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SPECTROPHOTOMETRIC METHODS FOR SIMULTANEOUS ESTIMATION OF CEFUROXIME SODIUM AND SULBACTAM SODIUM IN INJECTON

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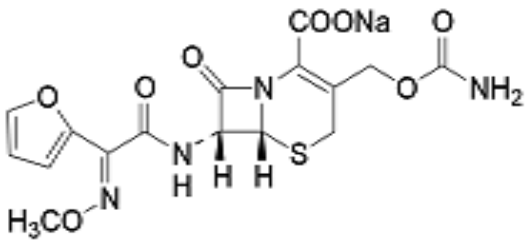
ABSTRACT

Cefuroxime is a 2nd-generation cephalosporin and Sulbactam is a β-Lactamase inhibitor. The combination formulation is used for the treatment of lower respiratory tract infection. Two new, simple, accurate and precise UV spectrophotometric methods have been developed and validated for the simultaneous determination of Cefuroxime Sodium (CEF) and Sulbactam Sodium (SUL) in their combined dosage forms. First method is based on simultaneous estimation of Cefuroxime at 279nm and Sulbactam at 259 nm, while other Q-absorption Ratio method using two wavelengths, 259nm (λmax of SUL) and 272nm (Isoabsorptive point). 0.01 N NaOH was the solvent used in all methods. Cefuroxime Sodium showed linearity in the range of 8-32µg/mL and Sulbactam sodium showed linearity in the range of 4-16µg/mL in all the methods. All methods were validated statistically and recovery studies were carried out. All methods were found to be accurate, precise and reproducible. These methods were applied to the assay of the drugs in marketed formulation, which were found in the range of 98.0% to 100.0% of the labelled value for both Cefuroxime and Sulbactam. Hence, the methods herein described can be successfully applied in quality control of combined pharmaceutical dosage forms.

INTRODUCTION: Cefuroxime Sodium is Sodium(7R)-3-carbamoyloxymethyl-7-[(z)-furan-2-yl-2-methoxyimino acetamido]-3-cephem-4-carboxylate. Cephalosporins are bactericidal and have the same mode of action as other beta-lactam antibiotics (such as penicillin) but are less susceptible to hydrolysis of β- Lactamase produced by microbes. Cephalosporins disrupt the synthesis of the peptodoglycan layer of bacterial cell walls [1, 2, 3].

Sulbactam sodium is Sodium(7R)-3-carbamoyl oxymethyl-7-[(z)-furan-2-yl-2-methoxyimino acetamide]-3cephem-4-carboxylate. It is an irreversible inhibitor of beta-Lactamase; it binds the enzyme and does not allow it to interact with the antibiotic. Hydrolysis of the β-Lactam ring either by enzymatic cleavage with β-Lactamase or by acid destroys the antibacterial activity of β-lactam antibiotic. Certain molecules can inactivate b-Lactamase, thus preventing the destruction of b-lactam antibiotics [1, 2, 3, 8, 9, 10].

The chemical structures of CEF and SUL are shown in **Fig. 1 (A) & (B).**



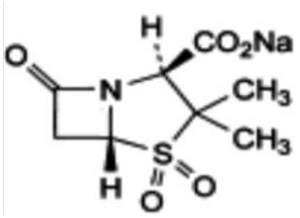


FIG. 1: CHEMICAL STRUCTURE OF (A) CEFUROXIME SODIUM AND (B) SULBACTAM SODIUM [8, 9, 10]

A detailed survey of analytical literature for CEF revealed several methods based on varied techniques, viz, HPLC [11, 12, 13], Spectrophotometery [14, 15, 16], Spectro-fluorimetry [17] and specific stability-indicating method by UV-Visible method [18]. Similarly, a survey of the analytical literature for sul revealed several methods based on varied techniques, viz HPLC[19, 20, 21, 22], Spectrophotometery [23, 24, 25], HPTLC [26].

According to, detailed survey of analytical literature none of the reported analytical procedures describes a simple and satisfactory UV spectrophotometric method for simultaneous determination of CEF and SUL in their combined dosage forms. So the objective of this work was to develop simple, precise and rapid spectrophotometric methods for combination drug products containing CEF and SUL.

MATERIALS AND METHODS:

Instrumentation: A Shimadzu model 1700(Japan) double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Spectra were automatically obtained by UV-Probe system software (UV Probe version 2.31). An Electronic analytical balance (Acculab) and an ultrasonic bath were used in the study.

Materials and Reagents: CEF and SUL bulk powder was gifted by Zydus Cadila Health Care Pvt. Ltd., Ahmadabad, India and Bharat Parentral ltd., Ahmadabad, India respectively. The commercial fixed dose combination product was procured from the local market. NaOH Pallet AR Grade was procured from S.D.Fine Chemicals Ltd., Mumbai, India.

