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Original Research Paper

STABILITY INDICATING HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF CIPROFLOXACIN AND PHENYLEPHRINE IN PHARMACEUTICAL DOSAGE FORM

Khushbu B. Patel*, Krupa C. Thula and Dilip G Maheshwari

Department of Quality assurance, L.J. Institute of Pharmacy, Ahmedabad-382 210, India

ABSTRACT

A simple, specific, accurate, and stability indicating reversed-phase high-performance liquid chromatographic method was developed for the simultaneous determination of ciprofloxacin hydrochloride and phenylephrine hydrochloride using a Zorbax Bonus RP C18 column and a mobile phase composed of Water : Acetonitrile : Triethylamine (85: 15: 0.1, v/v/v), pH 3 adjusted with orthophosphoric acid. The retention times of ciprofloxacin hydrochloride and phenylephrine hydrochloride were found to be 3.71 min and 2.17 min, respectively. Linearity was established for ciprofloxacin hydrochloride and phenylephrine hydrochloride in the range of 150-900 µg/ml and 5-30 µg/ml, respectively. The percentage recoveries of ciprofloxacin hydrochloride and phenylephrine hydrochloride were found to be in the range of 98.04-101.04%. Both the drugs were subjected to acid and base hydrolysis, oxidation, UV and thermal degradation conditions. Degradation peak was well resolved from the main peak of drug. This method can be successfully employed for simultaneous quantitative analysis of ciprofloxacin hydrochloride and phenylephrine hydrochloride in bulk drugs and formulations.

Keywords: Ciprofloxacin hydrochloride, Phenylephrine hydrochloride, Stability indicating HPLC method, Bulk drugs, Formulations, Hydrolysis, Oxidation, Thermal degradation.

INTRODUCTION

Ciprofloxacin hydrochloride (CIP), an antibacterial drug is widely used to treat a number of infections including infections of bones and joints, endocarditis, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax, chancroid among others^[1-3]. Chemically it is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Various analytical methods have been reported for the assay of CIP alone or in combination with other antibacterial agents in pharmaceutical formulations. They include UV spectroscopy^{4,5}, high performance liquid chromatography.⁶⁻⁹ The chemical structure of ciprofloxacin hydrochloride

is shown in figure 1. Phenylephrine hydrochloride (PHE), a synthetic sympathomimetic agent, is used in the treatment of sinusitis and bronchitis. Chemically it is benzenemethanol, 3-hydroxy- α [(methylamino) methyl]-hydrochloride (R). Various analytical methods have been reported for the assay of PHE alone or in combination with other sympathomimetic agents in pharmaceutical formulations. They include UV spectroscopy^{10,11}, high performance liquid chromatography.¹²⁻¹⁴ The chemical structure of phenylephrine hydrochloride is shown in figure 2. Both drugs are official in Indian pharmacopeia¹⁵, British Pharmacopeia¹⁶ and United States Pharmacopeia.¹⁷ The combination of CIP and PHE is used in treatment of eye infections.

Literature search reveals that various analytical methods like UV-visible spectrophotometry, HPLC have been reported for estimation of CIP and PHE individually. Literature survey describes that there is no reported method for degradation studies of CIP and PHE combination in various stress condition like alkaline, acidic, oxidative, UV and thermal degradation by RP-HPLC method. Therefore it was thought of interest to study the stability of CIP and PHE in various stress conditions like alkaline, acidic, oxidative, UV and thermal by RP-HPLC method. Because analytical methods must be validated before use by the pharmaceutical industry, the proposed method was validated in accordance with International conference in Harmonization ICH Q2 (R1) guidelines¹⁸ by assessing its linearity, accuracy, precision, limit of detection and limit of quantification.

MATERIALS AND METHODS

Apparatus

The chromatography was performed on a RP-HPLC instrument equipped with PDA detector and Zorbax Bonus RP C₁₈ column (250 mm × 4.6 mm, 5µm) was used as stationary phase. Shimadzu-AUX 220 analytical balance, Elico-L1 127 pH meter from Lab India, an ultrasonic cleaner (Frontline FS 4, Mumbai, India), Hot air oven (Lab India), UV stability chamber were used in the study.

Reagents and Materials

Ciprofloxacin hydrochloride and phenylephrine hydrochloride bulk powder were obtained from Cadila healthcare Ltd, Ahmedabad, India. Marketed Product (C-FLOXN Eye drop) was procured from the Calibre pharmaceutical. Label claim of C-FLOXN is ciprofloxacin HCl 0.3% w/v and phenylephrine HCl 0.01% w/v. Acetonitrile, methanol (HPLC grade), orthophosphoric acid (AR grade) were used. Sodium hydroxide, hydrochloric acid, hydrogen peroxide from Merck specialties Pvt Ltd, Mumbai, India were used in the study.

