

Research Article

Comparative evaluation of the biopharmaceutical and chemical equivalence of some commercially available brands of ciprofloxacin hydrochloride tablets

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Abstract

Purpose: This study was undertaken with the objective of evaluating the biopharmaceutical equivalency of ten brands of ciprofloxacin tablets and the chemical equivalency with the use of an analytical method, which will be easy to use, accurate, reproducible, simple, and inexpensive.

Method: The biopharmaceutical and chemical equivalence of ten brands of ciprofloxacin hydrochloride tablets were assessed through the evaluation of the uniformity of weight, friability test, hardness, disintegration test, dissolution rate, thin layer chromatography and non-aqueous titration procedure with the use of crystal violet solution indicator.

Result: All the brands complied with the official specification for uniformity of weight and friability test, while one of the brands failed the disintegration test. The dissolution rate profile revealed that four of the brands did not attain 70% dissolution throughout the period of the determination, while the other brands had above 70% dissolution at less than 45minutes. The non-aqueous titrimetric procedure showed that the excipients did not affect the procedure; with seven brands having values within the range specified in the USP, while the remaining three brands gave lower values.

Conclusion: Six of the brands evaluated in this study could be regarded as being biopharmaceutically and chemically equivalent, while a particular brand is obviously a fake product. The non-aqueous titrimetric procedure used in this study is simple, inexpensive, and easy to use and could be used in routine monitoring of the quality of ciprofloxacin HCl tablets, especially in the absence of high technology equipments that are not easily available in most developing countries.

Keywords: Ciprofloxacin hydrochloride tablets, non-aqueous titration, chemical equivalence, biopharmaceutical equivalence

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INTRODUCTION

The introduction of generic drug product from multiple sources into the health care delivery system of many developing countries was aimed at improving the overall healthcare delivery systems in such countries. However, this has been accompanied by a variety of problems of which the most critical is the widespread distribution of fake and substandard drug products.

The need to select one product from among several generic drug products of the same active ingredients during the course of therapy is a cause of concern to a healthcare practitioner. The first stage in ascertaining the therapeutic equivalence of any drug product involves ascertaining the chemical and biopharmaceutical equivalency of such drug products¹.

Drug products that are chemically and biopharmaceutically equivalent must be identical in strength, quality, purity as well as content uniformity, disintegration and dissolution rates². The need to ensure that the generic and branded drug products are pharmaceutically and therapeutically equivalent cannot be over emphasized. Variable clinical response to the same dosage form of a drug product supplied by different manufacturers has been reported^{3,4}; therapeutic inequivalences have been reported from the use of some generic brands of drug products such as tolbutamide⁵.

In Nigeria, chemical and biopharmaceutical inequivalencies have been reported for some brands of metronidazole⁶ tablets, ampicillin⁷ and tetracycline⁸ capsules. However, in a study on eight brands of sulphadoxine-pyrimethamine tablets, chemical as well as biopharmaceutical equivalency was observed with three out of eight brands tested, while the remaining five brands were found not to be equivalent⁹.

There are several brands of ciprofloxacin hydrochloride tablets available within the drug delivery system globally as well as in Nigeria. The increasing level of use of ciprofloxacin hydrochloride tablets as a result of its versatility

in the management of various cases of microbiological infections¹⁰ necessitated the need to evaluate the quality of the various brands available.

Ascertaining the quality of drug products involves the use of various procedures which includes both biopharmaceutical and chemical assay techniques. Various methods have been reported for the chemical assay of ciprofloxacin tablets. The United State Pharmacopoeia (USP)¹¹ and British Pharmacopoeia (BP)¹² recommend liquid chromatographic methods for the tablets, while non-aqueous titrimetry with potentiometric determination of end point is used for the pure drug compound.

Others workers have reported methods ranging from derivatization coupled with ion-pair complexation reaction, capillary electrophoresis, high performance liquid chromatography (HPLC), colorimetry to spectrophotometric technique^{13,14,15}. However, all these methods usually require the use of sophisticated equipment coupled with high cost of analysis. Thus, most developing countries are not able to use the methods.

