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## DEVELOPMENT OF A SPECTROPHOTOMETRIC METHOD FOR DETERMINATION OF CEPHALEXIN USING SODIUM 1, 2-NAPHTHOQUINONE-4-SULFONATE AND CENTRAL COMPOSITE DESIGN

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### Keywords:

Cephalexin, 1,2-naphthoquinone-4-sulfonate, Central composite design, Formulation, Recovery

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**ABSTRACT:** A spectrophotometric method for determination of cephalexin is proposed. This method is based on the formation of a colored compound in the reaction of cephalexin with sodium 1,2-naphthoquinone-4-sulfonate (NQS). The effects of various experimental parameters in this reaction were investigated and optimized using central composite design (CCD). Twelve experiments with two factors and five levels for each factor were designed. These factors include concentration of NQS and pH. A full-quadratic polynomial equation between the absorbance as the response and the studied parameters was established. After removing the non-significant terms from the model, response surface method was used to obtain the optimum conditions. The optimum values of factors were  $20.0 \times 10^{-4}$  M for concentration of NQS and 9.6 for pH. The maximum absorption wavelength and the value of absorptivity of the colored product were 475 nm and  $1.79 \times 10^3$  L mol<sup>-1</sup> cm<sup>-1</sup>, respectively. The absorbance of the reaction product obeys Beer's law in the range 1.5-34.0 mgL<sup>-1</sup>. The detection limit of the method was 0.43 mgL<sup>-1</sup>. This method is rapid and simple, and can be used for the determination of cephalexin in formulations (capsules and injections). Recovery of 98.8% was obtained in application of the method to the real samples.

**INTRODUCTION:** Cephalexin (7-[(aminophenyl acetyl)amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxyliacid) is a semi-synthetic  $\beta$ -lactam antibiotic which belongs to the group of cephalosporin antibiotics. They have antibacterial action against gram-positive and gram-negative bacteria. Cephalexin is a potent cephalosporin and exhibits a broad spectrum of antibiotic activity.

A great variety of methods have been reported to determine cephalexin, including microbiological,<sup>1, 2</sup> spectrophotometric<sup>3-5</sup>, fluorimetric,<sup>6, 7</sup> HPLC<sup>8-16</sup>, polystyrene-divinylbenzene column (PSDVB)<sup>17</sup>, high speed liquid chromatographic (HSLC)<sup>18</sup>, high-pressure thin layer chromatography (HPTLC)<sup>19-23</sup>, immunoanalysis<sup>24, 25</sup>, alternative assay technique<sup>26</sup> and electrochemical<sup>27-30</sup>.

The microbiological assay is highly sensitive and specific but it is time-consuming and expensive. The proposed polarographic and fluorimetric techniques for determination of cephalexin require tedious procedures including solvent extractions and chemical pretreatment. HPLC methods can be used to determine the cephalexin in pharmaceutical dosage forms, but it has poor reproducibility.

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PSDVB methods are related to the separation of drug from impurities. Other methods of analysis available in the literature are based on electrochemical techniques. These sophisticated instrumental methods are not suitable for counterfeit drug assay as they are expensive.

The present work provides a reliable, simple and less time-consuming method for the determination of cephalosporins and need no separation of drug from impurities. However, the use of sodium 1, 2-naphthoquinone-4-sulfonate (NQS) as a chemical derivative chromogenic reagent for the determination of cephalosporins by a condensation reaction has not been reported so far.

## EXPERIMENTAL:

**Apparatus:** An agilent 8453 spectrophotometer was used for spectrophotometric measurements in a 1 cm quartz cells. The pH values were measured by a Jenway model 3345 pH-meter. A Huber polystat model CC3 thermostat was employed for temperature controlling.

**Reagents:** All chemicals were of analytical grade and used as received without any further purification. These were NQS (Merck, >99%), sodium carbonate ( $\text{Na}_2\text{CO}_3 \cdot \text{H}_2\text{O}$ ) and Cephalosporin. Double-distilled water was used in all experiments.

Two different commercial capsules containing 500 and 250 mg cephalosporin per capsules from Tehranchemie pharmaceutical company were purchased and used as real samples.

**Solutions:** A  $1.0 \times 10^{-3}$  M standard solution of cephalosporin was prepared by dissolving 0.035g of drug in double-distilled water and diluting it to 100 mL.

A  $4.0 \times 10^{-3}$  M standard solution of sodium NQS was prepared by dissolving 0.026 g of solid in double-distilled water and diluting it to 25 mL. NQS solutions were freshly prepared for experiment any stage.

