ELSEVIER

www.elsevier.nl/locate/farmac

Il Farmaco 55 (2000) 680–686

IL FARMACO

Kinetic spectrophotometric determination of ampicillin and amoxicillin in dosage forms

F. Belal *, M.M. El-Kerdawy, S.M. El-Ashry, D.R. El-Wasseef

Department of Medicinal and Analytical Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt

Received 8 May 2000; accepted 31 July 2000

Abstract

A kinetic spectrophotometric method has been developed for the determination of ampicillin (I) and amoxicillin (II). The method involves hydrolysis of the antibiotics with 1.0 M HCl, neutralization with 1.0 M NaOH followed by addition of palladium(II) chloride in the presence of 2 M KCl. The produced yellow colour is measured at 335 nm. The proposed method is valid over the concentration range 8–40 μg/ml and 10–40 μg/ml for I and II respectively with minimum detectability of 0.73 μg/ml and 0.76 μg/ml for I and II respectively. The determination of the studied compounds adopting the fixed concentration method is feasible with the calibration equations obtained, but the fixed time method has been found to be more applicable. The proposed method was applied to commercial dosage forms and the results obtained were in good agreement with those given by USP method.

Keywords: Ampicillin; Amoxicillin; Kinetic determination; Dosage forms; Pharmaceutical analysis

1. Introduction

Ampicillin (I) is a semisynthetic broad spectrum penicillin active against Gram-positive organisms that are susceptible to other penicillins, and it is more active against some Gram-negative bacteria and enterococcal infections than other penicillins [1]. Amoxicillin (II) is the *p*-hydroxy analogue of ampicillin, its antibacterial spectrum is identical to that of ampicillin, but it possesses some significant advantages over ampicillin, including more complete gastrointestinal absorption, and little or no effect on absorption of food.

The literature reported several analytical procedures for the determination of amoxicillin and ampicillin in pure form or in pharmaceutical formulations as well as in biological fluids. Thus, the methods reported for amoxicillin included spectrophotometric [2–8], polarographic [9,10], fluorimetric [11,12], flow injection analysis [13,14] and HPLC methods [15–18]. Ampicillin, on the other hand, was assayed by spectrophotometric [7,19–21], polarographic [22,23], flow injection analysis [14], and HPLC methods [24,25].

Palladium(II) chloride was used for the determination of many pharmaceutical compounds including propylthiouracil [26] and 4-quinolone antibacterials [27].

In the present work a kinetically based spectrophotometric method is proposed for the determination of I and II. The method involves first hydrolysis with 1 M HCl, neutralization with 1 M NaOH followed by reaction with palladium(II)chloride in Britton–Robinson buffer of pH 6. The produced colour is measured at 335 nm.

2. Experimental

2.1. Apparatus

All the spectrophotometric measurements were made on a Shimadzu UV 1601 PC spectrophotometer.

* Corresponding author. Present address: Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, P.O. Box 2475, Riyadh-11451, Saudi Arabia. Fax: +966-1-4676 383 and +966-1-4675 220.

E-mail address: ffbelal@ksu.edu.sa (F. Belal).

0014-827X/00/$ - see front matter
PII: S0014-827X(00)00080-X

2.2. Reagents and materials

All the reagents used were of analytical reagent grade (A.R.) and the water was always double distilled water. Ampicillin sodium was supplied by Eipico Pharmaceutical Company, Cairo, Egypt. Amoxicillin sodium was supplied by Beecham Pharmaceutica, UK. Palladium(II) chloride was purchased from Merck, Germany; 1×10^{-3} M aqueous solution was prepared. Potassium chloride was prepared as 2M aqueous solution. Britton–Robinson buffer (BRb) was 0.08 M of pH 6.0.

Standard solutions: stock solutions of I and II were prepared by dissolving 40.0 mg of drug in 100 ml distilled water, and diluting as appropriate.

2.3. Procedures

2.3.1. Construction of calibration graphs

Into a series of 10 ml measuring flasks, increasing volumes of the stock solutions of I or II were transferred over the cited concentration range. 1 ml of 1 M HCl was added, and the solution was heated on a boiling water bath for fixed time of 1 h, cooled then neutralized with 1 M NaOH. 1 ml of palladium(II) chloride solution was added, followed by 2 ml of KCl solution, completed to volume with BRb pH 6.0. The absorbance of the coloured complex was measured at 335 nm. The absorbance was plotted versus the final concentration of the drugs to obtain the calibration graphs. Alternatively the corresponding regression equations were derived.

