ORIGINAL ARTICLE

Development of a spectrophotometric analytical approach for the measurement of cefdinir in various pharmaceuticals

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ABSTRACT

An accurate and sensitive determination procedure has been established for the quantification of cefdinir in pure and pharmacological formulas. The approach was dependent on derivatizing cefdinir with sodium anthraquinone-2-sulfonate (SAS) in an alkaline medium to produce a magenta-colored derivative with a maximum absorbance at 517 nm against the reagent blank. Different factors affecting the interaction of cefdinir with SAS were studied carefully and optimized, such as the buffer value, medium acidity, the duration of hydrolysis, and the reagent percentage. Under optimized conditions, a linear calibration curve with a correlation coefficient of R^2 = 0.9995 was obtained over the concentration range of cefdinir 0.5–100 μg/mL. The values of the parameters that represented the sensitivity of the method were satisfactory, i.e., the limit of detection, the limit of quantification, as well as Sandell's sensitivity (η) were 0.1 μg/mL, 0.5 μg/mL, and 0.064 μg/cm^2/0.001 Au, respectively. The relative standard deviation was below 1.35%, while the percentage recovery was 99.930%–102.257%. The mole ratio of the colored complex was estimated by following Job's method of continuous variation, which indicated that the cefdinir-SAS ratio was 1:1. The suggested approach was proven to be adequately accurate, precise, and without interfering with common excipients and additives. Thus, it could be implemented successfully for the standard determination of cefdinir in its pure and pharmaceutical forms.

Key words: Cefdinir, colorimetric, derivatization, sodium anthraquinone-2-sulfonate, spectrophotometry

INTRODUCTION

Cefdinir is a partially synthetic cephalosporin antibiotic of the third generation with broad antibacterial action that can be taken orally.[1] It has antibacterial properties for Gram-negative and Gram-positive bacteria due to the vinyl and (2-amino-4-thiazolyl)-2-(hydroxyimino) groups presented in its skeleton.[2] Cefdinir as a standard antibiotic[3] has been observed to *in vivo* interact with metals such as Zn (metal) and Mg (antacid) at pH 7.4, the stability constant of the resulting complexes was determined to assess the potential *in vivo* implications.[4]

Cefdinir has various forms, each with its solubility, liable for the acidity of the aqueous medium [Figure 1]. The least

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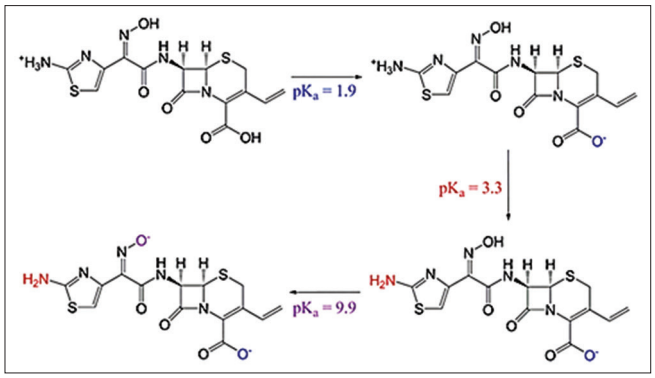

Figure 1: The acidity of the medium affecting the form and solubility of cefdinir

solubility is at pH 2.5 (0.52 ± 0.06 mg/mL) while it improves dramatically above pH 4.0 and reaches the best solubility of 17.11 ± 0.87 mg/mL over the range (pH 8–12).[5]

Sodium anthraquinone-2-sulfonate (SAS) exhibits strong oxidizing properties and possesses greater solubility in an aqueous medium.[6] However, light irradiation in alcoholic solutions reduces SAS to dioxyanthracene and, in alcohol-alkali solutions, to semiquinone anion radical.[7] It plays an important industrial role as a bioreduction agent in extracellular electron transfer processes.[8] A triplet exciplex is formed when an excited quinone molecule becomes a triplet state complex with an amino group.[9]

Spectrometrically, cefdinir is oxidized with 3-methylbenzothiazolone-2-hydrazone in the existence of FeCl3 in an acidic solution, resulting in a green-colored chromogen with a maximum wavelength of 660 nm,[10] also it has been estimated spectrometrically after cloud point extraction and diazotization with 2,5-dimethylphenol,[11] and high-performance thin layer chromatography (TLC), followed by densitometry to convert cefdinir dispersal on the TLC plate into digital data.[12] Cefdinir interacts with iron in an alkaline medium forming a violet-colored complex that absorbs at λmax of 550 nm.[13]

