Available online at http://ajol.info/index.php/ijbcs

Int. J. Biol. Chem. Sci. 5(1): 28-37, February 2011

International Journal of Biological and Chemical Sciences

ISSN 1991-8631

Original Paper

http://indexmedicus.afro.who.int

Simple and cost-effective spectrophotometric and titrimetric methods for the determination of ciprofloxacin in tablets

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ABSTRACT

Ciprofloxacin is a synthetic chemotherapeutic agent used in the treatment of infections caused by gram negative and gram positive bacteria. Due to its versatility in anti-bacterial chemotherapy, this study sets out to provide simple, in-expensive and sensitive analytical techniques involving UV-spectrophotometric and titrimetric methods. Method validation was by means of a precision assay. The methods were applied to the determination of ciprofloxacin hydrochloride in tablets available within the Nigerian drug distribution system. Ten different brands of ciprofloxacin tablets were analysed for ciprofloxacin by UV spectrophotometry at the λ_{max} of 271.5 nm and redox titration using KMnO4 in alkaline medium. The spectrophotometric results, expressed as a percentage of stated amounts of ciprofloxacin were 95.5 - 103.5%w/w, while the titrimetric results were 95.0 - 100.3%^{w}/w. Some 70% of the results from the two methods were in line with the high performance liquid chromatographic method specified by BP 2008. The results show that both the spectrophotometric and titrimetric methods described are suitable for the assay of ciprofloxacin in tablets.

Keywords: UV- Spectrophotometry; Redox titrimetry; Analytical methods; Ciprofloxacin; Tablets

INTRODUCTION

The introduction of generic drug products from multiple sources into the health care delivery system of many developing countries is aimed at improving the overall health care 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 generics is a major concern to health care providers (Olaniyi et al., 2001; Eboka and Oheri, 2005).

There are several brands of ciprofloxacin hydrochloride tablets within the drug distribution system globally, Nigeria included. The increasing rate of use of ciprofloxacin hydrochloride tablets as a result of its versatility in the treatment of various cases of microbial infections such as gastroenteritis; including cholera, travellers' diarrhoea; typhoid; gonorrhoea, legionnaire's disease; meningococal meningitis, respiratory tract infections including pseudomonal infection in cystic fibrosis (Shin et al., 2003; Noel et al., 2007) has necessitated the need to assess the quality of the various brands available using a simple, affordable and versatie techniques, such as spectrophoto-

metry and titrimetry (Corti et al., 1994; Clarke's, 2006).

Ciprofloxacin hydrochloride, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1–cyclopropyl-6-fluoro-1,4-dihydro-4-oxa-7-(piperazinyl)-3-uinolone carboxylic acid with an empirical formula of $C_{17}H_{18}FN_3O_3.HCl.H_2O$ and structural formula as shown in Fig. 1.

Most studies on analytical determination of fluoroquinolones in different matrices feature HPLC (Groeneveld and Brouwers, 1986; Griggs and Wise, 1989; Nangia et al., 1990; Samanidou et al., 2003). Although the authors eulogize the effectiveness of the HPLC technique, they also acknowledge the demerit of high cost involved.

Electrophoretic techniques such as, capillary zone electrophoresis (CZE) and micella electrokinectic capillary chromatography have also been reported for the determination of quinolone antibacterials. CZE is a good alternative to the HPLC in drug analysis as it combines high resolution, easy automation with modest sample requirements and low solvent consumption. CZE has a very good sensitivity based on UV, fluorescence and mass detection (Heshman, 2005). This is important when the size of the sample is very limited. Highly sensitive detection systems, such as a laser-induced florescence detection and electrochemical detection, have also been reported (El Ries et al., 2005). However, these methods are also highly expensive. Thin layer chromatographic (TLC) methods have also been proposed for ofloxacin in plasma and pleural fluid (Wang et al., 1999) and for norfloxacin, ciprofloxacin in urine (Simonovska et al., 1999) as well as for norfloxacin residues on pharmaceutical equipment surface (Abulkibash et al., 2003). These would seem however, to be of highly limited use in quantitative work.