2.3.2. Procedure for capsules

20 capsules were emptied and the contents mixed well. A quantity of the powder, equivalent to 40 mg of either I or II, was transferred into a small flask. About 80 ml of water was added and the solution shaken well, and filtered if necessary into a 100 ml volumetric flask. The flask was washed and filtered and the washings passed into the same volumetric flask and completed to the mark with the same solvent. The procedure was continued as described in Section 2.3.1. The nominal content of the capsules was determined either from the calibration graph or using the corresponding regression equation.

2.3.3. Procedure for vials

The contents of five vials were mixed. A quantity of the powder equivalent to 40 mg of the drug was transferred into 100 ml volumetric flasks. Sufficient water was added to dissolve the drug, and the solution completed to the mark with the same solvent. Aliquots were transferred into separate 10 ml volumetric flasks then the procedure was continued as in Section 2.3.1. The nominal content of the vials was determined either from the calibration graph or using the corresponding regression equation.

2.3.4. Procedure for suspensions

The contents of five bottles were mixed, then an aliquot of the powder equivalent to 40.0 mg of the drug was transferred into a small flask. This was extracted with 3×30 ml of water and filtered into a 100 ml volumetric flask. The flask was washed and filtered and the washings passed into the same volumetric flask, completed to the mark with the same solvent. The procedure was continued as described in Section 2.3.1. The nominal content of the suspension was determined either from the calibration graph or using the corresponding regression equation.

3. Results and discussion

3.1. Optimization of the reaction conditions

Penicillins are known to be hydrolysed in acidic medium to yield penicillamine and the corresponding peniloaldehyde [29] (Scheme 1). Penicillamine is reported to react with palladium(II) chloride forming a yellow complex peaking at 335 nm (Fig. 1).

As the hydrolysis of penicillins increases with time, it was deemed useful to elaborate a kinetically based method for the determination of ampicillin and amoxicillin. To realize this the reaction was investigated under various conditions of temperature, reagent concentration and acidity. The hydrolysis rate was apparently very slow at room temperature; only at 100°C was the rate increased substantially, as revealed by the intensification of the developed colour, suggesting higher analytical sensitivity. Therefore 100°C was selected as the optimum temperature. The optimum volume of palladium(II) chloride was found to be 1 ml of 1×10^{-3} M. Increasing the volume of palladium(II) chloride resulted in a decrease in absorbance. The pH of the reaction medium was adjusted at 6.0 using Britton–Robinson buffer; increasing the pH resulted in a decrease in the absorbance of the formed complex. These observations imply that the reaction between ampicillin or amoxicillin and palladium(II) chloride involves their degradation product, namely penicillamine [28]. The rate of the reaction proved to be dependent on the concentration of amoxicillin and ampicillin. The rates were followed at 100°C maintaining the amoxicillin concentration in the range of 8 to 40 μg/ml and ampicillin concentration in the range of 10 to 40 μg/ml, keeping the $[PdCl_2]$ fixed.

The graphs obtained, depicted in Fig. 2, clearly indicate that the reaction rate obeys the following equation:

$$\text{rate} = K'[\text{penicillin}]^n \quad (1)$$

where K' is the pseudo-order rate constant and n is the order of the reaction.

In Fig. 2, the composition of the formed complex was established by Job's continuous variation method [30]. The figure displayed a maximum at a mole fraction of 0.32, i.e. the ratio is 0.32:0.68 which indicates the formation of 1:2 (Pd:penicillamine).

Scheme 1 represents the proposed mechanism for the reaction between ampicillin and palladium(II) chloride after acidic hydrolysis [28].

