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Conductimetric determination of reproterol HCl and pipazethate HCl and salbutamol sulphate in their pharmaceutical formulations

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Abstract

A simple and sensitive conductimetric method for the determination of salbutamol sulphate and reproterol and pipazethate hydrochlorides is presented based on their ion associates with phosphotungstic and phosphomolybdic acids. The effect of solvent, molar ratio, reagent concentration and temperature were studied, and the solubility products of the formed ion associates were calculated. The method was applied to the determination of the drugs in their pure state or pharmaceutical preparations with mean recovery values of 99.82–100.54, 99.75–100.12 and 99.95–100.40%, and coefficient of variation 0.28–0.52, 0.16–0.36 and 0.19–0.33 for salbutamol sulphate, reproterol HCl and pipazathate HCl, respectively.

Keywords: Conductimetric titration; Salbutamol; Reproterol; Pipazethate; Salbovent; Asthmobronchin; Selgon

1. Introduction

The investigated drugs are very important bronchodilators that suppresses irritative and spasmodic cough. Several techniques have been adopted for the determination of salbutamol including high-performance liquid chromatography (HPLC) [1], HPLC/mass spectrometry (MS) [2], gas chromatography/MS [3], electrokinetic chromatography [4], MS [5], LC [6], immunoassay [7], capillary electrophoresis [8], spectrophotometry [9], voltammetry [10], polarography [11] and potentiometry using ion selective electrodes (ISE) [12]. Reproterol has been determined using electrophoresis [13], HPLC [14] and ISE [15], while pipazethate was determined by colorimetry [16], thin layer chromatography [17], HPLC [18]and ISE [19].

The present work, aims to introduce new conductimetric methods for the determination of salbutamol sulphate (Sl_2SO_4) and reproterol (RpCl) and pipazethate hydrochlorides (PiCl). These methods are very simple in application and of low expenses in comparison to the above mentioned techniques but as the same time offering a high degree of accuracy and precision when compared to the official method and could be used

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simply to determine the shelve-stability time of the studied drugs.

2. Experimental

2.1. Apparatus

A Hanna Research HI 9032 Conductivity Meter (Italy) was used for conductance measurements. The bridge is connected with a thermocouple for temperature measurements and the cell constant, K_{cell}, is 1.0.

2.2. Reagents

Doubly distilled water and analytical grade reagents were used to prepare all solutions. Pure-grade salbutamol sulphate (Sl_2SO_4) and its pharmaceutical preparations (Salbovent Forte tablets, 4 mg/tablet; and Salbovent syrup, 2 mg/5 ml syrup) were provided by Alexandria Company for Pharmaceuticals (Alexandria, Egypt), reproterol hydrochloride (RpCl) (Asthmobronchin tablets, 20 mg/tablet) were provided by Kahira Company for Pharmaceuticals (Cairo, Egypt), while pipazethate hydrochloride (PiCl) (Selgon; tablets, 20 mg/tablet and drops, 40 mg/ml) were provided by the Egyptian International pharmaceutical Industries Company, EIPICO (10th Ramadan City, Egypt). Concentrations were 10^{-2} M Sl_2SO_4, RpCl and PiCl.

Stock solutions were prepared by dissolving the accurate weights of pure solid in bidistilled water and adding a few drops of acid (HCl or H_2SO_4) to prevent fungi formation before completing to the required volume, and the solutions were kept in the refrigerator for no more than 1 week to avoid any degradation, if it occurred. Working solutions of lower concentrations were invariably prepared by appropriate dilutions.

2.3. General procedure

Volumes containing 17.30–103.80 mg Sl_2SO_4, 7.79–62.31 mg RpCl or 13.08–78.48 mg PiCl were transferred to a 50 ml volumetric flask and made to the mark with bidistilled water. The contents of the volumetric flask were transferred to a beaker and the conductivity cell was immersed. Then 10^{-2} M PTA or PMA was added from a microburette and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring. The conductance reading, taken after 1–2 min, after each addition was corrected for dilution [20] by means of the following equation, assuming that conductivity is a linear function of dilution:

$$\Omega_{corr} = \Omega_{obs}[(v_1 + v_2)/v_1]$$

where Ω is the electrolytic conductivity, v_1 is the initial volume and v_2 is the volume of the added reagent (corr., corrected; obs., observed).

