Utility of Spectroscopic Studies for Quantification of Cefditoren Pivoxil in Commercial Samples

[1]Salma Ali Al-Tamimi*, [1]Norah Sultan Abdulaziz Al-Motlaq and [2]Fatma Ahmed Aly
[1]*Department of Chemistry, College of Science, King Saud University, P. O. Box 22452, Riyadh 11495, Saudi Arabia.*
[2]*Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt.*
satamimi@ksu.edu.sa*

(Received on 17th August 2020, accepted in revised form 7th April 2021)

Summary: The current study is devoted to suggest new simple spectrophotometric probes for the estimation and quantification of cefditoren pivoxil (CFP) either in authentic or in commercial samples. Three simple kinetic and derivatize sensitive spectrophotometric methods were established. Two kinetic techniques (method A) and (method B) were based on the estimation of CFP using the oxidation properties of alkaline potassium permanganate at ambient temperature and the relation between the reduction in the absorbance of $KMnO_4$ and the added CFP were also investigated. The intensity of absorbance (A) of the colored MnO_4^- ions were recorded at wavelengths 610 and 525 NM for the two methods, respectively. Method C was based on derivatization of CFP with 1,2-naphthoquinone-4-sulphonate reagent in a basic solution (pH=11) to produce an orange red colored solution exhibited the highest absorption peak (λ_{max}) at 411 nm. The proposed systems displayed linearity over the concentration ranges of 1.0-16.0, 1.0-10.0 and 0.5-7.0 µg mL^{-1}.The suggested systems were validated obeying analytical methodology guidelines and the acceptance criteria for accuracy, precision, linearity, selectivity, and robustness were met in all cases.

Keywords: Cefditoren pivoxil, Kinetic spectrophotometry, Derivatization method, Commercial products.

Introduction

Antibiotics are chemical agents that act as bacteriostatic (stopping bacterial growth) or bactericidal (Killing bacterial cells). They are played an important role in the treatment of humans and animals. So, overuse and misuse of antibiotics have raised the development of bacterial resistant that provides a potential side effects to humans and animals health. Beside therapeutic potential of antibiotics, they have also been recommended to improve the production of agriculture and aquaculture. However, the appearance of resistant bacteria to frequently used potent antibiotics, emerged the require for powerful drugs [1].

Cefditoren Pivoxil, (CFP) is a 3rd generation cephalosporin with a potential activity against pathogens including both Gram-negative and Gram-positive bacteria. CFP is recommended for use as medication of acute exacerbations, chronic bronchitis, pharyngitis/tonsillitis, pneumonia, sinusitis, and uncomplicated skin infections. Thus, it is a superior option for the medicaments of adult patients with specific respiratory tract problems or skin infections [2]. Several analytical methods have been reported for its determination such as spectrophotometry [3-7], chemiluminescence [8], chromatographic techniques with photo diode array, UV and tandem mass spectrometry detection [9-11] and electrochemical methods [12 -14].

Chemical kinetics or the kinetic investigation of a chemical reaction is the branch of physical chemistry that is concerned with understanding the rates of chemical reactions. It relates to many scientific aspects including chemical engineering, biology, cosmology and even psychology and thus has extensive implications. The principles of chemical kinetics apply to investigate the rate of reactants are consumed or the products are formed in the chemical reactions [15].

The standard potential of $KMnO_4$ in acid solution, E^o, has been reported to be 1.51 V *vs* normal hydrogen electrode; hence the permanganate ion in acidic solution is a strong oxidizing agent [16]. The literature survey reported various studies of permanganate as oxidizing agent in spectrophotometric applications [17-19].

However, 1,2-Naphthoquinone-4-sulphonate sodium salt (NQS) is a widely used reagent in the ultraviolet-visible (UV-Vis) spectrophotometric estimation of amines and amino acids. It is able to produce colorimetric detectable derivatives in alkaline medium and moderate temperatures with 1ry and 2ry

***To whom all correspondence should be addressed.**

amino groups [20]. Folin in 1922 introduced this colorimetric reagent [21]. Many researchers exploited this reagent in their determination of amines [22, 23].

The objective of this investigation is to suggest three, sensitive, simple kinetic and derivative spectrophotometric probes suitable for the quantification of the CFP in authentic and its commercial products using alkaline solution of $KMnO_4$ as an oxidizing agent and NQS as colorimetric reagent.

Experimental

Chemicals and solvents

Pure CFP and its commercial products (MEIACT® 200 mg/tablet) were acquired by Tabuk Pharmaceutical, MFG. Co., Saudi Arabia. BDH, Poole, UK, supplied potassium permanganate, boric acid, phosphoric acid, acetic acid, tris-hydroxy methyl amino methane, hydrochloric acid, disodium hydrogen phosphate. However, NQS and sodium hydroxide were supplied by Sigma Aldrich, Hamburg, Germany and Winlab, East Midland, UK, respectively.

Preparation of reagent solutions

Aqueous solutions of 4.0×10^{-2} mol L^{-1} $KMnO_4$ and 1.0×10^{-1} mol L^{-1}, 1.0 mol L^{-1} sodium hydroxide and sulfuric acid were adapted by liquefying 0.632 g, 4.0 g and diluting 0.544 mL of concentrated H_2SO_4 (formula weight is 98.077 g mol^{-1}) to 100 mL distilled water, respectively. Freshly prepared of 0.3 % of NQS was obtained by liquefying 300 mg in 100 mL distilled water and kept in dark for further use.

Apparatus

All studies were performed using a UV-Vis Ultrospec 2100-Pro spectrophotometer (Biochrom, England).

Stock CFP solution

A supplying solution of CFP (100 µg mL^{-1}) was obtained by liquefying 10 mg of CFP in 100 mL 0.1 mol L^{-1} sulfuric acid (H_2SO_4). Investigating solutions were performed from supplying one by carrying out serial dilution with the same solvent.

Calibration graphs of kinetic methods

In 10-mL measuring flasks, aliquots of solutions containing 10.0-160.0 µg mL^{-1} (for 610 nm) or 10.0-100.0 µg mL^{-1} (for 525 nm) of CFP were mixed with 2.5 mL of 1.0 mol L^{-1} sodium hydroxide (for 610 nm) or 2.0 mL of 1.0 mol L^{-1} sodium hydroxide (for 525 nm), followed by 2.0 mL of 4.0×10^{-2} mol L^{-1} $KMnO_4$ (for 610 nm) or 0.1 mL of 4.0×10^{-2} mol L^{-1} $KMnO_4$ (for 525 nm). After well shaking, they completed to mark with distilled water. The increase or decrease in the absorbance at 610 nm or at 525 nm was measured after 10 min at 25°C *vs.* a blank. The calibration graphs were obtained by graphing the absorbance (A) at 610 nm or the difference in the absorbance (ΔA) at 525 nm *vs.* concentration of CFP in µg mL^{-1}. The corresponding regression equation was calculated.

Calibration graph of NQS method (method C)

Amounts of standard CFP solution in the concentration range 5.0-70.0 µg mL^{-1} was mixed with 1.5 mL of 0.3 % (w/v) NQS solution followed by 1.0 mL of Britton-Robinson buffer (pH 11). Then they mixed and completed to 10-mL with distilled water. The absorbance was recorded at 411 nm at 25°C *vs.* a reagent blank. The calibration graph was plotted using the absorbance *vs.* CFP concentrations. The corresponding regression equation was calculated.

Quantification of CFP in its commercial samples

An equivalent amount to 10.0 mg of CFP obtained from ten powdered tablets (200 mg/tablet) was liquefied with 100 mL of 0.1 mol L^{-1} H_2SO_4. Then the content was filtered after sonication for 30 min. The working solutions were analyzed according to the general procedures of method A, B and C, respectively. The real quantity of CFP in the commercial product was evaluated using the plotted curve or the regression equation.

