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Determination of cefdinir and cefditoren by zero order and first order derivative spectrophotometry

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ABSTRACT

Simple and rapid spectrophotometric methods (Zero order- methods M1 & M2 and first order derivative- methods M3 & M4) were developed and validated for the quantification of cefdinir and cefditoren in bulk and in pharmaceutical dosage form. Methanol is used as diluent in all the proposed methods. Absorbance of cefdinir and cefditoren solutions were measured at 286 nm (M1) and 230 nm (M2), respectively for the zero order. In methods, M3 and M4, zero-order spectra were derivatized into first-order and absorbance of cefdinir and cefditoren solutions were measured at 272 nm (M3) and 225 nm (M4), respectively. The linearity ranges were found to be 5-15 µg/ml for the methods M1-M4. The methods were validated as indicated by the ICH guidelines and applied to the estimation of cefdinir and cefditoren in pharmaceutical dosage forms. It was concluded that the methods developed were sensitive, precise, robust, rugged, accurate and useful for the quality control of cefdinir and cefditoren in pharmaceutical dosage forms.

Keywords: Zero order; First order Derivative; Cefdinir; Cefditoren; Analysis

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INTRODUCTION

Cefdinir [1-3], chemically known as 8-[2-(2-amino-1,3-thiazol-4-yl)-1-hydroxy-2-nitroso-ethenyl]amino-4-ethenyl-7-oxo-2-thia-6-azabicyclo[4.2.0]oct-4-ene-5-carboxylic acid, is a oral semisynthetic cephalosporin bacteriocidal antibiotic of third-generation. It is used to treat bacterial infections such as pneumonia, bronchitis, ear infection, sinusitis, pharyngitis, tonsillitis and skin infections. Analysis of cefdinir in bulk, pharmaceutical dosage forms and biological samples has been accomplished by several methods so far, including spectrophotometry [4-10], HPLC [11-14], LC-MS [15], electrochemical [16] and spectroflourometry [17].

Cefditoren [18-20], chemically known as (7*R*)-7-((*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino) acetamido) -3-((*Z*)-2- (4-methylthiazol-5-yl)vinyl)-8-oxo-5-thia-1- azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid, is a oral a semi-synthetic cephalosporin bacteriocidal antibiotic of third-generation. It is used in the management of infections such as community acquired pneumonia, flare-ups of chronic bronchitis, strep throat, tonsillitis and a number of types of skin infections. Literature survey reveals several analytical methods for the estimation of cefditoren in pharmaceutical preparations and biological fluids, including: spectrophotometry [21-26], UPLC [27], HPLC [28-36], HPTLC [37-40] and electrochemical [41].

The aim of the present study was the development and validation of simple, sensitive, rapid and reliable zero order and first order derivative spectrophotometric methods, appropriate for the quantification of cefdinir and cefditoren in bulk and pharmaceutical dosage forms.

MATERIALS AND METHODS

Apparatus:
A UV-VIS Spectrophotometer, model Systronics SL-2201 was employed with spectral bandwidth of 2.0 nm with a pair of matched quartz cells of 10 mm optical path length was used for spectral measurements. The spectra were obtained with the instrumental parameters are: Wavelength range: 200–400 nm; scan speed: Medium; sampling interval: 1.0 nm.

Standard solutions:
Ten milligrams each of pure cefdinir and cefditoren were weighed accurately and separately dissolved in the methanol (analytical reagent grade obtained from Qualigens Fine Chemicals, Mumbai, India) in a 100 ml volumetric flask and diluted up to the mark with the same solvent, to get a 100 µg/ml solution (stock standard solution).

Tablet sample solution:
Cefdinir capsule powder equivalent to 10 mg of drug was transferred to a 100 ml volumetric flask and sonication was done to dissolve it completely with approximately 70 ml of methanol. The solution was then diluted up to the mark with the same solvent (stock solution 100 µg/ml solution). The same procedure was followed for cefditoren tablets to get a stock solution with concentration 100 µg/ml of drug. The stock solutions of cefdinir and cefditoren were appropriately diluted with the methanol to get a final working concentration of 10 µg/ml of drug for the analysis by the proposed methods.