A graph of corrected conductivity versus the volume of titrant added was constructed and the end point was determined. One millilitre of 10^{-2} M PTA or PMA is theoretically equivalent to 17.301 mg Sl_2SO_4, 7.788 mg RpCl or 13.077 mg PiCl.

2.4. Procedure for determining the drug–titrant ratio

Six millilitres of 10^{-2} M Sl_2SO_4 or PiCl, or 4 ml of 10^{-2} M RpCl were transferred to a 50 ml volumetric flask and made up to the mark with bidistilled water. The contents were transferred to a beaker and the conductivity cell was immersed. Then 10^{-2} M PTA or PMA was added from a microburette and the conductance was measured subsequent to each addition of the reagent solution after thorough stirring for 1–2 min. A graph of conductivity versus volume was constructed.

2.5. Procedure for tablets

Twenty tablets containing salbutamol; reproterol or pipazethate were weighed and powdered. A quantity of powder equivalent to 1.0 g drug was transferred to a 100 ml volumetric flask and made up to the mark with distilled water. The general procedure was then followed in the concentration ranges already mentioned.

2.6. Procedure for syrup and drops

A volume of pipazethate drops (Selgon drops, 40 mg/ml) equivalent to 13.08–78.48 mg PiCl or salbutamol syrup (Salbovent, 2 mg/5 ml syrup) equivalent to 5.77–34.06 mg Sl_2SO_4 was transferred to a 50 ml volumetric flask and made to the mark by distilled water. The general procedure was then followed in the concentration ranges already mentioned.

2.7. Conductimetric determination of the solubility product of the ion associates

A series of solutions of different concentrations (c) was prepared for salbutamol; reproterol; pipazethate; PTA or PMA. The conductivities of these solutions were measured at 25°C and the specific conductivities (λ_0), corrected for the effect of solvent, were calculated and used to obtain the equivalent conductivities (λ) of the solutions. Straight-line plots of λ versus $\sqrt{c}$ were constructed and $\lambda_{0Sl2SO4}$; λ_{0RpCl}, λ_{0PiCl}, λ_{0PTA} or λ_{0PMA} were determined from the intercept of the respective line with the λ axis. The activity coefficients of the ions employed were taken as unity because all the solutions were sufficiently dilute (5×10^{-5} to 5×10^{-3} M). The values of $\lambda_{0(Sl\text{-}PTA)}$, $\lambda_{0(Sl\text{-}PMA)}$, $\lambda_{0(Rp\text{-}PTA)}$, $\lambda_{0(Rp\text{-}PMA}$, $\lambda_{0(Pi\text{-}PTA}$, and $\lambda_{0(Pi\text{-}PMA)}$ were calculated using Kohlrausch's law of independent migration of ions [21].

The solubility (s) and solubility product (K_{so}) of a particular ion associate were calculated using the following equations:

$$S = K_s \times 10000/\lambda_{0\ (\text{ion associate})}$$

$$K_{so} = 4S^3 \text{ for 1:2 ion associates}$$

$$K_{so} = 27S^4 \text{ for 1:3 ion associates}$$

where K_s is the specific conductivity of a saturated solution of the ion associate, determined at 25°C and corrected for the effect of solvent. The saturated solution was made by stirring a suspension of the solid precipitate in distilled water for 15 min at 25°C.

3. Results and discussion

Conductance measurements are used successfully in quantitative titration of systems in which the conductance of the solution varies before and after the equivalence point. In these cases, the titration curve can be represented by two lines intersecting at the end point. Titrations in different media were attempted to obtain the best results. Preliminary experiments in aqueous, ethanol, 50% ethanol water, 50% acetone water and 50% dioxan–water mixtures showed that the aqueous medium is the most suitable for obtaining a stable conductimetric readings.

The reagent concentration in each titration must not be less than ten times that of the drug solution in order to minimize the dilution effect on the conductivity through out the titration. The optimum concentration of the reagents is 10^{-2} M to achieve a constant and highly stable reading within 1–2 min of mixing. Concentrations less than this led to unstable readings and more time was needed to obtain constant conductance values. Temperatures up to 50°C show no effect on the end point.

