



Research Article

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## Kinetic spectrophotometric determination of cefadroxil in pure substance and pharmaceutical dosage form

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### ABSTRACT

A simple, reliable and sensitive kinetic spectrophotometric method was developed for determination of cefadroxil in pure substance and dosage form by the product of two conjugate reactions of peroxyacidic oxidation and perhydrolysis in a basic medium using potassium peroxomonosulfate as analytical reagent ( $\text{KHSO}_5$ ). The initial rate method was used at 294 nm. Linearity was studied over concentration range 1-7  $\mu\text{mL}^{-1}$  and correlation coefficient was found to be 0.999 for regression line. The proposed method was validated statistically and checked through recovery studies. Statistical comparisons of the results with the reference methods show excellent agreement and indicate no significant difference in accuracy and precision.

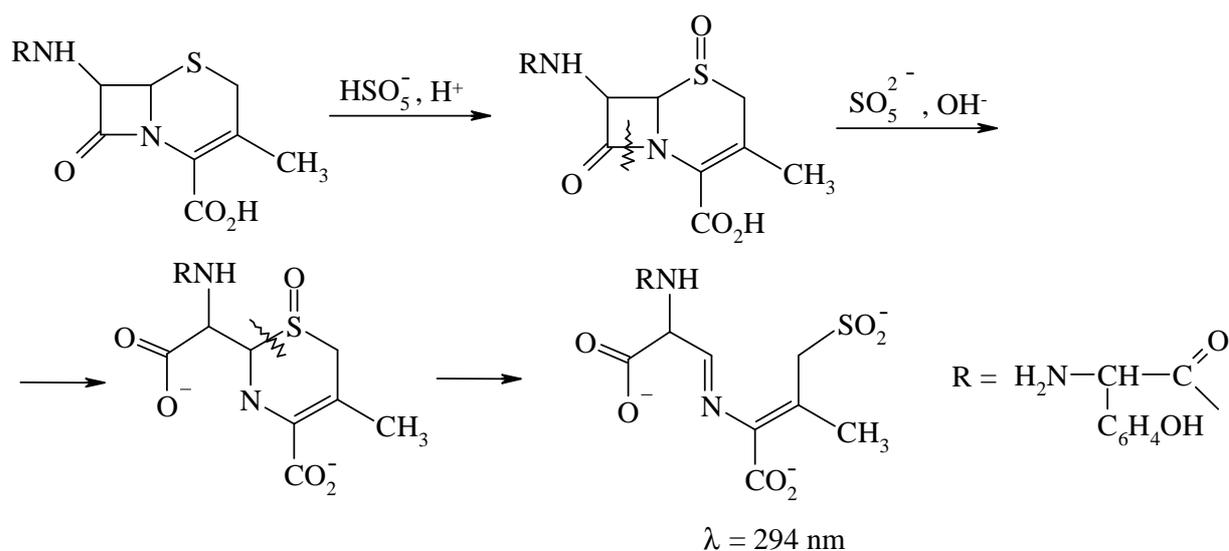
**Keywords:** Cefadroxil, kinetics, spectrophotometry, potassium peroxomonosulfate

### INTRODUCTION

Cefadroxil (Cefadroxil hemihydrate) is a semisynthetic first generation cephalosporin antibiotic. Chemically it is a (6R,7R)-7-[[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid [1]. It is a broad-spectrum antibiotic of the cephalosporin type, effective in gram-positive and gram-negative bacterial infections. It is a bactericidal antibiotic. The compound is active against bacteria due to the beta-lactam moiety and thus is similar to penicillin. It is a derivative of 7-aminocephalosporanic acid. It is produced in capsules containing 0.5 and film coated tablet for oral administration containing 1.0.

