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Utility of π and σ-Acceptor Reagents for the Spectrophotometric Determination of Cefotaxime Sodium Antibacterial Drug via Charge Transfer Complex Formation

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Abstract: Background: The antibacterial drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in humans. The considerable medical and their subsequent wide spread use were quickly reflected in the sharp decline in morbidity and mortality figures for the treatable infections diseases. Before penicillin became generally available, cefotaxime sodium was the mainstry of antibacterial chemotherapy. **The context and purpose:** A simple, sensitive and accurate spectrophotometric method has been developed for the determination of Cefotaxime sodium (CTX) in injection samples. The Charge Transfer (CT) reactions between CTX (n-electron donor) and 7,7,8,8-tetracyanoquinodimethane (TCNQ), 5,6-dicyano-1,4-benzoquinone (DDQ), 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinone (chloranilic acid, p-CLA) (π-acceptors) and I_2 (σ-acceptor) are studied where highly coloured CT complexes are formed. The experimental conditions for these CT reactions have been carefully optimized. Beer's law is valid over the concentration range from 5-300, 0.5-35, 1-500 and 0.2-15 μg mL^{-1} CTX using DDQ, TCNQ, p-CLA and I_2 reagents, respectively. Different analytical parameters namely molar absorptivity (ε), Standard Deviation (SD), Relative Standard Deviation (RSD), correlation coefficient, Limit Of Detection (LOD) and quantification (LOQ) are calculated. The optimum assay conditions are investigated and the recovery of the cited drug from its dosage forms is ranged from 98.00 to 102.0%. Good values of precision are obtained, intraday RSD are 0.171-1.91% and the correlation coefficients ranged from 0.996 to 0.999. The results obtained by the proposed methods are in good agreement with those obtained by the official method as indicated by the percent recovery values. **Conclusion:** Cefotaxime sodium have been successfully determined in pure and pharmaceutical preparations using charge transfer reagents.

Key words: Charge-transfer, CTX, spectrophotometry, TCNQ, DDQ, chloranilic acid, I_2

INTRODUCTION

The antibacterial drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in humans. The considerable medical and their subsequent wide spread use were quickly reflected in the sharp decline in morbidity and mortality figures for the treatable infections diseases. Before penicillin became generally available, cefotaxime sodium was the mainstry of antibacterial chemotherapy. Several methods have been reported for the determination of CTX in pharmaceutical dosage forms and in biological fluids including electrochemistry (Nigam *et al*., 2009), voltammetry (Aleksic and Kapetanovic, 2006; El-Maali *et al*., 2005; Yilmaz and Biryol, 1998), high performance liquid chromatography (Bafeltowska *et al*., 2002; Scanes *et al*., 2001) or by spectrophotometry (Nuevas *et al*., 1998). The molecular interactions between electron donors and acceptors are generally associated with the formation of coloured charge-transfer complexes which absorb radiation in the visible region (Mulliken, 1950; Mulliken and Pearson, 1969; Foster, 1969). Molecular Charge-Transfer complexes (CT) were of particular interest in pharmaceutical science (Muralikrishna and Krishnamurthy, 1985). Though the batch methods allowed for the determination of CTX, included time as a variable to be strictly controlled and require a stable reaction temperature.

This study describes simple, direct, sensitive and precise spectrophotometric methods for the determination of some antibacterial drugs via charge transfer complex formation with some π-acceptors, namely, TCNQ, DDQ, p-CLA and π-acceptor like I_2. Stoichiometry and molar

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absorptivity of the formed CT complexes were determined. Subsequent utilization of these charge transfer complexes for developing a new spectrophotometric method for the determination of CTX in pure and pharmaceutical preparations are discussed in detailed manner.