Standard and Test Solutions:

Preparation of Standard Solution: An accurately weighed quantity of CEF (10 mg) and SUL (10 mg) were transferred to a separate 100 ml volumetric flask and dissolved and diluted to the mark with 0.01 N NaOH to obtain standard solution having concentration of CEF (100µg/ml) and SUL (100µg/ml).

Preparation of Test Solution: From the Injection formulation, FASTGARD 2.25 (1500mg CEF & 750mg SUL), 30mg taken in 100 ml volumetric flask and the volume was adjusted to mark with 0.01 N NaOH. This was working sample solution having strength 200µg/ml of CEF & 100µg/ml of SUL.

Methods:

Simultaneous Equation Method: In this method, seven working standard solutions having concentration 8-32µg/ml for CEF and 4-16µg/ml for SUL were prepared in 0.01 N NaOH and the absorbance at 279 nm (λ_{max} of CEF) and 259 nm (λ_{max} of SUL) were measured and absorptivity coefficients

Were calculated using calibration curve.

The concentration of two drugs in the mixture can be calculated using following equations;

$$Cx = \frac{A2ay1 - A1ay2}{ax2ay1 - ax1ay2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$$Cy = \frac{A1ax2 - A2\,ax1}{ax2ay1 - ax1ay2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where, A_1,A_2 are absorbance of mixture at 2 nm79 (λ1) and 259 nm (λ2) respectively, ax1 and ax2 are absorptivities of CEF at λ1 and λ2 respectively, ay1 and ay2 are absorptivities of SUL at λ1 and λ2 respectively, Cx and Cy are concentrations of CEF and SUL respectively.

Q-Absorption Ratio Method: This method is applicable to the drugs that obey Beer's law at all wavelengths and the ratio of absorbance at any two wavelengths are a constant value, independent of concentration or path length [4, 5, 6, 7].

Two wavelengths, 272nm (Isoabsorptive point) and 259nm (λmax of SUL) were selected for the formation of Q-absorbance equation. The absorptivity co-efficient of each drug at both the wavelengths were determined.

The concentration of individual components, CEF and SUL may be calculated using the following equations

$C_{CT} = (Qm–Q_{BD}/Q_{CT}–Q_{BD}) * A1/ax1$ ..... (1)

$C_{BD} = (Qm–Q_{CT}/ Q_{CT}–Q_{BD}) * A1/ay1$ ..... (2)

$Qm= A2 / A1$..... (3)

$Q_{CT} = ax2 / ax1$ & $Q_{BD} = ay2/ay1$..... (4)

Where, A1 and A2 are absorbance of sample solution at Isoabsorptive point (272nm) and λmax of SUL (259nm) respectively; ax1 and ax2 are the absorptivities of CEF at 272 and 259 nm respectively and ay1 and ay2 are the absorptivities of SUL at the two wavelengths respectively.

Method Validation: All the methods were validated as per ICH guidelines for parameters like linearity, accuracy, precision, limit of detection, limit of quantitation [27].

RESULTS AND DISCUSSION: In the present work, two methods, namely, simultaneous equation method, and Q-absorption ratio method were developed for the simultaneous spectroscopic estimation of CEF and SUL in commercially available Parenteral dosage forms.0.01 N NaOH was used as the solvent since both the drugs exhibit good solubility in it and no interference due to excipients of the Parenteral formulation were observed.

Simultaneous Equation Method: Estimation of drugs by Simultaneous Equation method was carried out at 279 nm (λmax of CEF) and 259 nm (λmax of SUL). The standard solutions of CEF and SUL were prepared to determine the absorptivity values of the subject analyte at the two selected wavelengths. The method showed good linearity in the range of 2-14 µg/mL for CEF and 1-13 µg/mL for SUL. Overlain spectra of both drugs shown in **figure 1**.

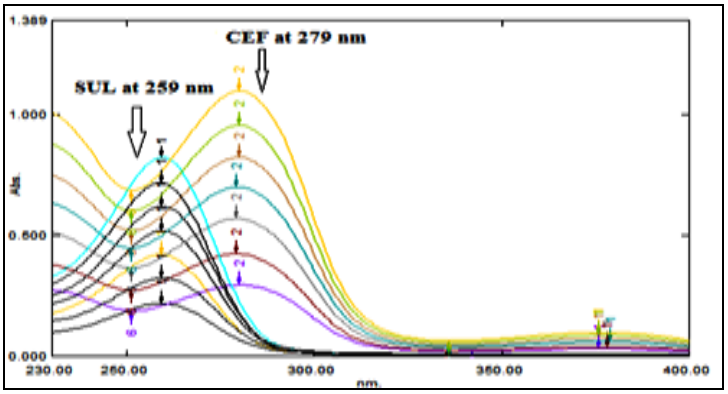


FIG. 1: OVERLAIN ZERO ORDER SPECTRA OF CEF AND SUL (SIMULTANEOUS EQUATION METHOD)

Q-Absorption Ratio Method: As shown in **Figure 2**, the overlain spectra of both drugs show a Reproducible Iso-absorptive point at 272nm. Thus, estimation of drugs by Q-absorbance ratio equation method was carried out at 272nm (Isoabsorptive point) and 259nm (λ_{max} of CEF). The standard solutions of CEF and SUL were prepared to determine the absorptivity values of the subject analyte at the two selected wavelengths. The method showed good linearity in the range of 8-32µg/mL for CEF and 4-16µg/mL for SUL.