Extensive literature survey reveals that a lot of analytical methods are reported for analysis of Cefadroxil like HPLC [2, 3], Capillary electrophoresis [4], Polarography [5, 6] and Chemiluminescence [7-9]. Spectrophotometric determination of Cefadroxil is reported using the bromination method [10], reactions with nitrate with further formation of chelate complex with metals [11], charge transfer process by fluorescence quenching method [12], oxidation with Ce (IV) or Fe (III) in acidic medium [13], in methanol medium with sonication [14], with Ninhydrin-Ascorbic acid and  $\beta$ -Naphthol- $\text{H}_2\text{O}_2$ -Cupric nitrate-2, 4-DNP-Ammonium hydroxide solutions [15]. Kinetic spectrophotometric methods became of great interest in chemical and pharmaceutical analyses [16-19]. The literature is still poor in analytical procedure based on kinetics, especially for determination of drug in pharmaceutical dosage forms. We aimed to improve on the current methods by employing the kinetic spectrophotometric oxidation of Cefadroxil to increase selectivity, avoid interference of colored and/or turbidity background of samples and consequently determination of low concentration of the drug as possible.

The proposed method is based on the determination of Cefadroxil in pure substance and capsules by the product of two conjugate reactions of peroxyacidic oxidation and perhydrolysis in a basic medium using potassium peroxomonosulfate as analytical reagent ( $\text{KHSO}_5$ ) and is therefore developed first. The reaction mechanism is proposed on the basis of the literature background [20] and our experimental study as shown in Scheme 1.



Scheme 1. Mechanism of Cefadroxil chemical transformations by means of potassium peroxomonosulfate in a basic medium

## EXPERIMENTAL SECTION

### Reagents and Chemicals

All the materials were of analytical reagent grade, and the solutions were prepared with double-distilled water. Cefadroxil was produced by Genom Biotek Ltd., India.

Peroxomonosulfate (Sigma-Aldrich) was employed as received. The solution of peroxomonosulfate was prepared by dissolving its potassium salt ( $\text{K}_2\text{SO}_5 \cdot \text{KHSO}_5 \cdot \text{K}_2\text{SO}_4$ ) in double-distilled water. The solution of peroxomonosulfate was standardized iodometrically.

Sodium hydroxide 0.51 M prepared by dissolving 2 g in 100 mL of double-distilled water.

### Equipment

A spectrophotometer SF-46 (LOMO) with 1 cm match quartz cells were used for spectral measurement.

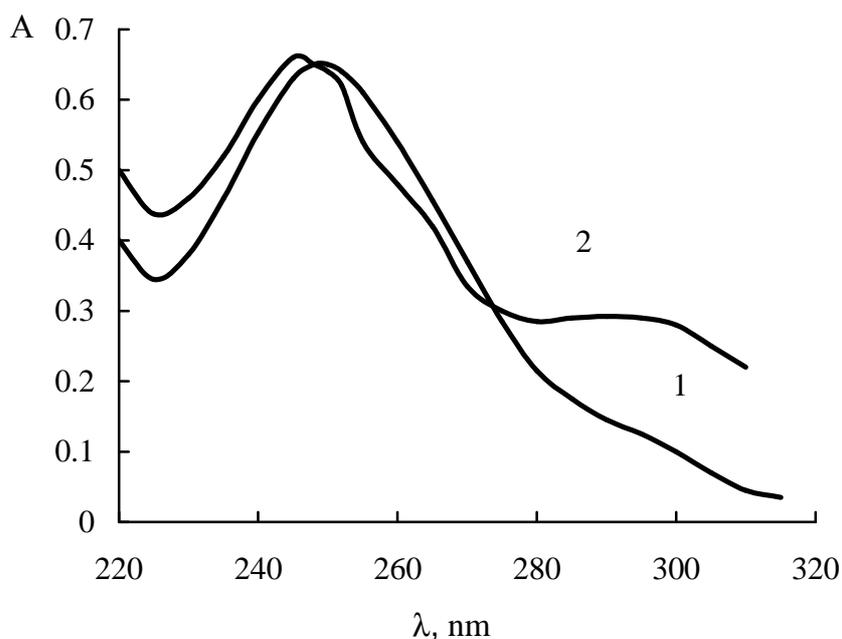


Fig. 1. Electronic spectra of Cefadroxil absorption (1) and product of conjugated reactions of S-oxidation and perhydrolysis with potassium peroxomonosulfate (2)

$c(\text{Cefadroxil}) = 4 \cdot 10^{-5} \text{ mol L}^{-1}$ ;  $c(\text{KHSO}_5) = 8 \cdot 10^{-4} \text{ mol L}^{-1}$ ;  $c(\text{NaOH}) = 0.02 \text{ mol L}^{-1}$

### Preparation of Standard Solution

Standard solution of Cefadroxil ( $1 \text{ mol L}^{-1}$ ): 39.12 mg of Cefadroxil was transferred in 100 mL volumetric flask and diluted to the mark with double distilled water at  $+20 \text{ }^{\circ}\text{C}$ .

