KINETIC SPECTROPHOTOMETRIC METHOD FOR DETERMINATION OF CEFTRIAXONE IN BULK AND VIALS

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An ultra-sensitive kinetic spectrophotometric method has been carried out to determine ceftriaxone in a simple and cost-effective manner. The method utilized the catalytic behavior of the drug in accelerating the reaction between iodine and sodium azide. The fixed time method was exploited to select the optimum reaction time and it was found to be 7.0 minutes after the addition of iodine at pH 2.0 using 0.1 M phosphate buffer. Experimental variables that affect the formation of the reaction product were studied and optimized. The method was validated following ICH guidelines and showed excellent linearity within 0.25–2.50 μg/mL at 348 nm. Kinetics of the reaction were investigated and the reaction rate constant was calculated. The method was successfully applied for the analysis of the drug in dosage forms with high selectivity. Comparing the results of the developed approach with the results of the reported spectrophotometric method showed no significant difference with respect to accuracy and precision. The developed method reached a sensitivity 20 folds greater than the reported method. Being selective and sensitive in analysis makes the method a suitable candidate for quality control monitoring of the cited drug.

Keywords: *ceftriaxone sodium, kinetic spectrophotometry, azide.*

КИНЕТИЧЕСКИЙ СПЕКТРОФОТОМЕТРИЧЕСКИЙ МЕТОД ОПРЕДЕЛЕНИЯ ЦЕФТРИАКСОНА В НЕРАСФАСОВАННОМ ВИДЕ И ВО ФЛАКОНАХ

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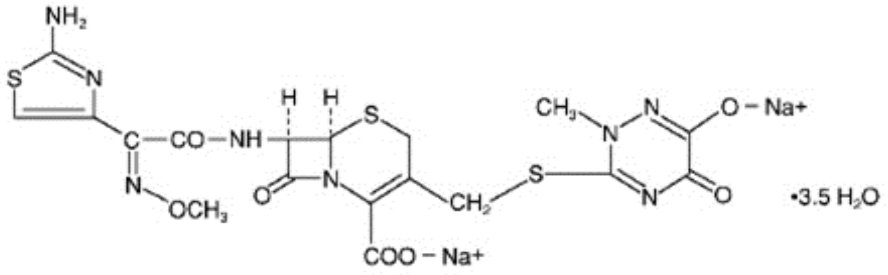
Разработан сверхчувствительный кинетический спектрофотометрический метод определения цефтриаксона. Каталитическое поведение препарата использовано для ускорения реакции между иодом и азидом натрия. Метод фиксированного времени применен для выбора оптимального времени реакции, которое составляет 7 мин после добавления иода при pH 2.0 с использованием 0.1 М фосфатного буфера. Изучены и оптимизированы экспериментальные параметры, влияющие на образование продукта реакции. Валидация метода в соответствии с рекомендациями ICH показала линейность в пределах 0.25–2.50 мкг/мл при 348 нм. Исследована кинетика реакции и рассчитана константа скорости реакции. Метод успешно применен для анализа препарата в лекарственных формах с высокой селективностью. Сравнение результатов разработанного подхода и предложенного ранее спектрофотометрического метода не показало существенной разницы в отношении точности и прецизионности, чувствительность разработанного метода в 20 раз больше.

Ключевые слова: *цефтриаксон натрия, кинетическая спектрофотометрия, азид.*

Introduction. Among diverse pharmaceutical analytical techniques, catalytic kinetic spectrophotometry has precious value in pharmaceutical analysis. It is characterized by selective monitoring owing to removing the interference that may occur from excipients or active components in the surrounding matrix, in addition

to the availability of spectrophotometers in most research laboratories [1]. In a neutral or acidic medium, iodine reacts slowly with azide and, upon the addition of sulfur (C-S-C) containing compounds, the reaction proceeds rapidly toward bleaching from a yellow color [2]. This reaction has been utilized to determine many compounds including but not limited to ranitidine [3], biotin [4], captopril, and ethamsylate [5]. The catalytic behavior of sulbutiamine [2], carbocisteine, ethionamide, thioctic acid and penicillamine [6] were also reported in the iodine–azide reaction. The suggested study will discuss the effect of ceftriaxone sodium (CTX) on the reaction.



CTX is disodium (6R,7R)-7-amino]-3-[[(2-methyl-6-oxido-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)sulphanyl] methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 3.5hydrate [7].