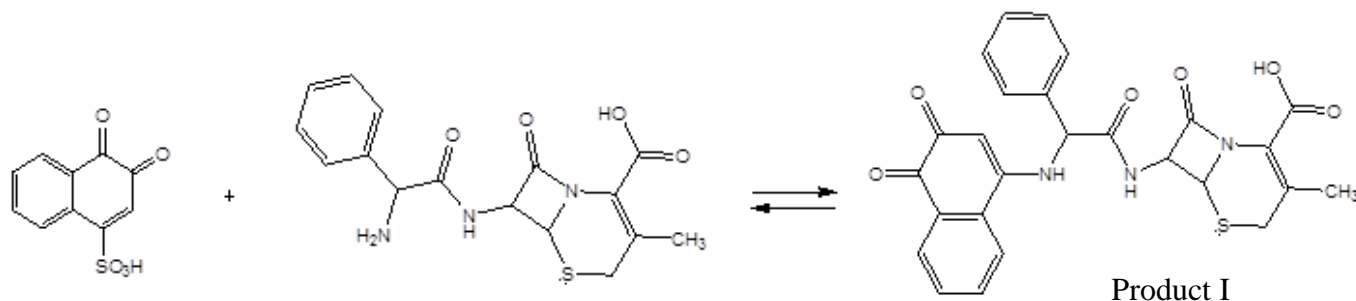
Buffer solutions of different pH were prepared by adding concentrated HCl or NaOH to the  $5.0 \times 10^{-3}$  M solution of  $\text{Na}_2\text{CO}_3$ .

**Procedure for recording spectra:** A 1.50 mL  $\text{Na}_2\text{CO}_3\text{-NaHCO}_3$  buffer solution of pH 9.6, 1.20 mL NQS and aliquots of cephalosporin stock solutions were transferred sequentially into a 10.00 mL standard flask, diluted to volume with double-distilled water and mixed well. The reaction was allowed to proceed at room temperature ( $25.00 \pm 1$  °C) for 30 min. The absorbance of the solution was measured at 475 nm against a reagent blank prepared with the same reagents concentration, but no cephalosporin.

**Preparation of the real capsule solutions:** The contents of ten capsules were weighed, finely powdered, and mixed thoroughly. A weight of the powder equivalent to the weight of the content of a capsule (containing 500 or 250 mg cephalosporin) was transferred into a 1000 mL volumetric flask, dissolved in about 50 mL water, sonicated for 15 min, filtered and diluted to the mark with double-distilled water, and mixed well. The resulting solution was analyzed based on the "Procedure for recording spectra".

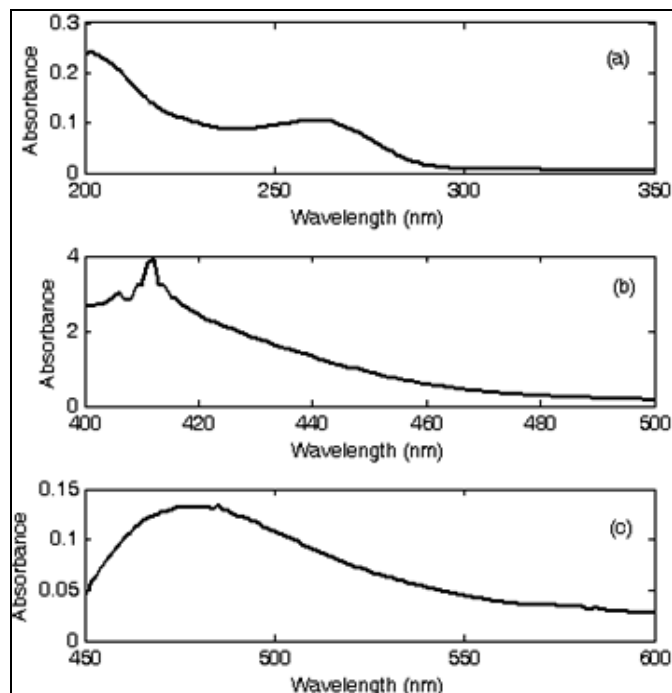
## RESULT AND DISCUSSION:

**Reaction between cephalosporin and NQS:** NQS reacts with amino group of cephalosporin to form a product.  $\lambda_{\text{max}}$  of the absorbance of the product is at 475 nm. The reaction has been shown in **Scheme 1**.