Although, the World Health Organization (WHO) issued guidelines for global standardization and requirements for the registration, assessment, marketing, authorization and quality control of generic drug products¹⁶, many developing countries do not have the technical, financial, or human resources required to monitor the quality of generic drug products being distributed within their regions¹⁷.

The objective of this study was to evaluate the biopharmaceutical equivalency of ten brands of ciprofloxacin tablets as well as their chemical equivalency through the use of an analytical method, which will be easy to use, simple, and inexpensive with results, which compare favourably with established official methods.

EXPERIMENTAL

Materials

Ciprofloxacin HCl pure powder was a gift from Gemini Pharmaceutical Industry, Lagos, Nigeria, while the various brands of the tablets were obtained from retail Pharmacies in Ibadan, Oyo State, Nigeria.

Reagents used include glacial acetic acid, perchloric acid, acetic anhydride, potassium hydrogen phthalate, hydrochloric acid, crystal violet powder, methanol and chloroform. They were all of analytical grade. Ten different brands of ciprofloxacin tablets and the innovator brand with labelled contents of 500mg each, were obtained from retail pharmacies in Ibadan Oyo State, Nigeria.

METHODS

Thin Layer Chromatographic identification: The 0.1%w/v pure ciprofloxacin HCl in methanol and equivalent solution of tablets were identified using thin layer chromatography (TLC) with ultraviolet spectroscopy detection.

Tablet description: The colour, shape and size were examined by visual observation.

Uniformity of weight determination: Twenty tablets from each of the ten brands was weighed individually using a Mettler 1180 weighing balance. The average weights of the tablet were calculated as well as their percentage deviation from the average weight.

Friability Test: Twenty tablets were weighed and subjected to abrasion using Veego tablet friability tester (Model VET – 2D, India) at 25 rev/minute. The tablets were weighed after five minutes and the weight compared to the initial weight.

Hardness Test: This crushing strength was determined using a Keetan tablet hardness tester.

Tablet Disintegration Test: This was determined at 37°C using Veego disintegration testing apparatus (model – VTDH3, Rutartek, India) until no particle remained on the basket of the system. The time taking for each of the four tablets tested in each of the brand was recorded.

Dissolution rate determination (B.P. 1998)¹²: This was determined using the Veego dissolution rate testing apparatus using 0.1M

HCl (900 ml) as the dissolution medium. The dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ and the basket was rotated at 100 r.p.m. Samples (10ml) were withdrawn at timed intervals of 10minutes for 1hour and replaced with 10ml fresh dissolution medium after each sampling. The samples were filtered and diluted appropriately before the absorbances were measured at 276 nm using ultraviolet/visible spectrophotometer (Perkin-Elmer model, Lambda 33). Six tablets were used from each brand.

The content of ciprofloxacin HCl in each sample was determined based on the calibration curve generated at a wavelength of 276nm. The regression equation for the calibration curve was $y = 713.33x + 0.0275$, $r^2 = 0.9773$.

The dissolution profiles of the different brands of ciprofloxacin HCl tablets were generated from the graph of the amount of ciprofloxacin HCl dissolved versus time. The average T_{70} (time for 70% of the active drug to be dissolved) and the amount dissolved at 45minutes were obtained for each brand.

Chemical content determination

Ciprofloxacin HCl pure powder: - 0.1g, 0.2g and 0.3g were dissolved in glacial acetic (15ml) acid, followed by the addition of freshly prepared mercuric (II) acetate solution (0.5ml, 1.0ml and 1.5ml respectively) and acetic anhydride (2ml, 4ml and 5ml respectively). The solutions were titrated against 0.1M acetous perchloric acid using 0.5%w/v crystal violet solution as indicator until a bluish – green end point.

Blank titrations were carried out using 15ml glacial acetic acid. Titre values were adjusted by deducting the blank determination from the assay. This was carried out in triplicate.