Chromatographic Condition

Separation was achieved by Zorbax Bonus RP C₁₈ column (250mm × 4.6 mm, 5µm) as

stationary phase with water : acetonitrile : triethylamine (85:15:0.1, v/v/v) as a mobile phase and PH of 3.0 adjusted by orthophosphoric acid at a flow rate of 1 ml/min and 10 min run time in isocratic mode. Quantification was achieved of CIP and PHE at 272 nm with PDA detector at 45°C temperature condition and 20 µL injection volume.

Preparation of Stock Solution

Accurately weighed 100 mg of CIP and 100 mg of PHE taken into two different 100 ml volumetric flask and made up volume with water (1000 µg/ml of CIP and PHE).

Preparation of Working Solution

CIP

From stock solution pipetted out 15 ml and diluted up to 100 ml with water (150µg/ml).

PHE

From stock solution pipetted out 1 ml and diluted upto 10 ml with water (100µg/ml). From that pipette out 0.5 ml and diluted up to 10 ml with water (5µg/ml).

Preparation of Calibration Curve

The calibration curves were plotted over a concentration range of 5-30 µg/ml for PHE and 150-900 µg/ml for CIP. Pipetted out 1.5, 3, 4.5, 6, 7.5 and 9 ml from stock solution (1000 µg/ml) of CIP and 0.5, 1, 1.5, 2, 2.5 and 3 ml from stock solution (100 µg/ml) of PHE into 10 ml volumetric flask and made up the volume up to the mark with water to get final concentration range from 150-900 µg/ml respectively for CIP and 5-30 µg/ml respectively for PHE.

Forced Degradation Study

- **Preparation of solution for acid degradation**

Acid decomposition study was performed by refluxing the working solution of both drugs (1 ml) in 1 ml of 0.1M HCl for 4 hr at 80 °C. After 4 hr solution neutralized with 1 ml of same strength of base and finally made up to 10 ml volume with water, sonicated and filtered through 0.45µm membrane filter paper and injected in to HPLC system.

- **Preparation of solution for basic degradation**

Alkali decomposition study was performed by refluxing the working solution of both drugs (1 ml) in 1 ml of 0.1M NaOH for 4 hr at 80 °C. After 4 hr solution neutralized with 1 ml of same strength of acid and finally made up to 10 ml volume with water, sonicated and filtered through 0.45µm membrane filter paper and injected in to HPLC system.

- **Preparation of solution for oxidative degradation**

Oxidative decomposition study was performed by refluxing the working solution of both drugs (1 ml) in 1 ml 3% H₂O₂ for 4 hr at 80 °C. After 4 hr volume made up to 10 ml with water, sonicated and filtered through 0.45µm membrane filter paper and injected into HPLC system.

- **Preparation of solution for thermal degradation**

Thermal decomposition study was performed by refluxing the working solution of both drugs (1 ml) for 4 hr at 80 °C. After 4 hr volume made up to 10 ml volume with water, sonicated and filtered through 0.45µm membrane filter paper and injected into HPLC system.

- **Preparation of solution for UV degradation**

UV degradation was performed by exposing the working solution of both drugs (1 ml) to UV radiation at 254 nm for 2 days. After 2 days volume made up to 10 ml volume with water, sonicated and filtered through 0.45µm membrane filter paper and injected into HPLC system.

METHOD VALIDATION

Linearity and Range

The linearity response was determined by analyzing 6 independent levels of calibration curve in the range of 5-30 µg/ml and 150-900 µg/ml for PHE and CIP respectively. Plot the

calibration curve of area versus respective concentration and find out correlation coefficient and regression line equation for PHE and CIP (figure 6 and 7).

Precision

Repeatability

From working solution of PHE and CIP, respectively 2 ml and 6 ml pipetted out and final concentration of PHE (20 µg/ml) and CIP (600 µg/ml) analysed six times in mixture. The areas of six replicate injections were measured and % RSD was calculated.

Intraday precision

From working solution of PHE and CIP, respectively 1.5, 2, 2.5 ml and 4.5, 6, 7.5 ml pipetted out and final concentrations of PHE (15, 20 and 25 µg/ml) and CIP (450, 600 and 750 µg/ml) were analyzed three times on the same day and %RSD was calculated.

Interday precision

From working solution of PHE and CIP, respectively 1.5, 2, 2.5 ml and 4.5, 6, 7.5 ml pipetted out and final concentrations of PHE (15, 20 and 25 µg/ml) and CIP (450, 600 and 750 µg/ml) were analyzed on three different day and %RSD was calculated.

