

The development and validation of an UV-Vis spectrophotometric method for the determination of ciprofloxacin in raw material and dosage forms

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ABSTRACT

Introduction

The quality control of medicines is crucial for market surveillance worldwide. With the growing problem of counterfeit drugs, it is important to protect the population from substandard medicines and equip professionals with effective analysis tools. Analytical methods such as UV-Vis spectrometry offer advantages over techniques like HPLC, which require more expensive equipment and solvents, especially in developing countries.

Purpose

This study aimed to develop and validate a simple, precise, accurate, reproducible, and less expensive UV-Vis spectrophotometric method for determining ciprofloxacin HCl in its pure form and dosage forms.

Methods

An appropriate wavelength was selected by scanning a ciprofloxacin HCl standard solution in 0.1M hydrochloric acid between 200–400 nm. The absorption maximum at 277 nm was chosen for further analysis. The method was developed and validated according to ICH guidelines, evaluating criteria such as linearity, precision, accuracy, specificity/selectivity, robustness, LOQ, and LOD.

Results

Ciprofloxacin HCl showed maximum absorption at 277 nm, following Beer-Lambert's law within the concentration range of 2.5 to 15 µg/ml. The linear regression equation was $Y = 0.1104x$, with a correlation coefficient of $R^2 = 0.999$. The LOD and LOQ were 0.4385 µg/ml and 1.4617 µg/ml, respectively. Intra- and inter-day precision had relative standard deviations under 2%, with recovery rates for selectivity (98.36–98.72%) and accuracy (100.10–100.83%) within acceptable ranges. Robustness standard deviations were below 2%, and ciprofloxacin levels in the samples ranged from 94.10% to 110%.

Conclusion

The validated method is suitable for routine quantification of ciprofloxacin HCl as raw API or in tablet forms, with revalidation needed for other pharmaceutical forms.

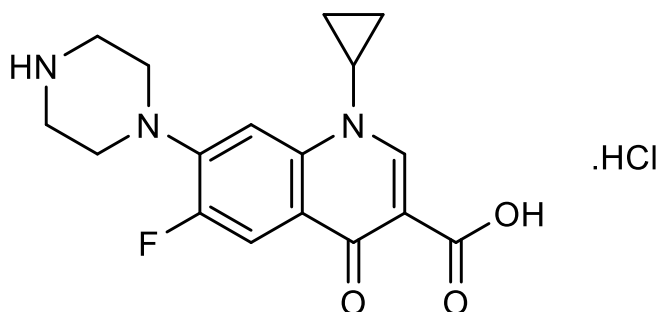
INTRODUCTION

Ciprofloxacin is a synthetic, broad-spectrum antibiotic of the second-generation quinolone family. It is used to treat a wide range of microbial infections, including acute bacterial diarrhoea, typhoid fever, meningitis, intra-abdominal infections, urinary tract infections, respiratory infections, eye infections, and skin structure infections (Solomkin et al., 2010; Sartelli et al., 2012; Mandell, et al., 2012).

Like all quinolones, ciprofloxacin acts by inhibiting bacterial DNA replication in susceptible species. It targets type II topoisomerases: DNA gyrase, the main target in Gram-negative bacteria, and topoisomerase IV, the main target in Gram-positive bacteria (Gilbert, 2013; François et al., 2003; European Pharmacopoeia [Ph. Eur.], 2007).

Scientifically, ciprofloxacin HCl is the hydrochloride salt of 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid, as shown in the structure below:

Figure 1:
Ciprofloxacin Hydrochloride Structure



For its quantitative analysis, high-performance liquid chromatography (HPLC) is described in various reference pharmacopoeias, including the British and American pharmacopoeias (USP, 2008; BP, 2003). Other advanced techniques, such as ultra-performance liquid chromatography (UPLC), have also been used for ciprofloxacin determination in raw materials and are considered more effective (Alabbas et al., 2023). Unfortunately, this technique is not available in all laboratories due to its high cost. Other sensitive and selective methods, such as direct infusion nano-electrospray ionization multi-stage mass spectrometry (DI-nano-ESI-MS³), have been used to identify and assay ciprofloxacin in pharmaceutical dosage forms and human urine (El Demeiry et al., 2020). However, like HPLC and

UPLC, this method is also expensive for laboratories in developing countries.