Ciprofloxacin HCl tablets (Innovator brand):- Amounts of the crushed tablet material equivalent to 0.1g, 0.2g, 0.3g of pure ciprofloxacin hydrochloride in the tablet dosage form of the innovator brand were weighed. These were dissolved in 15ml glacial acetic acid, followed by the addition of freshly prepared mercuric (II) acetate solution (0.5ml, 1.0ml and 1.5ml respectively) and acetic anhydride (2ml, 4ml and 5ml respectively). The solution was

titrated against 0.1M acetous perchloric acid using 0.5%w/v crystal violet solution as indicator until a bluish – green end point.

Blank titrations were carried out using 15ml glacial acetic acid. Titre values were adjusted by deducting the blank determination from the assay. The procedure was carried out in triplicate.

The procedure was then applied to ten other brands of ciprofloxacin HCl tablets sourced from various pharmacy outlets.

RESULTS

The TLC analysis of the pure drug and the various brands gave R_f values in the range of 0.70 – 0.73 for the different brands. However, a particular brand (Brand J) was observed to contain very little amount of the active drug compound as the intensity of the spot was very weak relative to the reference pure drug and the other brands.

The uniformity of weight determinations for all the brands gave values which complies with the official books specification for weight uniformity, as none of the brands deviated by up to 5% from the mean value (Table 1). Similarly, the friability results for all the brands also complied with official specification; all the brands gave a weight loss of less than the official specification of 1%w/w (Table 2). Also the mean crushing strength which is an indication of the hardness of the tablets showed that brands A, B and C gave the highest crushing strength of 10.3, 12.5 and 11.0 kg/cm² (Table 1).

The disintegration time obtained for nine out of the ten brands was less than the 15minutes official specification for uncoated tablets. However, brand J gave a disintegration time of 21.8 ± 6.29 minutes which is far higher than the specification for uncoated tablets (Table 2).

The obtained dissolution rate profile revealed that four of the brands i.e. E, G, I, and J did not attain 70% dissolution throughout the period of the determination. Of the remaining samples Brand F had the least time to achieve 70% dissolution. The obtained dissolution content at 45minutes was found to be highest with brand F

i.e. 99.82%w/v, while brand J gave the least value with 3.64%w/v (Table 2).

The result of the non-aqueous titration of ciprofloxacin HCl pure powder at 0.1g, 0.2g and 0.3g and the equivalent weights of the powdered tablets of the innovator brand is presented in Table 2. The values obtained with the different concentrations showed that the excipients did not affect the procedure.

The application of the method to ten other brands showed that seven brands (A, B, C, D, E, F and H) had values within the range specified in the USP (90–110%w/v), while the remaining three brands (G, I, J.) gave lower values (Table 3).

DISCUSSION

All the brands used were within their shelf life as at the time of the study. Ten different brands of ciprofloxacin hydrochloride tablets obtained from different retail pharmacy outlets within Ibadan metropolis were subjected to a number of tests in order to assess their biopharmaceutical and chemical equivalence. The assessments involved the use of both qualitative and quantitative methods of evaluation. The qualitative methods of evaluation includes tablet description i.e. colour size and shape, which were carried out by visual observation as well as thin layer chromatography (TLC), while quantitative evaluations used are uniformity of weight, friability, hardness, disintegration and dissolution tests as well as chemical content determination.

The initial identification procedure using TLC revealed that all the brands contained ciprofloxacin HCl as they all gave R_f values ranging between 0.70 – 0.73, which compares well with that of the reference pure ciprofloxacin HCl. However the intensity of the TLC spot obtained for brand J was very weak relative to the other brands at the same concentration. This is an indication that the ciprofloxacin HCl content in brand J is far lower than the labeled content.

