ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
18 (1999) 975–983

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

Spectrophotometric and atomic absorption spectrometric determination of certain cephalosporins

Magda M. Ayad, Abdalla A. Shalaby, Hisham E. Abdellatef *, Heba M. Elsaid

Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

Received 30 December 1997; received in revised form 16 March 1998; accepted 26 March 1998

Abstract

Two sensitive spectrophotometric and atomic absorption spectrometric procedures are developed for the determination of certain cephalosporins (cefotaxime sodium and cefuroxime sodium). The spectrophotometric methods are based on the charge-transfer complex formation between these drugs as n-donors and 7,7,8,8-tetracyanoquinodimethane (TCNQ) or *p*-chloranilic acid (p-CA) as π-acceptors to give highly coloured complex species. The coloured products are measured spectrophotometrically at 838 and 529 nm for TCNQ and p-CA, respectively. Beer's law is obeyed in a concentration range of 7.6–15.2 and 7.1–20.0 μg ml^{-1} with TCNQ, 95.0-427.5 and 89.0-400.5 μg ml^{-1} with *p*-CA for cefotaxime sodium and cefuroxime sodium, respectively. The atomic absorption spectrometric methods are based on the reaction of the above cited drugs after their alkali-hydrolysis with silver nitrate or lead acetate in neutral aqueous medium. The formed precipitates are quantitatively determined directly or indirectly through the silver or lead content of the precipitate formed or the residual unreacted metal in the filtrate by atomic absorption spectroscopy. The optimum conditions for hydrolysis and precipitation have been carefully studied. Beer's law is obeyed in a concentration range of 1.9–11.4 and 1.78–8.90 μg ml^{-1} with Ag(I), 14.2–57.0 and 13.3–53.4 μg ml^{-1} with Pb(II) for cefotaxime sodium and cefuroxime sodium, respectively (for both direct and indirect procedures). The spectrophotometric and the atomic absorption spectrometric procedures hold well their accuracy and precision when applied to the analysis of cefotaxime sodium and cefuroxime sodium dosage forms. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Cephalosporins; n-Donors; π-Acceptors; Charge transfer

1. Introduction

Cephalosporins are penicillinase-resistant antibiotics with significant activity against both gram-positive and gram-negative bacteria. The key intermediate for semi-synthetic production of a large number of cephalosporins is 7-aminocephalosporanic acid, which is formed by hydrolysis of cephalosporin C produced by fermentation [1].

Several procedures have been reported in the literature for the analysis of cephalosporins. These methods are spectrophotometry [1–4], high performance liquid chromatography [5,6], capillary

* Corresponding author.

0731-7085/99/$ - see front matter © 1999 Elsevier Science B.V. All rights reserved.
PII S0731-7085(98)00106-X

electrophoresis [7] fluorometry [8], polarography [9] and titrimetry [10] The USPXXIII [11] and the European Pharmacopoeia [12] specifies high performance liquid chromatography for the determination of cefotaxime sodium and cefuroxime sodium.

π-Acceptors such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), 7,7,8,8-tetracyanoquinodimethane (TCNQ), tetracyano-ethylene (TCNE), 2,4,7-trinitrofluoren-9-one (TNF) and 2,3,5,6-tetrachloro-*p*-benzoquinone (*p*-chloranil) are known to yield charge-transfer complexes and radical ions with a variety of electron donors such as amines [13–15], vitamin A [16], alkaloids [17], procaine [18], some drugs containing imidazoline ring [19], antihistamines [20], pentazocine [21], some sulpha drugs [22], some penicillins [23], some cephalosporins [24] and norfloxacin [25].

On the other hand, metal ions are widely used as precipitating agents for analysis of many pharmaceutical compounds [26–28].

The purpose of the present work is to describe the development of two simple and accurate spectrophotometric and atomic absorption spectrometric methods for the analysis of two cephalosporin derivatives.

2. Experimental

2.1. Apparatus

Shimadzu 260 UV recording spectrophotometer.

Shimadzu atomic absorption flame spectrophotometer, model AA-460-13.

Chemocadet pH-meter.

