WJPMR, 2026, 12(4), 242-247

Research Article

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Impact Factor: 7.555

ISSN (O): 2455-3301

ISSN (P): 3051-2557

Coden USA: WJPMBB

DEVELOPMENT OF NEW SPECTROSCOPIC METHOD FOR QUANTITATION OF CEFIXIME TRIHYDRATE CONTENT USING HYDROTROPHY PHENOMENON

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DOI: https://doi.org/10.5281/zenodo.19415912

How to cite this Article: R. Revathi*[1], V. Ganesan[2], E. Mohammed Thowfic Raja[2], A. Chelladurai[3], M. Premkumar[1], K. Sudharsan[1]. (2026). Development of New Spectroscopic Method for Quantitation of Cefixime Trihydrate Content Using Hydrotrophy Phenomenon. World Journal of Pharmaceutical and Medical Research, 12(4), 242–247.

Article Received on 05/03/2026 **Article Revised on 25/03/2026** **Article Published on 04/04/2026**

ABSTRACT

The aim to develop the new ultra violet spectroscopic method for estimating the content of cefixime trihydrate (CT) using hydrotrophy phenomenon is to reduce the cost, time and environmental friendly. The hydrotropic solubilizing agent is used to increase the drug's aqueous solubility and to avoid the usage of organic solvents. Approximately 1% sodium bicarbonate solution was used as solvent to dissolve the pure drug as well to make the suitable dilution of marketed formulations. Absorbance of CT was measured at 287 nm (λ max). Then linearity plot was made in the concentration range of 10-100 µg/mL with y = 0.0098x - 0.0157 as regression equation. In accordance with ICH guidelines, this method was validated with accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ). The percentage recovery of CT was found between 98.68% and 99.77%. The %RSD values for intermediate precision and repeatability were lower than 2% proved the method precision. The values of LOD and LOQ, which were observed as 3.133µg/mL and 9.494µg/mL, respectively, use the regression equation. The suggested procedure was employed to commercial formulation and showed an assay percentage ranging from 99 to 101 percent. Therefore, instead of using other sophisticated method for frequent analysis, this quick, affordable, and eco friendly method can be used as a substitute for analysis of CT content in pure drug and finished dosage forms.

KEYWORDS: Cefixime trihydrate, Hydrotrophy, Affordable, Robustness.

INTRODUCTION

Cefixime trihydrate (CT) is an orally active broad spectrum antibiotic under cephalosporin derivative. These are beta-lactam antibiotics and used for treating all type of bacterial infections including meningitis, pharyngitis, tonsillitis, urinary tract infections, skin infections, middle ear infections and uncomplicated gonorrhea. The mechanism of action based on the inhibition of cell wall synthesis of bacteria by incorporating with proteins with beta-lactam which leads to lysis. Furthermore, it has been proved that third generation cephalosporins are more stable than first and second generation in the presence of beta-lactamases.[1-3]

Numerous analytical methods were employed for analysis of CT in bulk, in finished formulations, in biological matrices, in combination with other drugs including UV-Vis spectroscopic[4-13], photocolorimetric[14,15] and hyphenated techniques such as HPTLC, RP-HPLC and LC-MS/MS[16-32] methods. In most of the above said methods, methanol could be used as solvent as well as mobile phase. Hence, to minimize the use of organic solvents, hydrotropes may be a method of choice to dissolve and extract the active ingredient from the formulation. This proposed UV spectroscopic method may not be a replacement for the above techniques; however it can be applied as an alternate choice for regular analysis of drug in bulk and formulation.

Here, various concentrations of hydrotropic solubilizers such as sodium benzoate, urea, polyethylene glycol, sodium acetate, sodium citrate and sodium bicarbonate have been used to dissolve the drug and also to separate

the active component from the solid dosage forms. If higher concentrations of hydrotropes are used in the above methods, it may potentially affect the stability of the drug and cause inconvenience in measuring absorbance. In this present communication, about 1% sodium bicarbonate solution is used for dissolving the drug and for further dilutions to avoid the use of organic solvents. Further, this developed analytical procedure was validated in accordance with ICH Q2(R1) – 2005 guidelines.