**SCHEME 1: REACTION BETWEEN CEPHALEXIN AND NQS**

**Absorption spectrum:** According to the procedure, the absorption spectrum of the product I produced by the reaction between cephalexin and NQS was recorded and shown in Fig. 1. As can be seen in Fig. 1, the maximum absorption wavelength of product I is at 475 nm and that for NQS is located at wavelengths lower than 400 nm. Obviously, cephalexin has no absorption in the range of 400–550 nm.



**FIG. 1: ABSORBANCE SPECTRUM OF (A) CEPHALEXIN AGAINST WATER AND BUFFER BLANK, (B) NQS AGAINST REAGENT BLANK AND (C) PRODUCT I AGAINST REAGENT BLANK.** Conditions: concentration of cephalexin 3.5 mg.L<sup>-1</sup>, concentration of NQS 20.0×10<sup>-4</sup> M and pH = 9.6.

**Optimization of reaction conditions:** Optimizing refers to improving the performance of a system, a process, or a product in order to obtain the maximum benefit from it. The term optimization

has been commonly used in analytical chemistry as a means of discovering conditions at which a procedure produces the best possible response. The experimental design is a method which can lead to this goal. The effect of NQS concentration and pH value on the formation of the reaction product was investigated by carrying out the reaction for different NQS concentrations (different volumes of 4.0×10<sup>-3</sup> M NQS solution) and pH (Table 1). Experiments were carried out at 25°C and reaction time was 30 min.

**TABLE 1: EXPERIMENTS DESIGNED BASED ON THE CCD FOR THE REACTION OF CEPHALEXIN WITH NQS**

Experiment number	pH	C (M)
1	9.0	20.0×10 <sup>-4</sup>
2	9.0	12.5×10 <sup>-4</sup>
3	11.0	12.5×10 <sup>-4</sup>
4	7.0	12.5×10 <sup>-4</sup>
5	7.6	18.0×10 <sup>-4</sup>
6	10.4	7.2×10 <sup>-4</sup>
7	9.0	12.5×10 <sup>-4</sup>
8	7.6	7.2×10 <sup>-4</sup>
9	9.0	5.0×10 <sup>-4</sup>
10	9.0	12.5×10 <sup>-4</sup>
11	10.4	18.0×10 <sup>-4</sup>
12	9.0	12.5×10 <sup>-4</sup>

1. **Design of experiments:** By using central composite design (CCD), twelve experiments (including four replicates at the central point) were designed. The factors (variables) were: initial concentration of NQS (C) and pH value. Although the initial concentration of cephalexin might be important, this factor was kept constant at a value of 1.0×10<sup>-5</sup> M. For each factor, five levels were defined. These values were designated by the codes: -2, -1, 0, +1 and +2 and are given in Table 2.

**TABLE 2: THE FACTORS, THEIR CODES AND THE REAL EXPERIMENTAL VALUES USED IN THE CENTRAL COMPOSITE DESIGN**

Factor	Name	Coded levels				
		-2	-1	0	+1	+2
F <sub>1</sub>	C (M)	5.0×10 <sup>-4</sup>	7.2×10 <sup>-4</sup>	12.5×10 <sup>-4</sup>	18.0×10 <sup>-4</sup>	20.0×10 <sup>-4</sup>
F <sub>2</sub>	pH	7.0	7.6	9.0	10.4	11.0

2. **Analysis of data:** After performing the experiments, the net absorbance for each experiment was calculated by ΔA= A<sub>s475</sub> - A<sub>b475</sub> where A<sub>bλ</sub> and A<sub>sλ</sub> are the absorbances of the blank and sample, respectively at the indicated wavelength.

The values of the difference between the absorbance of the blank and the absorbance of sample for each experiment are responses and are given in Table 3.

**TABLE 3: RESULTS OF THE EXPERIMENTS DESIGNED BY CCD (Table 1)**

Run No.	$\Delta A_{\text{experimental}}$	$\Delta A_{\text{predicted}}$
1	0.4267	0.4500
2	0.2518	0.2880
3	0.1796	0.2880
4	0.2912	0.2880
5	0.4004	0.4070
6	0.1901	0.1730
7	0.2724	0.2880
8	0.1767	0.1730
9	0.1339	0.1250
10	0.3219	0.2880
11	0.4777	0.4070
12	0.3376	0.2880

The closeness of the responses of the four replicate experiments can be a sign of the precision of the experiment process. The relation between the collected response and the variables conforms to the following polynomial equation (full quadratic model):

$$Y = b_0 + b_1F_1 + b_2F_2 + b_{11}F_1F_1 + b_{22}F_2F_2 + b_{12}F_1F_2 \dots \dots (1)$$

where  $Y$  is a response variable  $\Delta A$ ,  $b_i$  are regression coefficients for linear effects,  $b_{ik}$  are regression coefficients for quadratic effects and  $F_i$  are coded experimental levels of the variables. The analysis of variance (ANOVA) and least squares were used to evaluate the statistical significance of the variables and construct the model. The ANOVA consists of determining which factor(s) significantly affect the response. The significance and the magnitude of the estimated coefficients of each variable and all their possible interactions in the model (Eq. (1)) were determined and reported in **Table 4**.