Evaluation of reaction stoichiometric

The limiting logarithmic method was employed for the detection of the stoichiometric reaction ratio [24]. Two experimental sets were performed using the previously described procedure. The 1st set was performed using a fixed concentration of CFP drug and varying concentrations of ($KMnO_4$) or NQS reagent. In contrast, the 2nd set was performed using varying concentrations of CFP and a fixed concentration of ($KMnO_4$) or NQS reagent. The logarithm of the resulted absorbance was graphed *vs.* the logarithms of the concentrations of the reagent and CFP for the 1st and 2nd experimental sets, respectively. Then, the slopes were calculated. For method A, B and C, the selected concentrations were as: the 1st experimental set was carried out using $KMnO_4$

(0.2×10^{-3} – 0.8×10^{-3} mol L^{-1}) or NQS (0.23×10^{-3} - 1.73×10^{-3} mol L^{-1}) at a fixed concentration of CFP (2.58×10^{-5} mol L^{-1}) or CFP (0.81×10^{-5} mol L^{-1}), respectively. The 2nd experimental set was performed using CFP (0.16×10^{-5} – 2.58×10^{-5} mol L^{-1}) or (0.81×10^{-5} mol L^{-1}) at a fixed concentration of $KMnO_4$ (8.0×10^{-3} mol L^{-1}) or NQS (1.73×10^{-3} mol L^{-1}), respectively.

Results and discussion

CFP reacted with $KMnO_4$ in alkaline medium produces a green color as a result of manganate ions. The kinetic determination of CFP was achieved by color increasing with time. However, the presence of a 1ry aliphatic amino group in CFP is proper for its reaction to NQS [25].

Spectral evaluations

The aqueous solution of CFP showed one absorption band peak at 270 nm, however, that of alkaline $KMnO_4$ solution exhibited two absorption maxima at 525 and 545 nm. The reaction was conducted by adding the aqueous alkaline $KMnO_4$ solution to the solution of CFP forming another band peak at 610 nm (Fig 1a). This attributed to the formation of MnO_4^- with CFP. The increase of the green color intensity with time can be due to the formation of MnO_4^{2-}, whereas the disappearance of the MnO_4^- in the solution explains the absorbance of the solution at 525 nm.

These facts were applied to propose kinetically based spectrophotometric methods for the quantification of CFP. For method C, the absorption of CFP was measured *vs.* water. It was observed that CFP exhibited maximum absorption at (λ_{max}) 270 nm and NQS solution exhibited absorption maxima at 362 nm. Therefore, the reaction of CFP with NQS to initiate a more absorbing chromophore in the visible region was preferable. Under maximum experimental conditions, CFP was reacted with NQS forming an orange colored product displaying λ_{max} at 411 nm (Fig 1b).

Optimization of analytical conditions (method A and B)

To investigate the influence of $KMnO_4$ concentration on the absorbance, various volumes (0.5-3.0 mL) of 4.0×10^{-2} mol L^{-1} $KMnO_4$ were tested using CFP (8.0 μg mL^{-1}) at 610 nm. Fig 2a showed that the use of 1.0 mL $KMnO_4$ the highest absorbance was attained and no significant effect observed by adding excess volumes. Thus 2.0 mL of 4.0×10^{-2} mol L^{-1} $KMnO_4$ was employed for further studies at 610 nm. Also, 0.1 mL of 4.0×10^{-2} mol L^{-1} (A=1) was useful for evaluating the lower in the absorbance at 525 nm.

The influence of NaOH concentration on the absorbance of the reaction product was investigated using various volumes (0.5 - 4.0 mL) of 1.0 mol L^{-1} NaOH. It was noticed that A or ΔA of the reaction could be increased with increasing the volume of 1.0 mol L^{-1} NaOH up to 1.5 mL at 610 nm or 1.0 mL at 525 nm (Figs 2b and 2c). Thus 2.5 mL of 1.0 mol L^{-1} NaOH (at 610 nm) or 2.0 mL of 1.0 mol L^{-1} NaOH 525 nm) were used for further studies.

The reaction rate was studies with the change of temperature over the range of 25-80˚C. It was observed that, permanganate is reduced to manganate ion at temperature (25°C). However, the manganese dioxide is produced at higher temperature. Therefore, 25 °C was selected as the optimum temperature.

Optimization of analytical conditions (method C)

To optimize the experimental conditions, various parameters such as volume of NQS, pH, temperature, and time of heating were adjusted.

The effect of the NQS volume of the reaction product was studied using an increasing volume of 0.3% of NQS solution. Fig 3a, showed that maximum color intensity was achieved with 1.5 mL of 0.3% (w/v) NQS.

The influence of pH of the reaction of CFP with NQS was examined by changing the pH from 2 to 12. It was noticed that at pH < 8 no CFP-NQS product was formed. This can be due to the existence of the CFP amino group as the hydrochloride salt, thus it loses its nucleophilic substitution capability, whereas at pH > 8 the absorbance increased rapidly with increasing pH. The highest absorbance was achieved at pH 11, and then decreased due to competition by the OH^- ions for NQS. Thus, a pH value of 11 was selected for this study (Fig 3b). To study the effect of buffer type on the reaction, carbonate, Britton-Robinson, borate and phosphate buffers of pH 11 were used. The highest absorbance was achieved when Britton-Robinson buffer was used (Fig 3c) thus it was selected in all experimental studies. Furthermore, the effect of Britton-Robinson buffer on the absorbance was tested at 411 nm using different volumes (0.25-4.0 mL) of the buffer. It was found that 1.0 mL of this buffer solution gave the highest absorption value. Therefore, 1.0 mL of pH 11 from Britton-Robinson buffer solution was selected as the optimized volume of the buffer (Fig 3d).

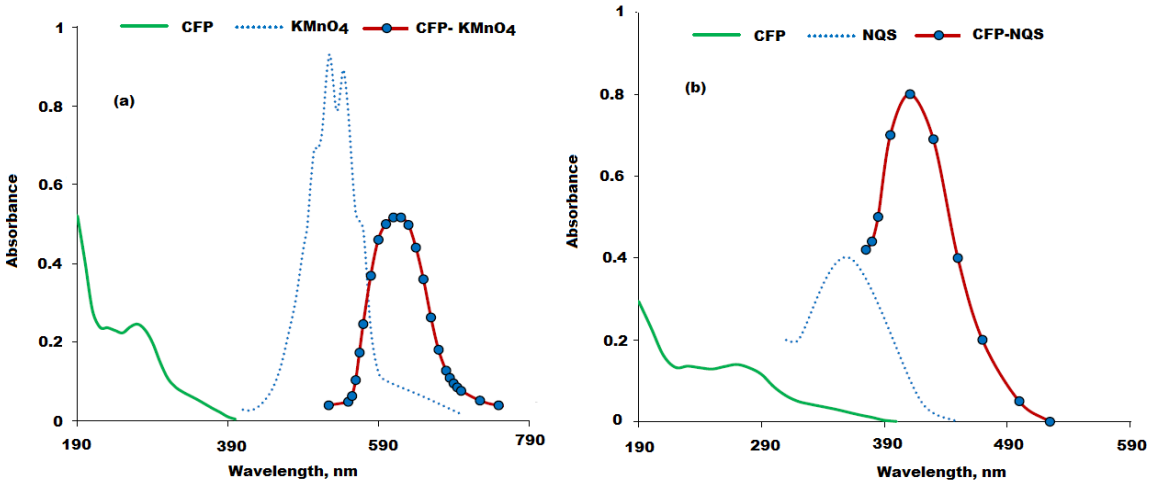


Fig 1: Absorption spectra of (a) CFP (8.0 µg mL^{-1}) against water, alkaline $KMnO_4$ (4.0×10^{-4}mol L^{-1}) against water and the reaction product of CFP with alkaline $KMnO_4$ against reagent blank and (b) CFP (5.0 µg mL^{-1}) against water, NQS (1.15×10^{-2}) against water and the reaction product of CFP with NQS against reagent blank.