MATERIALS AND METHODS

Reagents: All reagents and chemicals used were of analytical grade and all solutions were freshly prepared daily. 0.02% (w/v) 7,7,8, 8-Tetracyanoquinodimethane (TCNQ) was prepared in acetonitrile and 0.1% (w/v) of 5,6-dicyano-1,4-benzoquinone (DDQ) was prepared in methanol (all were supplied from Fluka) and 0.1% (w/v) of 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinone (p-CLA) was prepared in acetonitrile and 0.05% (w/v) I_2 was prepared in methanol. All solvents used throughout this study were of analytical grade including acetonitrile, 1,4-dioxane, ethanol, methanol, acetone, methylene chloride and 1,2-dichloroethane.

Market samples: Cefotax T3A (1 g) injection was supplied from T3A industrial, Ceforan (1 g) injection was supplied from Pharco B International Co. and Claforan (0.5 g) injection was supplied from Sanofi Aventis.

Materials

Pure sample: An accurate weight of the powder containing 100 mg of CTX was dissolved in 100 mL methanol for TCNQ, DDQ and p-CLA reagents. While in case of I_2 reagent, 10 mg of the drug was dissolved in 100 mL methanol.

Application to dosage forms: 2×10^{-3} and 2×10^{-4} mol L^{-1} solutions of CTX (drug) under investigation were prepared by dissolving the accurate weighed amount in a definite volume of methanol to get the required concentration.

Apparatus: The spectrophotometric measurements were carried out using the manual Unico 1200 (United Products and Instruments, Inc.) in the wavelength range from 325-1000 nm. Small values were taken using micropipette.

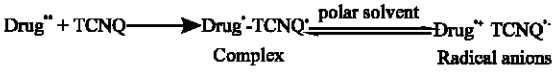
Stoichiometry of the formed CT complexes: Stoichiometry of the formed CT complexes was determined by applying the continuous variation and molar ratio methods (Job, 1928; Vosburgh and Cooper, 1941). Successive aliquots of CTX solutions (2×10^{-3} mol L^{-1}) in case of DDQ and TCNQ or p-CLA and (2×10^{-4} mol L^{-1}) in case of I_2 were added to the drug solution, so that the total number of moles was kept constant. The absorbance of the resultant CT complexes was measured at 450, 842, 510 and 360 nm for DDQ, TCNQ, p-CLA and I_2 reagents, respectively, against reagent blank.

Batch measurements: Aliquots containing CTX was transferred into 5.0 ml volumetric flask. 0.1, 0.02, 0.1 and 0.026 mg mL^{-1} of DDQ, TCNQ, p-CLA and I_2 reagents were added, respectively and the solution was completed to the mark with acetonitrile while in case of I_2 the solution was completed to the mark with dichloromethane. The complete colour development was attained after 30, 50, 10 and 10 min for DDQ, TCNQ, p-CLA and I_2 reagents, respectively. The absorbance of the formed complexes was measured at 450, 842, 510 and 360 nm for DDQ, TCNQ, p-CLA and I_2 reagents, respectively, against the blank solution prepared without the drug. The absorbance was plotted versus the final concentration to get the calibration graph.

RESULTS AND DISCUSSION

Spectral characteristics: CTX being an n-electron donor reacts with π- and σ-acceptors giving characteristic colour reaction products due to the formation of CT complexes (Abdel-Hamid and Abuirjeie, 1988). CTX shows negligible absorption in the wavelength range from 400-800 nm in acetonitrile and dichloromethane solvents, while addition of the different electron acceptors (namely, DDQ, TCNQ, p-CLA and I_2) to the drug solutions causes change in the absorption spectra due to the formation of CT complexes with new characteristic bands at maximum absorption depending on the type of the π-acceptors (Fig. 1). Interaction of CTX with TCNQ gives a green chromogen which exhibits strong absorption maxima at 842 and 740 nm. The wavelength 842 nm is selected as it gives reproducible results and higher molar absorptivity. These bands may be attributed to the formation of the radical anion $TCNQ^{\bullet-}$ (El-Dien *et al*., 2009; Frag and Mohamed, 2010) which was probably formed by the dissociation of an original donor-acceptor (D-A) complex which is promoted by the high ionizing power of the acetonitrile solvent (Scheme 1).