Such coefficients for each variable represents the improvement in the response, that is, to expect as the variable setting is changed from low to high level. Four replicates of the central points were performed to estimate the experimental error. In order to show the fitness of the model, regression coefficient ( $R$ ) maybe be used. However, the adjusted regression coefficient ( $R_{\text{adj}}$ ) is a better criterion than the absolute regression coefficient. Since the regression coefficient ( $R$ ) always decreases when a regression variable is eliminated from the model, in statistical modelling, the  $R_{\text{adj}}$ , which takes the number of regression variables into account, is usually selected.

Hence,  $R$  and  $R_{\text{adj}}$  together are very convenient to obtain a quick impression of the overall fit and the predictive power of a constructed model.  $R$  and  $R_{\text{adj}}$  values of the model are high. The values of these parameters indicate that the model explains more than 85% of the variations in the experimental data. The parameter  $F$  of the regression is also high which indicates that the model is reliable in prediction of the response based on the values of the factors studied.

In order to find the important factors and build a model to optimize the procedure, initially the full quadratic model including all terms in Eq. (1) was employed. Then by the back elimination process, those terms which were not significant enough were eliminated. These terms included the factors or the interactions which had no significant effect on the response. Each term with a  $p$ -value greater than 0.05 was removed from the main equation. As can be inferred from Table 4, initial concentration of NQS and the constant term of the model are significant at the 95% confidence level ( $p$ -value lower than 0.05). Although pH may be important in the reaction of the amines with NQS, the ANOVA results show that pH is not a significant factor. This may be due to the result of the range of pH studied. Moreover, interaction terms are not important.

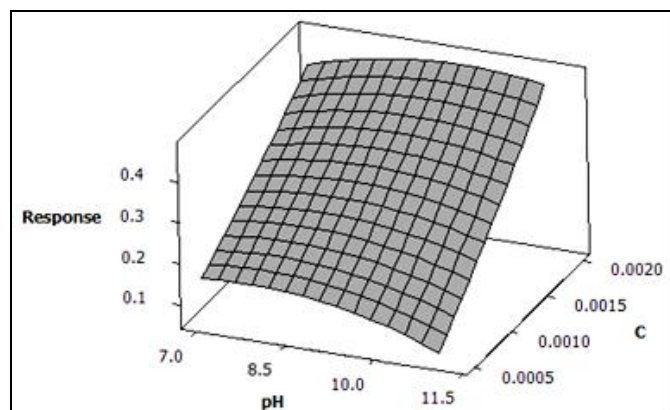
**TABLE 4: ANALYSIS OF VARIANCE (ANOVA) OF THE EXPERIMENTAL DATA**

Term	Coefficient	t	p
Constant	0.296	10.605	0.000
pH	-0.012	-0.441	0.674
C	0.162	5.880	0.001
pH×pH	-0.036	-0.803	0.453
C×C	0.011	0.258	0.805
pH×C	0.033	0.594	0.574
$R$	92.58%		
$R_{\text{adj}}$	85.91%		
$F$ regression	47.04		

3. **Response surfaces and selection of optimized values:** Response surface methodology (RSM) is a statistical method being useful for the optimization of chemical reactions and/or industrial processes and widely used for experimental design. Whenever multiple system factors may influence the responses, RSM can be utilized to assess the relationship between dependent (response) and independent variables (factors) as well as to optimize the relevant processes.



After analysis of the data, the response surface of the full quadratic model between the response and the factors was depicted. Via the surface, the relations between the response and the effective factors are graphically given. The surface is shown in **Fig. 2**. The optimized ranges for each factor that leads to the best response (the highest absorbance intensity) were extracted from this surface. The optimum values of variables were calculated as:  $20.0 \times 10^{-4}$  M for C and 9.6 for the reaction pH.