2.2. Materials and reagents

All the reagents were of analytical grade. Double distilled water was used.

1. Cefotaxime sodium, Hoechst orient Egypt, Cairo, under the licence from Hoechst AG Frankfurt (Main) Germany.
2. Cefuroxime sodium, Glaxo Egypt, SAE Cairo, under the licence from Glaxo Group, England.
3. Stock solutions of 2×1^{-3} M methanolic solution of cefotaxime sodium and cefuroxime sodium (solution A, for spectrophotometric procedures), 2×10^{-3} M aqueous solution of cefotaxime sodium and cefuroxime sodium (solution B, for atomic absorption procedure using Ag(I)), 2×10^{-3} M aqueous solution of cefotaxime sodium and cefuroxime sodium (solution C, for atomic absorption procedure using Pb (II)).

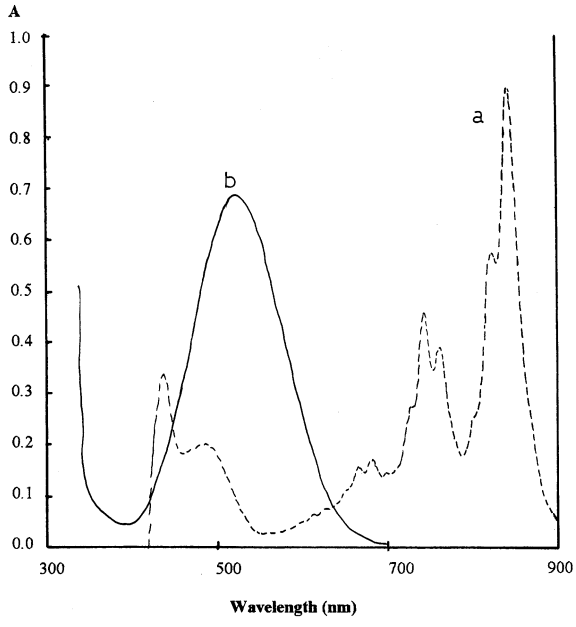


Fig. 1. Absorption spectra of: (a) cefotaxime sodium–TCNQ complex (20 μg ml^{-1}), (b) cefotaxime sodium–*p*-CA complex (330 μg ml^{-1}).

Table 1
Effect of solvent on the absorption intensity of reaction product of cefuroxime sodium with TCNQ and *p*-CA

Solvent	TCNQ[a] (at λ_{max} 838 nm)	*p*-CA[a] (at λ_{max} 529 nm)
Acetone	0.675	0.422
Acetonitrile	0.620	0.360
Methanol	0.274	0.320
Ethanol	0.030	0.226
Methylene chloride	0.600	0.358
Chloroform	—	0.353

[a] Final cefuroxime concentration 20, 180 μg ml^{-1} using TCNQ and *p*-CA, respectively.

Table 2
Parameters for the spectrophotometric determinations of cefotaxime sodium and cefuroxime sodium

Parameters	Cefotaxime sodium		Cefuroxime sodium	
	TCNQ	*p*-CA	TCNQ	*p*-CA
Beer's law limits (μg ml^{-1})	7.6–15.2	95.0–427.5	7.1–20.0	89.0–400.5
Molar absorptivity (mol^{-1} cm^{-1})	2.08×10^4	0.99×10^3.	1.82×10^4	1.03×10^3
Regression equation:				
Slope (*b*)	−0.01361	0.01255	−0.0880	0.00758
Intercept (*a*)	0.04365	0.00208	0.03814	0.0023
Correlation coefficient (*r*)	0.9991	0.9999	0.9998	0.9998
Relative standard deviation (%)	0.98	0.21	1.09	0.39
Range of error (%)	±0.44	±1.39	±0.42	±0.45

$A = a + b\ C$.
a = intercept.
b = slope.
C = concentration in μg ml^{-1}.

