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The Determination of Cefadroxil by Using Organic Reagent NQS

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Abstract: A simple spectrophotometric method to determine the cefadroxil has been investigated. The method is based on Schiff's base reaction of cefadroxil with 1,2-naphthoquinone-4-sulfonic acid (NQS) in an aqueous solution to give a dark yellow product for maximal absorption of 460 nm. It complied with Beer's Law with a range of 0.1 – 20 µg/ml. The limit of detection (LOD) and the limit of quantitation (LOQ) were 0.0339 and 0.169 ppm, respectively. It was found that the average recovery percent was 99.89% and 1:1 product. As the stability constant was 2.7×10^6 L/mol, this method was successfully applied for the determination of cefadroxil in the pharmaceutical formulations. The results obtained using this method are compatible with the method of the British Pharmacopoeia method.

Key Words: cefadroxil, Shiff's base

1. Introduction

Cefadroxil is an antibiotic [1] consumed and used to treat mild to moderate infections caused by susceptible microorganisms [2]. It is used to treat bacterial infection of the skin and strep throat for the urinary tract [3,4]. Figure 1 shows the structure of the drug.

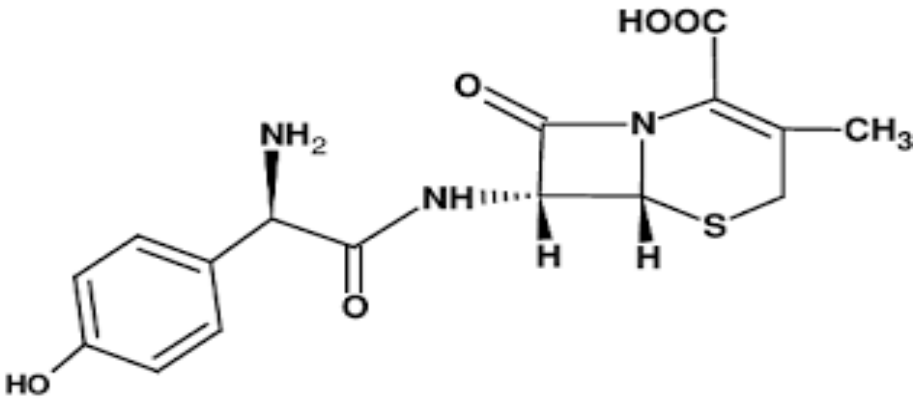


Figure 1. Structure of Cefadroxil [5]

Several scientific methods of analysis were available in the literature for the determination of cefadroxil in their pharmaceutical preparations, including fluorimetry [6] and polarography [7,8]. Thin layer chromatography [9], HPLC [10,11], sequential injection analysis [12], chemiluminescence [13,14], capillary electrophoresis [15], and spectrophotometric methods have been described to determine cefadroxil using various reagents based on the formation of complexes with copper (II) [16] Flow injection analysis (FIA) [17]. Additionally, another method is based on the liberation of hydrogen sulfide and followed by the reaction with N,N-diethyl-p-phenylenediamine [18]. Other spectrophotometric methods are reported for the determination of cefadroxil based on its reactivity with iodine [19]. Nitrosation and subsequent metal chelation reaction with 2,6-dichloro-quinone-4-aminoantipyrene in the presence of potassium hexacyanoferrate [20] or by oxidation in an acid medium [21].

These methods are time-consuming and required extraction steps or required indirect procedures. This work describes a simple and sensitive spectrophotometric method for the determination of cefadroxil. This method is based on the reaction of the drug with NQS and the formation of Schiff's base.

2. Experimental Apparatus

- Spectrophotometer using Ajena model 1100 (Germany) with a quartz cell with 1 cm path length, PW "9421" pH meter for a common glass electrode.

A meter electrical balance was used to weigh the sample. The reagent was supplied by BOH and Fluka. The standard solution of 100 ppm cefadroxil was prepared by dissolving 0.01 g in 2 ml of de-ionized water and then diluted to 100 ml. Also, 5×10^{-3} M of 1,2-naphthoquinone reagent was made by dissolving 0.06 g in 50 ml de-ionized water.

3. Results and Discussion

In a primary test, the NQS reagent reacted with cefadroxil in the presence of sodium hydroxide NaOH and formed a red color product with the highest absorption peak at 465 nm, where the reagent blank showed low absorbance at this wavelength.