It is a third-generation cephalosporin antibacterial medication that acts by inhibiting bacterial cell wall synthesis. CTX can treat urinary tract infections, endocarditis, gastro-enteritis gonorrhea, septicemia, syphilis, and typhoid fever. Also, it is used in intra-abdominal infections as well as bone and joint infections. Moreover, it is described as a prophylactic drug in surgical infections [8, 9].

The literature survey revealed different analytical methods to quantify CTX, these include spectrophotometric methods [10, 11], spectrofluorimetric methods [12–15], chemiluminescence method [16], electrochemical methods [17–19], and HPLC methods [20–25]. The novelty of the suggested method arises from developing an ultra-sensitive and nonextractive spectrophotometric method for the kinetic study of CTX. The method has been characterized by its cost-effectiveness due to the easy availability of spectrophotometers and the utilized reagents in most research laboratories, where there is no need for expensive organic solvents. Furthermore, its selective manner diminishes the interaction with other drugs or excipients in the matrix. Upon comparing the results of the reported spectrophotometric method [11] with the developed kinetic method, it was found that the suggested method provides a linearity range of (0.25–2.50 μg/mL), while the reported method has a linearity range of 5.0–50.0 μg/mL, which elucidates its ability to provide a 20-fold sensitivity enhancement. However, the reported method could not be used as a kinetic tool for CTX determination, as it includes direct measuring of the UV spectrum of the drug at 241 nm.

Experimental. A Shimadzu UV-Visible 1601 recording spectrophotometer (P/N 206-67001) was used for the experiment. The recording range was 0–1.0 at wavelength 348 nm. Consort NV P-901 pH-Meter (Belgium) was used for pH adjustment.

The reaction reagents and materials are of analytical grade. CTX with a purity of 99.90% was kindly supplied by Kahira Pharmaceuticals & Chemical Industries Co. (CPCI.CA), Shoubra. Cairo, Egypt. Sodium azide powder was bought from Sigma Aldrich, Germany. 1.0 M sodium azide solution was prepared by dissolving 6.50 g of the powder in 100 mL of distilled water. An aqueous solution of iodine (0.01 M) was prepared by dissolving 0.254 g of iodine and 4.50 g of potassium iodide in 100 mL of distilled water. Appropriate dilution was made by dilution with the same solvent to obtain 1.0×10^{-3} M. The solution was kept in an amber-colored glass bottle. To study the effect of different levels of pH, phosphate buffer solutions 2.0–8.0 were prepared in a concentration of 0.1 M by dissolving 0.1 M Na_2HPO_4 and then adjusted using 0.1 M NaOH; 0.1 M HCl. 0.1 M HCl was used to study pH 1.0. Ceftriazone® vial, batch # 0004203421, contained 250 mg ceftriaxone equivalent to 298.3 mg CTX per vial, batch # 010203621, contained 500 mg ceftriaxone equivalent to 596.5 mg CTX per vial, batch # 058203721, contained 1000 mg ceftriaxone equivalent to 1193 mg CTX per vial, the products were sourced from Pharco B International, New Borg El Arab City-3rd industrial zone, Alexandria, Egypt.

In a 100 mL volumetric flask, an accurately weighed amount (10.0 mg) of CTX was dissolved in 100 mL distilled water yielding a stock standard solution of CTX (100.0 μg/mL). A working standard solution of a concentration of 10.0 μg/mL was made by appropriate dilution utilizing the same solvent. Further dilutions

were made to obtain the required concentrations in the studied calibration range.

To a set of 10 mL volumetric flasks, different aliquots from CTX working standard solution were quantitatively transferred to obtain a final concentration range of 0.25–2.50 μg/mL. 0.60 mL of 0.1 M phosphate buffer (pH 2.0) was added followed by 1.0 mL of 1.0 M sodium azide solution, the flasks were mixed well and, lastly, 0.60 mL of 1.0×10^{-3} M iodine solution was added. The flasks were completed to the mark with distilled water. The absorbance of the test reaction (A_t) was recorded at 348 nm after 7.0 min against a blank (0.60 mL of buffer solution + 1.0 mL of sodium azide solution). The absorbance of the controlled experiment (A_c) was recorded following the same steps omitting the drug. The calibration graph was constructed by plotting the difference in absorbance ($\Delta A = A_c - A_t$) versus the drug concentrations (μg/mL) and the regression equation was computed.