The systems under investigation showed a regular rise in conductance up to the equivalence point where a sudden change in the slope occurs. This behaviour is probably related to the formation of RNH_x^+ and OH^- by hydrolysis. On adding PTA or PMA, the ion associate is formed by replacing the RNH_x^+ ions by mobile H^+ and the conductivity increases [22]. After the end point, more reagent acid is added and the conductivity increases more rapidly. A curve break is observed at a drug–reagent molar ratio of 3:1 in the case of salbutamol and pipazethate, while reproterol showed a drug–reagent ratio of 2:1 towards both reagents. Fig. 1 shows the conductimetric titration curves of the drugs versus PTA or PMA to calculate the molar ratio of the drug–reagent.

3.1. Analytical results

The results of the drug determination presented in Table 1 showed that good recoveries

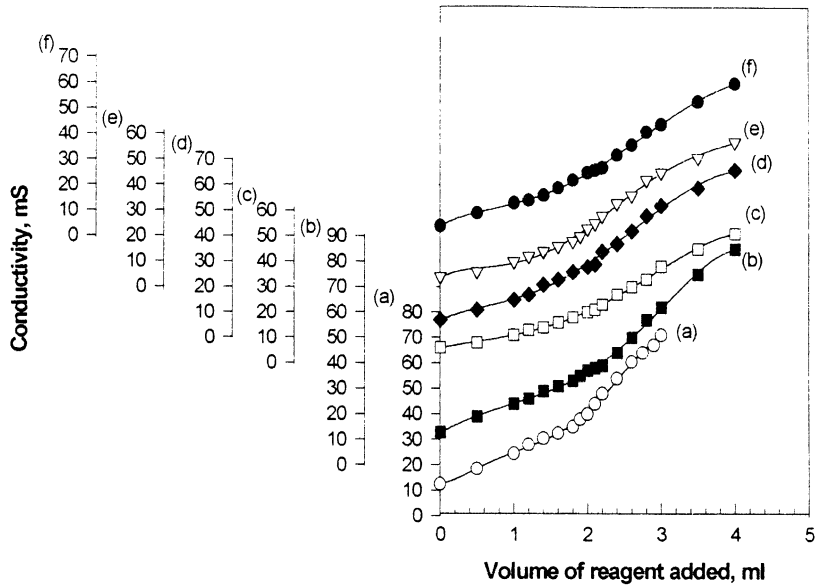

Fig. 1. Conductimetric titration of 34.06 mg Sl_2SO_4 against 10^{-2} M PTA (a) or 10^{-2} M PMA (b), 26.06 mg PiCl against 10^{-2} M PTA (c) or 10^{-2} M PMA (d), and 15.58 mg RpCl against 10^{-2} M PTA (e) or 10^{-2} M PMA (f).

Table 1
Conductimetric determination of pharmaceutical compounds in pure solution

Taken (mg)	PTA			PMA		
	Found[a] (mg)	Recovery (%)	RSD (%)	Found[a] (mg)	Recovery (%)	RSD (%)
Salbutamol sulphate						
17.30	17.27	99.82	0.36	17.25	99.71	0.27
34.60	34.44	99.54	0.52	34.48	99.66	0.16
51.90	51.76	99.73	0.31	51.87	99.95	0.30
86.50	86.76	100.30	0.28	86.52	100.02	0.25
103.80	104.36	100.54	0.41	104.22	100.41	0.22
Reproterol hydrochloride						
7.79	7.77	99.75	0.16	7.78	99.94	0.26
15.58	15.53	99.69	0.32	15.56	99.87	0.18
31.15	31.08	99.78	0.22	31.07	99.76	0.23
46.73	46.66	99.86	0.34	46.84	100.24	0.34
62.31	62.38	100.12	0.36	62.34	100.05	0.27
Pipazethate hydrochloride						
13.08	13.07	99.95	0.25	13.05	99.78	0.31
26.16	26.18	100.08	0.27	26.14	99.94	0.25
39.24	39.18	99.84	0.19	38.15	99.76	0.28
65.40	65.26	99.79	0.34	65.12	99.58	0.34
78.48	78.64	100.21	0.33	78.35	99.83	0.27

[a] Average of five determinations.