This study therefore sets to provide simple, inexpensive and sensitive methods, which can be used in monitoring of the quality of ciprofloxacin HCl tablets available within the drug distribution systems in a developing country like Nigeria.

MATERIALS AND METHODS

Materials

All reagents including ciprofloxacin reference standard were obtained from Sigma-Aldrich, USA. The ten (10) different Brands of ciprofloxacin hydrochloride tablets (500 mg), coded A to J, were procured from pharmacies in Yenagoa and environs in the Niger Delta region of Nigeria. Their batch and official registration (NAFDAC) numbers and the address of the manufacturer for each brand as well as their corresponding manufacturing and expiry dates were duly documented.

Equipment

These include: analytical balance (Shimadzu, Japan), volumetric flasks, measuring cylinder, spatula, pipettes, precision pipette (Eppendorf), water bath, burette, retort stand, funnel, matched 1 cm quartz cells, mortar and pestle, beakers, UV–Spectrophotometer (Thermo corporation, England).

Methods

Uniformity of weight

Twenty (20) tablets of each of the ten brands of ciprofloxacin were accurately weighed individually on an analytical balance and the average weight calculated. The percentage deviations of the individual weights from the average weight were computed.

Identification test

Ciprofloxacin HCl (0.1 g) standard was accurately weighed and dissolved in 25 ml of 0.01 M NaOH in a 100 ml volumetric flask. This was shaken and made up to volume with 0.01 M NaOH. The resulting solution was then scanned for the maximum wavelength of absorption (λ_{max}) using uv-vis-spectrophotometer at the wavelength range of 200–320 nm.

Standard curve for ciprofloxacin hydrochloride by UV- spectrophotometry

100 mg of ciprofloxacin HCl was weighed and transferred into a 100 ml volumetric flask. 10 ml of 0.01 M NaOH was then added initially to dissolve it. This was made up to volume with the same solvent. The resulting solution gave a concentration equivalent to 1 mg/ml as the stock solution. From this stock solution, working solutions of the following concentrations; 1 µg/ml, 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml were prepared using a precision pipette. The absorbance of these concentrations were measured and recorded at the λ_{max} of 271.5 nm. The absorbance versus concentration was plotted to obtain a calibration curve using the Microsoft Excel version 2007.

Method validation

Precision and accuracy

The precision and accuracy of the uv-spectrophotometric method were determined by performing five replicate analyses on the pure ciprofloxacin solutions at three different concentrations (i.e. 1 µg/ml, 5 µg/ml and 10 µg/ml). The intra-day precision was evaluated by running these concentrations five times within the day, while the inter-day precision was performed by replicate analyses on the three drug concentrations for a period of five days with fresh solutions on each day.

UV analysis of ciprofloxacin hydrochloride tablet samples

The ciprofloxacin hydrochloride tablet samples were assayed by accurately weighing 20 tablets on an analytical balance. The tablets were finely powdered in a mortar with the aid of a pestle. A portion of the powdered tablets equivalent to 100 mg of ciprofloxacin HCl was carefully weighed and transferred into a 100 ml volumetric flask. 10 ml of 0.01 M NaOH was added and shaken intermittently for 10 min before it was made to volume with 0.01 M NaOH to give a concentration of 1 mg/ml. The sample was then filtered to obtain a clear solution**.** Two solutions of 4 µg/ml and 8 µg/ml were prepared from the stock solution by serial dilution for each sample and their respective absorbance was taken at the λ_{max} of 271.5 nm. The absorbance was extrapolated on the standard curve to determine the actual concentration and the percentage content of each sample was calculated.