However, some methods of determination imply the separation of cefdinir from other impurities commonly available in medicines or biological specimens. However, spectrophotometric as well as colorimetric approaches are considered environmentally benign compared to other sophisticated analytical techniques.[14-17] Cefdinir was determined likewise by 0 and first-order derivative spectrophotometry.[18] While in another study, the approach of Taguchi experimental design was used for a spectrofluorometric determination of cefdinir.[19] Nevertheless, silver nanoparticles have been utilized for spectrophotometric assaying of cefdinir, as a degraded medicine in an alkaline medium to reduce silver ions to silver nanoparticles' presence of gelatin as a capping agent.[20] Several spectrophotometric methods were developed based on the alkaline hydrolysis of cephalosporin, followed by a reaction of the produced sulfide ions with chromogenic reagents.[21] Amines accelerate the photoreduction reaction when mixed with quinones, forming a colored charge-transfer exciplex.[22,23] The reagent of naphthoquinones was used for the spectrophotometric estimation of amino acids[24] and as a titrant.[25]

Accordingly, this study aimed to design a simple, sensitive, rapid, and affordable spectrophotometric technique for quantifying cefdinir in both pure form and pharmaceutical formulations through oxidizing the electron donor of the amino group located in the cefdinir molecule by coupling with SAS as an electron acceptor to form a colored complex that could be easily and sensitively quantified.

MATERIALS AND METHODS

All reagents and solvents were analytical grades. Cefdinir, purity 99% was provided from SDI, Samarra, Iraq. SAS 98%, Sigma-Aldrich. Spectrophotometric analysis was performed with ultraviolet-1800, Shimadzu Corporation, Kyoto, Japan.

500 mg/L SAS solution was prepared by mixing 50 mg in 100 mL of distilled water. A pH 10.5 buffer solution was formulated by combining 50 mL of 0.05 M $NaHCO_3$ with 31.7 mL of 0.1 M NaOH and made up the volume to 100 mL with distilled water. A cefdinir stock solution (500 µg/mL) was set in (pH 10.5) buffer. Then, a set of standard solutions in the concentrations of 0.01, 0.05, 0.1, 0.5, 1, 3, 5, 10, 15, 20, 30, 40, 60, 80, 100, 120, and 150 µg/mL were diluted from the freshly prepared stock solution of cefdinir.

A pharmaceutical sample of cefdinir powder has been collected out of 10 capsules, and then finely powdered. A mass of 100 mg of the powder was dissolved in 10 mL of (pH 10.5) buffer. The obtained stock was then diluted for examination following the developed procedure. The acidity of the reaction medium has to be buffered since it may affect the solubility of the analyte as well as the overall derivatization mechanism.[26] The calculations for the preparation of the buffer (pH 10.5) were performed according to the Henderson–Hasselbalch equation.[27]

The reaction of cefdinir with sodium anthraquinone-2-sulfonate

In a 10 mL volumetric flask, an aliquot of cefdinir solution was combined with 1 mL of SAS reagent, and the volume was completed with buffer pH 10.5. The reaction mixture was kept at room temperature for 10 min to develop the magenta color. The resulting colored derivative was analyzed at 517 nm.

The mole ratio of cefdinir and sodium anthraquinone-2-sulfonate in the colored derivative

The molar ratio of cefdinir and SAS in the resultant colored derivative was examined using Job's method of continuous

variation. This was accomplished by preparing two separate aqueous solutions of cefdinir and SAS with the same concentration of 10 µg/mL. From these solutions, a set of cefdinir-SAS mixtures were prepared in 10 mL volumetric flasks, in which the volume ratio of cefdinir was increased by 10% starting from 0 while the SAS volume ratio was decreased by 10% starting from 100%. The subsequent complementary solutions were kept aside for 10 min and then measured at 517 nm.

RESULTS

SAS is known to be a good chromogenic agent for derivatizing primary and secondary amines; nevertheless, its interaction with cefdinir has never been inspected beforehand. Therefore, the amino group presented in the pharmaceutical molecule of cefdinir was a good reaction center for being derivatized with the reagent of SAS for later spectrophotometric determination of cefdinir.

The maximum absorption peak of the magenta-colored product formed by the reaction between cefdinir and SAS was at 517 nm, while the maximum absorption peak (λmax) of SAS was at 371 nm [Figure 2].