The aim of this research is to develop and validate a simple, reliable, rapid, and economical UV-visible spectrophotometric method for the determination of ciprofloxacin hydrochloride

METHODS

Apparatus

The following equipment was used: Thermo Scientific GENESYS 10S UV/Vis spectrophotometer series, BRANSONIC CPX1800H-E series ultrasonic bath, and SV series precision analytical balance.

Chemicals

Ciprofloxacin HCl standard (lot: 104-200606-2, purity: 101%) was purchased from Zhejiang Cuobang Pharmaceutical Co. Ltd (China). Magnesium stearate, talc, corn starch, and microcrystalline cellulose were purchased from Prachin Chemical, Neelkanth Minechem, Universal Sarch, and Stannmarc Enterprise in India, respectively. Various batches of compressed ciprofloxacin HCl, including Cifin-500, Shalcip-500, Caisafloxin-500, Cipro-Med-500, Caisafloxacin, and Cypro-500, were purchased from the Kinshasa market in the Democratic Republic of the Congo. Hydrochloric acid (Merck KGaA, Germany) was of analysis grade.

Method Development

Preparation of 0.1M Hydrochloric Acid

0.1M hydrochloric acid was prepared by diluting 8.5 ml of concentrated hydrochloric acid to 1000.0 ml with distilled water (BP, 2021).

Preparation of Ciprofloxacin Hydrochloride Stock Solution

20 mg ciprofloxacin HCl was dissolved in 50 ml of 0.1M HCl in a 200 ml volumetric flask and stirred for 5 minutes using an ultrasonic bath. The volume was then made up to the mark with the same solvent to obtain a stock solution of 100 µg/ml.

Preparation of Ciprofloxacin Hydrochloride Standard Solution

0.5 ml of the ciprofloxacin HCl stock solution was diluted to 10.0 ml with 0.1M hydrochloric acid to obtain a solution containing 5 µg/ml ciprofloxacin HCl. This solution was scanned in a spectrophotometer between 200 and 400 nm.

Method Validation

The method was validated according to ICH guidelines, and validation criteria such as linearity, precision, accuracy, specificity/selectivity, robustness, LOQ, and LOD were selected. The validated method was used to assay 16 batches of ciprofloxacin HCl tablets.

Solutions for Linearity Study

Solutions were prepared by diluting 0.25, 0.5, 0.75, 1, 1.25, and 1.5 mL of ciprofloxacin HCl stock solution in different 10.0 mL volumetric flasks with 0.1 N HCl to obtain final concentrations of 2.5, 5, 7.5, 10, 12.5, and 15 µg/mL. The respective absorbances were measured at 277 nm on three consecutive days of the same week. By applying the method of least squares, the correlation coefficient was calculated, and the equation of the linear regression line was established (Kar, 2005; Toullec et al., 2005).

Solutions for Specificity/Selectivity

The 0.1M HCl solution, used as a blank, and the solution containing 5 µg of ciprofloxacin HCl were scanned to highlight any interference between the two solutions at the wavelength of maximum absorption selected for further experimentation (Pancham et al., 2020). Additionally, to assess the specificity/selectivity of the method, a placebo mixture consisting of 20 mg starch, 20 mg magnesium stearate, 20 mg talc, and 20 mg microcrystalline cellulose was placed in a 200 mL volumetric flask containing 100 mL of 0.1M hydrochloric acid. The mixture was stirred for 5 minutes in an ultrasonic bath, and the volume was made up to the mark with 0.1M HCl to obtain a solution containing 100 µg/mL of each component. After filtration using Whatman filter paper (No. 41), 4 mL, 5 mL, and 6 mL of the filtrate were transferred into three different 100 mL volumetric flasks. Then, 5 mL of the standard ciprofloxacin HCl solution was added to each of the three flasks to obtain solutions with concentrations of 80%, 100%, and 120% of each component of the placebo mixture. After adjusting the volume to the mark with 0.1 N hydrochloric acid, the recovery rate of ciprofloxacin HCl standard added to the placebo was calculated from the absorbances measured at each concentration level (Parakh et al., 2015).