4. Silver nitrate, 2×10^{-3} M solution (0.034% w/v).
5. Lead acetate, 6×10^{-3} M solution (0.195% w/v).
6. TCNQ, 2×10^{-3} M solution in acetonitrile.
7. *p*-CA, 4×10^{-3} M solution in acetonitrile.
8. Acetic acid (96% BP), 10% v/v solution.
9. N hydrochloric acid solution.
10. Ammonium hydroxide (99.9%), 10% v/v solution.
11. 0.1 M sodium hydroxide solution.

2.3. Formulations

The following commercial formulations were subjected to the analytical procedures: Claforan® vials (Hoechst orient Egypt, Cairo) containing 524 mg cefotaxime sodium equivalent to 500 mg cefotaxime per vial, Zinnat® vials (Glaxo SAE, Egypt, Cairo) containing cefuroxime sodium equivalent to 250 mg cefuroxime per vial.

2.4. General procedures

2.4.1. Spectrophotometric procedures

2.4.1.1. Using TCNQ. To different aliquots of stock solution (solution A, equivalent to 0.076–0.152 mg cefotaxime sodium or 0.071–0.200 mg cefuroxime sodium) 0.6 ml of TCNQ solution was added. The mixture was allowed to stand at 20–25°C for about 60–70 min. The volume was diluted to 10 ml with acetone, and the absorbance was measured at 838 nm against a reagent blank prepared in the same manner.

2.4.1.2. Using p-CA. To different aliquots of stock solution (solution A, equivalent to 0.950–4.275 mg cefotaxime sodium or 0.890–4.005 mg cefuroxime sodium) 2 ml *p*-CA solution was added. The volume was diluted to 10 ml with acetone and the absorbance was measured at 529 nm against a reagent blank prepared in the same manner.

2.4.2. Atomic absorption spectrometric procedures

2.4.2.1. Using Ag(I). To different aliquots of stock solution (solution B, equivalent to 0.19–1.14 mg of cefotaxime sodium or 0.178–0.890 mg cefuroxime sodium), 1 ml of 0.1 M NaOH solution was added. The solution was heated at 95°C in water bath for 25 min. The solution was cooled and neutralized with 10% acetic acid solution (pH, 7 using the pH-meter). A double volume of silver nitrate was added and the mixture was protected from light. The mixture was shaken and filtered through Whatman No 44 filter paper (9 cm in

diameter). The precipitate was washed with bidistilled water until silver free.

(a) Direct method: The precipitate obtained above was dissolved in the least amount of dilute ammonia solution and completed to 100-ml with bidistilled water.

(b) Indirect method: The filtrate and washings were collected in 100-ml volumetric flask and completed to volume bidistilled water.