Accuracy

The accuracy of the method was determined by calculating the recoveries of PHE and CIP by the standard addition method. Known amounts of standard solutions of PHE and CIP were added at 80, 100 and 120 % level to prequantified sample solutions of PHE and CIP (10 and 300 µg/ml respectively). The amounts of PHE and CIP were estimated by applying obtained values to the respective regression line equations, the solution was filtered through 0.45 µ Millipore PVDF filter; filtrate was collected after discarding first few ml. Each sample was prepared in triplicate at each level and injected.

Limit of Detection and Limit of Quantification

The limit of detection (LOD) and limit of quantitation (LOQ) of the method were determined by following equations.

$$LOD = 3.3 \times \sigma/S$$

$$\text{LOQ} = 10 \times \sigma/S$$

Robustness

Varying conditions of temperature, pH and mobile phase composition were carried out as per ICH Q2 (R1) guidelines to estimate the effects on the method.

RESULTS AND DISCUSSION

Optimized Chromatogram:

Mobile phase

Water: Acetonitrile: Triethylamine (85: 15: 0.1 v/v), pH adjusted to 3.0 with Orthophosphoric acid. Optimized chromatogram is shown in figure 3.

Stability results

The results obtained in acidic degradation, alkaline degradation, oxidative degradation, thermal degradation and UV degradation are depicted as chromatograms and given in figure 8, 9, 10, 11 and 12 respectively.

Specificity

Chromatographic condition of diluent was shown that there is no interference from the diluent (figure 4).

Linearity:

The linearity response was determined by analyzing 6 independent levels of calibration curve in the range of 5-30 µg/ml and 150-900 µg/ml for PHE and CIP respectively. The % RSD was found less than 2. The r^2 value was found 0.999 for both the drug (Table 4).

Precision

Repeatability

It was determined by analyzing PHE (20 µg/ml) and CIP (600 µg/ml) six times in mixture. The % RSD was found 0.375 for PHE and 0.234 for CIP (Table 5).

Intraday Precision

For intraday, PHE and CIP in the range of 15-25 µg/ml and 450-750 µg/ml were analyzed three times on the same day. The % RSD was found less than 2 (Table 6).

Interday Precision

For intraday, PHE and CIP in the range of 15-25 µg/ml and 450-750 µg/ml were analyzed on three

different days. The % RSD was found less than 2 (Table 7).

Accuracy

The accuracy of the method was determined by calculating the recoveries of PHE and CIP by the standard addition method at three concentration levels (80, 100 and 120%). The percentage recoveries of PHE and CIP were found to be in the range of 98.04-101.04% (Table 8).

LOD and LOQ

LOD was found to be 0.22 µg/ml and 2.19 µg/ml for PHE and CIP respectively. LOQ was found to be 0.75 µg/ml and 7.91 µg/ml for PHE and CIP respectively (Table 9).

Robustness

Varying conditions of temperature, pH and mobile phase composition were carried out and % RSD was found less than 2% (Table 10).

Applicability of the Method

Applicability of the proposed method was tested by analysing the commercially available Eye drops formulation C-FLOXN (Ciprofloxacin HCl 0.3% and Phenylephrine HCl 0.01%). 1 ml of eye drop solution was taken from 5 ml eye drop formulation and diluted with water upto 10 ml which gives 3000 µg/ml of CIP and 100 µg/ml PHE (Table 11).

CONCLUSION

A simple, accurate and precise stability indicating RP-HPLC assay method was developed for simultaneous estimation of Phenylephrine HCl and Ciprofloxacin HCl in pharmaceutical dosage form. No significant degradation was observed in acidic, basic, UV and thermal condition. Major degradation was observed in oxidative condition. Validation parameters prove that method is repeatable, sensitive and selective for the analysis of Phenylephrine HCl and Ciprofloxacin HCl in formulation. Based on this evidence the method can be stated as highly economical and it is recommended for routine use in quality control laboratories.