4. Study of Optimal Reaction Conditions

Impact of NQS Reagent

The impact of changing the reagent 1,2-naphthoquinone solution concentration on the absorbance of cefadroxil was performed. It was noticed that the absorbance increased and reached a maximum when 1 ml of 5 × 10^{-3} M 1,2 - naphthoquinone solution was used (Figure 2).

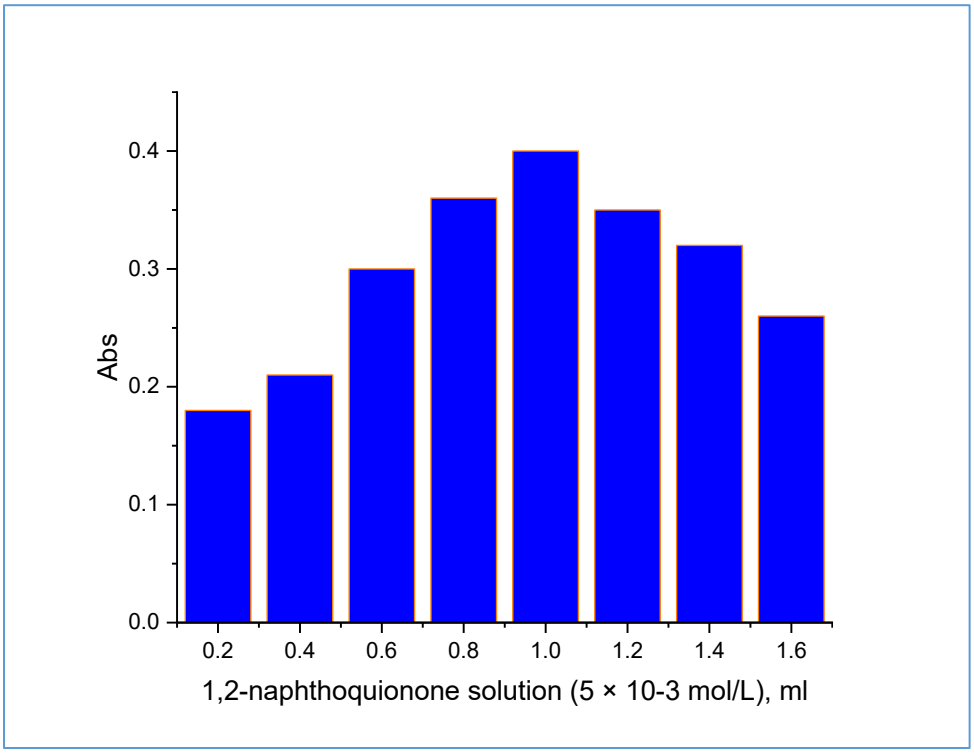


Figure 2. Impact of NQS Reagent Conc.

Impact of Base

The impact of bases (sodium hydroxide NaOH, potassium hydroxide KOH, ammonium hydroxide NH_4OH, and sodium carbonate Na_2CO_3) was investigated. It was found that potassium hydroxide gave maximum absorption at 460 nm (Figure 3).