The interaction of CTX with DDQ in acetonitrile at room temperature give red coloured chromogen with a strong absorption maximum at 450, 550 and 580 nm where the wavelength 450 is selected for the further studies (Abdel-Hamid *et al*., 1985; Abdel-Salam *et al*., 1985).



Scheme 1:

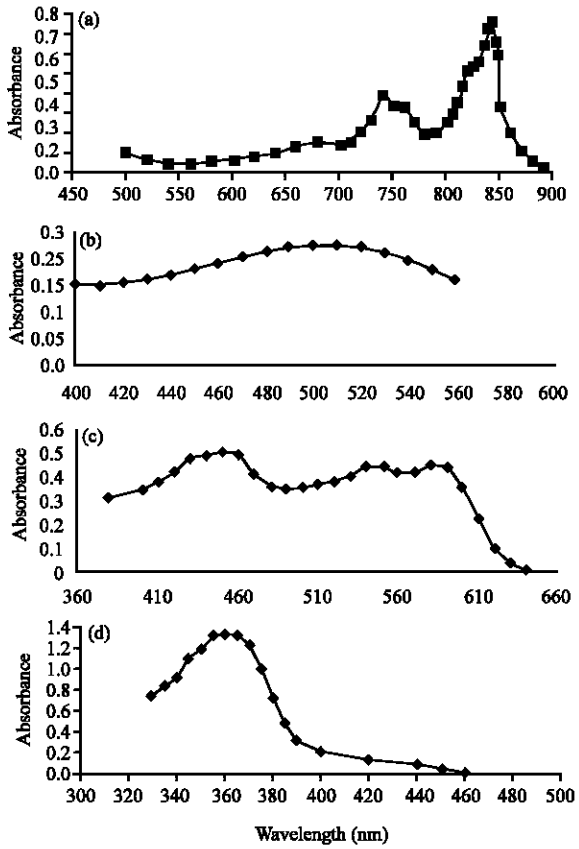


Fig. 1: Absorption spectrum of (a) CTX- TCNQ (b) CTX-p-CLA (c) CTX- DDQ CT complexes in acetonitrile and (d) CTX-I_2 CT complexes in methylene chloride

Interactions of CTX with p-CLA in acetonitrile give a purple product with absorption maximum at 510 nm. Some of the literatures reveal that the reaction of p-CLA with certain basic nitrogenous compounds (B) is probably due to CT complexation reaction according to Scheme 2 (Agarwal and Elsayed, 1981). Also according to the previous published data, the reaction may be suggested to be a proton transfer from p-CLA to the basic center of the drug (Scheme 3). Dissociation of the obtained ion pair salt is enhanced in the highly polar solvent such as acetonitrile to give the purple anion form of p-CLA (El-Dien *et al*., 2009; Elsayed *et al*., 1984).

The interaction of CTX with I_2 in dichloromethane at room temperature gives yellow coloured chromogen with a strong absorption maximum at 360 and 300 nm where the wavelength 360 is selected for the further studies (Pandeeswaran and Elango, 2009; Zayed and El-Habeeb, 2009).

$$B + p\text{-}CLAH_2 \rightleftharpoons [B \rightarrow p\text{-}CLAH_2] \rightarrow B^{+\cdot} + p\text{-}CLAH_2^{-\cdot}$$

Drug

Scheme 2:

$$p\text{-}CLAH_2 \rightleftharpoons H^+ + p\text{-}CLAH^- \text{ (purple)}$$

$$B + H^+ \rightleftharpoons BH^+ \text{ (colourless)}$$

Scheme 3:

$$Drug + I_2 \rightleftharpoons Drug - I_2 \text{ (outer complex)} \quad (1)$$

$$Drug - I_2 \rightleftharpoons [Drug - I]^+ I^- \text{ (inner complex)} \quad (2)$$