Solutions for Intra- and Inter-Day Precision Study

The intra-day and inter-day precision of the method were determined by analyzing three different solutions containing 5, 10, and 12.5 µg/mL ciprofloxacin HCl

standard, respectively, six times. Intra-day precision was determined on the same day, while inter-day precision was determined on three consecutive days of the same week. Absorbances were measured, and mean concentrations were found. Relative standard deviations (CV%) and relative biases were then calculated.

Solutions for Method Accuracy Study

The accuracy of the method was calculated by the dosed addition method. To a pre-analyzed sample of Caisafloxacin-500 tablet, precise quantities of ciprofloxacin HCl standard were added, and the recovery rate was calculated. Specifically, 20 Caisafloxacin tablets were individually weighed and averaged. A quantity of powder equivalent to 20 mg of ciprofloxacin HCl was finely ground, weighed accurately, and transferred to a 200 mL volumetric flask containing 100 mL of 0.1 M hydrochloric acid. The mixture was stirred in an ultrasonic bath for 5 minutes, and the volume was made up to the mark with the same solvent. After mixing and filtration through Whatman filter paper (No. 41), 5 mL of the filtrate was diluted to 100 mL, and the absorbance of the resulting solution was measured at 277 nm to determine the concentration of the active ingredient. Subsequently, 5 mL of the pre-analyzed solution was transferred to three different 100 mL volumetric flasks, to which ciprofloxacin HCl concentrations were fortified with 4 mL, 5 mL, and 6 mL of the standard solution, respectively. The volume was adjusted to the mark with 0.1M HCl to obtain spiked solutions with concentrations of 80%, 100%, and 120%. Absorbances were measured, and recovery was calculated at each concentration level using the following formula:

$$\% = \frac{C_f - C}{C_a \times 100}$$

Where:

- C_f is the concentration of the fortified sample,
- C is the concentration of the unfortified sample,
- C_a is the concentration of the added substance (Hussein, 2013; Aboud et al., 2017; Pritam et al., 2011).

Solution for Robustness Study

The robustness of the method was determined by performing six absorbance measurements of the stock solution containing 2.5 µg/mL ciprofloxacin HCl standard

at wavelengths equal to 277 nm ± 2 (Dange et al., 2017; Parakh et al., 2015; Jain, 2010; Gajjar et al., 2010). Results are expressed in standard deviations and relative standard deviations.

LOD and LOQ Determination

The limits of detection (LOD) and quantification (LOQ) were calculated based on data obtained from the linearity study. The slope of the regression line and the standard deviation of the y-intercept were calculated by the least-squares method. The two limits were then calculated using the following formulas:

$$LOD = \frac{S_b \times 3.3}{S}$$

$$LOQ = \frac{S_b \times 10}{S}$$

Where S_b is the standard deviation of the y-intercept and S is the slope of the regression line (Pancham et al., 2020; Gajjar et al., 2010).