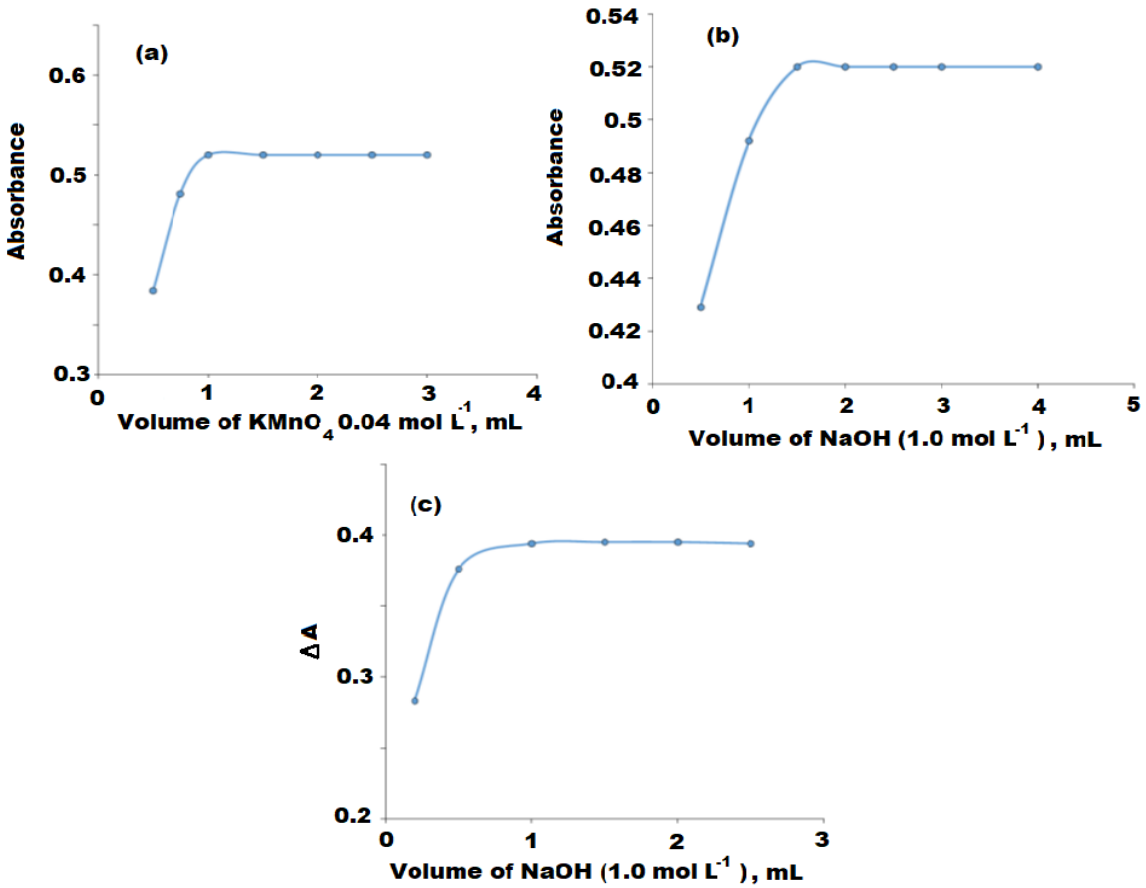


Fig 2: Effect of (a) volume of 4.0×10^{-2} mol L^{-1} $KMnO_4$ on its reaction with CFP (8.0 µgmL^{-1}) at 610 nm, (b) volume of 1.0 mol L^{-1} NaOH on the reaction of CFP (8.0 µgmL^{-1}) with $KMnO_4$ at 610 nm and (c) volume of 1.0 mol L^{-1} NaOH on the reaction of CFP (6.0 µgmL^{-1}) with $KMnO_4$ at 525 nm.

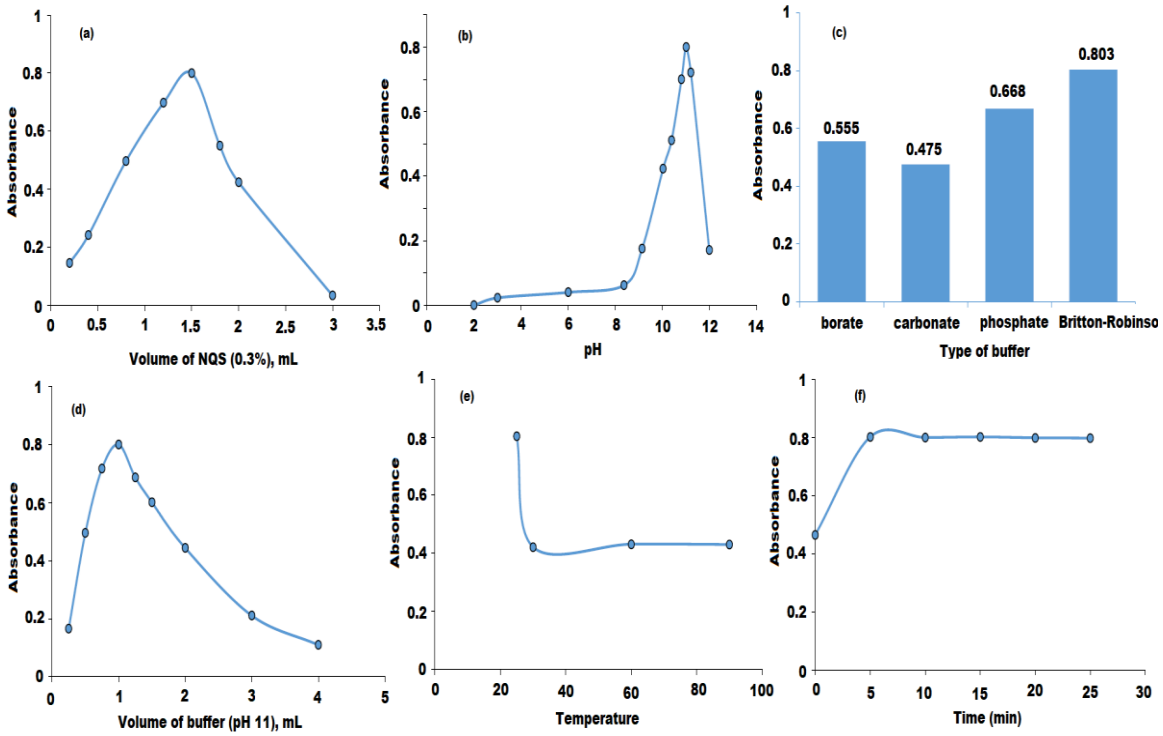


Fig 3: Effect of (a) Volume, (b) pH, (c) Type of buffer, (d) Volume of buffer solution, (e) Temperature and (f) standing time of the reaction of (0.3%, w/v) NQS with CFP (5.0 µgmL^{-1}) at 411 nm.

By using a thermostatically controlled water bath, the reaction was performed at different temperature settings (25, 30, 60, 90 °C). The temperature at 25°C gave the maximum absorbance values at demonstrated in Fig 3e. The completion of the reaction was studied by following various time intervals. It was noticed that the reaction was completed after 5 min (Fig 3f).

Stoichiometry and reaction mechanism

The stoichiometry of the reaction between CFP and $KMnO_4$ or NQS was studied by limiting logarithmic method [25]. The relation between log absorbance, log [$KMnO_4$] and log [CFP] was plotted. Straight lines, with slopes of 0.963 and 1.04 were plotted, respectively (Fig 4a). Therefore, the reaction proceeds in a ratio of 1:1 ($KMnO_4$: CFP). Scheme-1, postulated the pathway of the reaction on the bases of 1:1 ratio. In case of method C, two straight lines with 1.135 and 0.939 slopes were obtained revealing 1:1 reaction ratio (Fig 4b) and the reaction pathway was illustrated in Scheme 2.