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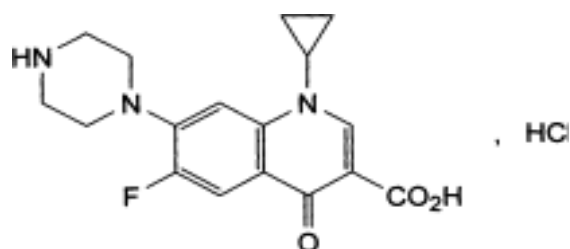


Figure 1: Chemical structure of ciprofloxacin hydrochloride

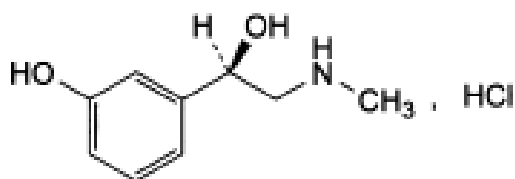


Figure 2: Chemical structure of phenylephrine hydrochloride

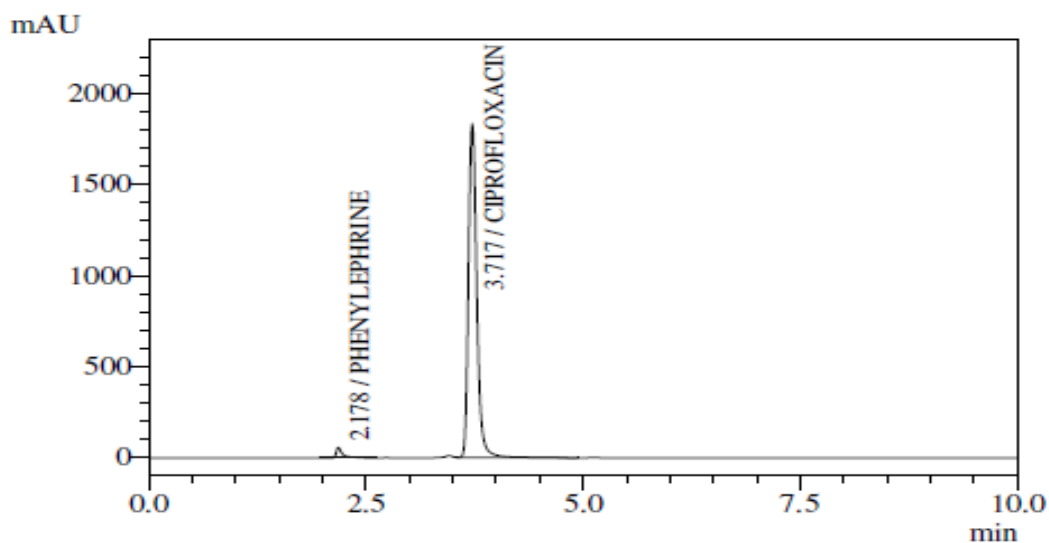


Figure 3: Optimized chromatogram of standard CIP (150 μ g/ml) and PHE (5 μ g/ml)

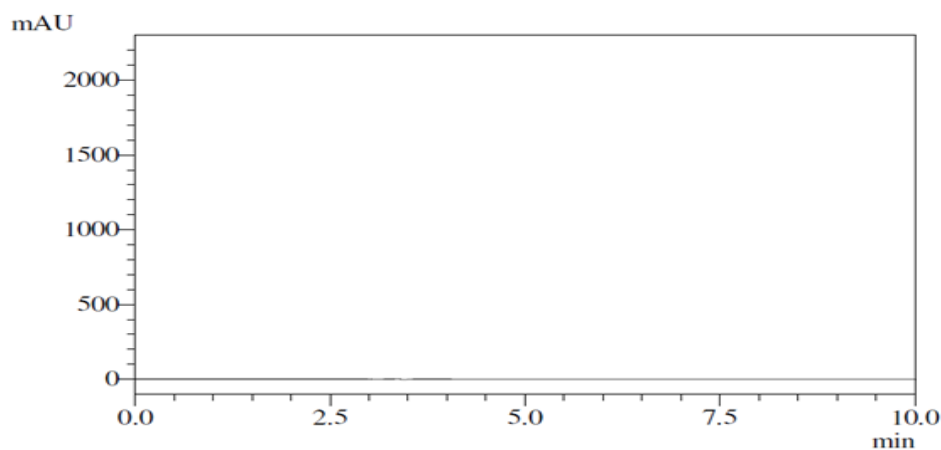


Figure 4: Chromatogram of Diluent (water)