Method Application on Dosage Forms

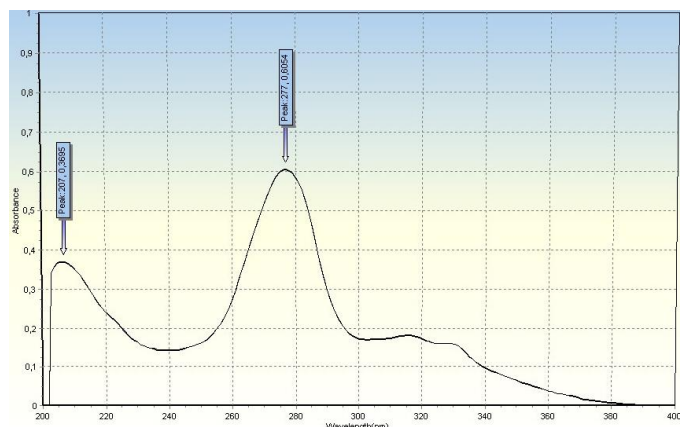
The preparation of solutions for the determination of drug samples was carried out in a similar manner to the method accuracy study. The absorbance of a dilution containing 5 µg/mL ciprofloxacin HCl was measured at 277 nm.

RESULTS AND DISCUSSION

Wavelength Selection

Ciprofloxacin HCl in 0.1M hydrochloric acid showed two absorption maxima at 207 nm and 277 nm, respectively, as shown in Figure 2. The 277 nm wavelength was retained for the remainder of this study (Kar, 2005; Toullec et al., 2005).

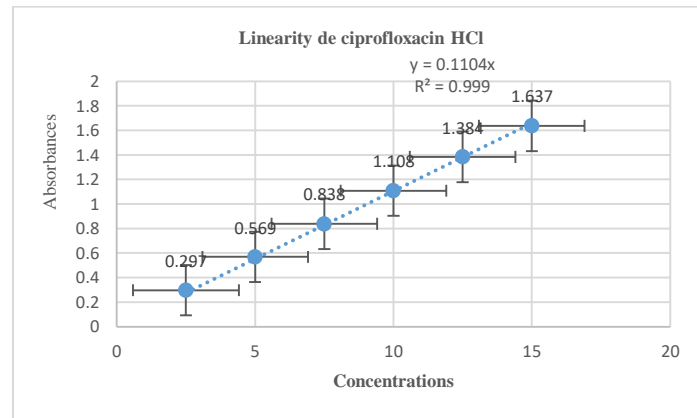
Figure 2:
Ciprofloxacin UV-Vis Spectrum in 0.1M HCl



Linearity Results

A strong correlation was observed between the concentration range of 2.5 to 15 µg/ml and the measured absorbances. The regression line equation obtained was $Y = 0.1104x$, with a correlation coefficient of $R^2 = 0.999$. Figure 3 illustrates the calibration curve for ciprofloxacin HCl in 0.1N hydrochloric acid (Ashutosh, 2005; Toullec et al., 2005).

Figure 3:
Calibration Line for Ciprofloxacin HCl in 0.1M HCl



The corresponding concentrations, absorbances, and specific absorbances are shown in Table 1.

Table 1:
Specific Absorbances of Ciprofloxacin HCl in 0.1M HCl (n = 6)

Concentrations (µg/ml)	Observed Absorbances	Specific Absorbances (A ^{1%} _{1cm})
2.5	0.297	1188
5.0	0.569	1138
7.5	0.838	1117.333
10.0	1.108	1108
12.5	1.384	1107.2
15.0	1.637	1091.333
Specific Absorbance Mean	1124.977	

The method's limits of detection (LOD) and quantification (LOQ) were found to be 0.4385 µg/ml and 1.4617 µg/ml, respectively. The results are summarized in Table 2.

Table 2:
Ciprofloxacin Linearity Study (n = 6)

Parameters	Ciprofloxacin HCl
λmax (nm)	277
Limit of the Beer-Lambert Law (µg/ml)	2.5-15
Linear regression equation	Y = 0.1104x
Correlation coefficient	0.999
Slope	0.1104
Coordinates at origin	0.0000
A1%1cm	1125
LOD	0.4385 µg/ml
LOQ	1.4617 µg/ml

Results of the Intra- and Inter-Day Precision Study

The biases calculated for all concentration levels were within the range of -2% to +2%. Intra-day and inter-day coefficient of variation (CV) values were less than 2% and 3%, respectively, confirming the method's high precision. The results of this test are presented in **Table 3**.