Standardization of 0.02 M $KMnO_4$ using oxalic acid

0.6 g of oxalic acid dihydrate was accurately weighed and dissolved in a 100 ml volumetric flask and made to mark with distilled water. 25 ml of this resulting solution was transferred into a 250 ml conical flask and 100 ml of 1M H_2SO_4 was added, warmed in a thermo stated water bath to about 60–70 ^oC and titrated immediately with KMnO4 solution and the end point was recorded as faint pink colour. Equation for the reaction:

$2MnO_4 + 5(COOH)_2 + 6H^+ \rightarrow 2Mn^{2+} + 10CO_2 + 8H_2O$

$H_2C_2O_4 \rightarrow 2CO_2 + 2H^+ + 2e^-$

$H_2C_2O_4.2H_2O \equiv 2e^- \equiv 2H^+$

126.067 g $H_2C_2O_4.2H_2O \equiv$ 2000 ml 0.2M $KMnO_4$ solution

0.006303 g $H_2C_2O_4.2H_2O \equiv$ 1 ml 0.02M $KMnO_4$ solution

Factor of solution = weight of standard solid/milliequivalent x titre volume

Assay of ciprofloxacin hydrochloride by visual titrimetry

A portion of the powdered tablets equivalent to 100 mg of ciprofloxacin HCl was carefully weighed and dissolved in 100 ml 0.02 M $KMnO_4$ solution in 100 ml flask. This was then filtered and 1ml of the filtrate was transferred into another 100 ml volumetric flask and made to volume with distilled water to give a solution of 10 µg/ml. An aliquot of 10 ml of the resulting solution was then transferred into 250 ml conical flask. To this, 10 ml of 0.02 M $KMnO_4$ was added by means of a pipette, the content thoroughly mixed and the flask was set aside for 15 mins.

Finally, the un-reacted oxidant was back titrated with 0.1M $FeSO_4$ solution. Simultaneously, a blank titration was performed, and the amount of ciprofloxacin (drug) in the measured aliquot was calculated from the amount of $KMnO_4$ reacted.

Equation for the reaction:

$C_{17}H_{18}FN_3O_3 + KMn0_4^- + 6H^+ \rightarrow C_{17}H_{18}FN_30_4^- + Mn^{2+} + 3H_2O$

Molar ratio: 1:1 (ciprofloxacin: oxidant)

331.4 g $C_{17}H_{18}FN_3O_3 \equiv$ 1000 ml 1M $KMnO_4$

331.4 g $C_{17}H_{18}FN_3O_3 \equiv$ 1000 ml 1M $KMnO_4$

0.3314 g $C_{17}H_{18}FN_3O_3 \equiv$ 1 ml 1M $KMnO_4$

0.006628 g $C_{17}H_{18}FN_3O_3 \equiv$ 1 ml 0.02M $KMnO_4$

6.628 mg $C_{14}H_{18}FN_3O_3 \equiv$ 1 ml 0.02M $KMnO_4$

Statistical analysis

Student t-test in the SPSS statistical software programme was used to compare the spectrophotometric and titrimetric methods assay results in this study with $p < 0.05$ as the level of significance**.**

RESULTS

Uniformity of weight

The percentage deviation of each tablet from the average weight for the samples A–J ranged from 0.000 to 5.195%.

Standard curve for ciprofloxacin by uv-spetrophotometry

The calibration curve for the standard ciprofloxacin was linear over a concentration range of 1.0 to 10 µg/ml with the regression line equation obtained as $y = 0.84x + 0.025$, which was in line with the Beer-Lambert's law.

Precision of the analytical method

The coefficient of variation, which is a measure of the precision, was < 1% for intra-day run and was < 10% for the inter-day run, which is a measure of reproducibility of the method for ciprofloxacin, is shown in Table 1. Also, the relative error (%), an indicator of accuracy was within 4%.

UV spectrophotometric assay for samples A-J

The % purity for samples A–J determined by UV spectrophotometry is shown in Table 2. Samples A–J showed % purity, which ranged from 95.5 to 103.5% with the highest % deviation of approximately 3% from the mean of all the samples.