The uniformity of weight determination for all the brands showed compliance with the official specifications (B.P 1998)¹², as none of the brands deviated by up to 5% from their mean

Table 1: Uniformity of weight, Friability and Hardness determination of ten brands of ciprofloxacin hydrochloride tablets

Sample	Friability (%)	Hardness (Mean Crushing strength) (Kg/cm ²)	Uniformity of Weight (g)
A	0.000	10.3 ± 0.57	0.785 ± 0.078
B	0.000	12.5 ± 0.5	0.775 ± 0.074
C	0.710	11 ± 0.0	0.705 ± 0.005
D	0.510	7.0 ± 1.0	0.980 ± 0.100
E	0.170	8.2 ± 0.76	0.785 ± 0.060
F	0.260	8.8 ± 1.89	0.785 ± 0.007
G	0.000	7.2 ± 2.75	0.799 ± 0.012
H	0.290	5.3 ± 1.04	0.980 ± 0.010
I	0.040	6.7 ± 0.29	0.786 ± 0.010
J	0.010	8.5 ± 3.5	0.960 ± 0.012

Table 2: Disintegration and Dissolution rate profile for ten brands of ciprofloxacin hydrochloride tablets

Sample	Disintegration Time (minutes)	Dissolution Rate Profile (% Dissolution)	
		Time to attain 70% dissolution (T ₇₀) (Minutes)	% Dissolution at 45 minutes (C ₄₅)
A	3.25 ± 0.95	41.5	72.80
B	2.63 ± 0.48	31.0	88.27
C	5.50 ± 1.29	43.0	71.89
D	2.63 ± 0.48	24.0	83.72
E	7.00 ± 1.83	-	38.22
F	2.50 ± 0.58	14.4	99.82
G	12.00 ± 0.82	-	30.94
H	1.25 ± 0.5	45.5	69.16
I	3.63 ± 1.11	-	50.96
J	21.75 ± 6.29	-	3.64

Table 3: Ciprofloxacin HCl content of pure and innovator brand of ciprofloxacin HCl tablet as determined by non-aqueous titration using acetous HClO₄ as titrant and crystal violet as indicator

Weight of sample (pure powd / equiv wts of tab.) (g)	Chemical content (%w/w)	
	Pure Ciprofloxacin powd	Powdered Ciprofloxacin tab. (Innovator brand)
0.1	99.12 ± 1.48	99.97 ± 2.78
0.2	100.17 ± 1.54	98.01 ± 1.89
0.3	100.37 ± 1.03	100.27 ± 2.05

Table 4: Ciprofloxacin HCl content of ten brands of ciprofloxacin HCl tablets as determined by non-aqueous titration using acetous HClO₄ as titrant and crystal violet as indicator

Brand	% Chemical content (%w/w)	Brand	% Chemical content (%w/w)
A	96.17 ± 1.92	F	90.39 ± 2.76
B	90.62 ± 2.05	G	84.14 ± 1.12
C	90.62 ± 2.04	H	90.59 ± 2.75
D	90.03 ± 3.45	I	87.27 ± 0.70
E	91.85 ± 3.36	J	19.72 ± 15.62

values and no tablet deviated by twice this value

(Table 1). This indicates that the weights of the tablets in each batch within each brand are within the expected official specifications.

Similarly, all the brands gave less than 0.8%w/w loss in weight with the friability test determination; this is less than the official specification of 1%w/w (B. P. 1998). This showed that all the brands could withstand abrasion without loss of tablet integrity. The mean crushing strength determination which is a measure of the degree of hardness of the tablets gave the highest values of 12.5, 11.0 and 10.3kgcm⁻² for brands B, C and A respectively, while the other brands had values less than 9.0kgcm⁻². Although, the crushing strength is not an official method of assessing tablet quality, it is still useful in assessing the integrity of tablet dosage forms.

All the brands except brand J passed the disintegration test (Table 2). The B.P. 1988 specifies 15 minutes and the inability of brand J to disintegrate within this time limit is an indication that the drug will show poor disintegration in the gastrointestinal tract. Hence, the tablet may not be broken down to facilitate release of content into the system. This usually has a direct effect on the dissolution and bioavailability of the drugs.