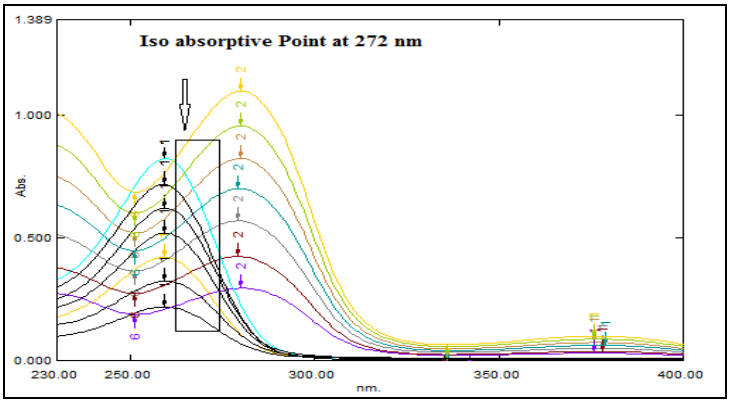


FIG. 2: OVERLAIN ZERO ORDER SPECTRA OF CEF AND SUL (Q-ABSORPTION RATIO METHOD)

Method Validation: The developed methods were validated for parameters like linearity, precision, accuracy, LOD, LOQ. the data for which are presented in the **Tables 1-5**. The low value of R.S.D. value indicates that all the methods are precise and accurate.

TABLE 1: DATA SHOWING LINEARITY OF THE DEVELOPED METHODS

Methods →	Simultaneous Equation Method		Q-Absorption ratio method	
Parameters ↓	CEF	SUL	CEF	SUL
Linearity range	8-32 µg/ml	4-16 µg/ml	8-32µg/ml	4-16µg/ml
Slope	0.033	0.050	0.031	0.050
Intercept	0.028	0.014	0.011	0.015
Correlation co-efficient	0.999	0.999	0.999	0.999

TABLE 2: DATA SHOWING ACCURACY OF THE DEVELOPED METHODS

DRUG	Amt. taken (µg/ml)	Amt. added (µg/ml)	Amt. added %	% mean recovery (±s.d.) n=3	
				Simultaneous Equation Method	Q-Absorption ratio method
CEF	20	5	25 %	101.6 ±0.92	97.6±0.86
	20	10	50 %	100.9 ±0.87	98.4±0.96
	20	15	75 %	98.66± 1.03	100.67±1.08
SUL	10	2.5	25 %	99.20 ±0.92	99.2±0.89
	10	5	50 %	101.8 ±0.85	100.8±.0.92
	10	7.5	75 %	98.10 ±0.74	101.33±0.82

SD=Standard Deviation, n = number of repetition

TABLE 3: DATA SHOWING PRECISION OF THE DEVELOPED METHODS

Methods		Simultaneous Equation Method (%RSD) (n=3)		Q-Absorption ratio method (%RSD) (n=3)	
		CEF	SUL	CEF	SUL
System precision	Intraday	0.59-0.90	0.63-0.85	0.60-0.92	0.63-0.85
	Interday	0.78-1.02	0.70-0.95	0.71-1.09	0.70-0.95
Method precision	Intraday	0.52-0.87	0.54-0.72	0.55-0.89	0.54-0.72
	Interday	0.70-0.98	0.69-0.84	0.65-1.02	0.69-0.84

%RSD=Relative Standard Deviation, n = number of repetition

TABLE 4: DATA SHOWING LOD AND LOQ OF THE DEVELOPED METHODS

Methods	Simultaneous Equation Method		Q-Absorption ratio method	
	CEF	SUL	CEF	SUL
LOD(µg/ml)	0.17	0.097	0.072	0.115
LOQ(µg/ml)	0.52	0.294	0.253	0.332

TABLE 5: RESULT OF ANALYSIS OF FORMULATION

Methods	Simultaneous Equation method		Q-Absorption ratio method	
	CEF	SUL	CEF	SUL
%Assay	97.33	98.85	96.43	97.75
S.D.(n=3)	0.039	0.026	0.049	0.028

S.D. =Standard Deviation, n = number of repetition

CONCLUSION: The developed spectroscopic methods are found to be simple, sensitive, accurate and precise and can be used for routine analysis of CEF and SUL. The developed methods were validated as par ICH guidelines. Statistical analysis proved that the method is repeatable and selective for the analysis of CEF and SUL in combination as a single drug in bulk as well as in pharmaceutical formulations.

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