Study of kinetic parameters

Under the controlled experimental conditions, the quantification of CFP was performed in an excess of $KMnO_4$ and NaOH according to to the initial concentration of CFP. Pseudo zero order reaction conditions were achieved according to their concentrations. Therefore, the kinetic equation for the oxidation of CFP by $KMnO_4$ in alkaline medium is written as: $\nu = k` C n$, where $\nu$ is the reaction rate, k` is pseudo rate constant, C is the molar concentration of CFP, and n is the order of the reaction. The logarithmic form of the equation was written as: $\log \nu = \log k` + n \log C$

The initial rates of reaction were determined using various concentrations of CFP (0.16×10^{-5} – 2.58×10^{-5} mol L^{-1}) at 610 and (0.16×10^{-5} – 1.61×10^{-5} mol L^{-1}) at 525 nm (Figs 5a and 5b). The outcome of the results is presented in Table 1. The log of reaction rates were graphed vs. log CFP concentration at 610 and 525 nm (Figs 6a and 6b).

The kinetic methods evaluation

To select the best quantitative kinetic method, different kinetic methods were tested. Initial rate, fixed concentration, and fixed time methods were applied and the most suitable analytical method with respect to its sensitivity, applicability, correlation coefficient (r) and the intercept was selected.

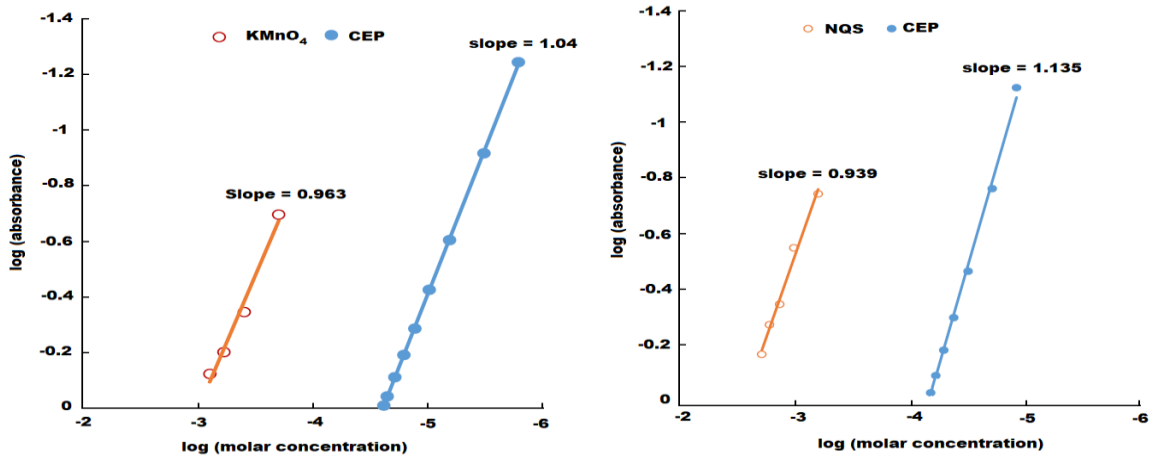


Fig 4: Limiting logarithmic plots for the determination of the molar ratio of the reaction between (a) CFP with alkaline $KMnO_4$ at 610 nm and (b) CFP with NQS.

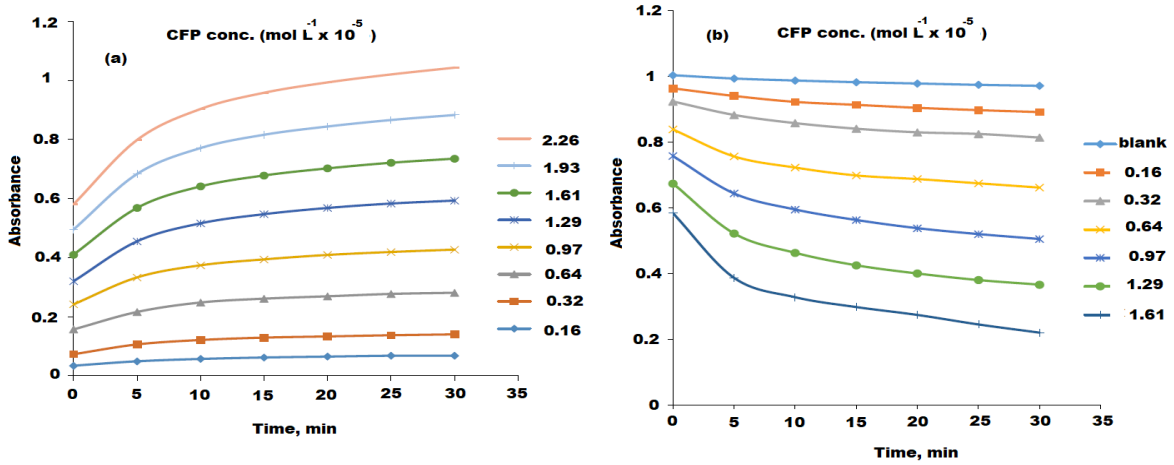


Fig 5: Absorbance time curves for the reaction of different concentrations of CFP with $KMnO_4$ at (a) 610 nm and (b) 525 nm

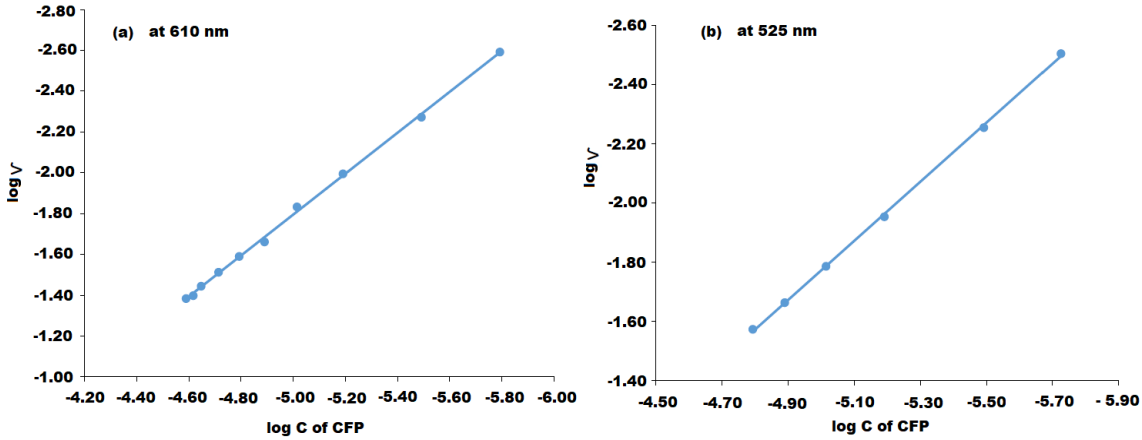


Fig 6: Linear plots of log v vs. log C for the kinetic reaction of CFP with alkaline $KMnO_4$ (a) at 610 nm and (b) at 525 nm.