$$[Drug - I]^+ I^- + I_2 \rightleftharpoons [Drug - I]^+ I_3^- \quad (3)$$

Optimization of reaction conditions

Effect of reagent concentration: To establish the optimum experimental conditions for CTX-CT complexes, the drug (2-50 μg mL^{-1}) are allowed to react with varying volumes of the different acceptors (DDQ, TCNQ, p-CLA and I_2). The data obtained are given in Fig 2. The maximum absorbance is obtained with (0.4 and 0.6) mg mL^{-1} of DDQ and p-CLA, respectively, while 0.1 mg mL^{-1} of TCNQ and I_2 are the suitable concentrations for quantitative determination of CTX. Higher concentrations of the reagents have no effect that may be useful for rapidly reaching equilibrium, thus minimizing the time required for attaining maximum absorbance at the corresponding wavelengths.

Effect of solvents: In order to select the suitable solvent for CT complex formation, the reaction of CTX with p-CLA, DDQ and TCNQ reagents is made in different solvents. Acetonitrile shows super priority over chloroform, 2-propanol, 1,2-dichloroethane, 1,4-dioxane, methanol and ethanol as the complex formed in these solvents either had low absorbance or precipitated on dilution. Further, acetonitrile, being a polar solvent, facilitates the complete transfer of charge from donor to acceptor with the formation of radical anion as the predominant chromogen indicated by high ε values which is attributed to its high dielectric constant (Vogel *et al*., 1989) but in case of I_2 methylene chloride shows super priority over chloroform, 2-propanol, 1,2-dichloroethane, 1,4-dioxane, methanol and ethanol as the complex formed in these solvents either had low absorbance values and hence low molar absorptivity.

Effect of reaction time and temperature: The effect of time on the CT complex formation is shown in Fig. 3. Reaction

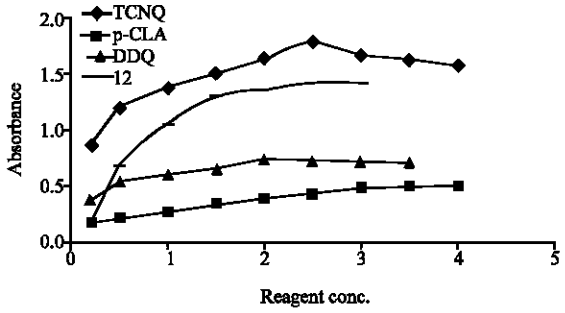


Fig. 2: Effect of TCNQ, p-CLA, DDQ and I_2 concentration on the formation of CTX CT complexe

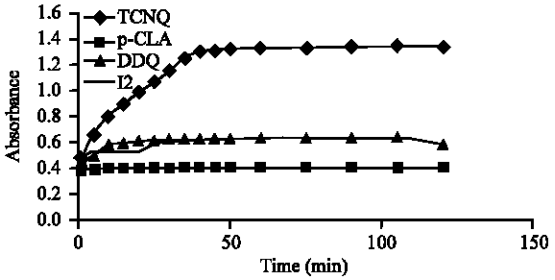


Fig. 3: Effect of time on the absorbance of CT complexes of CTX with (a) TCNQ (b) p-CLA (c) DDQ and (d) I_2

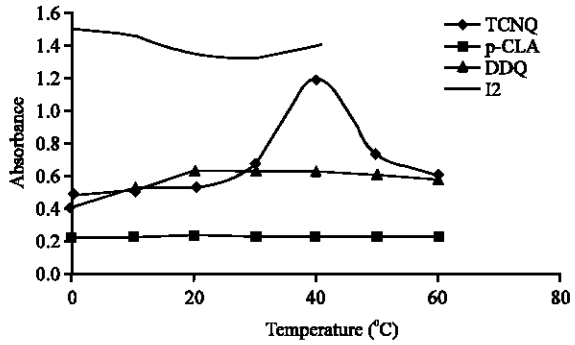


Fig. 4: Effect of temperature (0-60°C) on the absorbance of CT complexes of CTX with (a)TCNQ (b) p-CLA (c) DDQ and (d) I_2

time is determined by following the colour development. The results obtained indicate that complete colour development is attained immediately. DDQ, TCNQ, p-CLA and I_2 reagents form red, greenish yellow, purple and yellow chromogens with CTX under investigation after 30, 50, 10 and 10 min, respectively (Fig. 3). The effect of