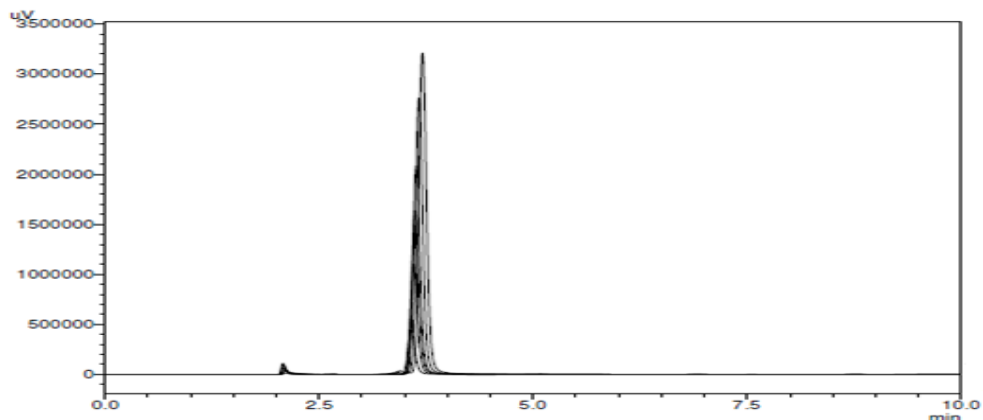


Figure 5: Overlain chromatogram of PHE (5-30 $\mu\text{g/ml}$) and CIP (150-900 $\mu\text{g/ml}$)

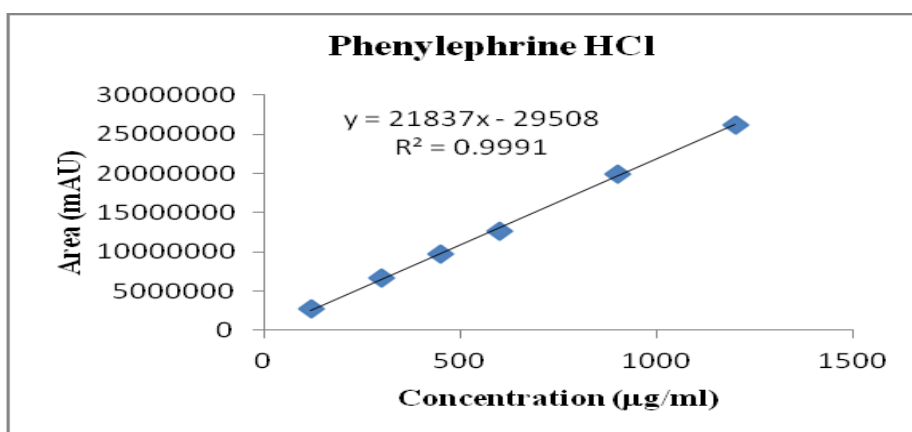


Figure 6: Calibration curve of PHE (5-30 $\mu\text{g/ml}$)

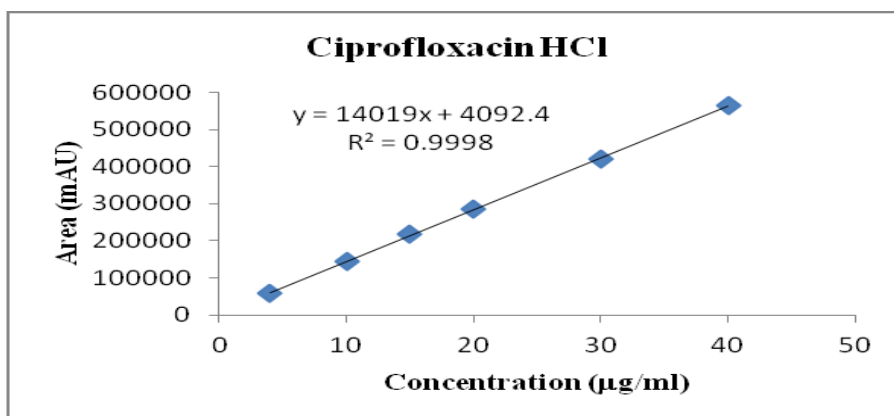


Figure 7: Calibration curve of CIP (150-900 $\mu\text{g/ml}$)