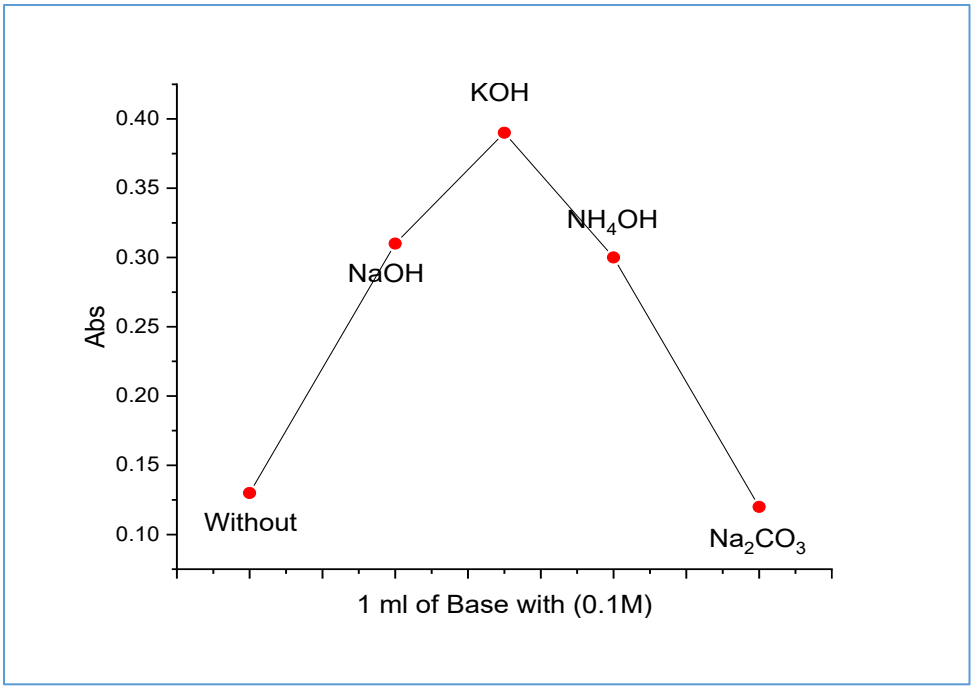


Figure 3. Bases (1 ml of 0.1M)

Furthermore, the impact of the potassium hydroxide volume and pH were studied. Maximum absorbance was observed when 1.5 ml of 0.1M KOH at pH 11.31 was used.

Table 1. The Impact of Increasing pH and the Volume of KOH 0.1 M on the Absorption of the Mixture (8 ppm Cefadroxil, NQS, KOH)

KOH V(ml)	0.5	1	1.5	2
pH	6.5	10.3	11.31	12.15
Absorbance	0.23	0.41	0.45	0.40

Impact of Surfactants

The impact of Tween 80 (TW-80), Triton X-100 (TX-100), and cetyltrimethyl ammonium bromide (CTAB) of 0.1% concentration was studied. However, the absorbance was decreased when CTAB was used (Figure 4). Therefore, it was excluded from the experiment.