From Fig. 3 the rate may be estimated using the variable time method measurement as $\Delta A/\Delta t$ where A is the absorbance and t is the time in seconds. Taking logarithms of rates and concentration (see Table 1) Eq. (1) is transformed into

$$\log(\text{rate}) = \log(\Delta A/\Delta t) = \log K' + n \log[\text{penicillin}] \quad (2)$$

Regression of log(rate) versus log[penicillin] by least square method yielded the calibration equation $\log(\text{rate}) = 0.406 + 0.992 \log C$ for amoxicillin with correlation coefficient $r = 0.9995$, hence $K' = 2.5\ s^{-1}$, and $\log(\text{rate}) = 0.3 + 0.993 \log C$ for ampicillin with correlation coefficient $r = 0.9980$, hence $K' = 2.00\ s^{-1}$. The reaction is first order ($n = 1$) with respect to both amoxicillin and ampicillin as shown in Fig. 4 for ampicillin as a representative example. Amoxicillin behaved similarly.

3.2. Evaluation of the kinetic methods

3.2.1. Pseudo first order method

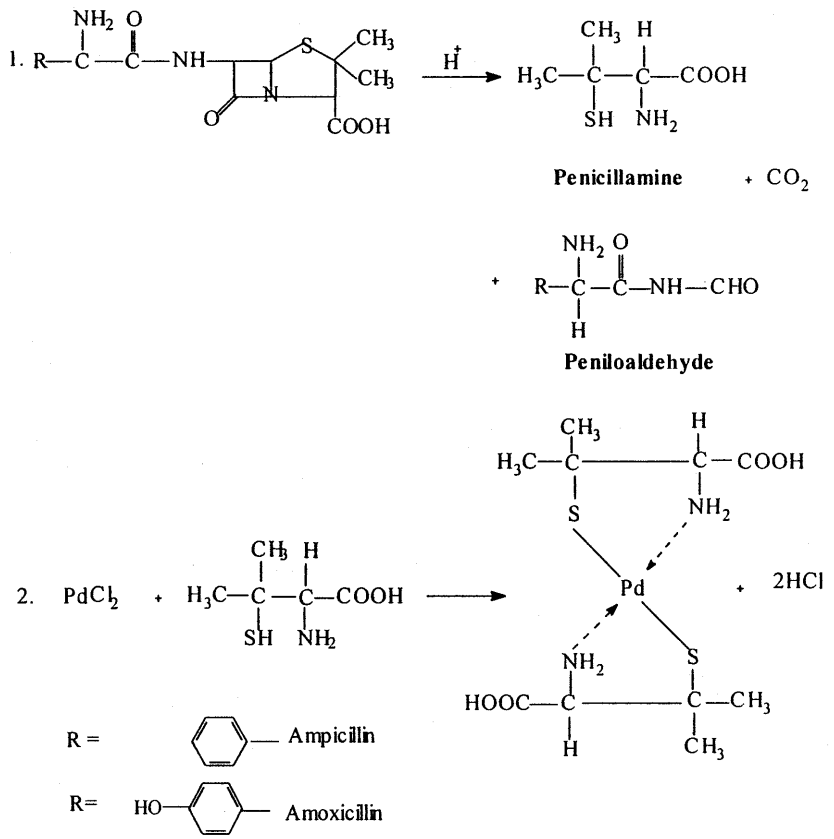
The rate will be directly proportional to the concentration of penicillins in a pseudo first order rate equation as follows:

$$\text{rate} = K'[\text{penicillin}] \quad (3)$$

where K' is the pseudo first order rate constant. Eq. (3) was the basis for several experiments which were run to obtain ampicillin or amoxicillin concentration using the rate data. Rate constant, constant concentration and fixed time methods [31,32] were tried and the most suitable analytical method was selected taking into account the applicability and sensitivity, i.e. the slope of the calibration graph, the correlation coefficient r and the intercept.

3.2.2. Rate constant method

Graphs of $\log(A)$ versus t for amoxicillin in the concentration range 5.2×10^{-5} to 1.057×10^{-4} M, and ampicillin in the concentration range 6.46×10^{-5} to 1.076×10^{-4} M were plotted and all appeared to be linear. Pseudo first order rate constants corresponding to different amoxicillin and ampicillin concentrations (C) were calculated from the slopes multiplied by -2.303 and are presented in Table 2.



Scheme 1. Proposal of the reaction pathway between the hydrolysed penicillins and palladium chloride.