The B.P. specifies that not less than 70%w/w labeled content should dissolved at 45minutes. The result obtained from this study revealed that four of the brands; E, G, I and J did not achieve this concentration at 45minutes (Table 2, Figure 1). Similarly the four brands could not achieve 70% dissolution throughout the 1 hour period of the determination. The obvious implication of this is that the four brands may exhibit poor bioavailability profile *in vivo*. Dissolution rate has been reported to have a direct bearing on the bioavailability profile of tablet dosage forms as it can be used to predict the drug release pattern *in vivo*¹. Brand J with the 3.64%w/v dissolution at 45minutes corroborates the disintegration rate result obtained for the brand. The disintegration time of 21.8 ± 6.29 minutes obtained for brand J may definitely indicate that the drug would not be released into the dissolution medium easily.

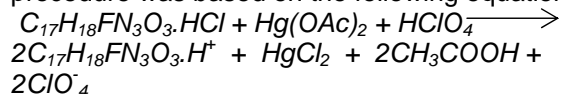
Although comparative bioavailability studies would be required to draw clinical conclusions, the failure of some of these products to meet the B.P. requirements for dissolution indicates formulation differences that could result in differences in bioavailability.

A study on 85 generic products from 21 countries reported that 91% of the generic piroxicam products evaluated failed to meet the routine in vitro USP quality assurance criteria for potency and or dissolution¹⁸. This difference in dissolution could result in altered bioavailability and hence potency, which may result in therapeutic failure.

One of the objectives of this study is to provide a simple easy to use, inexpensive and sensitive analytical technique, which could be used in the monitoring of the quality of ciprofloxacin HCl tablet available within the drug distribution system in a developing country.

The chemical content determination procedure used in this study involves the modification of the non- aqueous titration with potentiometric end point determination specified in B.P for ciprofloxacin HCl pure powder. The modification involves the addition of acetic anhydride and mercuric (II) acetate solution, using 5%w/v crystal violet solution as indicator.

The application of the non-aqueous titrimetric procedure was based on the following equation;



The pure ciprofloxacin HCl powder at 0.1, 0.2 & 0.3g gave 99.12 ± 1.48, 100.17 ± 1.54 & 100.37 ± 1.03%w/w respectively which is in line with the USP 1990 specification of 90 – 110%w/w. Similarly, equivalent weights of the powdered ciprofloxacin HCl tablets (innovator brand) gave 99.97 ± 2.78, 98.01 ± 1.89 & 100.27 ± 2.05w/w respectively. The procedure was repeatable with consistent results and very good interday and intraday precision. The excipients of the tablets did not interfere with the assay procedure and result as the colour end point was clear and stable.