Standardization of $KMnO_4$ for visual titration

$KMnO_4$ (0.02 M) was standardized with oxalic acid and the titre values are as shown in Table 3. The factor of solution is then worked out appropriately. The titration was controlled manually by running a blank titration against $FeSO_4$ and the results are shown in Table 4.

Assay of ciprofloxacin in tablet samples by visual titration

Titre values (Table 4) for sample A and the calculation for percent purity are shown below as an example. Samples B to J were similarly treated. The average titre values of 0.02 M $KMnO_4$ after titrations for samples A to J, the amount of ciprofloxacin in the sample, percent purity and the standard deviation obtained from the visual titration are as shown in Table 5. The upper percentage standard deviation for all the samples following titration with 0.02 M $KMnO_4$ is approximately 2.1%. This indicates a good control of the manual operation of the titration. The percentage purity was calculated by taking the ratio of the calculated amount of the ciprofloxacin tablet sample against the expected amount of the same tablet sample and multiplied by 100. All the ciprofloxacin HCl tablet samples had % purity ranging from 95.0 to 100.3%.

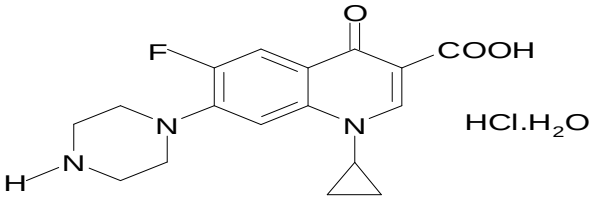

Figure 1: The structure of ciprofloxacin hydrochloride.

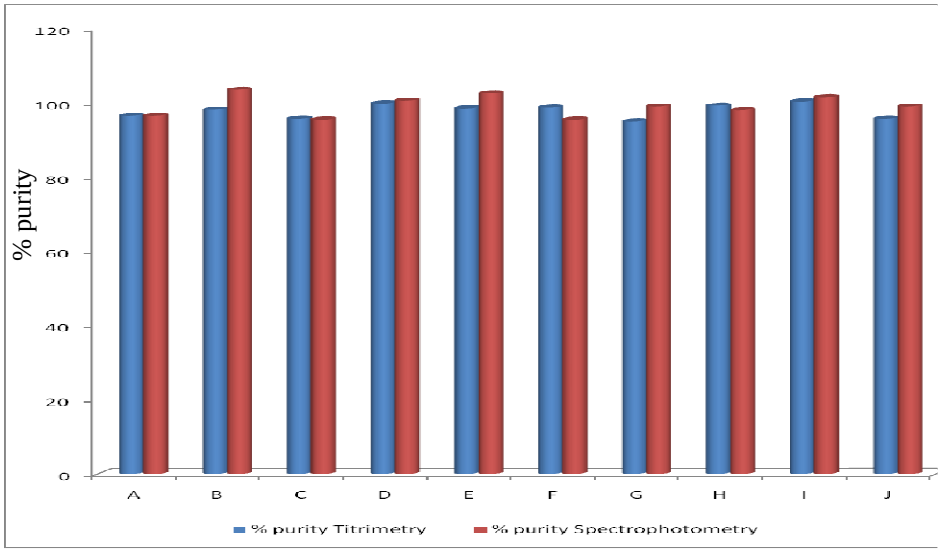

Figure 2: Comparative % purity of ciprofloxacin tablet samples A to J using titrimetric and UV-spectrophotometric methods.

Table 1: Precision and accuracy studies for ciprofloxacin (n=5).