### Determination of Absorption Maxima

In a basic medium Cefadroxil S-oxide undergoes hydrolytic cleavage. Figure 1 shows the electronic spectra of Cefadroxil and the reaction product. The appearance of a new band with absorption  $\lambda_{\text{max}} = 294 \text{ nm}$  demonstrates its formation in the reaction of alkaline hydrolysis of Cefadroxil S-oxide in the presence of potassium peroxomonosulfate (perhydrolysis reaction).

### Initial Rate Method

Aliquots of  $0.25\text{--}2.00 \text{ mol L}^{-1}$  of studied Cefadroxil test solutions were pipetted into a series of 100 mL volumetric flask containing 4 mL of  $0.02 \text{ mol L}^{-1}$   $\text{KHSO}_5$  solution and 4 mL of  $0.51 \text{ mol L}^{-1}$  NaOH solution. The content of mixture of each flask was mixed well and the increase in absorbance at 294 nm was recorded as a function of time for 15 minutes against reagent blank (Figure 2). It shows the dependence of Cefadroxil alkaline solutions absorption against time at 294 nm. They have linear dependence during first 10-15 minutes. This was a precondition for the possibility of using the kinetic method in the analysis of the drug.

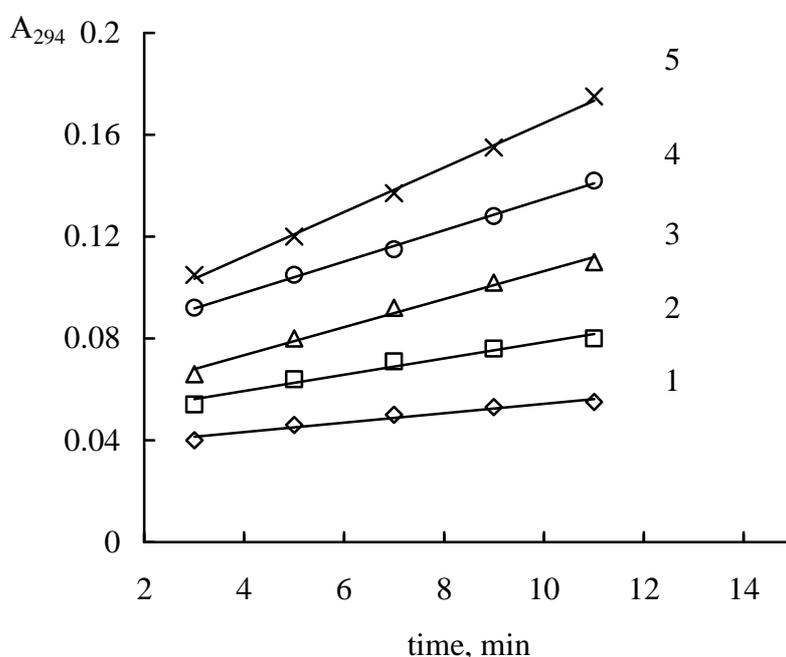


Fig. 2. Kinetic curves of formation of product of conjugated reactions of S-oxidation and perhydrolysis of Cefadroxil with potassium peroxomonosulfate

$c(\text{Cefadroxil})$ : 1 –  $0.25 \cdot 10^{-4} \text{ mol L}^{-1}$ ; 2 –  $0.5 \cdot 10^{-4} \text{ mol L}^{-1}$ ; 3 –  $1.0 \cdot 10^{-4} \text{ mol L}^{-1}$ ; 4 –  $1.5 \cdot 10^{-4} \text{ mol L}^{-1}$ ; 5 –  $2.0 \cdot 10^{-4} \text{ mol L}^{-1}$ ;  $c(\text{KHSO}_5) = 8 \cdot 10^{-4} \text{ mol L}^{-1}$ ;  $c(\text{NaOH}) = 0.02 \text{ mol L}^{-1}$

The initial rate of the reaction at different concentrations was obtained from the slope of the tangent to absorbance time curves. The calibration graph was constructed by plotting the tangent of the initial rate of the reaction versus molar concentration of Cefadroxil (Figure 3).