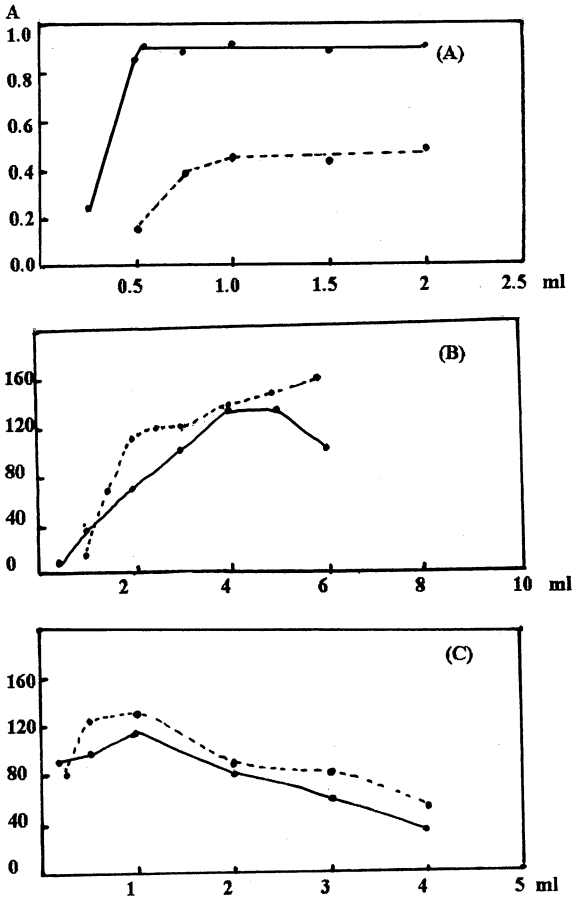


Fig. 2. Effect of the volume of : (A) TCNQ (2×10^{-3} M) on the absorbance of 20 μg ml^{-1} cefotaxime sodium (—) and *p*-CA (4×10^{-3} M) on the absorbance of 200 μg ml^{-1} cefotaxime sodium (---) Section 2.4.1. (B) Pb(II) (6×10^{-3} M) on the absorbance of 53.4 μg ml^{-1} cefuroxime sodium (—) and Ag(1) (2×10^{-3} M) on the absorbance of 9.1 μg ml^{-1} cefotaxime sodium (---) Section 2.4.2. (C) 0.1 M NaOH on the absorbance of 9.1 μg ml^{-1} cefotaxime sodium (—) and 1 M NaOH on the absorbance of 53.4 μg ml^{-1} cefuroxime sodium (---) Section 2.4.2.

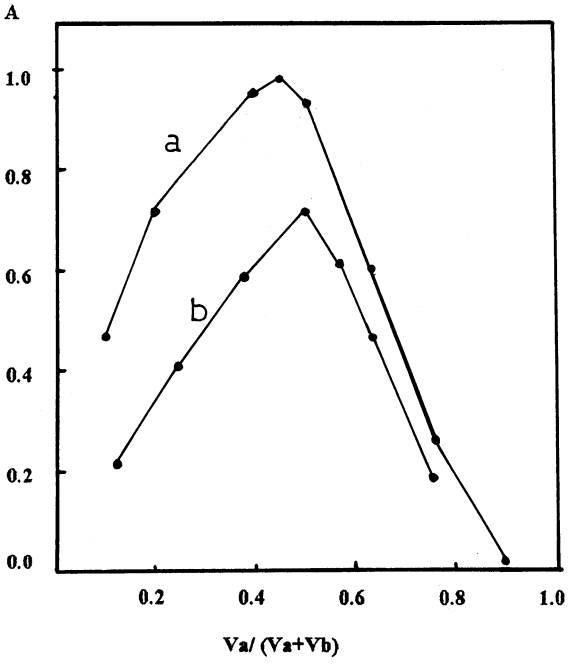
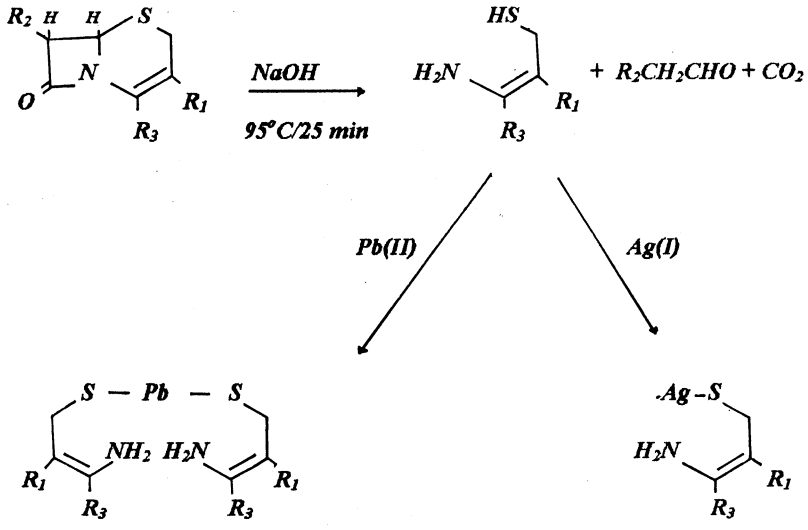


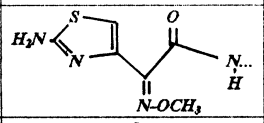
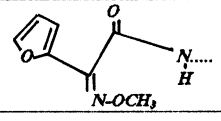
Fig. 3. Continuous variation plot of (a) cefuroxime sodium (2×10^{-3} M) with TCNQ (2×10^{-3} M) and (b) cefuroxime sodium (4×10^{-3} M) with *p*-CA (4×10^{-3} M).