General procedure:
Zero order (M1 & M2):
Suitable aliquots of standard stock solution (100 µg/ml) of both the drugs, that is, cefdinir and cefditoren (0.5, 0.75, 1.0, 1.25 and 1.5 ml) were taken in a 10 ml volumetric flask and diluted up to the mark, to get 5, 7.5, 10, 12.5 and 15 µg/ml solution of the drugs, with methanol. The absorbance of cefdinir solutions were measured at 286 nm (M1) and cefditoren solutions were measured at 230 nm (M2).

First order derivative (M3 & M4):
Suitable aliquots of standard stock solution (100 µg/ml) of both the drugs, namely, cefdinir and cefditoren (0.5, 0.75, 1.0, 1.25 and 1.5 ml) were taken in a 10 ml volumetric flask and diluted up to the mark with methanol, to get 5, 7.5, 10, 12.5 and 15 µg/ml solution of the drugs. The absorbances of cefdinir and cefditoren solutions were measured at 272 nm (M3) and 225 nm (M4), respectively.

In all the above methods (M1-M4), the calibration curve was plotted between absorbance and concentrations. Alternatively regression equation was derived. The concentrations of unknown samples were determined from the corresponding calibration curve or from the regression equation derived.

RESULTS AND DISCUSSION

Wavelength selection:
The selection of wavelength in all the methods (M1-M4) is based on the reproducibility of the results. The zero order spectra of cefdinir (M1) and cefditoren (M2) were recorded between 200 and 400 nm and the maximum wavelength of cefdinir and cefditoren in methanol was found to be 286 nm (M1) and 230 nm (M2), respectively. The zero order spectra of cefdinir and cefditoren are shown in Figures 3 and 4.

In Methods M3 and M4, zero-order spectra were derivatized into first-order. The working standard solutions of cefdinir (M3) and cefditoren (M4) were scanned in the first order derivative spectra. The cefdinir first order derivative spectra showed a maxima and minima at 272 and 300 nm, respectively (Figure 5). The first order derivative spectra showed a maxima and minima at 225 and 241 nm respectively for cefditoren (Figure 6). The wavelengths 272 nm and 225 nm were selected for analysis of cefdinir and cefditoren by methods M3 and M4, respectively.

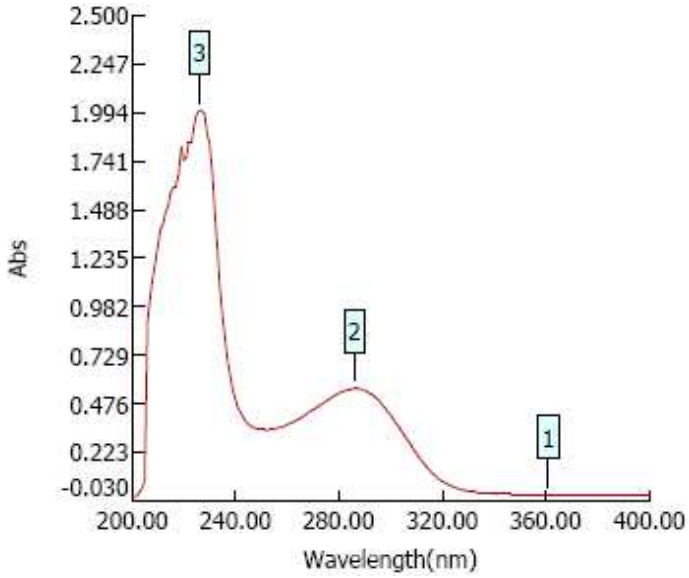

Figure 3. Zero order spectra of 10 µg/ml standard solution of cefdinir (M1)

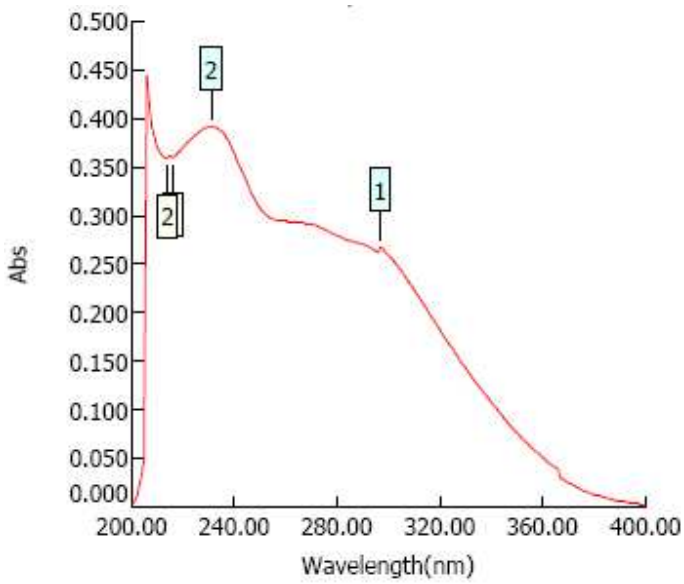

Figure 4. Zero order spectra of 10 µg/ml standard solution of cefditoren (M2)