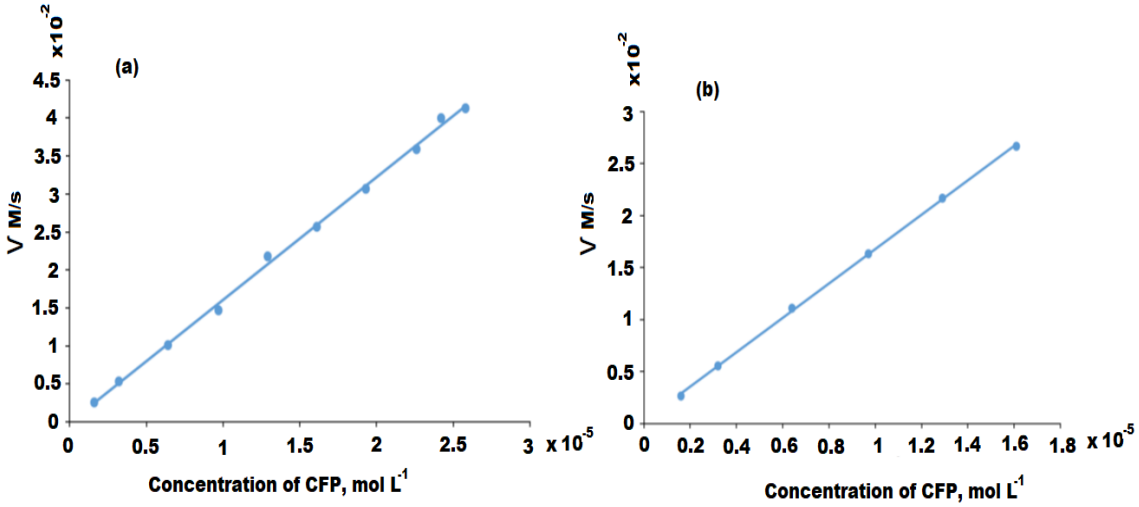
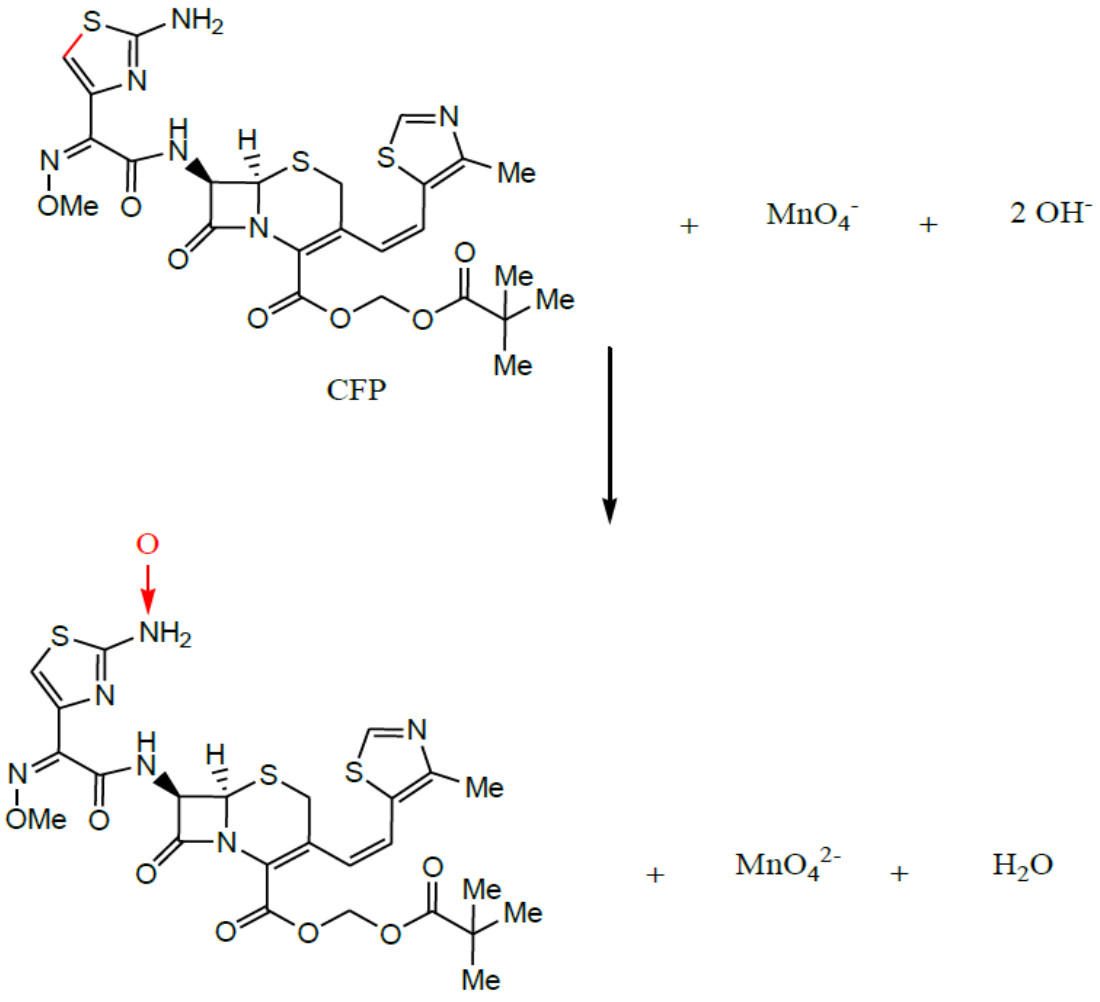
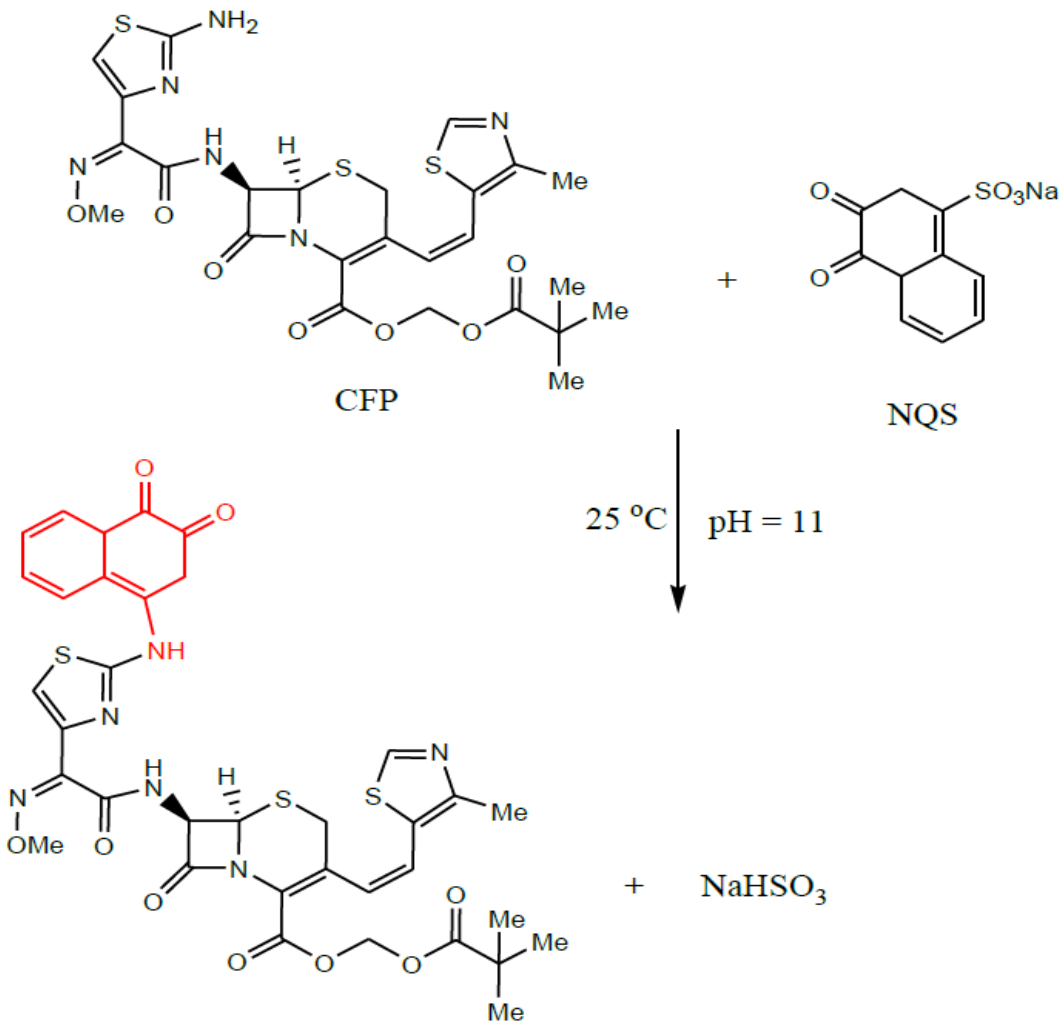


Fig 7: Linear plot of V *vs.* C for the kinetic reaction of CFP with alkaline $KMnO_4$ at (a) 610 nm and (b) 525 nm.