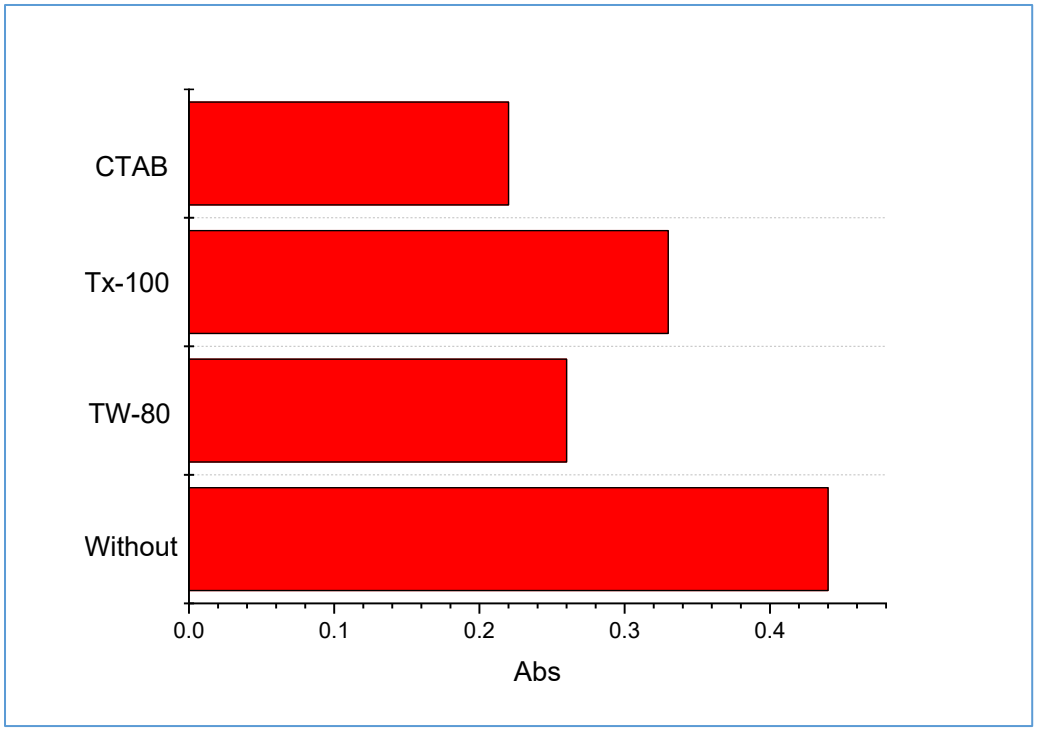


Figure 4. Impact of Surfactant on the Absorption of the Product

Impact of Temperature Versus Time on the Absorbance of the Complex

The effect of reaction time was performed at different temperatures. Figure 5 shows a decrease in the absorbance when time increased, attributed to the dissociation of the complex. It was found that the optimum time and temperature for the complex was 15 min at 40°C, respectively.

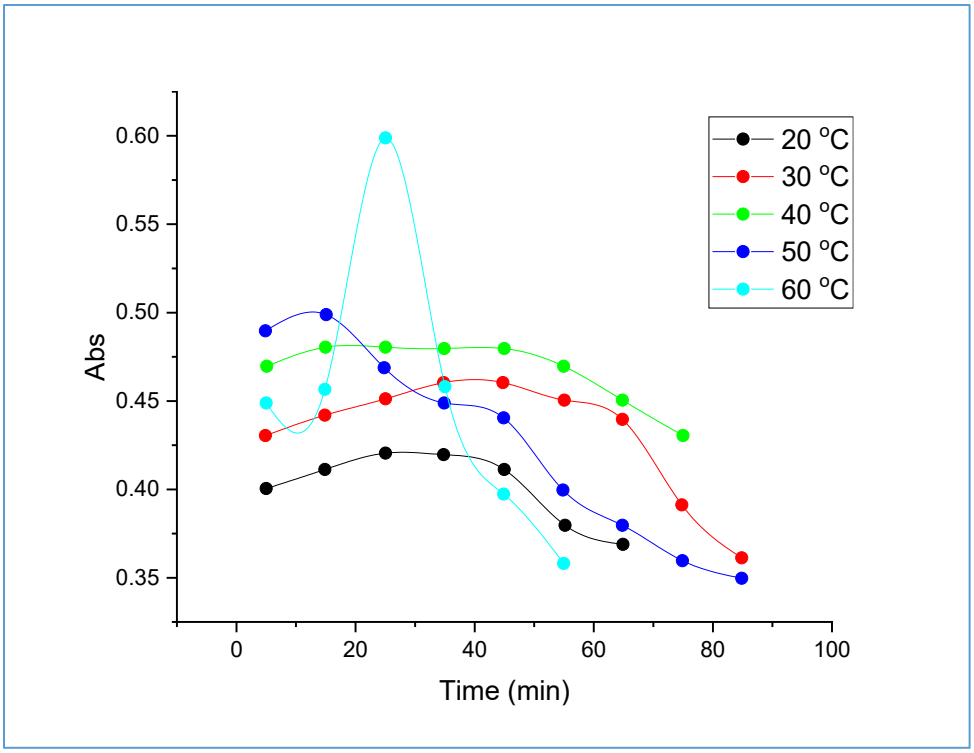


Figure 5. The Impact of Temperature Development and Time on the Stability of the Complex