### Application of the proposed method for the determination of Cefadroxil in pure substance and capsules

0.39 g (precise weight) of Cefadroxil was placed in a 100 mL volumetric flask, diluted to the mark with double distilled water. Then, 1 mL of this solution was further diluted to 100 mL with double distilled water at  $20^{\circ} \text{C}$ . 10,00 of obtained solution was introduced into 100 mL volumetric flask containing 4 mL of  $0.02 \text{ mol L}^{-1}$   $\text{KHSO}_5$  solution and 4 mL of  $0.51 \text{ mol L}^{-1}$  NaOH solution. The content was shaken and finally diluted to the mark with double distilled water. After the NaOH solution was added the stopwatch was switched on. The obtained solution was transferred to a 1 cm cell to measure the absorbance at the wavelength 294 nm during first 15 min every 2 min against water. A kinetic dependence curve of absorbance A against time, min was obtained. The calculation was

performed using the initial rate method (differential variant). Five replicate estimaytions were done in similar way. The content of Cefadroxil capsules was calculated and label claim was determined and results are shown in Table 3.

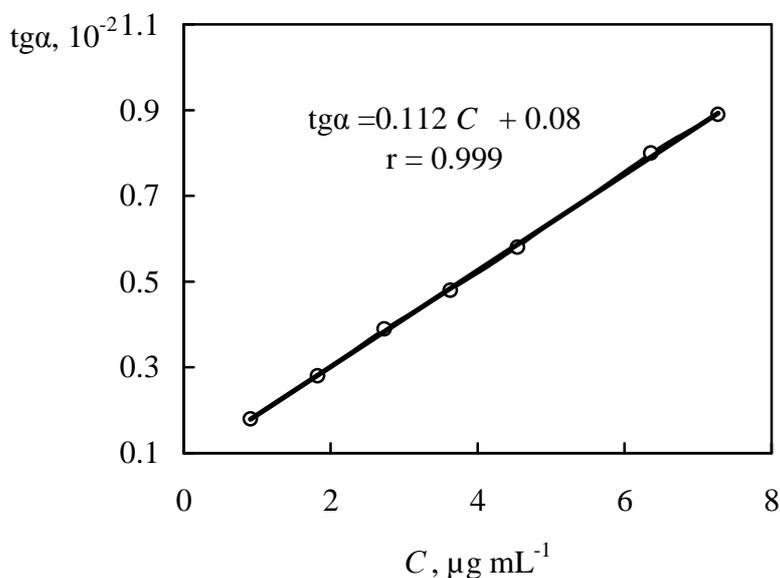


Fig. 3. Calibration plot for kinetic determination of Cefadroxil in pure substance  
 $c(\text{KHSO}_5) = 8 \cdot 10^{-4} \text{ mol L}^{-1}$ ;  $c(\text{NaOH}) = 2.00 \cdot 10^{-2} \text{ mol L}^{-1}$

### RESULTS AND DISCUSSION

The possibility of Cefadroxil analytical determination by the biologically active part of the molecule (alicyclic sulfur and  $\beta$ -lactam ring), reproducible results and accuracy are the advantages of the proposed procedure. It does not require expensive reagents and reference materials, toxic solvents and special equipment, as in HPLC, fast and simple in performance.