Accurately weighed amounts equivalent to 10.0 mg of CTX each from a Ceftriazone® vial of 250, 500, and 1000 mg were transferred separately to 100 mL volumetric flasks using distilled water as a diluting solvent. Further dilutions were made to obtain aqueous working standard solutions for each dosage form. The developed method was adopted using the working standard solutions to quantify CTX in the vials and the percentage recoveries were calculated according to the regression equation.

Results and discussion. The suggested work involves studying the catalytic influence of CTX on iodine–azide reaction. Iodine oxidizes azide slowly producing iodide and nitrogen. However, in an acidic medium and the presence of a (C-S-C) containing compound (like the studied drug), the reaction is much accelerated leading to a decrease in the absorbance of the iodine reactant as shown in Fig. 1. Furthermore, the decrease in the absorbance of iodine increases with time at 348 nm (Fig. 2), which makes the method a kinetic proposal for determining CTX in its authentic form and pharmaceutical formulations [4, 6]. The reaction proceeds as follows:

$$2N_3^- + I_2 \rightarrow 3N_2 + 2I^- \qquad \text{(slow reaction)}$$

$$2N_3^- + I_2 \xrightarrow{\text{CTX}} 3N_2 + 2I^- \qquad \text{(fast reaction)}$$

The most appropriate diluting solvent was selected by testing distilled water, methanol, ethanol and acetonitrile. Turbidity was observed when the flask was completed with ethanol. Testing acetonitrile showed a minor increase in ΔA compared with the completion with water; however, water was selected to conduct the methodology owing to its green and cost-effective properties.

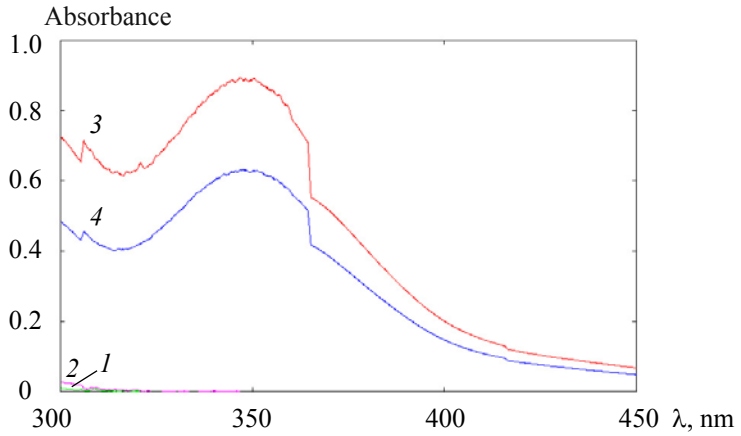


Fig. 1. Absorption spectra of (1) aqueous solution CTX (1.0 μg/mL) in 0.1 M phosphate buffer pH 2; (2) aqueous solution 1.0 M sodium azide in 0.1 M phosphate buffer pH 2; (3) controlled experiment of 1×10^{-3} M iodine and 1.0 M sodium azide in 0.1 M phosphate buffer pH 2 at instantaneous time; and (4) catalytic effect of CTX (1.0 μg/mL) on the reaction of 1.0 M sodium azide and 1×10^{-3} M iodine at instantaneous time.

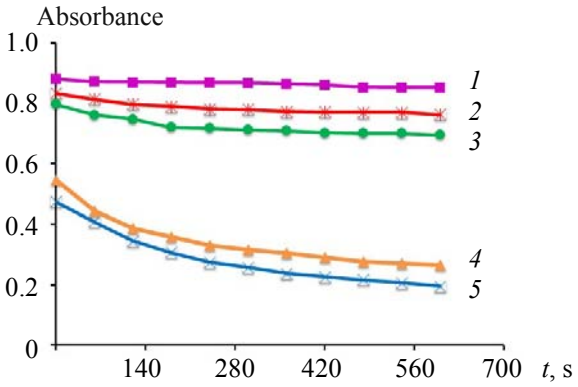


Fig. 2. Absorbance-time curve for (1) blank reaction of 1.0×10^{-3} M iodine and 1.0 M sodium azide in 0.10 M phosphate buffer of pH 2; (2–5) catalytic effect of CTX on the reaction of 1.0 M sodium azide and 1.0×10^{-3} M iodine in 0.1 M phosphate buffer of pH 2.0; [CTX] = 0.25 (2), 0.50 (3), 1.50 (4), and 2.0 μg/mL (5).