A blank (omitting the addition of the drug) was performed and absorbance was measured at the following conditions; wavelength 2833 Å, lamp current 7 mA, slit width 3.8 Å, air pressure 10 l min^{-1} and acetylene pressure 2.6 l min^{-1}.

The concentration of the consumed and the residual silver were calculated from the calibration graph of standard $AgNO_3$ solution.

2.4.2.2. Using Pb(II). To different aliquots of stock solution (solution C, equivalent to 1.42–5.70 mg of cefotaxime sodium or 1.33–5.34 mg cefuroxime sodium), 1 ml of 1 M sodium hydroxide was added. The solution was heated at 95°C in water bath for 25 min. The solution was cooled and neutralized with 10% acetic acid solution (pH, 7 using the pH meter). A double volume of lead acetate was added. The mixture was shaken and filtered through Whatman No 44 filter paper (9 cm in diameter). The precipi-



	R1	R2	R3
Cefotaxime sodium	-CH_2-O-$COCH_3$		-COONa
Cefuroxime sodium	-CH_2-O-$CONH_2$		-COONa

Scheme 1.

tate was washed with bidistilled water until lead free.

(a) Direct method: The precipitate obtained above was dissolved in the least amount of dilute HCl solution and completed to 100-ml with bidistilled water.

(b) Indirect method: The filtrate and washings were collected in 100-ml volumetric flask and completed to volume with bidistilled water.

A blank (omitting the addition of the drug) was performed and absorbance was measured at the following conditions, wavelength 3281 Å, lamp current 7 mA, slit width 3.8 Å, air pressure 10 l min^{-1} and acetylene pressure 2.6 l min^{-1}.

The concentration of the consumed and the residual lead were calculated from calibration graph of standard lead acetate solution.

2.4.3. Procedure for pharmaceutical formulations

For spectrophotometric method, the procedure described in Section 2.4.1 was followed using solution of claforan vial (0.95 mg ml^{-1} cefotaxime sodium) or Zinnat vial (0.89 mg ml^{-1} cefuroxime sodium) in methanol. For atomic absorption spectrometric method, the procedure given in Section 2.4.2 was adopted using solution of claforan vial (0.95 and 2.85 mg ml^{-1} cefotaxime sodium for procedure using Ag(I) and Pb(II), respectively) or zinnat vial (0.89 and 2.67 mg ml^{-1} cefuroxime sodium for procedure using Ag(I) and Pb(II), respectively) in bidistilled water.

Table 3
Parameters for the atomic absorption spectrometric determination of cefotaxime sodium and cefuroxime sodium

Parameters	Cefotaxime sodium				Cefuroxime sodium			
	Using Ag(I)		Using Pb(II)		Using Ag(I)		Using Pb(II)	
	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect
Beer's law limits (μg ml^{-1})	1.9–11.4		14.2–57.0		1.78–8.90		13.3–53.4	
Molar absorptivity (mol cm^{-1})	5.75×10^6	5.78×10^6	1.26×10^6	5.02×10^6	6.29×10^6	6.25×10^6	1.09×10^6	4.61×10^6
Regression equation:								
Slope (a)	0.3373	0.3591	0.3088	0.4210	0.8169	0.8002	0.4804	−0.3970
Intercept (b)	12.0481	12.1321	2.6455	10.5210	14.0845	13.9981	2.4340	10.330
Correlation coefficient (r)	0.9979	0.9996	0.9989	0.9992	0.9994	0.9979	0.9994	0.9979
Relative standard deviation (%)	0.99	1.19	0.97	1.16	0.53	0.45	1.02	1.16
Range of error (%)	±0.36	±0.52	±0.84	±0.55	±0.19	±0.73	±0.29	±0.66

$A = a + b\ C$
a = Intercept.
b = Slope.
C = Concentration in μg ml−1.