**FIG. 2: RESPONSE SURFACE FOR THE VARIATION OF THE FACTORS CONCENTRATION OF NQS (C) AND pH**

**Effect of factors:** The optimum values of the factors show that higher values of concentration of NQS and intermediate pH are suitable for the reaction between cephalixin and NQS. The coefficient of the concentration of NQS (C) is positive (Table 4) and it is the largest ones among the coefficients except the constant term. This indicates the importance of the concentration of NQS in the reaction studied. From Fig. 2, the significant effect of concentration of NQS (C) on the response is clearly observed. On the other hand, the coefficient of pH is negative and it is one of the smallest ones in the model. Therefore, pH is not as important as the concentration of NQS in the

reaction studied. This can be simply inferred from Fig. 2. With variation of pH, response changes only slightly. However, the overall effect of pH is such that the production of the colored product favors in the intermediate studied pHs.

**Calibration:** Under the optimum conditions, a linear relationship between concentration of cephalixin and  $\Delta A$  was obtained in the range of 1.5–34.0 mg.L<sup>-1</sup>. In addition, based on the absorbance and concentration of the cephalixin, molar absorptivity of product I at 475 nm was  $\epsilon_{475} = 1.79 \times 10^3$  L mol<sup>-1</sup>cm<sup>-1</sup>. Statistical analyses of the calibration have been collected in **Table 5**.

**TABLE 5: STATISTICAL ANALYSIS OF THE CALIBRATION BY THE PROPOSED METHOD**

Parameter	Parameter
$\lambda_{max}$ (nm)	475
Linear range (mg.L <sup>-1</sup> )	1.5-34.0
slope (n=11)	0.0090
intercept (n=11)	0.0900
Correlation coefficient (R)	0.9960
Detection Limit (mg.L <sup>-1</sup> )	0.4316
Standard deviation of blank	0.0022
Standard deviation of slope	0.0008
Standard deviation of regression	0.0305

**Analysis of the real samples:** The applicability of the method was assayed by analyzing two different pharmaceutical formulations. The assays were carried out as described under the *preparation of the real capsule solutions*. In all cases, the concentration of cephalixin was obtained by reaction of the real samples with NQS in the optimum conditions and using the standard calibration graph.

The results have been shown in **Table 6**. Accuracy of the proposed method is evident from the percent recoveries very close to 100%. The method is also precise since the RSD% values are below 3%.

**TABLE 6: RESULTS OF DETERMINATION OF CEPHALEXIN IN PHARMACEUTICAL FORMULATIONS BY THE PROPOSED METHOD**

Sample no.	Real sample (mgL <sup>-1</sup> )	Mean found (mgL <sup>-1</sup> ) (n=5)	RSD (%)	Recovery (%)
(Cephalixin Tehranchemie 500 mg capsule)	10	9.88	2.6	98.8
(Cephalixin Tehranchemie 250 mg capsule)	10	9.95	1.5	99.5

**Comparison of the proposed method with the reported spectrophotometric method:** Statistical analysis of the results obtained (**Table 7**) indicates that lower limit of the linear range of the proposed method is smaller and molar absorptivity of

product I at 475 nm is  $\epsilon_{475} = 1.79 \times 10^3$  L mol<sup>-1</sup> cm<sup>-1</sup>. Linear range or the reported spectrophotometric method<sup>5</sup> is relatively wide. The relative standard deviation (RSD) of the two methods is less than 2% and recoveries are over 98%.

**TABLE 7: ANALYTICAL DATA FOR DETERMINATION OF CEPHALEXIN BY THE PROPOSED METHOD AND THE REPORTED SPECTROPHOTOMETRIC METHOD.**

	Linear range (mg.L <sup>-1</sup> )	Molar absorptivity (L mol <sup>-1</sup> cm <sup>-1</sup> )	RSD (%)	Recovery (%)
Proposed method	1.5-35	1.79×10 <sup>3</sup>	1.50	99.5
Spectrophotometric method <sup>5</sup>	10-150	0.19×10 <sup>3</sup>	1.11	98.5

**CONCLUSION:** The present spectrophotometric method describes the evaluation of NQS as analytical reagent in the development of simple, sensitive and accurate method for the determination of cephalexin in pharmaceutical formulations. Central composite design can be used to find more precise conditions for the system studied. The reagent utilized in the proposed method is cheap and readily available and the procedure does not involve any critical reaction conditions or tedious sample preparation and extraction. Statistical analysis proved that the proposed method could be applied for the analysis of cephalexin in their pure forms and in pharmaceutical formulations. Therefore, this method can be recommended for the routine analysis of cephalexin in quality control laboratories.

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