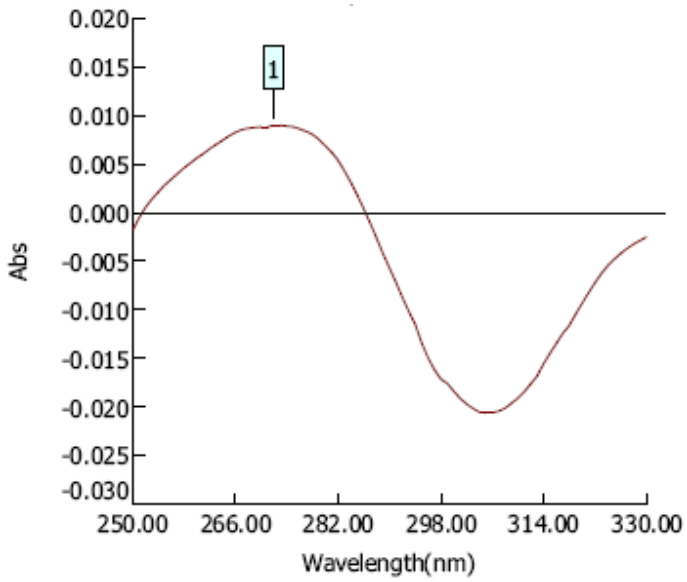

Figure 5. First order derivative of 10 µg/ml standard solution of cefdinir (M3)

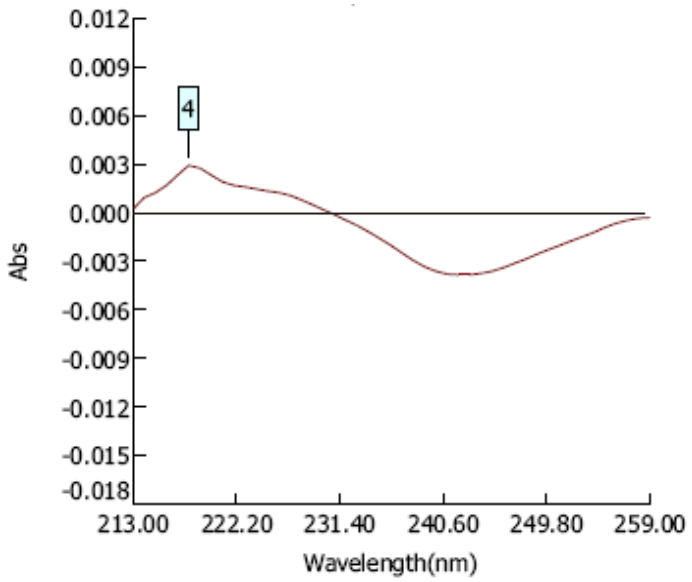

Figure 6. First order derivative spectra of 10 µg/ml standard solution of cefditoren (M4)

Validation of the proposed methods:

The proposed methods were validated with respect to linearity, sensitivity, precision, accuracy and robustness as per the guidelines of ICH [42].

Linearity:

In all the methods (M1-M4), the calibration curves were constructed by plotting an increase in absorbencies *vs* concentrations. A linear correlation was found between absorbance and concentration of EZT in the ranges given in Table 1. The statistical parameters given in the regression equation were calculated from the calibration graphs. The high values of the regression coefficient (R^2) and low values y-intercepts of the regression equations, proved the linearity of the calibration curves (Table 1).