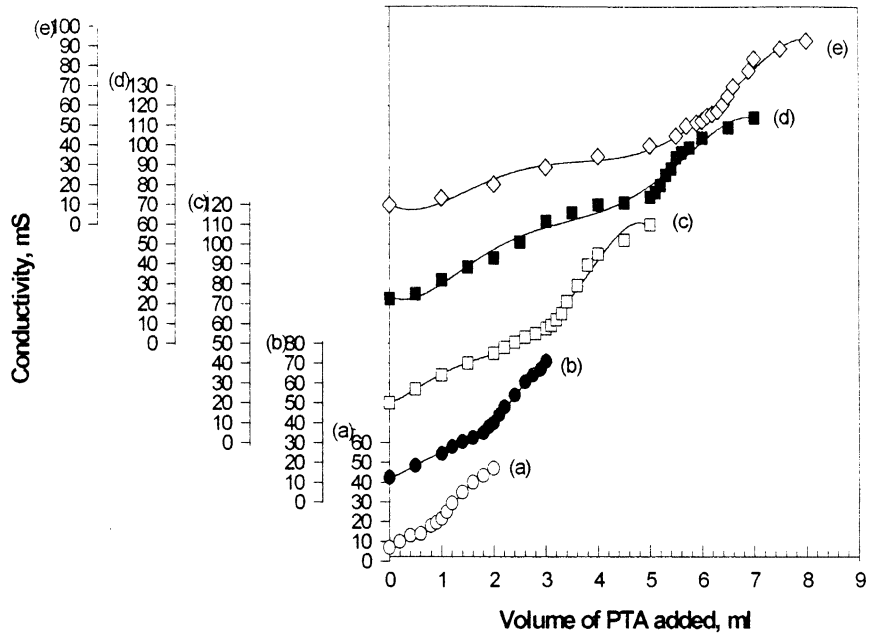

Fig. 2. Conductimetric titration of 17.30 mg (a), 34.60 mg (b), 51.90 mg (c), 86.50 mg (d) and 103.80 mg (e) Sl_2SO_4 against 10^{-2} M PTA.

and low standard deviations were obtained. The optimum concentration ranges for determination are 17.30–103.80, 7.79–62.31 or 13.08–78.48 mg with mean recovery values of 99.82–100.54, 99.75–100.12 and 99.95–100.40% and coefficient of variation 0.28–0.52, 0.16–0.36 and 0.19–0.33 for salbutamol sulphate, reproterol HCl and pipazathate HCl, respectively, at which sharp inflections and stable conductance readings are obtained. Fig. 2 represents the titration curves for 17.30–103.80 mg Sl_2SO_4 against PTA as a representative figure.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression of observed drug concentration against the theoretical values obtained using the official method was calculated. The Student *t*-test (at 99.9% confidence level) and *F*-test were applied [23]. The calculated *t* values ranged from 1.36 to 2.34, which is lower than the tabulated values at the 99.9% confidence level (4.03), while the *F* values were found to range from 2.37 to 3.71, which is lower than the tabulated value (6.61 for five determinations) at the 95% confidence limit. This means that there is no systematic differences between the determined and true concentrations; thus, the proposed method is of the same accuracy as the official methods [24–26]. The results of statistical treatment of data are presented in Table 2.

3.2. Analytical applications

The validity of the proposed method was assessed by its application to the determination of Sl_2SO_4, RpCl and PiCl in their pharmaceutical preparations (tablets, syrup and drops). The mean recovery values were 99.65–100.12, 98.97–100.14, 98.75–100.13, 99.90–99.98 and 99.85–100.12 with coefficients of variation 0.15–0.37, 0.21–0.38, 0.24–0.33, 0.19–0.37 and 0.18–0.35 for salbovent tablets, salbovent syrup, asthmobronchin tablets, selgon tablets and selgon drops, respectively (Table 3). This is nearly the same as in the case of determining pure drug samples, indicating the high selectivity of the method towards the studied drugs. Thus, the other excipients and binders, maize starch, magnesium stearate, lactose or sucrose and sodium lauryl sulphate, in the formulations did not interfere in the determination.

Table 2
Linear regression analysis of data obtained from determination of the investigated drugs using PTA and PMA

Ion associate	Slope of the regression line[a]	Intercept of the regression line	*t* value (4.03)[b]	*F* value (6.61)[c]
Sl_3-PTA	0.998	0.041	1.36	2.37
Sl_3-PMA	0.997	0.028	2.14	3.25
Rp_2-PTA	0.995	0.035	1.76	3.64
Rp_2-PMA	0.998	0.064	1.52	2.98
Pi_3-PTA	0.999	0.057	2.34	3.54
Pi_3-PMA	0.997	0.039	1.68	3.71

[a] Observed versus theoretical.
[b] Tabulated 99.9% confidence limit at five degrees of freedom.
[c] Tabulated 95.0% confidence limit at five degrees of freedom.