3. Results and discussion

3.1. Spectrophotometric methods

The reaction of cefotaxime sodium and cefuroxime sodium with TCNQ results in the formation of an intense blue colour, causing characteristic long wavelength absorption bands, frequently with numerous vibrational maxima in the electronic spectrum (Fig. 1). The predominant with TCNQ is the blue radical anion $TCNQ^-$, which was probably formed by the dissociation of an original donor–acceptor (DA) complex with cefotaxime sodium and cefuroxime sodium.

$$D^{\cdot\cdot} + A \rightarrow \left(\underset{DA\ complex}{D:} - A \right) \overset{Polar\ solvent}{\rightarrow} \underset{Radical}{A^{-\cdot}} + \underset{ions}{D^{+\cdot}}$$

In addition to TCNQ radical anion, the reaction of cefotaxime sodium and cefuroxime sodium with p-CA results in the formation of intense pink colour with maximum absorption at 529 nm (Fig. 1).

Concerning the effect of solvent; different solvents such as acetone, methanol, ethanol, methylene chloride, acetonitrile and chloroform were examined. Acetone afforded the maximum sensitivity when compared with all other solvents (Table 1). However, acetone has poor solvent power for TCNQ reagent and also, for cefotaxime sodium and cefuroxime sodium. So, TCNQ and p-CA were prepared in acetonitrile and the cephalosporins in methanol and acetone added-only-for dilution after mixing the contents of the reaction.

The relative sensitivities of the two acceptors can be determined by comparing the molar absorpitivities (ε) of the chromogens (Table 2).

When various concentrations of TCNQ or p-CA were added to a fixed concentration of cefotaxime sodium and cefuroxime sodium, 0.6 ml of 2×10^{-3} M solution of TCNQ and 1 ml of 4×10^{-3} M solution of p-CA were found to be sufficient for the production of maximum and reproducible colour intensity. Higher concentrations of reagent did not affect the colour intensity (Fig. 2A).

The optimum reaction time was determined by following the colour development at ambient temperature (20–25°C). The time required for the reaction used cepalosporins with p-CA to give maximum absorbance was not specified as the colour was produced immediately upon mixing the contents of the reaction. However, the reaction with TCNQ required 60–70 min.

Table 4
Assay of cefotaxime sodium in Claforan vials by spectrophotometric, atomic absorption and official [11] methods

Statistic	Official method [11]	Spectrophotometric method		Atomic absorption method			
		TCNQ	*p*-CA	Ag (I)		Pb (II)	
				Direct	Indirect	Direct	Indirect
Mean recovery	99.07	100.92	99.99	100.52	98.91	99.89	98.73
± SD	0.821	1.153	0.562	1.038	1.031	0.913	0.923
N	4	7	7	6	6	6	6
Variance	0.674	1.329	0.316	1.077	1.063	0.834	0.852
t-Test		1.23 (2.26)	0.81 (2.26)	1.93 (2.31)	2.11 (2.31)	1.55 (2.31)	1.98 (2.31)
F-test		1.97 (8.94)	2.13 (8.94)	1.60 (9.01)	1.58 (9.01)	1.24 (9.01)‘	1.26 (9.01)

Values in parenthesis are the tabulated values of t and F at $p = 0.05$.
N is the number of experiments where each result is the average of triplicate measurements.

Job's continuous variation graph for the reaction between cefotaxime sodium or cefuroxime sodium and TCNQ or *p*-CA (Fig. 3) shows that the interaction between these two compounds occurs on an equimolar basis (1:1)

3.2. Atomic absorption spectrometric methods

The neutral solutions of the hydrolysis products of cefotaxime sodium and cefuroxime sodium were found to give brown precipitate with both lead acetate and silver nitrate. These precipitates are the basis for the micro-quantitative determination of the cited drugs. The reaction product can be represented by the following structure [29] Scheme 1

Concerning the effect of pH on precipitation buffer solutions covering the acid to the alkaline range have been tried. Acid media have a solubilizing effect on the precipitate leading to lower results for the direct technique and higher ones for the indirect technique while alkali media precipitate the metal as its oxide or hydroxide leading to higher results for the direct technique. The optimum pH was found to be neutral.

For the complete precipitation of the hydrolysis product of cephalosporins double amount of lead acetate or silver nitrate must be added. Excessive reagents must be avoided. (Fig. 2B).