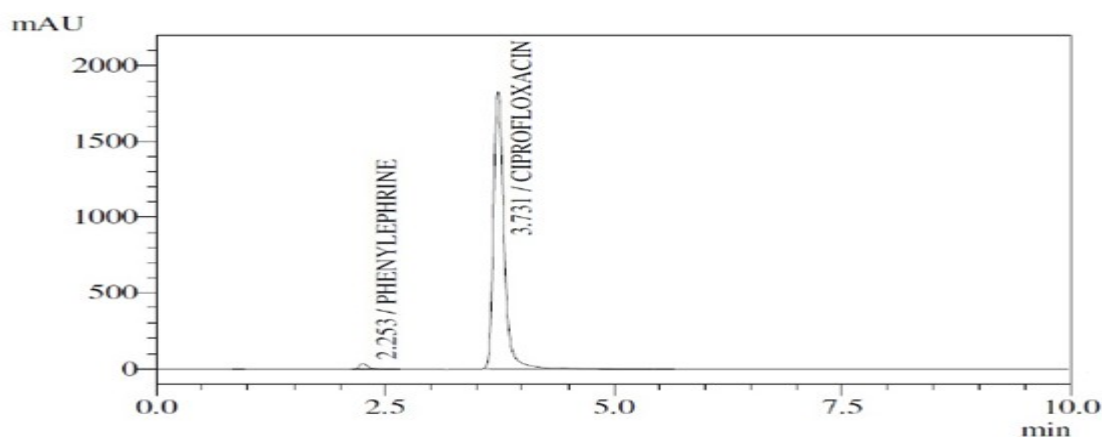


Figure 8: Chromatogram of acid degradation in 0.1N HCl after 4 hr

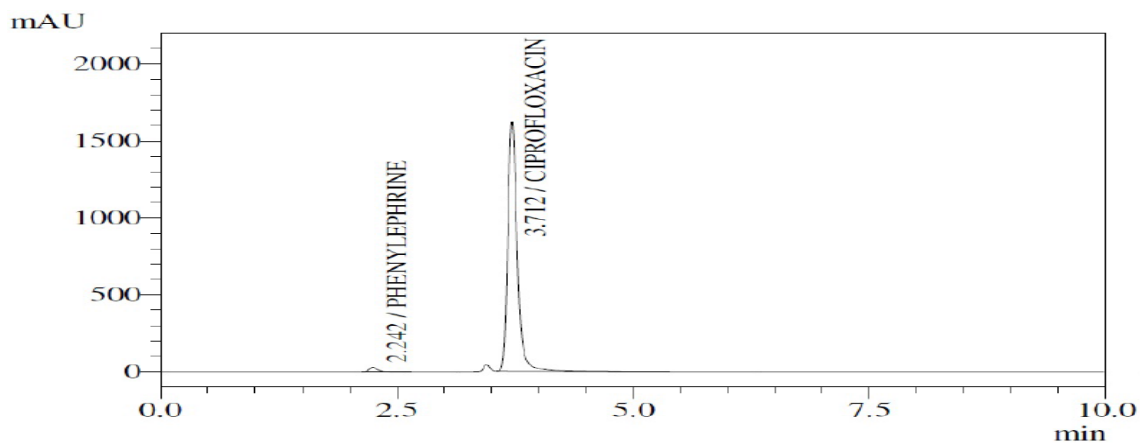


Figure 9: Chromatogram of alkali degradation in 0.1N NaOH after 4 hr

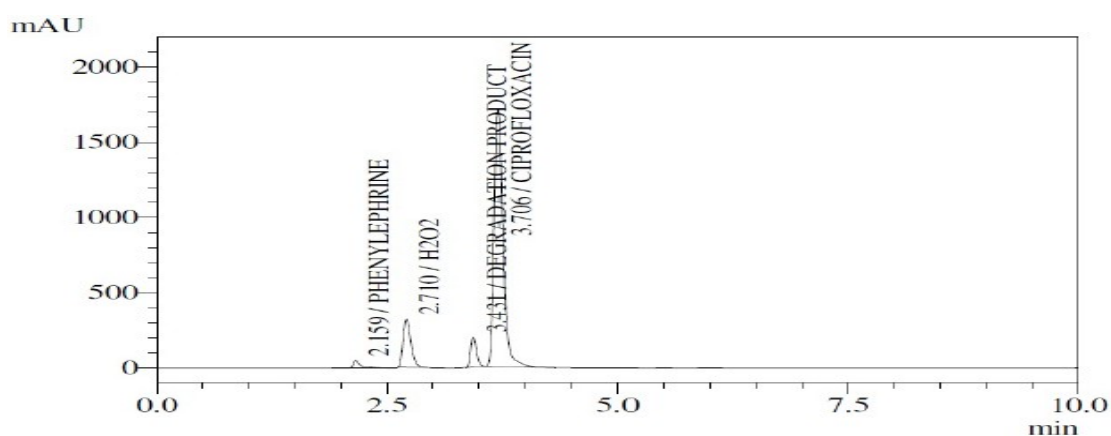


Figure 10: Chromatogram of oxidative degradation in 3% H₂O₂ after 4 hr

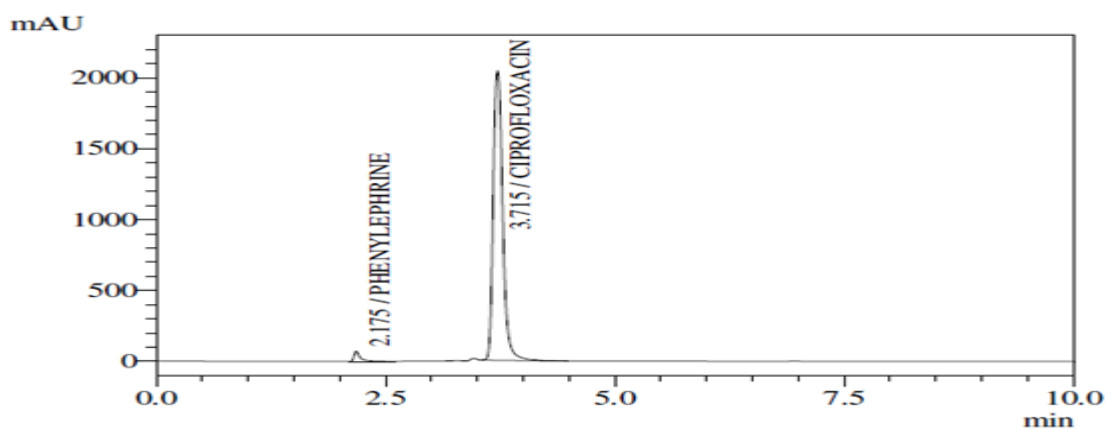


Figure 11: Chromatogram of thermal degradation at 80°C after 4 hr

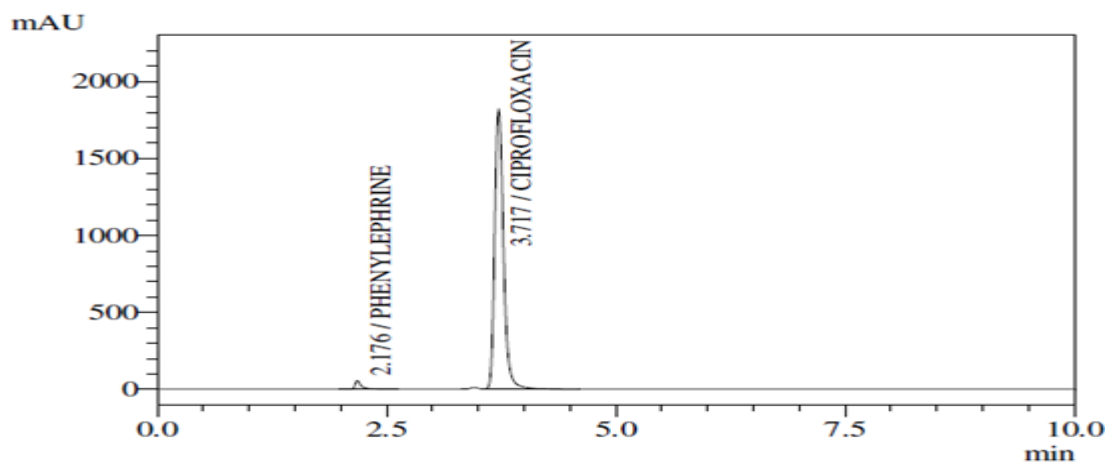


Figure 12: Chromatogram of UV degradation after 2 day

Table 1: System suitability parameters

Parameters	CIP	PHE
Retention time (min)	3.71±0.092	2.17±0.102
Theoretical plate	7356	6794
Tailing factor	1.73	1.49
Area (µv*sec)	14836037	298907
Resolution	5.1	

Table 2: Stability study results of PHE

Conditions	Conc. (µg/ml)	Time period	Peak area		% Degradation
			Before	After	
Acid degradation	20	4 hr	298907	251192	15.96
Base degradation	20	4 hr	298907	276863	7.38