Table 3
Conductimetric determination of salbutamol sulphate and reproterol and pipazethate hydrochlorides in their pharmaceutical preparations

	Taken (mg)	PTA		PMA	
		Recovery (%)	RSD (%)	Recovery (%)	RSD (%)
Salbutamol sulphate					
Salbovent tablets (4 mg/tablet)	17.30	99.65	0.23	99.85	0.22
	34.60	99.82	0.15	98.76	0.30
	51.90	98.79	0.46	99.85	0.27
	86.50	99.63	0.37	100.02	0.25
	103.80	99.96	0.28	100.12	0.19
Salbovent syrup (2 mg/5 ml)	5.77	98.97	0.21	99.97	0.31
	11.53	99.86	0.28	99.92	0.38
	23.01	99.90	0.34	99.98	0.29
	28.00	99.98	0.29	99.99	0.35
	34.60	100.14	0.31	100.00	0.27
Reproterol hydrochloride					
Asthmobronchin tablets (20 mg/tablet)	7.79	98.75	0.27	99.76	0.28
	15.58	99.80	0.24	99.85	0.24
	31.15	99.97	0.36	99.92	0.31
	46.73	99.90	0.28	99.98	0.25
	62.31	100.13	0.33	99.95	0.29
Pipazethate hydrochloride					
Selgon tablets (20 mg/tablet)	13.08	99.90	0.25	99.96	0.30
	26.16	99.96	0.31	99.87	0.28
	39.24	99.95	0.28	99.85	0.24
	65.40	99.93	0.34	99.96	0.32
	78.48	99.98	0.37	99.98	0.19
Selgon drops (40 mg/ml)	13.08	99.97	0.28	99.89	0.21
	26.16	99.95	0.31	99.92	0.25
	39.24	99.96	0.33	99.85	0.18
	65.40	100.00	0.35	99.98	0.34
	78.48	100.12	0.24	100.05	0.27

Table 4
Statistical treatment of data for drugs formulations in comparison with the official methods

	Official method	PMA	PTA
Salbovent tablets			
$X \pm$ S.E.	100.00 ± 0.42	99.72 ± 0.25	99.57 ± 0.29
Probability		<0.05	<0.05
Relative error (%)		0.28	0.43
$F^{(5,5)}$ value (5.05)		1.98	2.14
Salbovent syrup			
$X \pm$ S.E.	100.30 ± 0.52	99.97 ± 0.32	99.77 ± 0.29
Probability		<0.05	>0.01
Relative error (%)		0.33	0.53
$F^{(5,5)}$ value (5.05)		3.21	2.68
Asthmobronchin tablets			
$X \pm$ S.E.	99.50 ± 0.62	99.89 ± 0.27	99.71 ± 0.30
Probability		>0.01	>0.01
Relative error (%)		0.39	0.21
$F^{(5,5)}$ value (5.05)		2.34	1.72
Selgon tablets			
$X \pm$ S.E.	99.70 ± 0.52	99.92 ± 0.27	99.94 ± 0.31
Probability		>0.01	<0.05
Relative error (%)		0.22	0.24
$F^{(5,5)}$ value (5.05)		1.94	2.39
Selgon drops			
$X \pm$ S.E.	100.50 ± 0.61	99.94 ± 0.25	100.00 ± 0.30
Probability		>0.01	>0.01
Relative error (%)		0.06	0.50
$F^{(5,5)}$ value (5.05)		2.61	3.37

The results of the formulations determination were compared with those obtained from the official methods applying the F-test and the t-test (Table 4). This comparison indicated that the proposed methods are not only as accurate as the official methods, but they use simple reagents and apparatus; they are also applicable to a wide range of concentration beside being time saving (20 min are required for each complete titration), thereby encouraging their application in quality control of these drugs in their pure form and pharmaceutical preparations.

3.3. Solubility products of ion associates

Ion-associate formation is the main controlling factor in many chemical reactions, such as precipitation reactions, where the degree of feasibility of titration depends on the degree of completeness of the precipitation reaction. The equilibrium constant of the precipitation reaction is inversely proportional to the solubility product, whereas the smaller the solubility product of the formed ion associate, the sharper is the end point. It is noteworthy to mention also that the solubility of ion associates is one of the main factors controlling the life span of solid-state ion-selective electrodes built up from these ion associates, and which are widely used as an analytical tool for determining those drugs under investigation.