A calibration curve was constructed for the determination of the cefdinir-colored derivative. Across the range of quantification concentration range (0.5–100 µg/mL), a linear correlation was observed. The regression equation observed was A = 0.0155C + 0.1155 with a correlation coefficient R^2 = 0.9995, where A depicted absorbance at 517 nm and C was cefdinir concentration (µg/mL). The molar absorptivity (ε) was 0.0155 L.mol^{-1}.cm^{-1} as illustrated in Figure 3.

Statistical analysis of the results obtained indicated the high accuracy and precision of the proposed procedure. The standard cefdinir solutions were analyzed by three replicates for each concentration. The results were satisfactory, indicating the excellent reproducibility of the developed method. Relative standard deviation was <1.4%, the percentage recovery was 99.930%–102.257% [Table 1], and the limit of detection and limit of quantification were 0.1 µg/mL and 0.5 µg/mL, respectively.

Sandell's sensitivity (λ), defined as the minimum concentration in (µg/mL) that produces an absorbance of 0.001 within a path length of 1.0 cm, was determined through the following calculation:

λ = (0.001 cm × 1.0 cm)/slope (cm^3/µg)

=0.064 µg/cm^2/0.001 Au

DISCUSSION

Transformation of SAS into its hydroxyl derivatives might take place in the presence of molecular oxygen. In the current investigation, SAS formed a colored derivative with cefdinir which was absorbed at 517 nm under alkaline conditions.

The impact of the SAS reagents' concentration was investigated by employing various volumes of SAS, each with a consistent concentration of 10 µg/mL. The reaction of SAS with cefdinir was initiated upon adding 0.2 mL

Table 1: Evaluation of accuracies and precisions for the proposed method

Concentration (µg/mL)		Relative error* (%)	Recovery (%)	RSD* (%)
Taken	Found*			
10	9.9930	−0.070	99.930	1.221
20	20.066	+0.330	100.330	1.184
60	60.154	+0.257	102.257	1.316

*Average of three measurements. RSD: Relative standard deviation

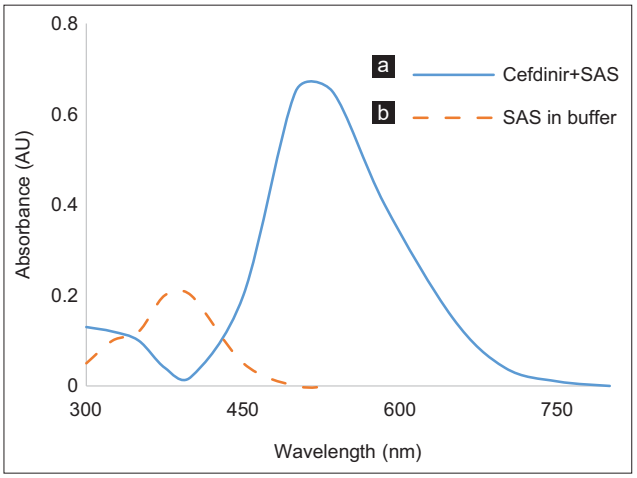

Figure 2: Absorption spectra of (a) Cefdinir/sodium anthraquinone-2-sulfonate (SAS) complex, and (b) SAS in buffer pH 10.5. SAS: Sodium anthraquinone-2-sulfonate

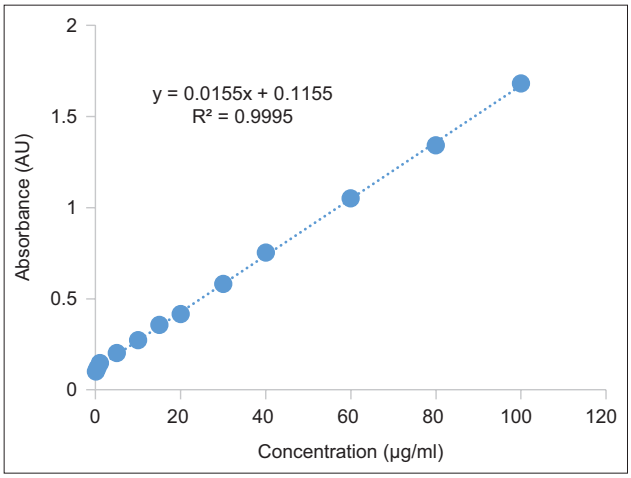

Figure 3: The calibration curve of cefdinir under optimum conditions. Lambert–Beer's law was obeyed over the concentration range of 0.5–100 µg/mL

of SAS to 1 mL of 10 µg/mL of cefdinir. The addition of SAS continued with an increment of 2 mL at a time which resulted in a proportionate rise in the absorbance for the derivatized product. The absorbance was stabilized upon the addition of 0.8 mL of SAS, then remained constant until the addition of 1.2 mL, after which absorbance began to decline. Figure 4 showed that 1.0 mL of SAS solution was the optimal volume since the highest average absorbance was achieved.