Different pH values of 0.1 M phosphate buffer solutions in the pH range of 2.0–8.0 and pH 1.0 of 0.1 M HCl were examined. The results revealed that pH 2.0 of 0.1 M phosphate buffer solution achieved the highest Δ*A*. BRB of pH 2.0 was also studied; however, better results were not noted. A phosphate buffer was selected to conduct the methodology. Different volumes of 0.2–1.0 mL of 0.1 M phosphate buffer solution (pH 2.0) were investigated, whereby 0.6 mL was found to give the optimum results.

Increasing volumes of 0.2–1.4 mL of 1.0 M sodium azide solution were tested to attain the maximum Δ*A*. It was found that Δ*A* was increased by increasing the volume of sodium azide solution up to 1.0 mL after which Δ*A* was almost constant; therefore, 1.0 mL of 1.0 M sodium azide was used throughout the study (Fig. 3).

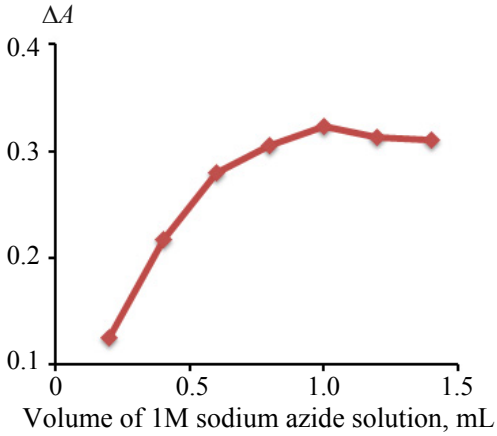


Fig. 3. Effect of 1.0 M sodium azide solution volume on the reaction between CTX (1.0 μg/mL) and 1 mL (1×10^{-3} M) iodine aqueous solution.

Results revealed that Δ*A* was increased by increasing the volume of 1.0×10^{-3} M iodine solution. However, 0.6 mL was chosen as a suitable volume after which the absorbance value exceeds 1.0, which could lead to experimental error and affect the method's reproducibility.

Different orders in the addition of the reaction components were studied to obtain the maximum Δ*A*. The results showed that the best order was to start with the drug, add phosphate buffer, then sodium azide solution, and finally iodine.

Upon addition of the (C-S-C) containing compound to the iodine-azide reaction, the yellow color of iodine decreased with time. Accordingly, the reaction was utilized as a salutary tool to develop a kinetic study for CTX determination. In order to determine the reaction rate constant and order of the reaction, the following equation was applied: $R = K'[\text{drug}]n$, where R is the reaction rate, K' is the reaction rate con-

stant, n is the reaction order, and [drug] is the molar concentration of CTX. By taking logarithms for the previous equation:

$$\log R = \log K' + n\log[\text{drug}].$$

Since the rate is equivalent to $\Delta A/\Delta t$, a relationship was plotted between $\log\Delta A/\Delta T$ and log[CTX], where ΔA is the change in absorbance and Δt is the time change in seconds [1, 26]. A linear relationship was obtained with $K' = 0.0023$ s^{-1} and $n = 0.99$, which confirmed a first-order reaction (Fig. 4). Due to the presence of a high concentration of sodium azide, the reaction was assigned as a pseudo first-order reaction.

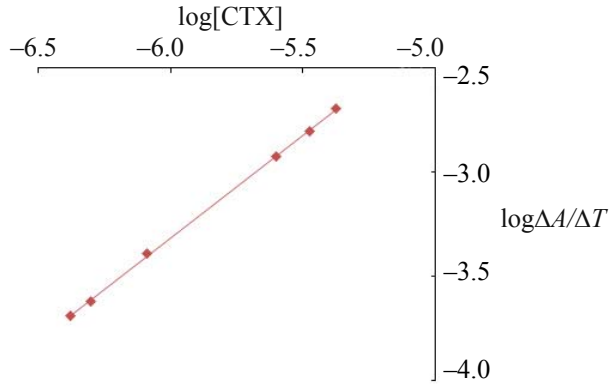


Fig. 4. Plot of logarithm rate of the reaction versus logarithm molar concentration of CTX.

To study the fixed time method [26], ΔA values were calculated at a preselected time for different concentrations of CTX in the range of 0.25–2.50 μg/mL. The absorbance was recorded at different times instantaneous, 1, 2, 3, 4, 5, 6, 7, and 8 min after the addition of iodine. Calibration graphs were then constructed between ΔA against the initial concentration of CTX at the preselected times. The most suitable reaction time to perform the procedure was found to be 7.0 min after the addition of iodine to achieve the best slope and correlation coefficient of the calibration curve (Table 1).