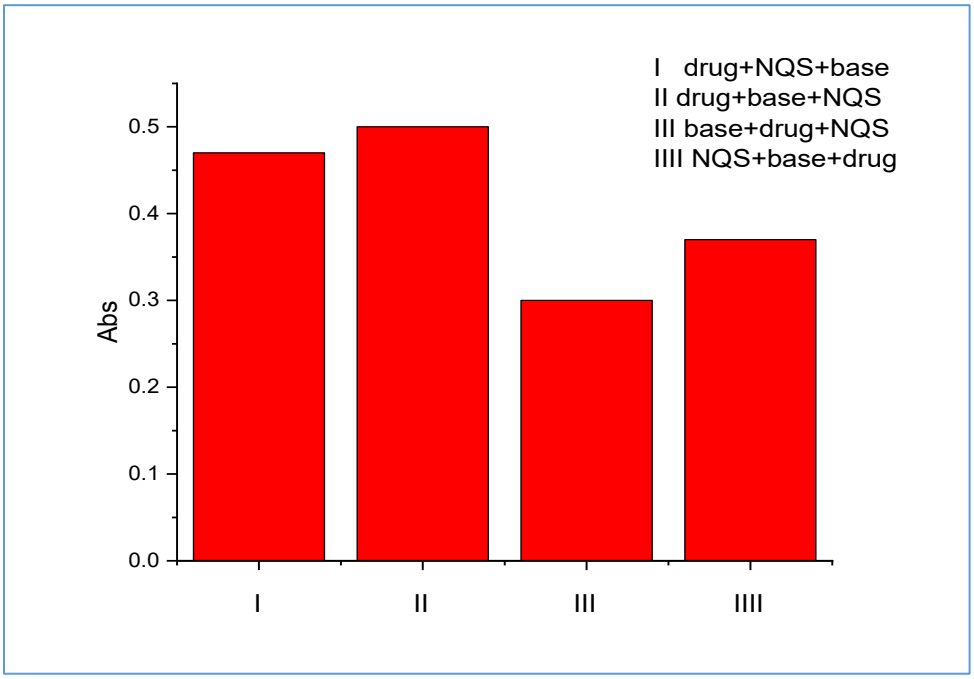


Figure 6. Impact of the Order of Addition on the Absorption

Impact of the Order of Addition

Under the optimum conditions, the order of addition was investigated. Figure 6 shows that in the order of addition, no. II was the best.

Absorption Spectra

Figure 7 shows the absorption spectra for the best condition that has been confirmed above.

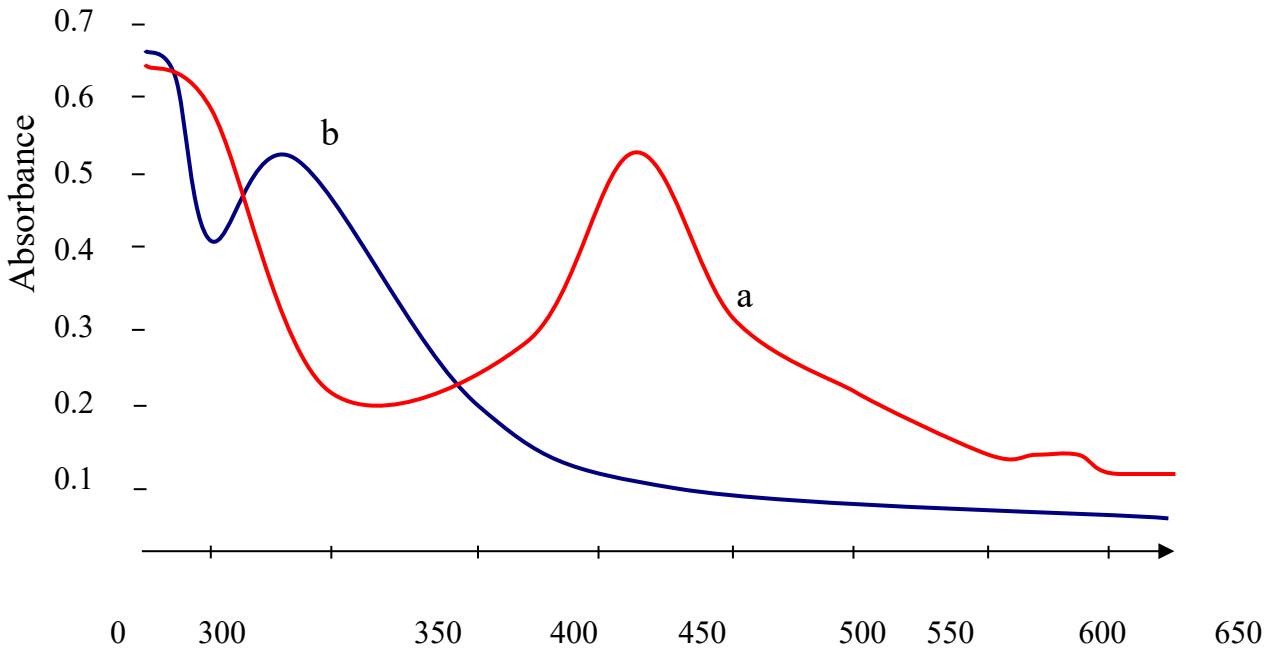


Figure 7. (a) The absorption Spectra of Cefadroxil with 1,2-Naphthoquinone Versus Reagent Blank at 460nm (b) Reagent Blank Versus Distilled Water

The Details of the Statistical Data and Optical Characteristics of the Suggested Method

The absorbance of the complex was measured at 460 nm. Beer's law limits and molar absorptivity values are shown in Table 2. In addition, the relative standard deviation (RSD) and the accuracy of analysis on six replicates for three different concentrations of cefadroxil indicate that the method is valid. Also, the limit of detection (LOD) is accepted as well.