The effect of different factors on the hydrolysis of cephalosporins was studied and optimized. Heating for about 25 min at 95°C gives the maximum absorbance after the addition of metal ions. Several trials have been made to stabiles the normality and the volume of NaOH used in hydrolysis step for both procedures using Ag(I) and Pb(II). It was found that 1 ml 0.1 M NaOH solution sufficient for complete hydrolysis of the two cited drugs for the procedure using Ag(I) (Fig. 2C),but this concentration was not enough for the procedure using Pb(II) which may be referred to the high concentrations of drugs used in this procedure, Table 3, (at least 5 times more than that used in the procedure using Ag(I)). Maximum absorbance was obtained when 1 ml of 1 M NaOH was used (Fig. 2C).

Concerning the stoichiometric relationships, the molar ratio method indicated a molar ratio 1:1 and 2:1 cephalosporins to silver ion and lead ion, respectively. According to this ratio it was found that:

2.16 mg Ag^+ = 8.93 mg Cefuroxime sodium
= 9.56 mg Cefotaxime sodium

1.24 mg Pb^{2+} = 5.34 mg Cefuroxime sodium
= 5.71 mg Cefotaxime sodium

Table 5
Assay of cefuroxime sodium in Zinnat vials by spectrophotometric, atomic absorption and official methods [11]

Statistic	Official method [11]	Spectrophotometric method		Atomic absorption method			
		TCNQ	*p*-CA	Ag(I)		Pb(II)	
				Direct	Indirect	Direct	Indirect
Mean recovery	101.02	101.25	100.16	100.67	101.01	100.28	101.36
± SD	1.021	1.262	0.525	1.114	1.150	0.694	0.733
N	4	7	7	6	6	6	6
Variance	1.042	1.593	0.276	1.241	1.323	0.482	0.537
t-Test		1.04 (2.26)	1.57 (2.26)	2.01 (2.31)	0.84 (2.31)	0.12 (2.31)	1.58 (2.31)
F-test		1.53 (8.94)	3.78 (8.94)	0.84 (9.01)	1.27 (9.01)	2.16 (9.01)	1.94 (9.01)

Values in parenthesis are the tabulated values of t and F at $p = 0.05$.
N is the number of experiments where each result is the average of triplicate measurements.

3.3. Quantification, accuracy and precision

A linear correlation was found between absorbance and concentration in the ranges given in Tables 2 and 3.The correlation coefficients, intercepts and slopes for the calibration data for the two cited drugs are calculated using the last-squares method.

The precision and accuracy of the two methods were tested by estimating six replicates of the two cited drugs within the Beer's law limits.The percentage standard deviation and the percentage range of error at 95% confidence level are given in Tables 2 and 3.

The utility of each method was verified by means of replicate measurements of pharmaceutical formulations and recovery experiments. Recoveries were determined by adding standard drug to the pre-analyzed mixture of pharmaceutical preparations. The results of the recovery experiments by the proposed methods are listed in Tables 4 and 5.

The performance of the methods was assessed by calculation of the t-and F-values compared with the official methods [11] The results showed that the calculated t- and F-values did not exceed the theoretical values (95% confidence limits for five degree of freedom) Tables 4 and 5. From which we can conclude that the proposed methods do not differ significantly from official methods [11].

3.4. Conclusion

The proposed methods are advantageous when compared to many of the reported spectrophotometric and titrimetric methods in having higher sensitivity. The data given above reveal that the proposed methods are simple,accurate and sensitive (atomic absorption spectrometric method > spectrophotometric method) with good precision and accuracy. With these methods, one can do the analysis at low coast without losing accuracy. They must be considered non specific regard to differentiation between them or between them and many of other electron donors compounds (for the spectrophotometric method), or any compounds that containing free thiol and form precipitate with silver or lead ions (for the atomic absorption spectrometric method). These shortcomings do not affect the utility of the methods in routine analysis and content uniformity determination of these drugs as they are singly prescribed. Also, the nonspecificity of the methods due to the presence of degradation products and related substances containing free thiol could generally be overcome by prior chromatographic separation [30]. The proposed methods can be used as alternative methods to the reported ones for the routine determination of cefotaxime sodium and cefuroxime sodium in the pure form and in pharma-

ceutical formulations depending upon the availability of chemicals and the equipment.