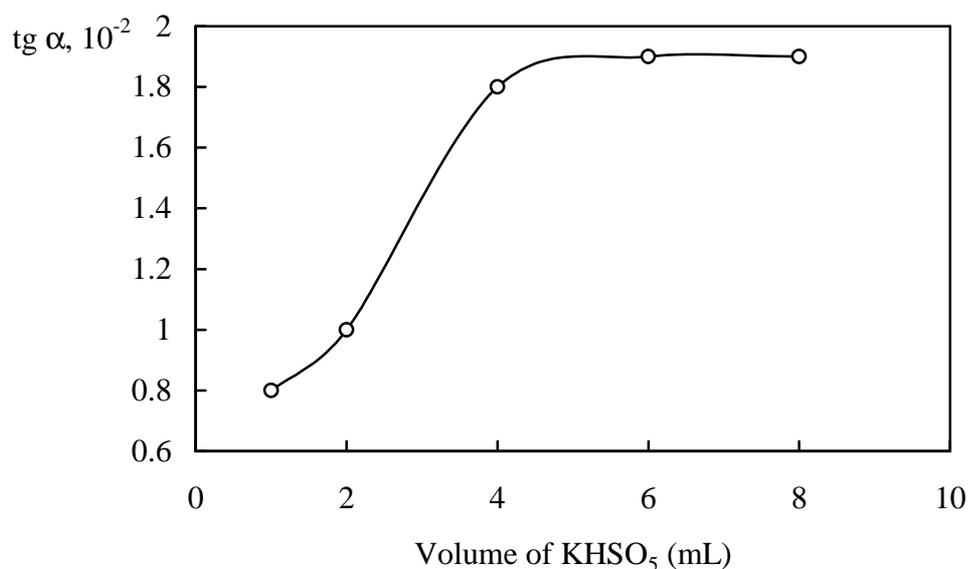


Fig. 4: Effect of potassium peroxomonosulfate 0.02 M on the reaction between the Cefadroxil ( $0.4 \cdot 10^{-4} \text{ mol L}^{-1}$ ) and alkaline potassium peroxomonosulfate

### Optimization of Reaction Conditions

#### Effect of potassium peroxomonosulfate

The absorbance increases substantially with increasing the concentration of potassium peroxomonosulfate (Figure 4). Maximum absorbance was obtained when 4.0 mL of 0.02 M of potassium peroxomonosulfate was used.

#### Effect of Sodium Hydroxide Concentration

Maximum absorption was obtained when 4 mL of 0.51 M NaOH was used. Over this volume no change in absorbance could be detected. So 4 mL of 0.51 M of NaOH was used as an optimum value (Figure 5).

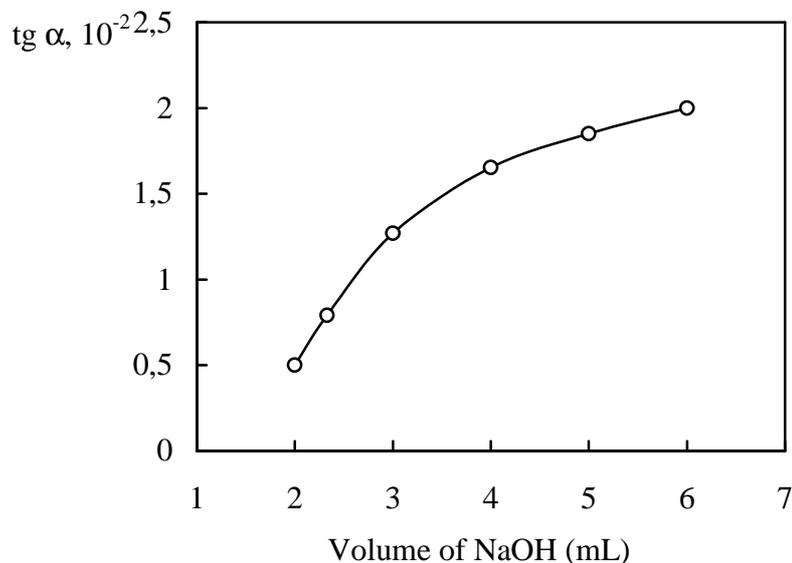


Fig. 5: Effect of sodium hydroxide concentration (0.51M) on the reaction between the Cefadroxil ( $0.4 \cdot 10^{-4} \text{ mol L}^{-1}$ ) and alkaline potassium permanganate.

The redox interaction between Cefadroxil and potassium peroxomonosulfate in acidic medium ( $\text{pH} = 3-5$ ) is stoichiometrical and fast: 1 mol of Cefadroxil per 1 mol of  $\text{KHSO}_5$  (observation time is 1 min) was determined by iodometric method. The reaction product is corresponding S-oxide (found by voltammetry method data).