MATERIAL AND METHODS

Preliminary Solubility Studies and Selection of Solvent

The solubility study of CT was ascertained in various hydrotropic solubilizers, including sodium benzoate, sodium citrate, urea, polyethylene glycol, sodium acetate, and sodium bicarbonate. It has found that the solubilization of pure drug in sodium bicarbonate solution was improved. Pure drug was completely dissolved in sodium bicarbonate solution at different concentrations such as 1%, 5%, 10% and 20%. Hence, the minimum concentration of 1% w/v sodium bicarbonate solution was used for subsequent analytical work.

Selection of Wavelength

Primary standard stock solution having 1 mg/mL concentration was prepared by dissolving the drug of 100 mg of CT in 1% w/v solution of sodium bicarbonate solution and made upto the level of 100 mL. Then it was sonicated for 15 minutes and filtered to get clear solution. Volumes ranging from 1 to 10 mL of the primary stock solutions were displaced into a series of 100 mL standard flasks and diluted up to the level using sodium bicarbonate solution to get 10–100 µg/mL concentration. The medium-concentrated solution was then scanned in the range of 200–400 nm against the blank in UV spectrometer. The absorption maximum of CT was obtained at 287 nm against blank. (Fig.2).

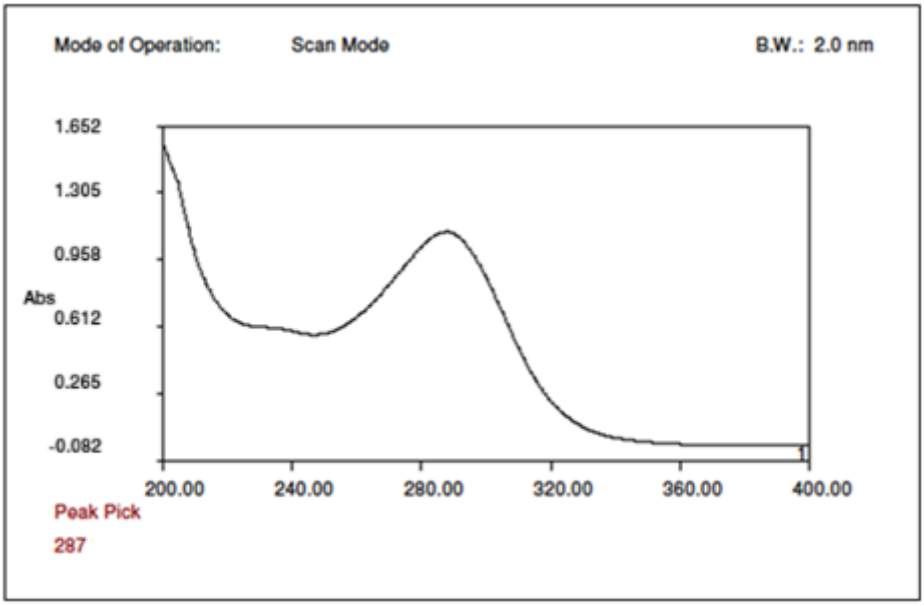

Fig 2: UV spectra of Cefixime Trihydrate scanned from 200-400 nm.

Assay of Marketed Formulation

About 20 tablets of marketed brand were weighed, pulverized and the tablet powder corresponding to 100 mg of CT was weighed and transferred to a 100 ml volumetric flask and then dissolved in 1% sodium bicarbonate solution and brought to volume with the same solvent. The flask was then shaken in a rotary shaker for approximately 20 minutes to dissolve the drug. The solution was filtered through Whatman No. 40 filter paper and an aliquot of the solution was diluted to obtain a concentration of 50µg/mL. The absorbance was measured at the respective λ max and then the drug content of the tablet formulation was calculated. The results (Table 1) are statistically validated to obtain the mean percent drug content, standard deviation and %RSD.