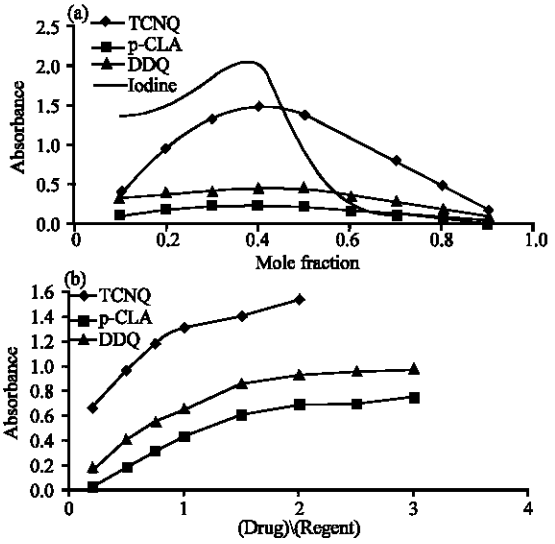
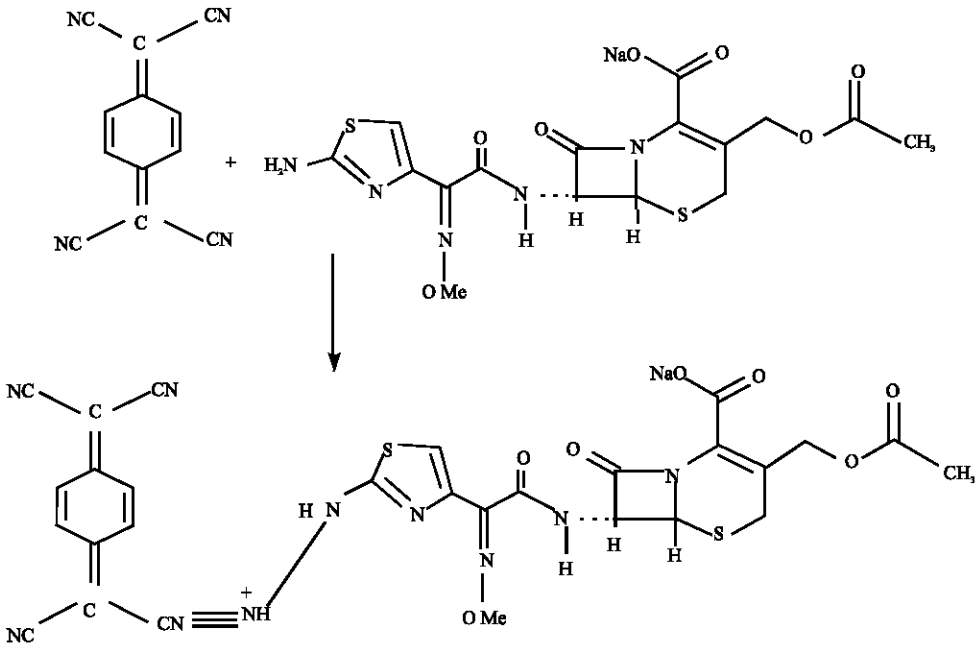


Fig. 5: Stoichiometric ratio of CTX CT complexes with TCNQ, p-CLA, DDQ and I_2 by: (a) Job's method (b) Molar ratio method

temperature on the CT complex formation is shown in Fig. 4. Reaction temperature is determined by following the colour development. The results obtained indicate that complete colour development is attained immediately. DDQ, TCNQ, p-CLA and I_2 reagents form red, greenish yellow, purple and yellow chromogens with CTX under investigation at 20, 40, 20 and 10°C, respectively (Fig. 4). The absorbance of the complexes remains stable for at least one day for DDQ, TCNQ, p-CLA and I_2, respectively thus is permitting quantitative determination of CTX to be carried out with good reproducibility.