Table 3:
Statistical Data for Intra- and Inter-Day Precision (n = 6)

Introduced Concentrations (µg/ml)	5.0	10.0	12.5
<i>Intra-day Recovered Concentrations (µg/ml)</i>	5.00	9.902	12.320
% Recovered	100	99.02	98.56
Relative Bias (%)	0.00	-0.98	-1.44
Standard Deviations	0.00285	0.00134	0.00134
CV (%)	0.50	0.12	0.09
<i>Inter-day Recovered Concentrations (µg/ml)</i>	5.02	9.911	12.33
% Recovered	100.44	99.11	98.64
Relative Bias (%)	0.4	-0.89	-1.36
Standard Deviations	0.00249	0.00082	0.00090
CV (%)	0.44	0.07	0.06

Results of the Method Accuracy Study

The recovery rates calculated at all concentration levels ranged from 98% to 102%, demonstrating the accuracy of the developed method. The results are shown in **Table 4**.

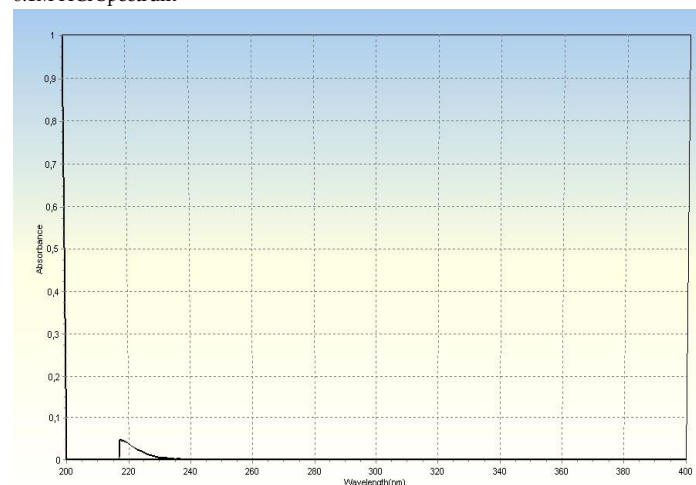
Table 4:
Method Accuracy (n = 3)

No	Caisafloxin (µg/ml)	%Introduced standard	Recovered Standard (µg/ml)	% Recovery	Means ± CV %
1	5.56	80	3.96	100.22	100.44 ± 0.18
		80	3.98	100.67	
		80	3.97	100.44	
2	5.56	100	4.97	100.26	99.81 ± 0.51
		100	4.95	99.10	
		100	4.96	100.08	
3	5.56	120	5.94	98.86	99.38 ± 0.37
		120	5.93	99.71	
		120	5.92	99.57	

Results of Specificity/Selectivity Study

The spectrum of the 0.1M HCl solution used as a blank showed no absorption maxima across the entire wavelength range, indicating that there was no interference between the analyte and the matrix used. Figures 2 and 3 illustrate the spectra of ciprofloxacin HCl and 0.1M HCl, respectively.

Figure 4:
0.1M HCl Spectrum



Additionally, the recovery rates of ciprofloxacin HCl in the reconstituted matrix (placebo) ranged from 98% to 102% across all concentration levels. The difference between the mean analyte contents obtained before and after the addition of placebo was not significant. The results of this test are shown in the **Tables** below:

Table 5:
Recovery Rate of Specificity/Selectivity Study

N ^o	% Excipients	Standard without placebo(Abs)	Average standard contents ± CV %	Standard with placebo (Abs)	Average recovery ± CV (%)
1	80	0.555	98.48 ± 0.14	0.554	98.54 ± 0.22
	80	0.553		0.556	
	80	0.554		0.553	
2	100	0.554	98.72 ± 0.22	0.552	98.36 ± 0.22
	100	0.557		0.555	
	100	0.555		0.553	
3	120	0.556	98.72 ± 0.17	0.558	98.48 ± 0.44
	120	0.556		0.552	
	120	0.554		0.552	