Method Validation as per ICH Guidelines

The proposed method was validated according to ICH guidelines Q2 R1 for validation of the analytical procedure. Some critical parameters such as accuracy, precision, linearity, LOD, LOQ and robustness were carried out to demonstrate the validation of the developed method.

Accuracy

The accuracy of an analytical method expresses the closeness of agreement between the test result and the actual result. The accuracy of the method was determined by the recovery studies which was carried out by taking three different concentrations of 80%, 100% and 120% of the standard drug and diluted accordingly and analyzing to obtain the percentage

recovery with triplicate determination at each level (Table 2).

Precision

The precision was demonstrated by intra-day and inter-day studies by performing the assay of the tablet formulation using the developed method. The experiment was repeated six times per day to determine intra-day precision (repeatability) and on six consecutive days to determine inter-day precision (ruggedness). The mean percentage drug content and the percentage relative standard deviation (%RSD) were calculated, values are given in Table 3.

Linearity, LOD and LOQ

The absorbance of various diluted solutions with concentration ranges of 10–100 µg/mL were measured at its corresponding λ max and the calibration curve (Fig. 3) was plotted using the least squares method. The linear regression equation was derived from the standard graph, slope and intercept and their 95% confident interval values were calculated. The Limit of Detection (LOD) and Limit of Quantification (LOQ) were also calculated using the same regression equation. The results for the linearity data are shown in Table 4.

Robustness

It is a measure of the ability of the analytical method to remain unaffected by small but deliberate variations in method parameters such as variations in detection wavelength ± 1 nm, variations in solvent strength by using two different concentrations of hydrotropes such as 0.8% and 1.2% and the study report shown on Table 5.

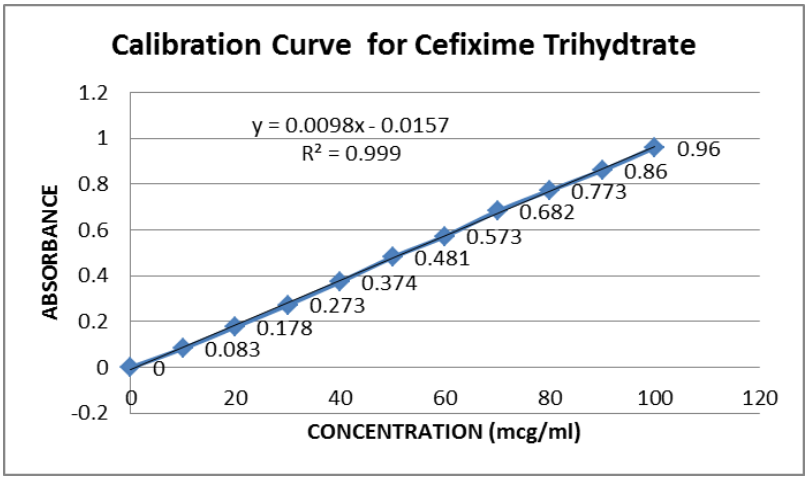

Fig. 3: Calibration graph for Cefixime trihydrate.

Table 1: Results for percentage drug content of marketed formulation.

Brand with Label claim (mg)	Amount of drug estimated (mg)	Percentage drug content (%w/w)	Mean % Content ± SD (%w/w)	%RSD	SEM	95% CI
Brand-I 200 mg	198.68	99.34	99.59 ± 0.2902	0.2914	0.33828	99.262 – 99.918
	199.83	99.91				
	199.06	99.53				
Brand-II 200 mg	200.21	100.10	99.72 ± 0.38	0.3810	0.44168	99.290 – 100.150
	198.68	99.34				
	199.45	99.72				

Table 2: Results for accuracy by percentage recovery method.