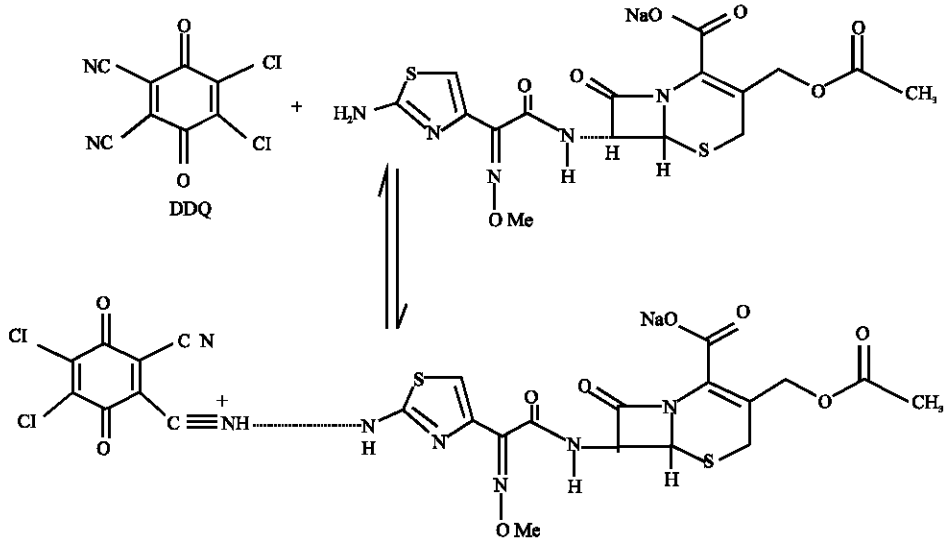
Stoichiometry of the formed CT complexes: The stoichiometry of the formed CT complexes is determined by applying the molar ratio and continuous variation methods (Job, 1928; Vosburgh and Cooper, 1941) and data obtained are given in Fig. 5. It is obvious from Fig. 5 that 1:2 (Drug): (Reagent) CT are formed. This finding is anticipated by the presence of basic electron-donating center (nitrogen atom) in the drugs under investigation. The structures of CT complexes are given in Schemes (4-6).

Validity of Beer's law: Under the optimum conditions described above, the calibration graphs are constructed for the investigated drug applying the four different acceptors. The molar absorptivities, standard deviations, concentration ranges, regression equations, Limits Of Detection (LOD) and quantification (LOQ) for each acceptor is tabulated in Table 1. Beer's law is valid over