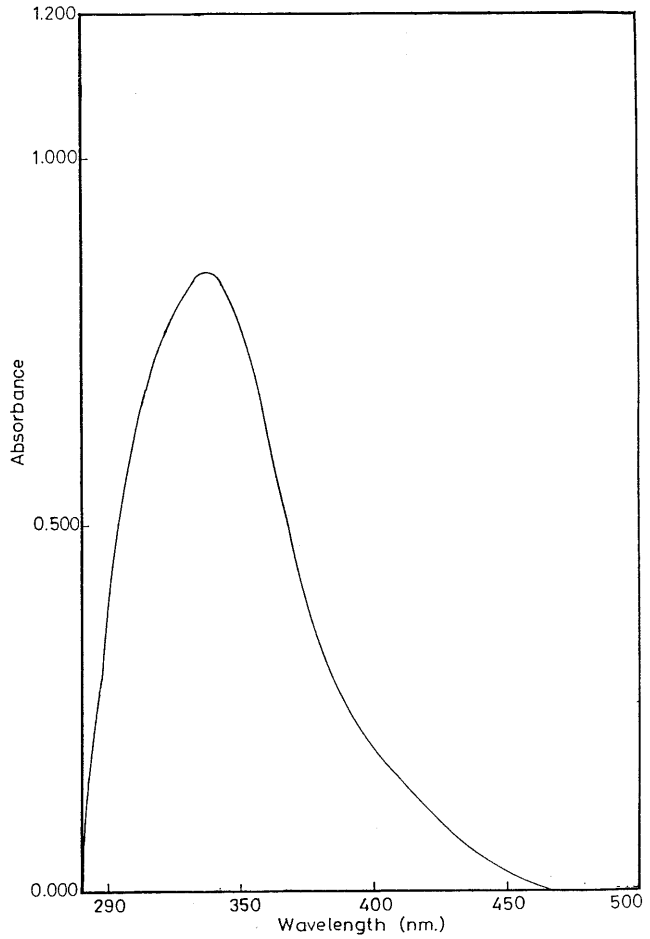


Fig. 1. Absorption spectrum of the reaction product of palladium(II) chloride with the hydrolysis product of ampicillin.

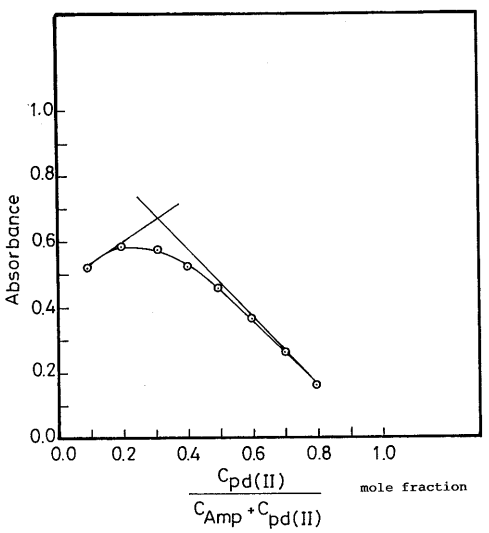


Fig. 2. Continuous variation graph for the ampicillin–$PdCl_2$ reaction product (1×10^{-3} M each).

Regression of C versus K' gave the equations: $K' = -2.723 \times 10^{-4} + 0.23C$, $r = 0.787$ for amoxicillin; $K' = -2.77 \times 10^{-4} + 1.24C$, $r = 0.746$ for ampicillin.

The values of r indicate poor linearity which is probably due to inconsistency of K' as a result of slight changes due to the elevated temperature of the reaction.

3.2.3. Fixed absorbance method

Reaction rates were determined for different amoxicillin and ampicillin concentrations in the range 5.02×10^{-5} to 1.057×10^{-4} M for amoxicillin and 6.64×10^{-5} to 1.076×10^{-4} M for ampicillin. A preselected value of absorbance was fixed and the time was measured in seconds, the reciprocal of time (i.e. $1/t$) versus the initial concentrations of amoxicillin or ampicillin (Table 3) was plotted and the following equations of the calibration graphs were worked out by the linear regression: $1/t = -4.3 \times 10^{-4} + 14.326C$, $r = 0.9957$ for amoxicillin; $1/t = -5.64 \times 10^{-4} + 13.92C$, $r = 0.9978$ for ampicillin.