Oxidative degradation	20	4 hr	298907	277789	7.07
Thermal degradation	20	4 hr	298907	276036	7.69
UV degradation	20	2 day	298907	287868	3.7

Table 3: Stability study results of CIP

Conditions	Conc. (µg/ml)	Time period	Peak area		% Degradation
			Before	After	
Acid degradation	600	4 hr	14836037	13771294	7.18
Base degradation	600	4 hr	14836037	11728982	20.95
Oxidative degradation	600	4 hr	14836037	11473473	22.67
Thermal degradation	600	4 hr	14836037	14710806	0.85
UV degradation	600	2 day	14836037	12208955	17.71

Table 4: Linearity data of PHE and CIP (n = 3)

Sr. No.	Conc. (µg/ml)		Mean Area. (mAU) ± S.D.		% RSD	
	PHE	CIP	PHE	CIP	PHE	CIP
1	5	150	57750 ± 236.45	2711801 ± 9510.64	0.409	0.352
2	10	300	143156 ± 530.95	6646235 ± 21079.9	0.370	0.317
3	15	450	218504 ± 424.14	9770091 ± 19658.8	0.195	0.201
4	20	600	287187 ± 1479.14	12568423 ± 20956.55	0.511	0.163
5	25	750	421626 ± 933.94	19899458 ± 53574.69	0.226	0.269
6	30	900	564831 ± 1864.83	26196114 ± 99024.18	0.331	0.378