CTX-TCNQ CT complex

Scheme 4: Structure of CTX-TCNQ CT complex



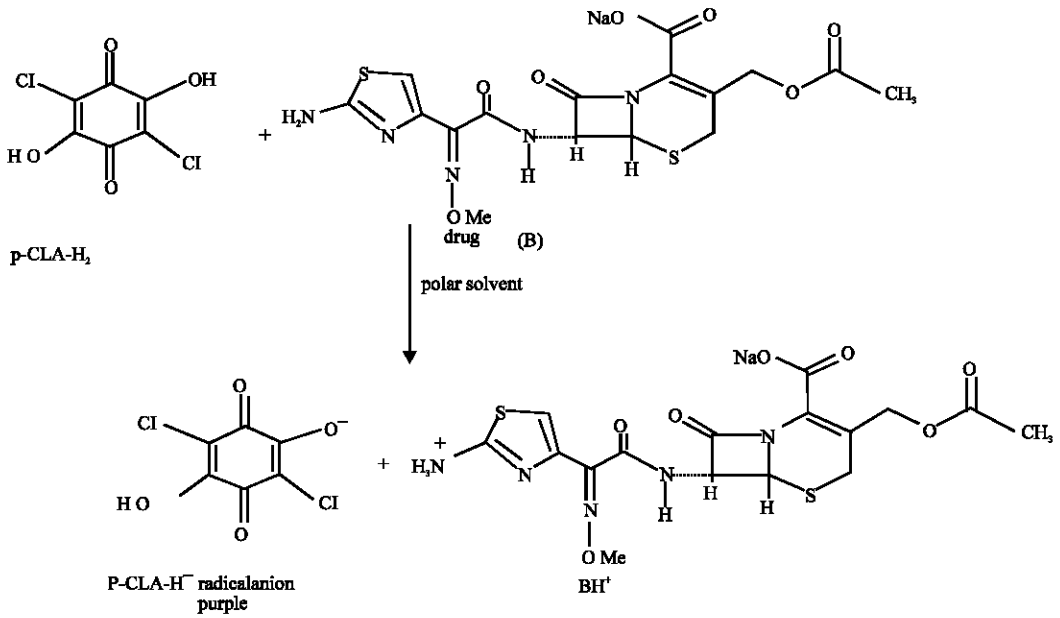
DDQ-CTX complex

Scheme 5: Structure of CTX-DDQ CT complex.

the concentration range from 5-300, 0.5-35, 1-500 and 0.2-15 μg mL^{-1} of CTX using DDQ, TCNQ, p-CLA and I_2 reagents, respectively.

The high correlation coefficients and low values of the relative standard deviations indicate the high accuracy and precision of the method.

Between-day determination of CTX: In order to prove the validity and applicability of the proposed method and reproducibility of the results obtained, four replicate experiments at four concentrations of CTX are carried out. Table 2 shows the values of the between-day relative standard deviations for different concentrations of the



Scheme 6: Structure of CTX-p-CLA CT complex

Table 1: Spectral characteristics of CTX-DDQ, CTX-TCNQ, CTX-P-CLA and CTX-I_2 coloured reaction products and the analytical characteristics (accuracy and precision) of these reactions

Drugs parameters	DDQ	TCNQ	p-CLA	I_2
λ_{max} (nm)	450	842	510	360
[Drug] (μg mL^{-1})	5-300	0.5-35	1-500	0.2-15
ε (L mol cm)	5.06×103	7.4×103	2.7×103	3.3×105
S (μg cm^{-2})	0.4139	0.283	0.776	0.006347
A = mC + z,				
m	0.517	2.02	0.26	1.109
z	0.222	0.066	0.214	0.116
r^2	0.999	0.999	0.996	0.997
%Recovery	98.66-101.4	98.60-102.0	99.43-102.0	99.00-101.8
LOD (μg mL^{-1})	0.0189	0.0052	0.0402	0.009
LOQ (μg mL^{-1})	0.0631	0.0173	0.1341	0.0315
SD	0.017-0.013	0.009-0.01	0.009-0.026	0.001-0.008
RSD (%)	1.14-1.86	1.51-1.97	0.759-1.91	1.31-1.633

*A = Z+ mC, where C is the concentration in μg mL^{-1}

Table 2: Between-day precision of the determination of CTX using DDQ reagent

Compound	Drug, taken (μg mL^{-1})	Drug, found (μg mL^{-1})	Percentage recovery (%)	SD*	RSD*
CTX- DDQ	10.00	10.10	101.00	0.006	0.250
	70.00	71.00	101.40	0.010	1.720
	100.00	99.00	99.00	0.011	1.500
	250.00	254.00	101.60	0.014	0.960
CTX-TCNQ	2.50	2.54	101.60	0.002	1.140
	5.00	4.90	98.00	0.002	0.906
	25.00	25.50	102.00	0.004	0.395
	35.00	34.50	98.60	0.002	0.171
CTX-p-CLA	30.00	30.00	100.00	0.002	0.586
	100.00	99.00	99.00	1.108	1.116
	250.00	255.00	102.00	0.004	0.420
	400.00	400.00	100.00	0.003	0.235
CTX-I_2	2.00	2.00	100.00	0.003	0.880
	5.00	4.98	99.60	0.009	1.260
	9.00	8.90	98.88	0.005	0.453
	15.0	15.00	100.00	0.010	0.590

*The average of four replicates

drugs, obtained from experiments carried out over a period of four days. It is found that, the within day relative standard deviations are less than 1% which indicates that the proposed method is highly reproducible and DDQ, TCNQ, p-CLA and I_2 reagents are successfully applied to determine CTX via the charge transfer reaction.