The initial number of moles of cefdinir:

$$n_{cefdinir} = C_M \times V_{mL} = 50_{\mu\alpha/mL} \times 1.0_{mL} = 50 \text{ mmole}$$

The optimal number of moles of SAS:

$$n_{SAS} = C_M \times V_{mL} = 50_{\mu\alpha/mL} \times 1.0_{mL} = 50 \text{ mmole}$$

Accordingly, the optimal number of moles of cefdinir and SAS were equal for both.

An alkaline medium was required to create nucleophiles from cefdinir and activate the nucleophilic substitution processes. To determine the optimal basicity that yielded the highest absorbance, an aqueous solution of sodium hydroxide in the range of 0.01–1.0 M was used as an alkali modifier for the reaction medium. The maximum absorption was seen when 1 mL of 0.01 M sodium hydroxide was added [Figure 5].

However, the impact of the temperature on the reaction was examined by conducting the reaction at different temperature settings in the range of 25°C–90°C. Based on the results obtained, the elevated temperature had a detrimental impact on the absorption intensity. This could be attributed to the instability of the colored derivative of cefdinir-SAS. Similarly, the duration required to complete the interaction was taken into account. After 4 min, the maximum absorbance intensity was reached; however, during the next 20 min, there was no change in the absorbance intensity, which then started to gradually decline [Figure 6].

The mole ratio of cefdinir to SAS in the colored derivative was estimated by following Job's method of continuous variation. Job's plot as depicted in Figure 7 had a

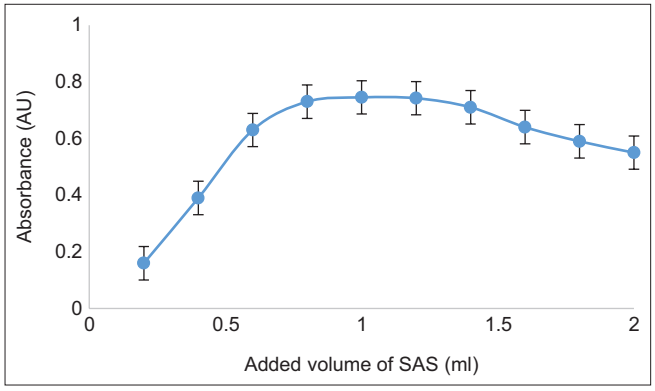

Figure 4: Effect of SAS (10 µg/mL) volume on the absorbance intensity of the colored-derivative when added to cefdinir (10 µg/mL). SAS: Sodium anthraquinone-2-sulfonate

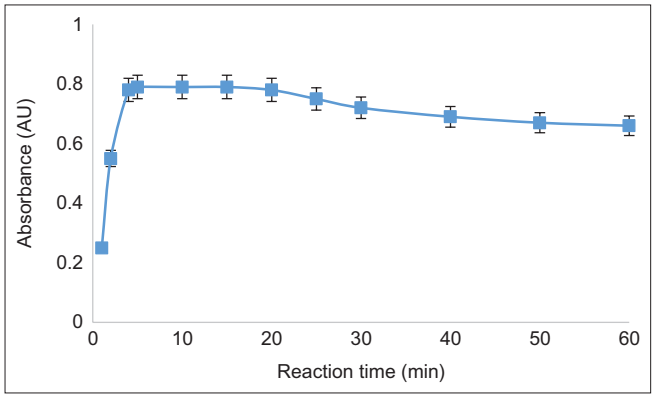

Figure 6: Time of reaction of cefdinir with sodium anthraquinone-2-sulfonate at 517 nm

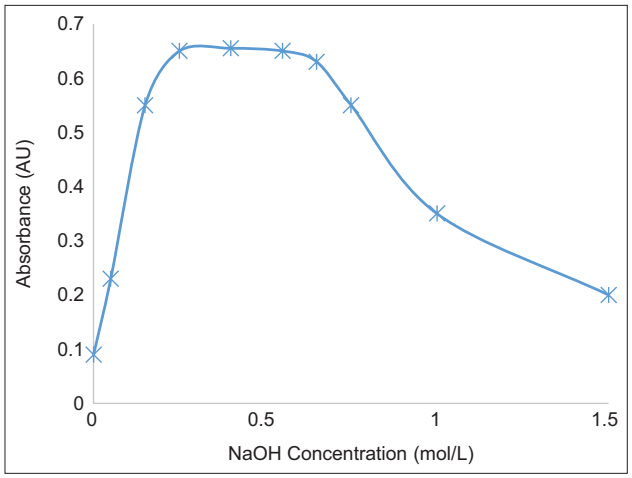

Figure 5: Effect of NaOH concentration as a basicity controller on the absorbance of cefdinir-derivative (10 µg/mL)