The fixed absorbance method was investigated by recording the reaction times required for different concentrations of CTX to reach a specific ΔA [26]. To reach a preselected value of ΔA (0.57), the required time was measured in seconds. The calibration graph was then constructed by plotting the initial concentration of CTX against the reciprocal of time $1/t$, whereby the following regression equation was obtained: $1/t = 10297.7C - 0.016$ ($r = 0.9437$). The concentrations achieved the previous equation are 1.51, 2.26, 3.02, 10^{-6} [CTX] at 1.11, 4.17, 16.67, 10^{-3} $1/t$, respectively.

TABLE 1. Feasibility of the Fixed Time Method for the Determination of CTX by the Developed Method

Time, min	Regression equations	Correlation coefficient
1.0	$\Delta A = 0.2755\ C - 0.0207$	0.9959
2.0	$\Delta A = 0.2948\ C + 0.0161$	0.9960
3.0	$\Delta A = 0.3082\ C + 0.0412$	0.9964
4.0	$\Delta A = 0.3138\ C + 0.0379$	0.9980
5.0	$\Delta A = 0.3179\ C + 0.0392$	0.9988
6.0	$\Delta A = 0.3326\ C + 0.01$	0.9993
7.0	$\Delta A = 0.3338\ C + 0.0006$	0.9999
8.0	$\Delta A = 0.3250\ C + 0.0226$	0.9999

According to the initial reaction rates method [26], initial reaction rates were obtained from the slopes of tangents of absorbance-time curves at 348 nm (Fig. 2). The initial rate was constructed against a concentration of CTX to plot the calibration curve. The results showed a linear relationship over the concentration range of 1.0–2.5 μg/mL. Table 2 summarizes the results of the method:

$$R = 0.0008\ C + 1\times10^{-5}\ (r = 0.9954).$$

From the obtained results, it was found that fixed absorbance and initial rate methods had the drawbacks of poor linearity and small concentration range with low sensitivity. Because the fixed time method was

characterized by excellent linearity and high sensitivity, it was selected to construct the calibration curve and conduct the work. ICH directives [27] were followed to validate the proposed assay in terms of linearity, LOQ, LOD, precision, accuracy, and robustness.

The calibration curve was established by plotting ΔA against a concentration of CTX in μg/mL. A linear relationship was attained within the concentration range 0.25–2.50 μg/mL with a correlation coefficient of 0.9999. The linear regression analysis is presented by the following equation: $\Delta A = 0.3338C + 0.0006$. Different analytical parameters of the developed methodology were listed in Table 3.

TABLE 2. Initial Rate Method for the Proposed Method Using Different Concentrations of CTX

[CTX], 10^{-6}	Rate of the reaction
1.51	9.0×10^{-4}
2.26	1.15×10^{-3}
3.02	1.5×10^{-3}
3.77	2.0×10^{-3}

TABLE 3. Analytical Performance Data for the Determination of CTX by the Developed Method

Parameter	The developed method
Linearity range, μg/mL	0.25–2.5
LOD, μg/mL	0.04
LOQ, μg/mL	0.11
Correlation coefficient, r	0.9999
Slope	0.33
Intercept	0.0006
$S_{y/x}$	0.005
S_a	0.003
S_b	0.002
%Error	0.45
%RSD	1.09
No. of experiments	6
Mean found (%) ± SD	100.21 ±1.09

N o t e. $S_{y/x}$ standard deviation of the residuals; S_a standard deviation of the intercept of regression line; S_b standard deviation of the slope of regression line; % Error – RSD%/$\sqrt{n}$.

To calculate LOD and LOQ, ICH equations [27] were utilized as follow:

$$\text{LOD} = 3.3 \times \text{standard deviation of intercept/slope},$$

$$\text{LOQ} = 10 \times \text{standard deviation of intercept /slope},$$

where LOD and LOQ were 0.04 and 0.11 μg/mL, respectively. The obtained small values reflect the highly sensitive property of the suggested method.

The two levels of precision were tested by analyzing three different concentrations of CTX (0.5, 1.5, 2.0 μg/mL) by adopting the developed method. Repeatability (intra-day precision) was studied by performing the analysis three times within the same day, while reproducibility (inter-day precision) of the analysis was conducted on three consecutive days. The listed results in Table 4 show that SD and %RSD were lower than 2 and %error values were lower than 1, giving a sign of the good precision property of the developed method [27].