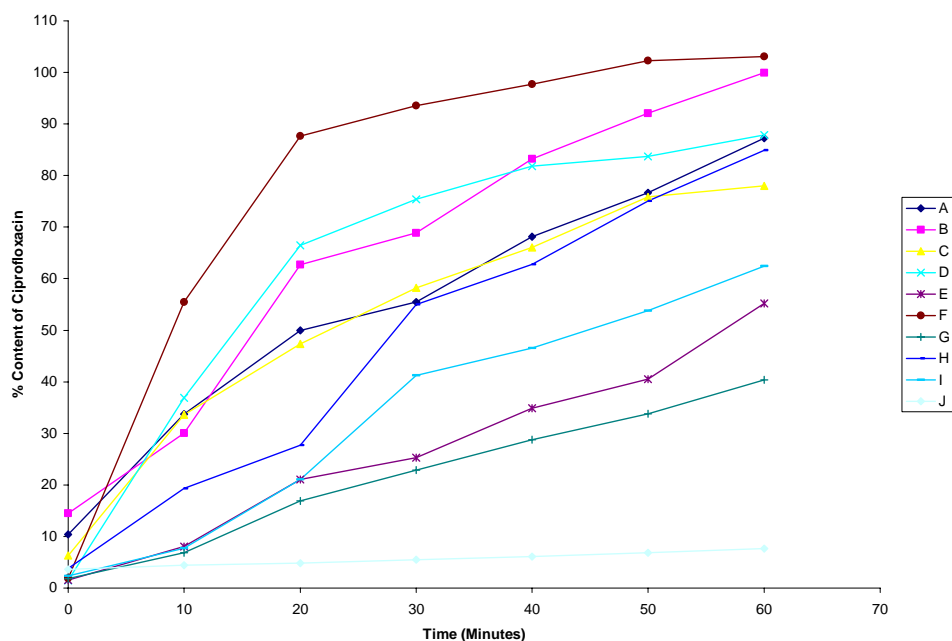


Figure 1: Dissolution profile of the ten different brands of ciprofloxacin hydrochloride in 0.1M HCl at $37 \pm 0.5^\circ \text{C}$.

The suitability of this method for the assay of ciprofloxacin HCl tablets was determined by applying the method to ten other brands of the drug. Seven of the brands (A, B, C, D, E, F and H) gave values that conform to the U.S.P specification of ciprofloxacin HCl content, while the remaining three brands (G, I and J), gave lower contents (Table 3). The percentage deviation from the mean for all the samples at different concentrations was not greater than $\pm 3.5\%w/w$, except Brand J, which deviated by $\pm 15.62\%w/w$.

The method was able to detect an apparently fake brand of ciprofloxacin HCl tablets i. e. brand J, which gave a percentage content of $19.72 \pm 15.62\%w/w$; thus confirming the result obtained from the thin layer chromatographic analysis of the brand, which raises questions as to the quality of the brand. This implies that the method can be successfully used to detect apparently fake ciprofloxacin tablets.

Non-aqueous titration procedure has been reported for the chemical content determination

of various drugs such as chlodiazepoxide, chlorpromazine, pyrimethamine, metronidazole, salbutamol phosphate, promethazine HCl, methyl dopa, lignocaine, ofloxacin and norfloxacin^{5, 12}. Earlier reports on ciprofloxacin HCl tablet dosage by colorimetric method gave $101.23 \pm 2.85\%w/w$, while microbiological assay gave $97.96 \pm 0.87\%w/w$ ¹⁰. Liquid chromatographic technique is the official method specified in the official books for ciprofloxacin HCl tablets. However, the equipment is not readily affordable due to high cost of purchase and maintenance. Hence the need to develop a simple method which can easily be used to monitor the quality of the drug products cannot be over emphasized.

It is quite interesting to note that brand J is obviously a fake product based on the results obtained for the critical quality control parameters such as TLC identification, disintegration, dissolution and chemical content determinations.

Brands G and I could be regarded as substandard products; their failure of the chemical content determination is reflected in their dissolution rate profile in which both of them could not achieve 70% dissolution at 45 minutes and none of them achieved 70% dissolution throughout the 1 hour period of the determination.

Brand E with $91.85 \pm 3.36\%$ w/w chemical content could not achieve 70% dissolution, while its dissolved content at 45 minutes was 38.22% w/v. This obviously indicates a problem with dissolution which may indicate formulation problem. Thus the fact that a product passes the chemical content determination does not indicate that the product will be the therapeutically useful.

Ironically, brands A, B and C with very high crushing strength still exhibited very good quality control parameters such as dissolution profile, disintegration rate and chemical content determination. This indicates that hardness test is not a critical quality control parameter.

It was quite interesting that all the brands had NAFDAC registration numbers indicating that the brands were duly registered for use in the country.

CONCLUSION

The differences in quality control parameters observed in this study with respect to the ciprofloxacin HCl tablet dosage form used in the study have implications in terms of product equivalency and standards of multisourced products available within the study area. Healthcare providers should take this into account.

The non- aqueous titrimetric procedure for the assay of ciprofloxacin HCl used in this study is simple, inexpensive, reproducible and easy to use and could be used in routine monitoring of the quality of ciprofloxacin HCl pure powder and tablets, especially in the absence of high technology equipment that are not easily available in most developing countries.

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