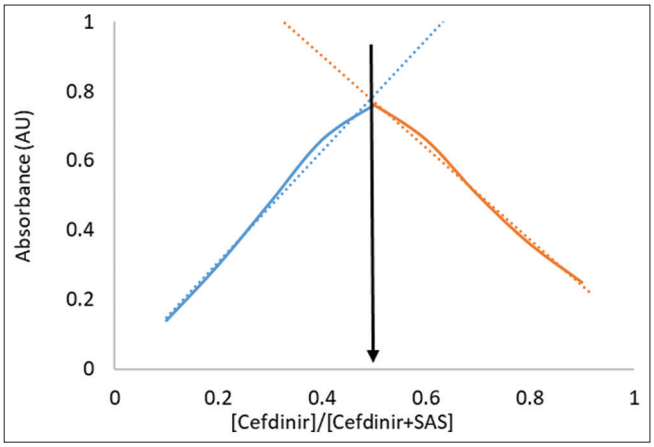

Figure 7: Estimating the mole ratio of cefdinir to SAS in the colored product using the continuous variation method. SAS: Sodium anthraquinone-2-sulfonate

symmetrical bell shape where the point of intersection of the two tangents corresponded to the mole fraction of cefdinir in the colored product. The mole fraction of cefdinir was 0.5 indicating that the cefdinir-SAS ratio was 1:1.

Based on the mole ratio, in addition to the presence of the amino functional group in cefdinir that is ready for substitution, the suggested mechanism may proceed as shown in Figure 8.

Analysis of dosage forms

The method was specific toward assaying cefdinir within medical matrices where active pharmaceutical ingredients usually present with some excipients and common additives that usually be added during medicinal formulation. Real pharmaceutical samples were quantified following the planned procedure after getting spiked by a known quantity of cefdinir. The recovery maintained its value around (98.435%–99.895%) which confirmed the robustness of the proposed method, as well as the absence of interferences, proceed as shown in Table 2.

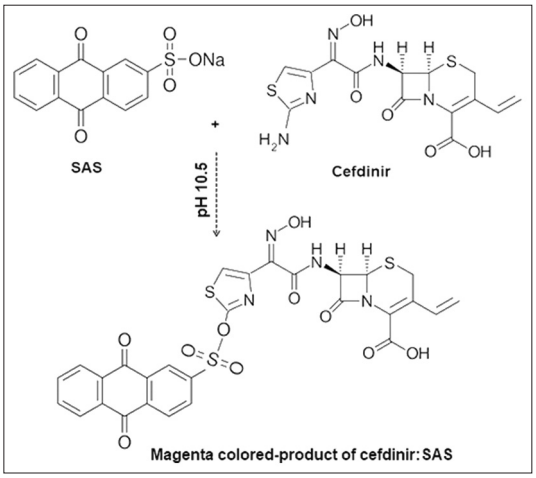

Figure 8: The suggested colored-product of cefdinir-SAS in an alkaline medium. SAS: Sodium anthraquinone-2-sulfonate

Table 2: Spectrophotometric determination of cefdinir in various pharmaceuticals

Sample	Taken	Found	Recovery (%)	RSD*
Cefdine® 300 mg Capsules, NOVARTIS Switzerland	20	19.847	99.235	1.479
	60	59.722	99.537	1.521
Cefdine 300 mg Capsule, Citron Pharma, India	20	19.687	98.435	1.668
	60	59.346	98.910	1.606
Sefarin® 300 mg Capsule, Pharma International Co., Jordan	20	19.779	99.895	1.509
	60	59.652	99.420	1.475

*Average of three measurements. RSD: Relative standard deviation

CONCLUSION

The proposed quantification procedure for cefdinir was simple, affordable, and satisfactory in terms of accuracy and precision. SAS reagent was used to turn cefdinir into a colored derivative for easier and more sensitive spectrophotometric assaying of cefdinir in pure and pharmaceutical form. The common interferences in medicinal formulas did not affect the proposed approach. Therefore, it could be reliably recommended for standard analysis of cefdinir in different matrices.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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