Spectrophotometric determination of CTX in pharmaceutical preparations: The spectrophotometric microdetermination of CTX via its reactions with DDQ, TCNQ, p-CLA and I_2 (strong electron acceptors) reagents are carried out. The results obtained are given in Table 3. These data show that, the determined concentrations of CTX by the proposed methods are closed to that calculated from the applied standard method (The United States Pharmacopeia, 2006). In order to check the confidence and correlation between the suggested spectrophotometric procedures and the official spectrophotometric determination using paramolybdate anion method (Issopoulos, 1989) for determination of CTX, the percent recovery for all the results are calculated. The percentage recovery values obtained by the proposed methods are higher than or close to those obtained by the official method. In addition, the SD values obtained by the proposed methods are lower than those obtained by the official method. The results obtained are given in Table 3. The small values of SD and RSD indicate the reliability, accuracy and precision of the suggested procedures.

Table 3: Spectrophotometric determination of CTX drug in different pharmaceutical preparations using DDQ, TCNQ, p-CLA and I_2 by proposed methods compared with that by the official method

Samples	Drug taken (g mL^{-1})	Drug found (g mL^{-1})	Percentage recovery (%)	SD	RSD (%)
Using DDQ					
Cefotax	50.00	51.00	102.00	0.008	0.008
	200.00	203.00	101.50	0.009	0.009
Ceforan	50.00	50.50	101.00	0.008	0.008
	200.00	204.00	102.00	0.012	0.012
Claforan	50.00	50.90	101.80	0.010	0.010
	200.00	202.00	101.00	0.015	0.015
Using TCNQ					
Cefotax	5.00	5.10	102.00	0.005	0.005
	25.00	25.20	100.80	0.013	0.013
Ceforan	5.00	5.40	101.00	0.005	0.005
	25.00	25.40	101.60	0.018	0.018
Claforan	5.00	5.40	101.00	0.005	0.005
	25.00	25.40	101.60	0.018	0.018
Using p-CLA					
Cefotax	100.00	100.90	100.90	0.008	0.008
	300.00	295.00	98.30	0.014	0.014
Ceforan	100.00	99.80	99.80	0.005	0.005
	300.00	296.00	98.67	0.011	0.011
Claforan	100.00	100.50	100.50	0.009	0.009
	300.00	294.00	98.00	0.011	0.011
Using I_2					
Cefotax	5.00	4.90	98.00	0.010	0.010
	9.00	9.10	101.10	0.007	0.007
Ceforan	5.00	5.10	102.00	0.007	0.007
	9.00	8.90	98.88	0.007	0.007
Claforan	5.00	5.00	100.00	0.009	0.009
	9.00	9.00	100.00	0.006	0.006
Using Official method					
Cefotax	200.00	200.40	100.20	5.800	5.800
	300.00	299.90	99.99	6.900	6.900
Ceforan	200.00	200.20	100.10	6.600	6.600
	300.00	299.90	99.99	4.300	4.300
Claforan	200.00	200.00	100.00	3.700	3.700
	300.00	300.00	100.00	8.700	8.700

Cefotax T3A (1g) injection was supplied from T3A industrial, Ceforan (1 g) injection was supplied from Pharco B International Co. and Claforan (0.5 g) injection was supplied from Sanofi Aventis

CONCLUSION

This study demonstrated that CT complexes can be utilized as useful reagents for the spectrophotometric determination of CTX under investigation. Rapid formation of stable CT complexes and no need for extraction or separation processes are advantages of the suggested method over the previously reported spectrophotometric methods. The proposed spectrophotometric methods are simpler, time saving and they involve very simple procedures, that can be applied in routine analysis.

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