Table 6:
Comparison of Two Averages

Concentrations	80%	100%	120%
Average Standard Contents \pm CV % without Placebo	98.48 \pm 0.14	98.72 \pm 0.22	98.72 \pm 0.17
Average Recovery \pm CV (%)	98.54 \pm 0.22	98.36 \pm 0.22	98.48 \pm 0.44
t-Student Calculated	0.47	2.833	0.824
First-Class Error (α)	0.05		
Degree of Freedom (v)	2		
t-Student Theoretical t (0.05; 2)	4.303		

Method Robustness Results

The robustness of the method was assessed by deliberately changing the maximum absorption wavelength ($\lambda_{\max} \pm 2\text{nm}$). In all cases, the calculated coefficient of variation values were less than 2%. Statistical data for this test are provided in **Table 7**.

Table 7:
Method Robustness (n = 6)

Sr.N ^o	$\lambda \pm 2\text{nm}$ (243)	Conc.($\mu\text{g/ml}$)	Absorbances	Averages	%RSD
1.	276	2.5	0.308	0.304	0.003
2.	276	2.5	0.308		
3.	276	2.5	0.302		
4.	276	2.5	0.302		
5.	276	2.5	0.301		
6.	276	2.5	0.306		
1.	278	2.5	0.306	0.302	1.360
2.	278	2.5	0.301		
3.	278	2.5	0.300		
4.	278	2.5	0.300		
5.	278	2.5	0.300		
6.	278	2.5	0.306		
1.	280	2.5	0.296	0.291	0.860
2.	280	2.5	0.290		
3.	280	2.5	0.290		
4.	280	2.5	0.290		
5.	280	2.5	0.290		
6.	280	2.5	0.293		

Quantification of Pharmaceutical Dosage Forms

The method was used to assay 16 batches of ciprofloxacin tablets, and the analyte contents obtained for each batch ranged from 90% to 110%, in line with the United States Pharmacopeia standard (USP, 2020). The results are shown in **Table 8**.

Table 8:
Active Ingredient Content of Batches of Ciprofloxacin Tablets Analyzed

Samples N ^o	Brand Names	Batches N ^o	Absorbances	Average Content \pm CV %
1	Cifin-500	A037	0.610 0.607 0.608	108.14 \pm 0.20
2	Chalcip 500	K3015	0.613 0.614 0.614	109.09 \pm 0.08
3	Caisafloxin-500	4CFX02	0.626 0.628 0.628	110 \pm 0.14
4	Caisafloxin-500	3CFX01	0.611 0.611 0.612	108.68 \pm 0.08
5	CYPRO-500	Cip 228	0.545 0.545 0.549	97.12 \pm 0.35
6	Shalcip 500	K3008	0.611 0.611 0.608	108.44 \pm 0.23
7	Cifin-500	A032	0.621 0.618 0.618	109.92 \pm 0.70
8	CYPRO-500	Cip 211	0.529 0.530 0.529	94.10 \pm 0.09
9	Chalcip 500	K3016	0.607 0.606 0.605	107.73 \pm 0.13
10	Caisafloxin-500	4CFX01	0.622 0.622 0.621	110 \pm 0.00
11	Cifin-500	A038	0.605 0.605 0.605	107.55 \pm 0.00
12	Ciprofloxacin	BB220101	0.612 0.612 0.613	108.85 \pm 0.07
13	CYPRO-500	CIP 212	0.539 0.536 0.536	95.46 \pm 0.26
14	Cifin-500	A035	0.601 0.602 0.601	106.90 \pm 0.07

CONCLUSION

The method developed for the quantification of pure ciprofloxacin HCl and tablets is linear, with a good correlation between the concentrations introduced and the absorbances observed. It is simple, selective, reliable,

robust, economical, and can be applied to the routine determination of pure ciprofloxacin HCl and tablets.

Ethical Approval: Not applicable

Conflicts of Interest: None declared.

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 Mbenza, P. A.²: Nil identified
 Mana, K. D.²: Nil identified
 Tayey, M. M. J.²: Nil identified
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