Scheme-1: The reaction pathway of CFP with alkaline $KMnO_4$.



Scheme-2:The reaction pathway of CFP with NQS.

Initial rate method:

The slopes of tangents of absorbance-time curves at 610 and 525 nm were used to determine the initial reaction rates (Figs 5a and 5b). The calibration curves were obtained by graphing the initial rate (ν) *vs.* CFP concentrations as demonstrated in Figs 7 (a and b). Linear relationships were obtained over the concentration ranges of 0.16×10^{-5} – 2.58×10^{-5} mol L^{-1} (1.0- 16.0 µgmL^{-1}) at 610 nm and 0.16×10^{-5} – 1.61×10^{-5} mol L^{-1} (1.0-10.0 µgmL^{-1}) at 525 nm. Regression equations using the method of least squares [26] were found as:

At 610 nm, log ν = 1.0025 log C + 3.2178 (r = 0.9995) and At 525 nm, log ν = 0.998 log C + 3.2168 (r = 0.9998). Hence k` = 1651.20 s^{-1}, 1647.40 s^{-1} and n = 1.0025, 0.998 (≈ 1) respectively, thus according to CFP the reaction was pseudo-first order.

Fixed time method

The absorbance was measured at 610 nm and ΔA was measured at 525 nm. Calibration graphs were obtained by graphing the absorbance at 610 nm or ΔA at 525 nm *vs.* initial concentrations of CFP at fixed times (5 min) from 1-30 min were established. The regression equations, correlation coefficients, and standard deviations of slope and intercept are reported in Table-2 and 3. The results indicated good correlation coefficient (r) values and the intercept achieved at a fixed time of 10 min which was selected as the btime interval for the proposed study. Figs. 8a and 8b, showed the calibration graphs of CFP determination over 1.0 - 16.0 µg mL^{-1} and 1.0 – 10.0 µg mL^{-1} ranges by the fixed time method at 610 and 525 nm, respectively.

Fixed concentration method

To reach to a specific absorbance at 610 nm or ΔA at 525 nm, reaction times were recorded for various

concentrations of CFP. A previously selected value of absorbance (0.50) was fixed and the time was recorded in seconds. Calibration graphs were obtained by graphing (1/t) *vs.* initial drug concentration (C). Straight lines were obtained using 8.0 - 12.0 µg mL^{-1} and 6.0 -10.0 µg mL^{-1} CFP at 610 and 525 nm respectively, with regression equations: At 610 nm, 1/t = 0.0045 C - 0.0342 (r = 0.99995) and At 525 nm 1/t = 0.001 C - 0.0058 (r = 0.99998). The outcome of data revealed that, the initial rate method has poor linearity, poor accuracy, and poor sensitivity than the fixed concentration and fixed time methods. Moreover, it possesses some experimental difficulty in the accurate determination of the initial rate. Also the fixed concentration method gave very limited range of CFP concentration. Therefore, the fixed time method was selected for the quantification of the CFP in its authentic and commercial samples.

Method validation

For methods A and B, under optimal conditions, the fixed time method was employed to the kinetic quantification of CFP over the concentration ranges 1.0 -16.0 and 1.0 -10.0 µg mL^{-1} at 610 nm and 525 nm, respectively (Table-2 and 3). For method C, a straight line over the concentration range 0.5 – 7.0 µg mL^{-1} was obtained. Least squares [26] analysis of the outcome of data gave excellent correlation coefficient (r) and small values of standard deviations of intercept (S_a) and slope (S_b) as indicated in Table-4.

Table-1: Initial rate reaction of varying concentrations of CFP with alkaline $KMnO_4$.

		At 610 nm		At 525 nm	
$C\times10^{-5}$, M	**Log C**	**V, M/s**	**Log V**	**V, M/s**	**Log V**
0.16	**-5.79**	**2.56×10^{-3}**	**-2.59**	**2.57×10^{-3}**	**-2.57**
0.32	**-5.49**	**5.33×10^{-3}**	**-2.27**	**5.56×10^{-3}**	**-2.26**
0.64	**-5.19**	**1.01×10^{-2}**	**-2.00**	**1.10×10^{-2}**	**-1.95**
0.97	**-5.01**	**1.47×10^{-2}**	**-1.83**	**1.63×10^{-2}**	**-1.79**
1.29	**-4.89**	**2.18×10^{-2}**	**-1.66**	**2.67×10^{-2}**	**-1.66**
1.61	**-4.79**	**2.57×10^{-2}**	**-1.59**	**2.57×10^{-2}**	**-1.57**
1.93	**-4.71**	**3.07×10^{-2}**	**-1.51**		
2.2	**-4.65**	**3.59×10^{-2}**	**-1.45**		
2.42	**-4.62**	**4.00×10^{-2}**	**-1.40**		
2.58	**-4.59**	**4.13×10^{-2}**	**-1.38**		

Table-2: Analytical data for the proposed fixed time spectrophotometric method for the quantification of CFP using alkaline $KMnO_4$ at 610 nm

Time (min)	**Linear range (µgmL^{-1})**	**Regression equation A=bC+a****	**Correlation coefficient (r)**	**(S_b)**	**(S_a)**	**LOD (µgmL^{-1})**	**LOQ (µgmL^{-1})**
1	**1-18**	**A=0.0422C-0.0115**	**0.99989**	**0.0002**	**0.00204**	**0.1592**	**0.4825**
5	**1-18**	**A=0.0585C-0.0148**	**0.99989**	**0.0003**	**0.00328**	**0.1851**	**0.5608**
10	**1-16**	**A=0.0655C-0.0122**	**0.99995**	**0.0002**	**0.00248**	**0.1249**	**0.3786**
15	**1-16**	**A=0.0685C-0.0084**	**0.99962**	**0.0007**	**0.00680**	**0.3274**	**0.9921**
20	**1-16**	**A=0.014C-0.0109**	**0.99984**	**0.0005**	**0.00462**	**0.2137**	**0.6474**
25	**1-14**	**A=0.0738C-0.0132**	**0.99977**	**0.0006**	**0.00541**	**0.2419**	**0.7331**
30	**1-14**	**A=0.075C-0.0131**	**0.99984**	**0.0005**	**0.00454**	**0.1997**	**0.6051**

**A = absorbance, C = Concentration in µgmL^{-1}

Table-3: Analytical data for the proposed fixed time spectrophotometric method for the quantification of CFP using alkaline $KMnO_4$ at 525 nm

Time (min)	**Linear range (µgmL^{-1})**	**Regression equation ΔA=bC+a****	**Correlation coefficient (r)**	**(S_b)**	**(S_a)**	**LOD (µgmL^{-1})**	**LOQ (µgmL^{-1})**
1	**1-10**	**ΔA=0.042C-0.0037**	**0.99987**	**0.00034**	**0.0020**	**0.1599**	**0.4844**
5	**1-10**	**ΔA=0.0611C-0.0104**	**0.99970**	**0.00074**	**0.0045**	**0.2440**	**0.7395**
10	**1-10**	**ΔA=0.066C-0.0012**	**0.99998**	**0.00023**	**0.0014**	**0.0709**	**0.2150**
15	**1-10**	**ΔA=0.0686C-0.005**	**0.99981**	**0.00066**	**0.0040**	**0.1938**	**0.5873**
20	**1-10**	**ΔA=0.0706C-0.0083**	**0.99962**	**0.00097**	**0.0059**	**0.2748**	**0.8326**
25	**1-10**	**ΔA=0.0731C-0.0068**	**0.99972**	**0.00087**	**0.0053**	**0.2373**	**0.7191**
30	**1-10**	**ΔA=0.0747C-0.0094**	**0.99981**	**0.00073**	**0.0044**	**0.1953**	**0.5920**