	Expected conc. (µg/ml)	Observed mean conc. ± SD (µg/ml)	Coefficient of variation/Relative error (%)
Intra-day run	1.0	0.96 ± 0.003	0.34
	5.0	4.80 ± 0.038	0.79
	10.0	10.50 ± 0.05	0.48
Inter-day run	1.0	0.92 ± 0.039	4.2
	5.0	5.30 ± 0.47	8.8
	10.0	9.50 ± 0.72	7.6
Accuracy	1.0	1.02 ± 0.04	4
	5.0	4.95 ± 0.15	3
	10.0	10.2 ± 0.36	3.5

Table 2: Percent purity of ciprofloxacin tablet samples A to J using UV Spectrophotometry.

Sample	Average weight of 20 tablet (g)	λ_{max} at 271.5nm	% purity	% deviation
A	0.931	0.908	96.5	1.882
B	0.774	0.970	103.5	3.082
C	0.763	0.902	95.5	2.589
D	0.780	0.942	100.5	0.961
E	0.747	0.957	102.5	2.375
F	0.667	0.897	95.5	2.589
G	0.781	0.927	99.0	0.107
H	0.630	0.917	98.0	0.814
I	0.693	0.948	101.5	1.668
J	0.751	0.925	99.0	0.107

Table 3: Titre values for the standardization of $KMnO_4$ with oxalic acid.

Burette Readings (ml)	Titration			Mean titre value ± SD
	1st	2nd	3rd	
Final reading	85.00	84.00	86.00	85.00
Initial reading	0.00	0.00	0.00	0.00
Volume of $KMnO_4$ used	85.00	84.00	86.00	85.00 ± 1

Factor of solution = weight of standard solid / milliequivalent x titre value = 0.6 / 0.006303 x 85 = 1.12

Table 4: Blank titration and titre values for sample A with $FeSO_4$.

Burette readings (ml)	Blank titration			Titre value for sample A	
	1st	2nd	3rd	1st	2nd
Final reading	18.00	18.25	17.30	4.70	4.80
Initial reading	0.00	0.00	0.00	0.00	0.00
Volume of $FeSO_4$ used	18.00	18.25	17.30	4.70	4.80
Mean titre value (ml)	17.85 ± 0.5			4.75 ± 0.071	

Volume of $FeSO_4$ used = KMnO4 (volume) ; Amount of ciprofloxacin = (B – T) x F x Meq where; B = Blank titire value ; T = Titire value of 0.02M$KMnO_4$ used. Meq = Milliequivalent of Ciprofloxacin; F = Factor of $KMnO_4$;
Amount of Ciprofloxacin = (B – T) x F_{KMnO4} x Meq ciprofloxacin ;
Calculated amount = 17.85 - 4.75 x 1.1111 x 0.006628g/ml; = 0.0964733 g; Expected amount = 0.1 g;
% purity = 0.0964733/0.1 x 100 = 96.5%$^{w}/_{w}$

Table 5: Percent purity of Ciprofloxacin HCl tablet samples by visual titrimetry.

Sample	Average wt. of tablet taken (g)	Average titre (B-T) (ml)	Amount of ciprofloxacin (mg)	% purity	% deviation
A	0.751	13.1	482.4	96.5	0.92
B	0.931	13.3	490.5	98.1	0.21
C	0.763	13.0	478.7	95.7	1.48
D	0.747	13.5	498.9	99.8	1.41
E	0.780	13.4	492.4	98.5	0.49
F	0.781	13.4	493.4	98.7	0.64
G	0.630	12.9	475.0	95.0	1.97
H	0.717	13.5	496.1	99.2	0.99
I	0.774	13.6	500.8	100.3	1.77
J	0.667	13.0	478.7	95.7	1.48

DISCUSSION

The standards for uniformity of weight are applied to tablets, which are supplied in unit dose forms because they are subject to more variations than comparable preparations supplied in multi dose forms. For tablets with average weight above 250 mg, the percentage deviation from the average weight permissible in the official compendium (BP, 2008) is ± 5 %. The ten different brands (samples A-J) of ciprofloxacin tablets passed the test for uniformity of weight. However, two tablets of samples B and E exceeded the 5% deviation from the average weight; it still conformed to the official compendium specification, which stipulates that not more than two tablets must deviate by 5% from the average weight, if twenty tablets are used for the test. The ten samples were assayed by spectrophotometry and visual titrimetry developed in this study.