During the experiment it was determined that the order of mixing influences the kinetics and yield of the reaction. The highest rate of product accumulation was observed only after prior adding of potassium peroxomonosulfate to cephalosporin (formation of Cefadroxil S-oxide), and then to a basic solution, optimal concentrations: potassium peroxomonosulfate  $8 \cdot 10^{-4} \text{ mol L}^{-1}$ , alkaline  $2.1 \cdot 10^{-2} \text{ mol L}^{-1}$  at 298-299 K. The reaction product wasn't formed without oxidant during the first 30 min. The product formation rate was assessed by the slope ( $\text{tg}\alpha, \text{min}^{-1}$ ) of linear plots of kinetic absorption curves, A against time, t (in minutes). The  $\text{tg}\alpha$  linear concentration dependence was observed within the Cefadroxil content in solution  $1-7 \mu\text{g mL}^{-1}$ .

On the basis of the results new procedures of quantitative determination of Cefadroxil in the pure substance and its dosage form was performed by the kinetic spectrophotometric initial rate method (differential version of the method of tangents).

### Development and validation of analytical method

Validation of the proposed method was carried out for the parameters like linearity, precision, accuracy, LOD and LOQ. Detection wavelength selected for analysis was 294 nm.

#### Linearity

Linearity was studied over a small drug concentration range from  $1-7 \mu\text{g mL}^{-1}$ . The correlation coefficient  $r=0.999$  obtained for regression line showed good relationship between the tangent of the initial rate of the reaction and molar concentration of cefadroxil (Figure 3, Table 1).

**Table 1: Analytical parameters for the initial rate method for the determination of Cefadroxil with potassium hydrogenperoxomonosulfate**

Linear range ( $\mu\text{g mL}^{-1}$ )	Intercept ( $a$ )	Standard deviation of intercept ( $S_a$ )	Slope ( $b$ )	Standard deviation of slope ( $S_b$ )	Correlation coefficient ( $r$ )	LOD ( $\mu\text{g mL}^{-1}$ )	LOQ ( $\mu\text{g mL}^{-1}$ )
1-7	0.0757	0.0099	0.1119	0.0022	0.999	0.265	0.885

**Accuracy, Precision Limit of Detection and Quantification**

The validity of the proposed method is studied by performing recovery studies. Precision and accuracy were studied by analyzing five replicates of sample solutions at three concentrations levels. The calculated relative standard deviations were all below 2.2% indicating excellent precision of the proposed procedure.

The LOD and LOQ were calculated based on standard deviation of response and the slope of calibration curve and expressed as

$$\text{LOD}=3\times S_a/b, \text{ LOQ}=10\times S_a/b,$$

where  $S_a$  is the standard deviation of response,  $b$  is the slope of calibration curve.

The results are summarized in Table 2.

**Table 2: Evaluation of accuracy and precision of the initial rate method for determination of Cefadroxil pure substance**

Amount taken (g)	Amount found (g)	Recovery (% $\pm$ SD)	RSD (%)
0.1956	0.1952 $\pm$ 0.0018	99.80 $\pm$ 2.04	2.04
0.3912	0.3903 $\pm$ 0.0098	99.77 $\pm$ 2.03	2.03
0.5868	0.5856 $\pm$ 0.0020	99.80 $\pm$ 0.90	0.90

**Table 3: Results of determination of Cefadroxil capsules by the reactions of peroxiacidic oxidation and perhydrolysis (P=0.95; n=5)**

Analyte	Amount taken (g)	Amount found (g)	Recovery (% $\pm$ SD)	RSD (%)	$\delta$ (%)
Cefadroxil capsules	0.5000 0.4953*	0.4979 $\pm$ 0.0180	99.58 $\pm$ 2.97	2.98	+0.42

\* Cefadroxil content to reference standard pharmacopoeia method.

**CONCLUSION**

So, spectrophotometric determination of Cefadroxil by the conjugated reactions of S-oxidation and perhydrolysis by means of potassium peroxomonosulfate in a basic medium was optimized and proposed for the first time.

The initial rate method can be easily applied for determination of Cefadroxil in pure substance and capsules that do not require elaborate treatment and expensive materials. The proposed method is sensitive enough to enable determination of lower amounts of drug, these advantages encourage the application of proposed method in routine quality control of Cefadroxil in industrial laboratories. Finally our method provides advantages of improving selectivity, quick and easy in performance.

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