Testing the accuracy of the developed approach was achieved by comparing the results of the drug in raw material following the suggested method with the reported spectroscopic one [11]. The reported spectroscopic method involves direct measuring of the CTX absorbance maxima at 241 nm using water as a diluting solvent. Table 5 points out that results from Student's t- and variance ratio F-tests showed no significant difference between the two methods and they were in good agreement, thereby proving the method's accuracy [28].

TABLE 4. Precision Data for the Determination of CTX by the Proposed Method

Sample concentration	Repeatability	Intermediate precision
0.5 μg/mL		
Mean found (%) X	99.82	101.43
± SD	1.26	0.28
%RSD	1.26	0.28
%Error	0.73	0.16
1.5 μg/mL		
Mean found (%) $\bar{X}$	99.39	98.99
± SD	1.53	1.11
%RSD	1.54	1.12
%Error	0.89	0.65
2.0 μg/mL		
Mean found (%) $\bar{X}$	99.9	99.85
± SD	1.64	1.26
%RSD	1.64	1.27
%Error	0.95	0.73

TABLE 5. Application of the Developed and Reported Method for the Determination of CTX in Raw Material and Vials

Parameter	Suggested spectrophotometric method		Reported spectrophotometric method [11]	
	Conc. taken, μg/mL	Found, %	Conc. taken, μg/mL	Found, %
CTX (raw material)	0.25	101.20	7.0	99.46
	0.30	99.33	10.0	100.43
	0.50	101.40	15.0	99.79
	1.50	99.73		
	2.00	98.75		
	2.50	100.84		
$\bar{X}$ ±SD		100.21 ± 1.09		99.89 ± 0.49
Student's *t*-test		0.47 (2.36)[28]		
Variance ratio (*F*-test)		4.88 (19.30)[28]		
Ceftriazone ® vial 250 mg	0.50	100.10	7.0	99.47
	1.50	100.30	10.0	100.42
	2.00	99.91	15.0	99.79
$\bar{X}$ ±SD		100.1 ± 0.21		99.89 ± 0.49
Student's *t*-test		0.65 (2.78)[28]		
Variance ratio (*F*-test)		6.04 (19.00)[28]		
Ceftriazone ® vial 5000 mg	0.50	101.00	7.0	101.23
	1.50	99.96	10.0	99.19
	2.00	99.14	15.0	101.43
$\bar{X}$±SD		100.03 ± 0.93		99.89 ± 0.49
Student's *t*-test		0.65 (2.78)[28]		
Variance ratio (*F*-test)		1.77 (19.00)[28]		
Ceftriazone ® vial 1000 mg	0.50	99.96	7.0	101.23
	1.50	97.50	10.0	100.42
	2.00	100.80	15.0	98.14
$\bar{X}$ ±SD		99.42 ± 1.71		99.89 ± 0.49
Student's *t*-test		0.38 (2.78)[28]		
Variance ratio (*F*-test)		1.15(19.00)[28]		

The screening robustness of the developed approach was assessed by introducing deliberate changes in the reaction parameters. The studied parameters were: pH of the selected buffer, volume of phosphate buffer and volume of the azide solution. The obtained results point out the method retained was unchanged by the small variations that may occur throughout the work, thus assuring that the method is robust.

The developed approach was utilized to quantify CTX in Ceftriaxone® vials 250, 500, and 1000 mg. Table 5 recaps the accepted percentage recoveries for testing the vials. Additionally, the tested vials were analyzed by the published spectroscopic method [11]. The outcomes of both methods were statistically compared using Student's *t*- and variance ratio *F*-tests [28]. The statistical results revealed the close similarity between the suggested system and the reported method, thereby affirming the method's accuracy.

Conclusions. A facile and cost-effective kinetic spectrophotometric method was suggested for determining ceftriaxone sodium in raw materials and pharmaceutical formulations. The method depended on the catalytic behavior of the drug on the acceleration iodine–azide reaction. The experimental conditions were optimized and the reaction kinetics were discussed. Upon adopting the fixed time method, the optimum reaction time was found to be 7 min directly after the addition of iodine. Linearity, accuracy and precision of the method were investigated. The availability of instrumentation and the sensitivity of the method makes it a suitable candidate for quality control monitoring of ceftriaxone sodium.

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