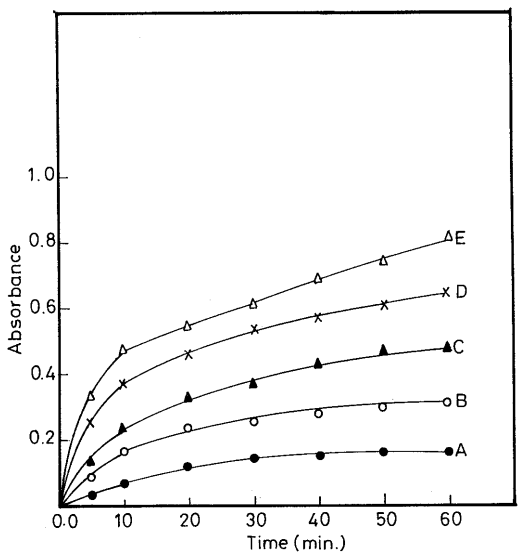


Fig. 3. Absorbance versus time graph for the reaction between Pd and the hydrolysis product of ampicillin over the range 8–40 μg/ml. A = 8 μg/ml; B = 16 μg/ml; C = 24 μg/ml; D = 32 μg/ml; E = 40 μg/ml.

Table 1
Logarithms of rates of different concentrations of amoxicillin and ampicillin at constant concentration of palladium(II) chloride of 1×10^{-3} M

Log rate ($\Delta A/\Delta t$)	Log[penicillin]
Amoxicillin	
−4.14	−4.585
−3.85	−4.277
−3.76	−4.2
−3.66	−4.1
−3.54	−3.98
Ampicillin	
−4.34	−4.666
−4.013	−4.366
−3.88	−4.189
−3.73	−4.064
−3.64	−3.968

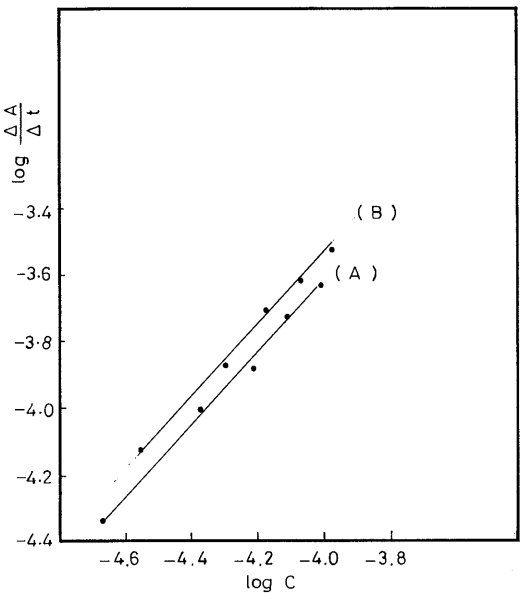


Fig. 4. Plot of log rate of the reaction for different concentrations of ampicillin (A) and amoxicillin (B) at constant concentrations of $PdCl_2$ (1×10^{-3} M).

Table 2
Values of K' calculated from slopes of log$A$ versus t graphs multiplied by -2.303 for different concentrations of penicillins and constant concentration of $PdCl_2$ of 1×10^{-3} M

K' (s^{-1})	[Penicillin]
Amoxicillin	
-2.6×10^{-4}	2.6×10^{-5}
-2.65×10^{-4}	5.2×10^{-5}
-2.64×10^{-4}	6.3×10^{-5}
-2.53×10^{-4}	7.93×10^{-5}
-2.44×10^{-4}	1.057×10^{-4}
Ampicillin	
-2.97×16^{-4}	2.5×10^{-5}
-1.79×10^{-4}	4.3×10^{-5}
-1.726×10^{-4}	6.46×10^{-5}
-1.6×10^{-4}	8.6×10^{-5}
1.727×10^{-4}	1.076×10^{-4}

The range of amoxicillin and ampicillin concentration giving the most satisfactory calibration was limited and therefore this method was abandoned.