Table 5: Repeatability data for PHE and CIP (n=6)

Concentration ($\mu\text{g/ml}$)		Area (mAU)	
PHE	CIP	PHE	CIP
20	600	287026	12591150
		284526	12554698
		285362	12549686
		286423	12579854
		288121	12562311
		286123	12619854
Avg. of Area		286889	12587340
S.D		1077.43	29492.81
%RSD		0.375	0.234

Table 6: Intraday precision data for PHE and CIP (n=3)

Conc. ($\mu\text{g/ml}$)		Area (mAU) \pm S.D.		% RSD	
PHE	CIP	PHE	CIP	PHE	CIP
15	450	218417.3 \pm 501.54	9771117.6 \pm 20793.60	0.229	0.212
20	600	287036 \pm 1516.02	12603776 \pm 21889.66	0.528	0.173
25	750	422352.3 \pm 969.52	19908600.6 \pm 53306.03	0.231	0.267

Table 7: Interday precision data for PHE and CIP (n=3)

Conc. ($\mu\text{g/ml}$)		Mean Area (mAU) \pm S.D.		% RSD	
PHE	CIP	PHE	CIP	PHE	CIP
15	450	218961 \pm 519.38	9769784.3 \pm 22796.7	0.237	0.233
20	600	287306 \pm 1572.80	12600442.6 \pm 25278.2	0.547	0.2
25	750	421239.3 \pm 1047.5	19905267.3 \pm 56997.8	0.248	0.286

Table 8: Accuracy data of PHE and CIP

Sample	Concentration level	Average area \pm S.D	% Recovery
PHE	80%	256739 \pm 1688.26	99.92
	100%	301792 \pm 715.19	99.98
	120%	355648 \pm 1684.16	101.04
CIP	80%	11325896 \pm 48937.98	100.03
	100%	14201569 \pm 58045.13	98.04
	120%	17451236 \pm 91509.73	99.98

Table 9: LOD and LOQ for PHE and CIP

Parameter	PHE	CIP
LOD ($\mu\text{g/ml}$)	0.22	2.19
LOQ ($\mu\text{g/ml}$)	0.75	7.91

Table 10: Robustness study of PHE and CIP (n=3)

Condition	Variation	PHE		CIP	
		Mean Area \pm S.D.	% R.S.D	Mean Area \pm S.D.	% R.S.D
Temp. (45 \pm 5°C)	40°C	287372.6 \pm 1484.6	0.516	12603109.3 \pm 22489.7	0.178
	50°C	287409.3 \pm 1437.8	0.5	12604409.3 \pm 21361.7	0.169
Mobile phase composition (1 \pm 0.1 mL/min)	0.9 ml/min	287339.3 \pm 1528.2	0.531	12618776 \pm 24051.2	0.19
	1.1 ml/min	287416 \pm 1429.4	0.497	12609776 \pm 18453.4	0.146
pH(3.0 \pm 0.1)	pH 3.1	287372.6 \pm 1484.6	0.519	12613109.3 \pm 19654.2	0.155
	PH 2.9	287359.3 \pm 1502.4	0.522	12614109.3 \pm 20182.6	0.160

Table 11: Analysis of market formulation (n=3)

Eye drops	Label claim		Amount found (mg)		% Assay \pm S.D	
	PHE	CIP	PHE	CIP	PHE	CIP
C-FLOXN	0.1 mg	3 mg	0.099	3.04	98.9 \pm 0.25	101.33 \pm 0.1

Table 12: Validation summary

Sr. No.	Parameter	PHE	CIP
1	Linearity Range	5-30 μ g/ml	150-900 μ g/ml
2	Correlation coefficient (R ²)	0.999	0.999
3	Precision (% R.S.D)		
	1. Repeatability (n=6)	0.375	0.234
	2. Intraday precision (n=3)	0.229-0.528	0.173-0.267
	3. Interday precision (n=3)	0.237-0.547	0.20-0.28
4	Accuracy (% recovery), n=3	99.92-101.04	98.04-100.03
5	% Assay (n=3) \pm S.D	98.9 % \pm 0.25	101.33 % \pm 0.19
6	Limit of Detection (μ g/ml)	0.22	2.19
7	Limit of Quantitation (μ g/ml)	0.75	7.91

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Correspondence Author:

Khushbu B. Patel

Department of Quality assurance, L.J. Institute of Pharmacy, Ahmedabad-382 210, India

Email: khushbupatel18@yahoo.com

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