Table 2. The Summary of Optical Characteristics

Parameter	Cefadroxil
Beer law limit (ppm)	0.1-20
Molar abs (L/mol . cm)	3.152×10^3
LOD (ppm)	0.0399
LOQ (ppm)	0.169
Average recovery percent (%)	99.89
Correlation Coefficient	0.989
Slop a	0.122
Intercept b	0.0169
R.S.D.	≤ 0.44

Analytical Implementation

The results showed that the experimental F-Test and T-Test were less than the theoretical value (t = 2.50, f = 6.41). However, it was observed that there was no significant variation between the suggested method and the formal method [22].

Quantities and Stability Constant

Quantities of a reaction of cefadroxil for NQS were studied through the molar ratio as well as job method [23,24].

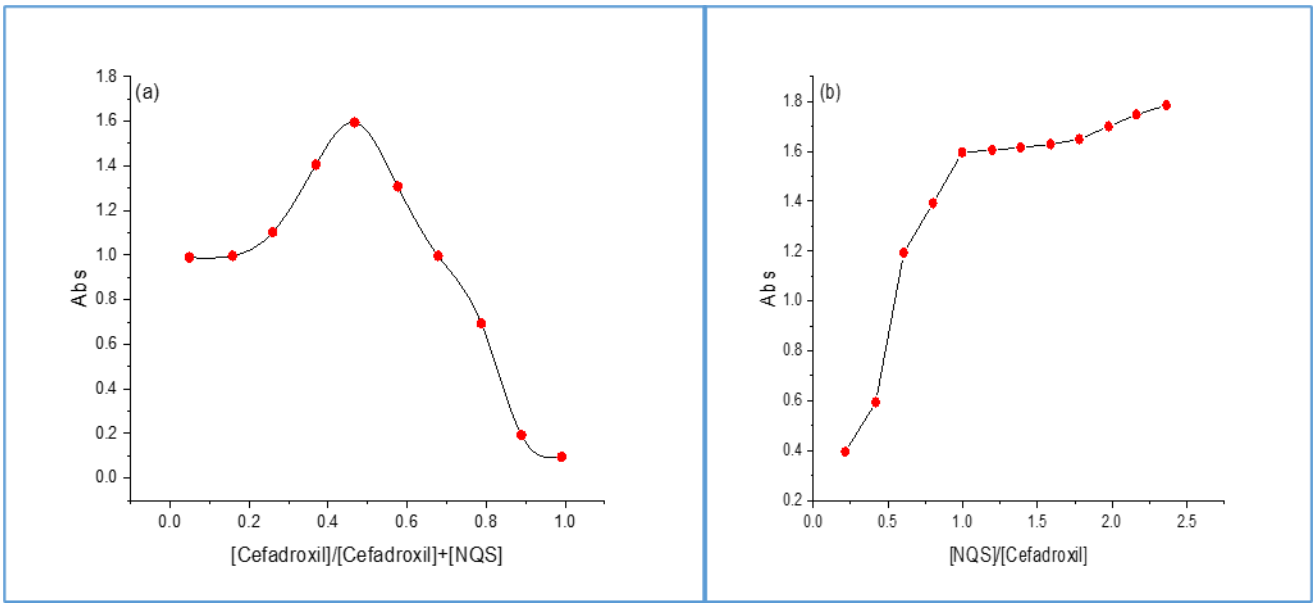


Figure 8. (a) Continuous Variations (b) Mole Ratio

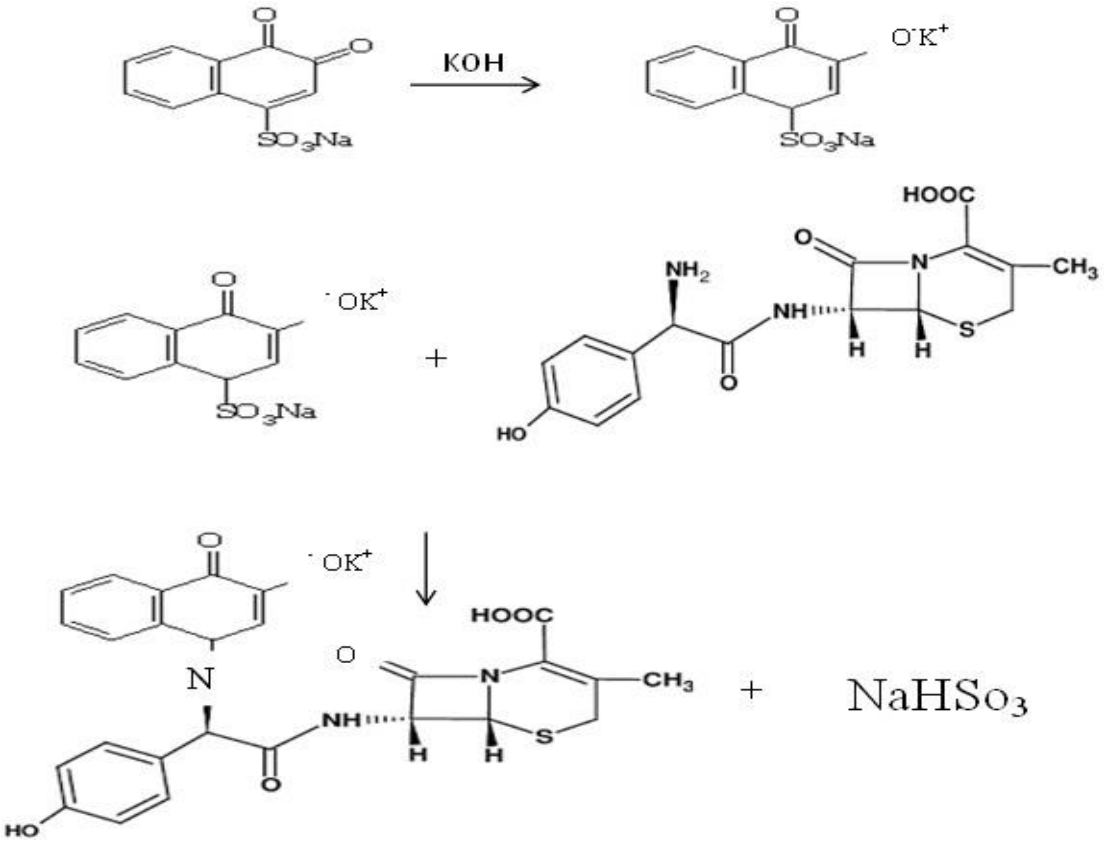
Figure 8 (a) and (b) showed that the results were 1:1 and the average conditional stability constant for the resulting complex was calculated using the equation (1) below:

$$K_{st} = 1 - \propto / (\propto^2 C)$$
$$\propto = (Am - As) / (Am) \quad (1)$$

where K_{st}: the stability constant (L/mol), (∝): the dissociation degree, and (C): the concentration of the resulting complex. The average K_{st} is 2.7×10^6 which illustrates that the resulting product is stable.

Mechanism of the Reaction

Under the experimental conditions, the mechanism of the reaction is shown in Scheme 1.



Scheme 1. The Suggested Mechanism of the Product

The mechanism suggests that the NQS was converted into a quinoidal which reacts with phenol amine via the replacement of the hydrogen atom of the primary aromatic amine group to produce paraquinoidimide-condensation (Schiff's base) $NaHSO_3$.

5. Conclusion

The suggested spectrophotometric method is simple, sensitive, and low cost. In addition, this method does not involve a solvent extraction step. Also, it gives accurate and precise results. The calibration curve shows high linearity. The coefficient correlation was higher than 0.99. The limit of detection and limit of quantitation values were very acceptable as well. Finally, the suggested mechanism of the product formation shows the NQS was converted to a quinoidal that reacts with phenol amine to produce paraquinoidimide-condensation (Schiff's base) and $NaHSO_3$.

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