3.2.4. Fixed-time method

Reaction rates were determined for various concentrations of amoxicillin and ampicillin. Each time, the reaction was quenched by cooling under tap water at a preselected fixed time which was accurately measured. Calibration graphs of absorbance versus initial concentration of amoxicillin or ampicillin were established at fixed times of 5, 10, 20, 30, 40, 50 and 60 min with the calibration equation assembled in Table 4. It is clear that the slope increases with time and the most acceptable values of correlation coefficients r and intercepts were obtained at a fixed time of 60 min which was therefore chosen as the most suitable time interval for measurement.

3.3. Applications

The fixed time method was applied for the determination of amoxicillin and ampicillin in the supplied drug formulations. The concentrations of amoxicillin and ampicillin were calculated using the corresponding calibration equation shown in Table 4 at a fixed time of 60 min. The results obtained for the analysis in drug formulations were compared with those obtained using the official USP method [33] (Table 5).

Table 3
Values of reciprocal of time taken at fixed absorbance values for different rates of variable concentrations of penicillins with constant concentration of $PdCl_2$ of 1×10^{-3} M

t (min)	$1/t$ (s^{-1})	[Penicillin]
Amoxicillin		
50	3.3×10^{-4}	5.2×10^{-5}
45	3.7×10^{-4}	6.3×10^{-5}
25	6.66×10^{-4}	7.93×10^{-5}
15	1.1×10^{-3}	1.057×10^{-4}
Ampicillin		
50	3.3×10^{-4}	6.4×10^{-5}
30	5.5×10^{-4}	8.077×10^{-5}
25	6.6×10^{-4}	6.46×10^{-5}
18	9.26×10^{-4}	1.076×10^{-4}

Table 4
Calibration equations for amoxicillin of different concentrations ranging from 2.6×10^{-5} to 1.05×10^{-4} M and for ampicillin of different concentrations ranging from 2.15×10^{-5} to 1.076×10^{-4} M at different time intervals with [$PdCl_2$] of 1×10^{-3} M

Time (min)	Calibration equation	Correlation coefficient r
Amoxicillin		
5	$A = 0.014 + 0.0007C$	0.992
10	$A = 0.0055 + 0.01125C$	0.9997
20	$A = 0.002 + 0.0152C$	0.9967
30	$A = -0.006 + 0.0197C$	0.9989
40	$A = -0.005 + 0.0206C$	0.9905
50	$A = 0.0345\ 6\ 0.0222C$	0.9991
60	$A = 0.008 + 0.02162C$	0.09994
Ampicillin		
5	$A = 0.069 + 0.0098C$	0.988
10	$A = 0.0239 + 0.013C$	0.998
20	$A = 0.0012 + 0.0138C$	0.993
30	$A = 0.0257 + 0.0149C$	0.996
40	$A = 0.0108 + 0.017C$	0.9995
50	$A = 0.0172 + 0.018C$	0.998
60	$A = -0.0068 + 0.0206C$	0.9997

Table 5
Spectrophotometric determination of the studied compounds in pharmaceutical preparations by the proposed and official method

Preparation	Taken (μg)	Found (μg)	Recovery (%)	Reference method [33]
Amoxil capsule [a] (250 mg amoxicillin trihydrate/capsule)	10	9.92	99.2	
	20	20.10	100.5	
	30	30.28	100.94	
	40	40.48	101.20	
$X' \pm SD$			100.46 ± 0.89	100.66 ± 1.034
t				0.29 (2.36)
F				2.03 (6.59)
Amoxil suspension [a] (250 mg amoxicillin trihydrate/5 ml)	10	9.92	99.2	
	20	20.1	100.5	
	30	30.27	100.9	
	40	40.40	101.0	
$X' \pm SD$			100.4 ± 0.82	100.83 ± 0.5
t				0.37 (2.36)
F				0.80 (6.59)
Amoxil vial [a] (500 mg amoxicillin sodium)	10	9.9	99.0	
	20	20.1	100.5	
	30	30.23	100.77	
	40	40.36	100.9	
$X' \pm SD$			100.29 ± 0.87	100.68 ± 0.46
t				0.41 (2.36)
F				0.61 (6.59)
Epicocillin capsule [b] (250 mg ampicillin trihydrate/capsule)	8	8.09	101.10	
	16	15.89	99.30	
	24	24.22	100.91	
	32	32.11	100.34	
X‘ $\pm$ SD			100.41 ± 0.81	100.77 ± 0.61
t				0.65 (2.36)
F				0.56 (6.59)
Epicocillin suspension [b] (125 mg ampicillin trihydrate/5 ml)	8	8.064	100.8	
	16	15.92	99.5	
	24	24.12	100.5	
	32	32.61	101.9	
$X' \pm SD$			100.68 ± 0.98	99.7 ± 0.7
t				0.34 (2.36)
F				0.51 (6.59)
Epicocillin vial [b] (500 mg amipicillin sodium/vial)	8	7.94	99.25	
	16	15.81	98.81	
	24	24.27	101.12	
	32	32.11	100.34	
$X' \pm SD$			100.34 ± 0.71	100.55 ± 0.77
t				0.51 (2.36)
F				0.92 (6.59)