**ΔA = difference in absorbance, C = Concentration in µgmL^{-1}

Table-4: Analytical performance data for the determination of FP with NQS reagent

Parameter	**Results**
Measurement wavelength (nm)	**411**
Linear range (µgmL^{-1})	**0.5-7.0**
Regression equation	**A = 0.1653C-0.0287**
Correlation coefficient (r)	**0.99998**
Standard deviation of the intercept (S_a)	**1.40×10^{-3}**
Standard deviation of the slope (S_b)	**3.00×10^{-4}**
Limit of detection LOD (µgmL^{-1})	**2.77×10^{-2}**
Limit of detection LOQ (µgmL^{-1})	**8.38×10^{-2}**
Molar ratio (drug/reagent)	**1:1**

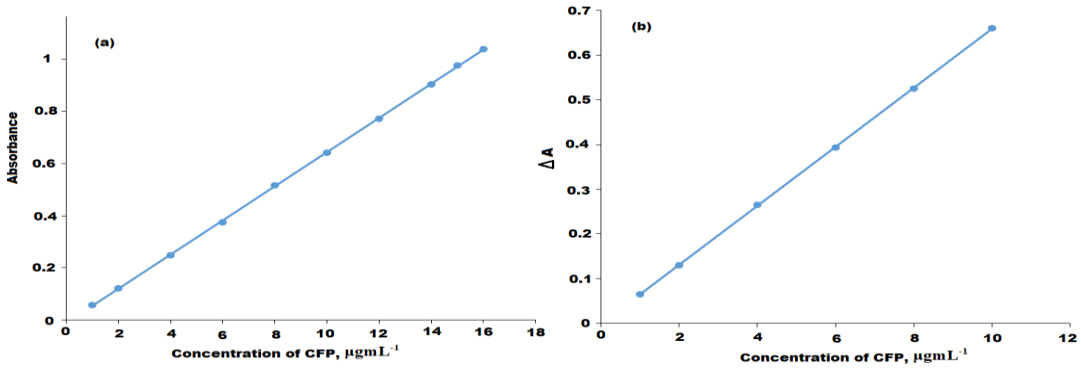


Fig 8: Linear plot of (a) A *vs*. C for the kinetic reaction of CFP with alkaline $KMnO_4$ at 610 nm and (b) ΔA *vs*. C for the kinetic reaction of CFP with alkaline $KMnO_4$ at 525 nm using fixed time method.

To study the accuracy of the current methods the % error was determined over the concentration ranges 1.0 - 16.0 and 1.0 – 10.0 and 0.5 – 7.0 µg mL^{-1}, for method A, B and C, B, respectively. The % errors were -0.61 – (0.15) % at 610 nm, -0.61 – (0.83) % at 525 nm and were (-0.14) – (0.45) % at 411 nm, for the three methods respectively. The outcome of data from the quantification of the CFP in its authentic samples using the developed methods was compared with other results obtained from previously addressed spectrophotometric method [3]. Student's t-test and variance ratio F-test [26] were used to assess the analytical results and no significant differences observed (Table-5). Further validation study was performed to evaluate the precision of the current methods using intra-day and inter-day tests. The obtained small standard deviations confirming intermediate precision and the reasonable repeatability of the proposed methods as summarized in (Table-6).

Table-5: Analysis of CFP in authentic samples using the published and proposed spectrophotometric methods A, B and C

	Taken range (µgmL^{-1})	Found range (µgmL^{-1})	% Error	% Found Mean±SD	t-test (2.22)*	F-test (5.05)*
Method A at 610 nm	**1-16**	**0.99-16.02**	**-0.24-0.15**	**99.70±0.26**	**0.91**	**1.78**
Method B At 525 nm	**1-10**	**1.00-10.02**	**-0.61-0.30**	**99.67±0.26**	**0.77**	**1.86**
Method C At 411 nm	**0.5-7.0**	**0.50-7.01**	**-.0.14-0.45**	**99.84±0.22**	**1.81**	**2.51**
Published method				**99.54±0.3**		

*Tabulated values of t and F at P = 0.05 [26]

After optimizing the analytical conditions, the selectivity of the suggested probes was examined in the presence of MEIACT tablet's co-additives [27] e.g., D-mannitol hydroxyl propyl cellulose, hypromellose, magnesium stearate, croscarmellose sodium, sodium caseinate, sodium tripolyphosphate, polyethylene glycol, titanium dioxide and propylene glycol. The printed tablets with ink containing opacode blue S-1-10533 was tested. No remarkable interference from co-additives. Therefore, these analytical systems are selected for the drug quantification.

Limits of detection and quantitation, LOD and LOQ were evaluated with respect to ICH [28] guidelines. The following equations were obeyed 3.3 (Sa)/b and 10 (Sa)/b for LOD and LOQ, respectively. The results were mentioned above in Tables 3 and 4.

Robustness, this study performed by inducing insignificant changes in the analytical parameters, e.g. 2.0 ± 0.2 mL of 4.0×10^{-2} mol L^{-1} $KMnO_4$, and 2.5 ± 0.2 mL of 1.0 mol L^{-1} NaOH or 1.5±0.2 mL of NQS for method A, B and C, respectively. No significant effect on the absorbance intensity was noticed by taking place these changes in the analytical parameters. Finally, a comparative study has been carried out between the three suggested spectrophotometric methods and the outcomes were presented in Table-7.

Application by analysis of commercial tablets

To investigate the analytical suitability of the developed kinetic spectrophotometric methods, CFP was quantified in its commercial samples. The % recoveries of the average triplicate determinations were calculated as 99.72±0.33, 99.68±0.57 and 99.99±0.55 for the three methods, respectively. The comparative results between the published spectrophotometric method [3] and the studied results gave good agreements (Table-8). The assessed statistical data using t-test and F-test [26] revealed the excellent accuracy and precision of the developed procedures.

Table-6: Precision data for the determination of CFP by using the three proposed spectrophotometric methods.

Parameter		CFP concentration µg mL^{-1}								
		Method A at 610 nm			Method B at 525 nm			Method C at 411 nm		
		2.0	6.0	10.0	2.0	6.0	10.0	1.0	3.0	7.0
Intra-day	% Found[a]	99.73	99.29	100.6	98.79	98.77	99.67	99.79	100.66	100.08
		100.23	99.45	99.87	99.31	99.68	98.93	98.71	98.87	100.21
		99.56	101.1	99.33	99.69	100.4	99.86	100.21	100.38	99.77
	Mean	99.84	99.63	99.26	99. 61	99.49	99.92	99.57	99.97	100.02
	±SD	±0.35	±1.43	±0.45	±0.81	±0.49	±0.62	±0.77	±0.96	±0.23
	S_{mean} [b]	0.20	0.83	0.26	0.47	0.28	0.36	0.45	0.56	0.13
Inter-day	% Found	98.83	99.39	100.4	100.8	99.55	101.12	101.08	99.49	99.83
		100.74	98.91	98.85	99.62	99.93	98.03	99.56	98.86	98.33
		99.76	100.1	99.96	98.84	100.8	98.68	98.94	100.07	100.79
	Mean	99.78	99.45	99.73	99.75	100.1	99.28	99.86	99.47	99.65
	±SD	±0.96	±0.57	±0.79	±0.98	±0.63	±1.63	±1.10	±0.61	±1.24
	S_{mean} [b]	0.55	0.33	0.45	0.56	0.36	0.94	0.64	0.35	0.72

[a] Each result is the average of three separate experiment; [b] Calculated as SD/√n

Table-7: Comparative results of the three suggested spectrophotometric methods with respect to linearity, accuracy, precision and interference.