UV spectrophotometric method is suitable for the analysis of ciprofloxacin tablets since it contains suitable chromophore that absorbs radiation in the UV region at the maximum wavelength (λ_{max}) of 271.5nm. The calibration curve for reference ciprofloxacin was linear over a concentration range of 1.0 to 10.0 µg/ml with the regression line equation obtained as y = 0.84x + 0.025, which is in conformity with the Beer-Lambert's law. The correlation coefficient of (R=0.999) allowed for accurate reading of the concentrations of all the test samples. The coefficient of variation (%), an indicator of precision and the relative error (%), a measure of accuracy of the analytical method, which were evaluated by replicate analyses of the pure drug solution at three different concentrations within working range, indicate high precision and accuracy of the method. The inter-day precision, which is a measure of the reproducibility of the method with coefficient of variation being less than 10% shows that the method was highly reproducible. The spectrophotometric method was therefore sensitive and reproducible. The assay of samples, A–J by spectrophotometric method showed that seventy percent of the samples fell within the BP limit. Samples A, C and F had % purity levels below the official stated limit while sample B had % purity slightly above the upper limit. The overage of sample B may not be unconnected with its deviation from the average uniformity of weight.

The titrimetry was based on an oxidative reaction of ciprofloxacin with $KMnO_4$ yielding N-oxide or pyridinium oxide depending on the site of reaction on the piperazine moiety of ciprofloxacin as an oxidative product. Sixty percent of the brands of ciprofloxacin tablets conformed to the official limits of 98 –102% (USP, 2007; BP, 2008) following the use of redox titrimetry. Samples A, C, G and J had % purity below the official permissible limit when visual titrimetric method was employed. The highest percent deviation of approximately 2% for the samples after the visual titration shows that the manual operation of the titration was efficient to produce a highly sensitive and reproducible method, which is comparable with the non-aqueous titrimetric method described by Adegbolagun et al. (2007). In comparison however, sample F conformed to the stated standard with visual titrimetry while samples G and J, which had percent purity below the stated standard with titrimetric method, conformed to the stated BP requirement with UV-spectrophotometric method.

On comparing the two analytical methods, it was obvious that the assay results of the classical visual titrimetric method was not significantly different (P>0.05) from the UV-spectrophotometry as shown in Fig 1, except for slight variations in the % purity of samples F, G and J with respect to the stated compendia limits. The finding indicates that the redox titrimetric method, though relatively inexpensive and simple, may not be less sensitive and less selective than the UV spectrophotometric method. In most cases, the success of an analytical assay depends on the effective validation of the method used and not really the sophistication of the method. However, where a large number of sample determinations are required the UV spectrophotometric analytical method may be

preferred (Ebeshi et al., 2009). Compliance with official standards as stipulated in the monographs is a measure of the authenticity of a preparation. Therefore, the efficacy of these methods to validate all the test samples was quite essential. The implication of the results in this study was that no single method is adequate to authenticate the quality of particular drug samples, especially when large numbers of such samples are involved.

This study suggests that in carrying out post market surveillance of the quality of pharmaceutical products, manufacturers or regulatory authorities should employ the use of more than one analytical method to authenticate the quality of such products, since in such cases; large amounts as well as wide range of products are considered for evaluation.

Conclusion

The study showed that simple and cost-effective methods (spectrophotometric and tritrimetric) with sufficient accuracy and reproducibility can be developed for the assay of ciprofloxacin in tablets; and that these methods can be used to effectively monitor the quality of ciprofloxacin marketed in a developing country like Nigeria. The study highlights the fact that simplicity and cost-effectiveness of an analytical method are necessary when considering the choice of analytical method to use in monitoring the quality and efficacy of pharmaceutical products.

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