Sensitivity:

The sensitivity of the proposed methods was determined by calculating such as molar absorptivity, Sandell's sensitivity, limit of detection (LOD) and limit of quantification (LOQ). The results are summarized in Table 1 and indicated the sensitivity of the proposed methods

Table 1: Linearity, regression and sensitivity characteristics

Parameters	M1	M2	M3	M4
Linearity (µg mL^{-1})	5-15	5-15	5-15	5-15
Regression equation (A= mC + I)[$]	-	-	-	-
Slope (m)	0.0538	0.0385	0.0009	0.0003
Intercept (I)	0.0084	0.0096	0.0004	-0.0004
Regression coefficient (R^2)	0.9992	0.9985	0.9997	0.9996
Molar Absorbitivity ($L\ mole^{-1}\ cm^{-1}$)	2.178×10^5	2.439×10^5	3.588×10^3	1.862×10^3
Sandell's sensitivity (µg cm^{-2})	1.814×10^{-4}	2.544×10^{-4}	1.111×10^{-2}	3.333×10^{-2}
LOD (µg mL^{-1})	0.025	0.060	0.187	0.300
LOQ (µg mL^{-1})	0.076	0.181	0.566	0.909

[$]A = mC + I, where A is the absorbance and C is the concentration of drug in µg mL^{-1}

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Precision:

The precision of the proposed methods (M1-M4) was expressed as the percent relative standard deviation of the series of measurements. Precision was ascertained by estimation of cefdinir (by methods M1 & M3) and cefditoren (by methods M2 & M4) at 10 µg/ml concentration level. It involves intraday precision and intermediate precision (also known as Ruggedness). For intraday precision, the analysis was carried out five times on the same day, and for intermediate precision, the analysis was carried out on different day by using same dimensions. Results are summarized in Table 2. As the percent relative standard deviation vales are within the acceptable limit (<2%), the proposed methods are considered as precise and rugged.

Table 2: Precision of the proposed methods

Method	Concentration (µg/ml)	Absorbance*	% RSD
Intra-day precision			
M1	10	0.556	0.080
M2	10	0.392	0.180
M3	10	0.009	0.600
M4	10	0.003	1.401
Intermediate precision			
M1	10	0.563	0.079
M2	10	0.394	0.212
M3	10	0.009	0.600
M4	10	0.003	1.480

**average of five determinations*

Table 3: Accuracy of the proposed methods

Method	Spiked level (%)	Amount Added (µg/ml)	Amount Found (µg/ml)*	Recovery (%)	Mean Recovery (%)
M1	50	5.0	4.99	99.9	99.9
	100	10.0	9.99	99.9	
	150	15.0	14.99	99.9	
M2	50	5.0	4.99	99.9	99.5
	100	10.0	10.0	100.0	
	150	15.0	14.8	98.7	
M3	50	5.0	4.99	99.8	99.8
	100	10.0	9.98	99.8	
	150	15.0	14.9	99.8	
M4	50	5.0	4.99	99.8	99.8
	100	10.0	9.98	99.8	
	150	15.0	14.9	99.8	

**average of three determinations*

Accuracy:
The accuracy of the proposed methods (M1-M4) was determined by performing recovery study at 50, 100, and 150% level (with respect to target assay concentration) for cefdinir (by methods M1 & M3) and cefditoren (by methods M2 & M4). The recovery study was done by adding pure drug solution to the preanalyzed sample, and concentrations of cefdinir and cefditoren was determined. The results of the recovery study are shown in Table 3. The values of recovery studies were showing acceptable accuracy of the proposed methods.

Robustness:
As part of the robustness, deliberate change in the wavelength is made. The wavelength was varied by ±2 nm. Standard solution (10 µg/ml) of cefdinir and cefditoren was prepared and analysed using the varied wave length along with method wave length. The results are summarized in Table 4. On evaluation of the results, it can be concluded that the variation in wave length did not affected the methods significantly. Hence it indicates that the methods (M1-M4) are robust by change in the wave length ±2 nm.

Table 4: Robustness of the proposed methods

Method	S.No.	Wave length (nm)	Absorbance
M1	1	284	0.550
	2	286	0.553
	3	288	0.551
M2	1	228	0.389
	2	230	0.391
	3	232	0.393
M3	1	270	0.008
	2	272	0009
	3	274	0.009
M4	1	223	0.002
	2	225	0003
	3	227	0.004

CONCLUSION

Zero order and first order derivative spectrophotometric methods were developed and validated for the assay of cefdinir (methods M1 & M3) and cefditoren (methods M2 & M4) in bulk and in its pharmaceutical formulations. The developed methods (M1-M4) proved to be simpler in procedure, sensitive, precise, robust and produced accurate results. Hence, the proposed methods (M1-M4) are effective for the routine analysis of cefdinir and cefditoren in bulk and pharmaceutical formulations.

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