References

[1] B. Morelli, P. Peluso, Anal. Lett. 18 (1985) 1113–1129.
[2] M.A. Korany, M.A. El-Sayed, S.M. Galal, Anal. Lett. 22 (1989) 159–175.
[3] P.B. Issopoulos, J. Pharm. Biomed. Anal. 7 (1989) 619–625.
[4] P.B. Issopoulos, Analyst 113 (1988) 1083–1086.
[5] S.C. Zarapkar, S.A. Shivalkar, A.A. Dhanvate, P.M. Deshpande, Indian Drugs 33 (1995) 232–235.
[6] M.J. Loudhl, K.E. Reher, H.Q. Russlie, D.M. Canafax, J. Chromatogr. B, Biomed. Appl. 653 (1994) 227–232.
[7] P.G. Castaneda, E. Julien, H. Fabre, J. Chromatogr. 42 (1996) 159–164.
[8] J.A. Murillo, J.M. Lemus, L.F. Garcia, J. Pharm. Biomed. Anal. 12 (1994) 875–881.
[9] F.I. Sengun, K. Ulas, I. Fedai, J. Pharm. Biomed. Anal. 3 (1985) 191–199.
[10] A.G. Fogg, M.A. Abdalla, H.P. Honriques, Analyst 107 (1982) 449.
[11] United States Pharmacopeia XXIII, NF, US Pharmcopeial Convention, Rockville, MD, 1995, p. 299, 315.
[12] European Pharmacopeia, 3rd edition, Council of Europe, Strasbourg, 1997, p. 564, 571.
[13] L.R. Melby, in: S. Patai (Ed.), In the Chemistry of the Cyano Group, Interscience, New York, 1970, pp. 639–670.
[14] R. Foster, Organic Charge-Transfer Complexes, Academic Press, London, 1969.
[15] C.N.R. Rao, S.N. Bhat, P.C. Dwivedi, in: E.G. Brame (Ed.), Applied Spectroscopy Reviews, 5, Marcel Dekker, New York, 1972, pp. 1–170.
[16] F.U. Lichti, A.J. Lucy, Biochem. J. 112 (1969) 221.
[17] A. Taha, G. Rucker, Arch. Pharm. 310 (1977) 485.
[18] K.A. Kovar, W. Mayer, H. Auterhoff, Arch. Pharm. 314 (1981) 447.
[19] K.A. Kovar, M. Abdel-Hamid, Arch. Pharm. 317 (1984) 246.
[20] M. Abdel-Khalek, M. Abdel-Hamid, M. Mahrous, J. Assoc. Off. Anal. Chem. 68 (1985) 1057.
[21] M. Abdel-Hamid, M. Mahrous, M. Abdel-Salam, J. Pharm. Belg. 40 (1985) 237.
[22] A.M. Nour El-Din, Arch. Pharm. 319 (1986) 143.
[23] F.A. Hassan, A.S. Gamal, M.O. Nabil, Analyst 116 (1991) 387–390.
[24] S.A. Alaa, O.E. Gamal, M.I. Yousery, Analyst 120 (1995) 1189–1193.
[25] M. Ayad, L. Abd El Aziz, A. Abou El Khair, Anal. Lett. 16 (1983) 1335–1342.
[26] S. Belal, A. Abou El Kheir, A. El-Shanawani, Anal. Lett. 18 (1985) 617–628.
[27] M.E. Mohamed, H.Y. Aboul-Enein, E.A. Gad-Kariem, Anal. Lett. 16 (1983) 45.
[28] S.M. Galal, S.M. Blaih, M.E. Abdel-Hamid, Anal. Lett. 25 (1992) 725.
[29] M.I. Walash, M. Rizk, S.S. Toubar, S.M. Ahmed, N.A. Zakhari, Anal. Lett. 27 (1994) 2499.
[30] M.A. Elsayed, S.P. Agarwal, Talanta 29 (1982) 535.