	Linear concentration range (µg mL^{-1})	Precision (% RSD)		Accuracy Mean ± SD	Interferences
		Intra-day	Inter-day		
Method A at 610 nm	1.0-16	0.35 - 1.43 %	0.57 - 0.96 %	99.70±0.26	NO
Method B At 525 nm	1.0-10	0.49 - 0.81 %	0.63 - 1.63 %	99.84±0.22	NO
Method C At 411 nm	0.5-7.0	0.23 - 0.96 %	0.61 - 1.24 %	99.54±0.30	NO

Table-8: Analysis of CFP in commercial tablets using the published and proposed spectrophotometric methods A, B and C

	Taken range (µgmL^{-1})	% Found Mean ± SD	t-test (2.22)*	F-test (5.05)*
Method A at 610 nm	1-16	99.72±0.33	0.19	1.30
Method B At 525 nm	1-10	99.68±0.57	0.03	3.82
Method C At 411 nm	0.5-7.0	99.99±0.55	1.19	3.55
Published method		99.69±0.29		

*Tabulated values of t and F at P = 0.05 [26]

Conclusion

The recent study concerned with developing more reliable kinetic and colorimetric spectroscopic systems for the quantification of the CFP in its authentic and commercial tablets. The develop fixed time methods displayed some advantages over many previously published UV-Vis methods that they are simple, fast in detection time and provide a wide concentration range for determination of the CFP in its authentic and dosage form samples. Moreover, the suggested systems can be used for analytical estimation of the drug without any expensive devices of harmful reagents. The outcome of results gave the developed methods great attention and encourages the utility of these procedures in quality control analysis of drugs.

Conflict of interest

No conflict of interest associated with this work.

References

1. J. Dugassa and N. Shukuri, Review on antibiotic resistance and its mechanism of development. *J. Health, Med. Nurs.*, **1**, 1 (2017).
2. A. Rodriguez-Gascon, A. Aguirre-Quinonero and A. Canut-Blasco, Are oral cefuroxime axetil, cefixime and cefditoren pivoxil adequate to treat uncomplicated acute pyelonephritis after switching from intravenous therapy? A pharmacokinetic/pharmacodynamic perspective. *Enferm. Infecc. Microbiol. Clin.*, **38**, 306 (2020).
3. S. R. Narala and K. Saraswathi, Application of oxidants to the spectrophotometric determination of cephalosporins (Cefditoren Pivoxil and Cefdinir) in formulations. *Tablet*, **1**, 187 (2011).
4. S. R. Narala and K. Saraswathi, Validated spectrophotometric methods for the determination of cefditoren pivoxil in drug formulations, *J. Pharm. Sci. Res.*, **3,** 1025 (2011).
5. A. B. Karadi, S. A. Raju, S. Manjunath, D. Darak, Development and validation of visible spectrophotometric methods for determination of Cefditoren Pivoxil in pharmaceutical

formulations. *Res. J. Pharm. Tech*., **4**,1269 (2011).
6. V. Niraimathi, A. Aruna, A. J. Suresh and V. Prema, Spectrophotometric estimation of cefditoren pivoxil in pharmaceutical oral solid dosage form, *Int. J. Chem. Sci.,* **8**, 724 (2010).
7. V. Prema, V. Niraimathi, A. Aruna and A. J. Suresh, Estimation of cefditoren pivoxil in pharmaceutical oral solid dosage form by difference spectroscopy and Q-absorbance method, *Res. J. Pharm. Tech.,* **3,** 610 (2010).
8. N. A. Alarfaj, F. A. Aly and M. F. El-Tohamy, Application of silver nanoparticles to the chemiluminescence determination of cefditoren pivoxil using luminol-ferricyanide system, *Luminescence*, **300,** 91 (2015).
9. A. Dewani, N. Kochar, H. Abooj, R. Bakal, A. Chandewar and B. Barik, Determination of cefditoren pivoxil in bulk by RP-HPLC in presence of its degradation products, *J. Pharm. Res.,* **3,** 2588 (2010).
10. H. M. Albishri, Simple stereoselective HPLC method for studying the isomerisation of cefditoren pivoxil and its isomeric purity in pharmaceuticals, *Chromatographia,* **75,** 1327 (2012).
11. S. Vidhya, B. L. Narayanan, P. Malairajan, R. J. Sahayaraja, E. Kumar, S. Mahibalan, M. Karpakavalli and C. Balakumar, Analytical method development and Validation for the quantitative estimation of cefditoren pivoxil in tablet formulation by RP-HPLC, *Int. J. Drug Dev. Res.,* **4**, 186 (2012).
12. I. H. Tasdemir, Electrochemistry and determination of cefdinir by voltammetric and computational approaches. *J. Food Drug Anal.*, **22**, 527 (2014).
13. S. A. Al-Tamimi, A. M. Al-Mohaimeed, N. A. Alarfaj and F. A. Aly, Ion selective electrodes for determination of cefditoren pivoxil in pharmaceutical formulations and biological fluids, *Int. J. Electrochem. Sci.,* **8**, 3988 (2013).
14. I. H. Tasdemir, Electrochemistry of cefditoren pivoxil and its voltammetric determination. *Arabian J. Chem.,* **9**, 86 (2016).
15. K. J. Laidler, J. H. Meiser, B. C. Sanctuary, *Physical Chemistry* Boston, N. Y, (2003).
16. A. P. Gervasio, P. R. Fortes, S. R. Meneses, C. E. Miranda and E. A. Zagatto, An improved flow-injection system for spectrophotometric determination of molybdenum and tungsten in tool steels, *Talanta,* **69**, 927 (2006).
17. C. Tu and X. Wen, November. Determination of Methimazole by Potassium Permanganate Spectrophotometry, *J. Phys.,* **1635**, 012103 (2020).
18. H. Rahman, Analytical Applications of Permanganate as an Oxidant in the Determination of Pharmaceuticals Using Chemiluminescence and Spectrophotometry: A Review, *Curr. Anal. Chem.*, **16**, 670 (2020).
19. S. T. McBeath, D. P. Wilkinson and N. J. Graham, Analytical quantification of aqueous permanganate: Direct and indirect spectrophotometric determination for water treatment processes, *Chemosphere*, **251**, 126626 (2020).
20. A. A. Elbashir, A. A. Ahmed, S. M. Ali Ahmed and H. Y. Aboul-Enein, 1, 2 Naphthoquinone-4-sulphonic acid sodium salt (NQS) as an analytical reagent for the determination of pharmaceutical amine by spectrophotometry, *Appl. Spec. Rev.*, **47**, 219 (2012).
21. O. Folin, A system of blood analysis supplement iii. A new colorimetric method for the determination of the amino-acid nitrogen in blood, *J. Biol. Chem.* **51,** 377 (1922).
22. D. Rosenblatt, P. Hlinka and J. Epstein, Use of 1, 2-Naphthoquinone-4-sulfonate for Estimation of Ethylenimine and Primary Amines, *Anal. Chem.*, **27**, 1290 (1955).
23. T. Gurkan, Reaction of some sympathomimetic amines with sodium 1, 2-naphthoquinone-4-sulphonate. *Microchim. Acta* **65**, 165 (1976).
24. J. Rose, *Advanced Physicochemical Experiments*. John Wiley, New York, p. 348 (1964).
25. S. A. M. Ebraheem, A. A. Elbashir and H. Y. Aboul-Enein, Spectrophotometric methods for the determination of gemifloxacin in pharmaceutical formulations, *Acta Pharm. Sinica B*, **1**, 248 (2011).
26. R. Caulcutt and R. Boddy, *Statistics for analytical Chemists.* Chapman and Hall, London, (1983).
27. http://www.rxlist.com/spectracef-drug/pateint-avoid-while-taking.htm,28/1/2015.
28. International Conference on harmonization ICH, Q2(R1), validatiom of analytical procedures, Text and Methodology, Switzerland, (1995).