[a] Product of Beecham Pharm. Co., UK.
[b] Product of Eipico Pharma. Co., Cairo, Egypt.

Statistical analysis of the results was carried out adopting Student's t-test and the variance-ratio F test and the results obtained show no significant difference in the performance of the two methods regarding accuracy and precision, respectively [34].

4. Conclusion

The kinetically based method proposed in this work for the quantitation of ampicillin and amoxicillin is direct and more sensitive compared to the USP method. Furthermore, the proposed method does not require elaboration of procedures which are usually associated with chromatographic methods. The proposed method could be applied successfully for determination of ampicillin and amoxicillin either in pure form or in pharmaceutical preparations.

References

[1] J.N. Delgado, W.A. Remers (Eds.), Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, Lippincott, Philadelphia, PA, 10th ed., 1995, Chapter 7.

[2] H.K. Li, L.S. Chen, Y.P. Zhao, Spectrophotometric determination of amoxicillin in dry syrup, Fenxi Huaxue 27 (1999) 370.
[3] F.S. El-Shafie, E.S. Gad-Kariem, K.A. Al-Rashood, H.A. Al-Khamees, H.A. El-Obeid, Colorimetric method for the determination of ampicillin and amoxicillin, Anal. Lett. 29 (1996) 381.
[4] G.A. Saleh, Two selective spectrophotometric methods for the determination of amoxicillin and cefadroxil, Analyst 121 (1996) 641.
[5] B. Devani, I.T. Patel, T.M. Patel, Spectrophotometric determination of amoxicillin in its dosage forms, J. Pharm. Biomed. Anal. 10 (1992) 355.
[6] H.E. Abdel Fattah, M.N. El-Bolkiny, A. Aboul-Kheir, pH induced difference spectrophotometric of amoxicillin in presence of dicloxacillin and flucloxacillin, Egypt. J. Pharm. Sci. 33 (1992) 805.
[7] H.F. Askal, G.A. Saleh, N.M. Omer, Utility of certain pi-acceptors for the spectrophotometric determination of some penicillins, Analyst 116 (1991) 387.
[8] E.M. Abdel Moety, Spectrophotometric determination of amoxicillin and dicloxacillin in binary mixture and capsules, J. Pharm. Biomed. Anal. 9 (1991) 187.
[9] B. Uslu, I. Biryol, Voltammetric determination of amoxicillin using a poly(*N*-vinylimidazole) carbon paste electrode, J. Pharm. Biomed. Anal. 20 (1999) 591.
[10] I. Biryol, B. Uslu, Z. Kucukyavuz, Voltammetric determination of amoxicillin using carbon paste electrode modified with poly(4-vinyl)pyridine, STP Pharm. Sci. 8 (1998) 383.
[11] V. Kapetanovic, D. Veselinovic, Fluorescence studies of amoxicillin, Arch-Pharm. 321 (1998) 559.
[12] P. Gutierez-Navarro, A. El-Bekkouri, E. Rodriguez-Reinoso, Spectrofluorimetric study of the degradation of alpha amino beta lactam antibiotics catalysed by metal ions in methanol, Analyst 123 (1998) 2263.
[13] M.A. van Opestel, R. Wolters, J.S. Blaww, P.C. van Krimpen, A. Bult, Determination of penicillins in pharmaceutical formulations by flow injection analysis, J. Pharm. Biomed. Anal. 8 (1990) 49.
[14] M.C. Garcia, M.I. Alberto, V. Rodenas, Determination of ampicillin or amoxicillin in pharmaceutical samples by flow injection analysis, J. Pharm. Biomed. Anal. 12 (1994) 1585.
[15] J.O. Boison, L.J.Y. Keng, Ampicillin and amoxicillin by liquid chromatography in bovine muscle, J. Assoc. Off. Anal. Chem. 81 (1998) 1113.