Conc of Std Drug Taken (µg/ml)	Level	Amount Recovered (µg/ml)	Percentage Recovery (%)	Mean % Recovery ± SD	%RSD	SEM	95 % CI
40 µg/ml	80 %	39.20	98.00	99.77% ± 1.5390	1.5434	0.31184	98.028 – 101.512
		39.72	99.30				
		40.28	100.70				
50 µg/ml	100%	49.11	98.22	99.68% ± 0.5547	0.5621	0.16653	99.052 – 100.308
		49.27	98.54				
		49.67	99.30				
60 µg/ml	120%	58.80	98.00	99.13% ± 1.2050	1.2155	0.50972	97.766 – 100.494
		59.41	99.01				
		60.54	100.90				

Table 3: Precision study data.

Label Claim	Repeatability				Ruggedness			
	Time of Analysis	Amount found (mg)	% Drug Content	Mean ± SD* & %RSD*	Day of Analysis	Amount found (mg)	% Drug Content	Mean ± SD* & %RSD*
200 mg	10.00 am	201.6	100.8	99.73 ± 0.8640 & 0.866	Day 1	201.1	100.5	99.72 ± 0.7503 & 0.752
	11.00 am	200.8	100.4		Day 2	200.8	100.4	
	12.00 pm	200.0	100		Day 3	200.3	100.1	
	01.00 pm	199.2	99.6		Day 4	199.1	99.5	
	02.00 pm	198.4	99.2		Day 5	198.31	99.1	
	03.00 pm	96.8	98.4		Day 6	197.2	98.6	

*(n=6)

Table 4: Results for linearity data.

Parameters	Values
λ max	287 nm
Linearity	10-100 µg/ml
Regression equation	Y = 0.009808 X - 0.01573
Correlation coefficient	0.9996
Slope	0.009808
95% CI of Slope	0.009653 to 0.009963
Intercept	-0.01573
95% CI of Intercept	-0.02537 to -0.006093
LOD	3.133 µg/ml
LOQ	9.494 µg/ml

Table 5: Results for Robustness study data.

Parameters	Conc Taken for Analysis	Absorbance	Conc Found (µg/ml)	Mean ± SD*	%RSD*
At 286 nm	**50 µg/ml**	0.495	48.90	49.07 ± 0.1582	0.3223
		0.498	49.21		
		0.497	49.11		
At 288 nm		0.496	49.01	49.07 ± 0.2122	0.4323
		0.495	48.90		
		0.499	49.31		
Using 0.8 % $NaHCO_3$		0.497	49.11	49.31 ± 0.2050	0.4157
		0.499	49.31		
		0.501	49.52		
Using 1.2 % $NaHCO_3$		0.506	50.03	49.99 ± 0.3564	0.7129
		0.509	50.33		
		0.502	49.62		

*(n=3)

RESULTS AND DISCUSSION

According to the solubility studies, the drug was satisfactorily soluble in 1% sodium bicarbonate solution compared to its solubility in other solvents. Beer's law obeys in the concentration range of 10-100 µg/ml with a correlation coefficient of 0.9996 and a regression equation of Y = 0.009808 x - 0.01573. The percentage drug content was estimated with the marketed formulation using the proposed UV spectroscopic method and the results ranged from 99.34% to 100.10% w/w with a %RSD less than 0.5%. The method was then validated according to ICH guidelines for % recovery, precision (repeatability and robustness), linearity, LOD, LOQ and robustness. The % recovery and % drug content of more than 99% and %RSD of less than 2% at each level clearly demonstrate that the method is accurate and precise enough for content analysis of drug in pure and pharmaceutical dosage forms. Furthermore, in robustness studies, the method demonstrated an %RSD value of less than 1% when measuring drug concentration at the detection wavelength of 286 nm and 288 nm and when selectively changing the concentration of hydrotropic agents (using 0.8% and 1, 2% sodium bicarbonate solution).

CONCLUSION

An accurate, precise, user-friendly, and trustworthy UV spectroscopy method was developed to estimate CT in bulk and its formulation in compliance with the ICH Guidelines. The approach is found to be very simple,

reproducible, and in good accordance with the label claim of active drug. Both pharma companies and academic institutions can use this method to estimate CT for frequent analysis in least cost.

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