.68 ± 21.79	68.92	6.94	Failed
B *(DF – 4001)*	455.70 ± 7.10	22.46	4.93	Passed
C *(FT -02)*	967.00 ± 259.45	820.44	84.84	Failed
D *(A – 86)*	945.05 ± 50.50	159.96	16.98	Failed
E *(E-613)*	917.40 ± 74.22	234.71	25.58	Failed

Table 3: Friability characteristics of the sampled brands of ciprofloxacin HCl caplets

Brands	Initial weight (mg)	Final weight (mg)	Abrasion resistance, B, (%wt. loss)
A *(E090 B)*	7323.00	7322.00	0.014
B *(DF – 4001)*	4559.00	4558.00	0.022
C *(FT -02)*	9669.00	9661.00	0.083
D *(A – 86)*	6837.00	6826.00	0.161
E *(E-613)*	9155.00	9152.00	0.033

Table 4: Disintegration time (sec) of the sampled brands of Ciprofloxacin HCl caplets

Brands	Disintegration time (sec)	Disintegration range (sec)	Remark
A *(E090 B)*	450.00	410-450	Passed
B *(DF – 4001)*	125.00	120-125	Passed
C *(FT -02)*	235.00	85-235	Passed
D *(A – 86)*	482.00	305-482	Passed
E *(E-613)*	105.00	55-105	Passed

Table 5: Average absolute drug content of the sampled brands of Ciprofloxacin HCl caplets

Brands	Average absolute drug content (mg)	% ave. abs. drug content	Remark
A *(E090 B)*	390.40	78.08	Under dosage (Failed)
B *(DF – 4001)*	235.20	94.08	Normal dosage (Passed)
C *(FT -02)*	390.40	78.08	Under dosage (Failed)
D *(A – 86)*	449.80	89.96	Normal dosage (Passed)
E *(E-613)*	533.40	106.68	Normal dosage (Passed)

Table 6: Mean bactericidal activity, d, of the sampled brands of ciprofloxacin HCl caplets against *Staphylococcus aureus* and *Salmonella paratyphimurium*

Brand	Bactericidal activity, d, (mm) against micro organism			
	Staphylococcus aureus		*Salmonella paratyphimurium*	
	Mean d ± S.E.M	Stand. dev.	Mean d ± S.E.M	Stand. dev.
A *(E090 B)*	6.80 ± 0.03	0.09	5.20 ± 0.37	0.83
B *(DF – 4001)*	10.90 ± 0.09	0.19	4.90 ± 0.53	0.18
C *(FT -02)*	6.10 ± 002	0.05	4.00 ± 0.17	0.38
D *(A – 86)*	7.10 ± 0.02	0.05	2.90 ± 0.08	0.18
E *(E-613)*	8.40 ± 0.02	0.05	3.40 ± 0.02	0.05

d = (IZD – 8) mm / 2; Where: IZD = inhibition zone diameter. (mm); 8 = cork diameter (mm). d = measure of bactericidal activity (mm).

Table 7: Minimum inhibitory concentration (MIC), μg/ml, of the sampled brands of ciprofloxacin HCl caplets

Bacteria	MIC (μg/ml)				
	A *(E090 B)*	B *(DF – 4001)*	C *(FT -02)*	D *(A – 86)*	E *(E-613)*
Staphylococcus aureus	2.19	2.45	1.81	2.33	
Salmonella paratyphimurium	> 125.00	44.62	≈ 125.00	≈ 125.00	

Conclusion

This study showed that there were variations in the hardness and weight uniformity characteristics of the five selected brands of Ciprofloxacin HCl caplets in Nigeria. Two brands, A and C, could be considered to have failed the content of active ingredient test being below the acceptable pharmacopoeia limits. Three brands, A, B and C exhibited bioequivalent activity against the Gram-negative *Salmonella paratyphmurium*, while A and D were bioequivalent in activity against the gram-positive Staphylococcus aureus. These bioequivalent pairs could be used interchangeably in the treatment of the respective clinical conditions. All brands however passed the disintegration time and friability tests. None of the brands examined met all the bench marks stipulated in the official compendia [BP (2004) and USP (2004)]: Thus, they could be declared sub-standard.

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