[16] J. van Zijveld, E.J. van Hoogdalem, Application of semipermeable surface column for the determination of amoxicillin in human blood serum, J. Chromatogr. B. 726 (1999) 169.
[17] Z.F. Zhang, Y. Lu, G.J. Liang, Y.D. Wang, W. Liu, Study on the determination and stability of amoxicillin sodium and clavulanate potassium for injection by HPLC, Chin. J. Pharm. Anal. 16 (1996) 366.
[18] T.L. Tsou, J.R. Wu, C.D. Young, T.M. Wang, Simultaneous determination of amoxicillin and clavulanic acid in pharmaceutical products by HPLC. With beta-cyclo dextrin stationary phase, J. Pharm. Biomed. Anal. 15 (1997) 1197.
[19] H.A. Al-Khamees, F.S. ElShafie, M.E. Hagga, M.E. Alawady, E.A. Gad-Kareim, Kinetic method for the quantitation of ampicillin trihydrate in bulk and in drug formulations, Sci. Pharm. 63 (1995) 191.
[20] S.Y. Sun, W. Chen, Z.X. Pan, M.S. Zhang, J. Qu, P.F. Li, A modification of B.P network and application for simultaneous determination of four drugs, Fenxi Shinyanshi 15 (1996) 39.
[21] C.S.P. Sastry, S.G. Rao, P.Y. Naidu, K.R. Srinivas, New spectrophotometric method for the determination of some drugs with iodine and wool fast blue BL, Talanta 45 (1998) 1227.
[22] F. Belal, M.S. Rizk, M. Eid, Polarographic determination of some penicillins through nitrosation, J. Pharm. Biomed. Anal. 17 (1998) 275.
[23] G.O. El-Sayed, A.S. Amin, Y.M. Issa, DC polarographic determination of ampicillin in pharmaceutical dosage forms, Anal. Lett. 27 (1994) 2515.
[24] E. Verdon, P. Couedor, Multiresidue analytical method for the determination of eight penicillin in muscle tissue by ion pair-reversed phase HPLC after precolumn derivatization, J. Assoc. Off. Anal. Chem. 82 (1999) 1083.
[25] M. Ishida, K. Kobayashi, N. Awata, F. Sakamoto, Simple high performance liquid chromatographic determination of ampicillin in human serum using solid-phase extraction cartridge, J. Chromatogr. 727 (1999) 245.
[26] B. Stankovic, T. Jovanovic, S. Masic, Z. Koricanac, Use of palladium(II) chloride as colour forming reagent in spectrophotometric determination of propylthiouracil in aqueous solution and tablet, Farmaco 51 (1996) 679.
[27] Y. Fujita, I. Mori, K. Fujita, Y. Nakahashi, T. Tanaka, Determination of chloropromazine, thiamine, lincomycin, ofloxacin and theophylline by ternary complex formation with eosin and palladium, Chem. Pharm. Bull. 35 (1987) 5009.
[28] P.M. Issopoulos, S.E. Salta, High-sensitive spectrophotometric determination of micromolar concentrations of penicillamine by means of a coupled redox- complexation reaction, Farmaco 52 (1997) 113.
[29] E. Ivashkiv, in: K. Florey (Ed.), Analytical Profiles of Drug Substances, vol. 2, Academic Press, New York, 1973, p. 1.
[30] R.D. Braun, in: Introduction to Instrumental Analysis, McGraw-Hill, New York, 1987, p. 291.
[31] K.B. Yatsimirskii, Kinetic Methods of Analysis, Pergamon, Oxford, 1966.
[32] H.A. Laitinen, W.E. Harris, Chemical Analysis, McGraw-Hill, New York, 2nd ed., 1975.
[33] The United States Pharmacopeia XXIII US Pharmacopeial Convention, Easton-Pennsylvania, 1995.
[34] J.C. Miller, J.N. Miller, Statistics for Analytical Chemistry, Wiley, New York, 1984.