The solubility products of the ion associates were found to be 8.36×10^{-5}, 3.75×10^{-6}, 6.93×10^{-9}, 1.58×10^{-9}, 3.89×10^{-6} and 4.69×10^{-6} for Sl_3-PTA, Sl_3-PMA, Rp_2-PTA, Rp_2-PMA, Pi_3-PTA and Pi_3-PMA, respectively. Consequently, the equilibrium constants of the ion-associate formation reaction can be calculated as follows:

$$3Sl^+ + PTA \rightleftarrows Sl_3\text{-PTA} \qquad K = 1.19 \times 10^4$$

$$3Sl^+ + PMA \rightleftarrows Sl_3\text{-PMA} \qquad K = 2.67 \times 10^5$$

$$2Rp^+ + PTA \rightleftarrows Rp_2\text{-PTA} \qquad K = 1.44 \times 10^8$$

$$2Rp^+ + PMA \rightleftarrows Rp_2\text{-PMA} \qquad K = 6.31 \times 10^8$$

$$3Pi^+ + PTA \rightleftarrows Pi_3\text{-PTA} \qquad K = 2.57 \times 10^5$$

$$3Pi^+ + PMA \rightleftarrows Pi_3\text{-PMA} \qquad K = 2.13 \times 10^5$$

These equilibrium constant values are very high, indicating that the degree of completeness of the ion-associate formation reaction is 99.99%. In the equilibria, the solubility product of the undissociated ion associate in water (i.e. the intrinsic solubility) was omitted as this term makes a negligible contribution to the total solubility because the ion associates are sparingly soluble in water and its saturated solution is, therefore, very dilute [27,28].

References

[1] K.M. Fried, P. Koch, I.W. Wainer, Chirality 10 (1998) 484 (Anal. Abstr. 60 (1998) 12G194).
[2] G. Biancotto, R. Angeletti, R. Piro, D. Favretto, P. Traldi, J. Mass Spectrom. 32 (1997) 781.
[3] C. Demir, R. Brereton, Analyst 122 (1997) 631.
[4] H. Jakubetz, M. Juza, V. Schurig, Electrophoresis 18 (1997) 897.
[5] E. Redenti, M. Fiaschi, M. Zanol, P. Ventura, Eur. Mass Spectrom. 3 (1997) 89.
[6] E.A. Hogendoorn, P. Vanzoonen, A. Polettini, G.M. Bowand, M. Montage, Anal. Chem. 70 (1998) 1362.
[7] K. Vanoosthuyze, C. Arts, C. Vanpeteghem, J. Agric. Food Chem. 45 (1997) 3129.
[8] A. Esquisabel, R.M. Herandez, A.R. Gascon, M. Igartua, B. Calvo, J. Pharm. Biomed. Anal. 16 (1997) 357.
[9] I. Singhui, S.C. Chaturvedi, Indian Drugs 35 (1998) 421.
[10] D. Boyd, J. Barreira, A. Miranda, P. Tunon, M. Smyth, Analyst 119 (1994) 1979.
[11] Y. Zhan, Fenxi Huaxue 20 (1992) 199.
[12] N.T. Abdel Ghani, M.S. Rizk, R.M. El-Nashar, Analyst 125 (2000) 1129.
[13] Y.E. Sun, Y.F. Guan, Fenxi-Huaxue 25 (1997) 745 (Anal. Abstr. 60 (1998)).
[14] N.G. Knebel, M. Winkler, J. Chromatogr. B: Biomed. Appl. 119 (1997) 702.
[15] Y.M. Issa, M.S. Rizk, R.M. El-Nashar, Mikrochim. Acta (in press).
[16] S.S. Zarapker, R.V. Rele, V.M. Shah, Indian Drugs 24 (1987) 445.
[17] H.D. Revanasiddappa, P.G. Ramappa, Indian Drugs 32 (1995) 73.
[18] H.D. Revanasiddappa, P.G. Ramappa, Indian Drugs 32 (1995) 534.
[19] N.T. Abdel-Ghani, A.F. Shoukry, Analyst 126 (2001) 79–85.
[20] J.J. Lingane, Electroanalytical Chemistry, 2nd ed., Interscience, New York, 1958, p. 90.
[21] L.L. Antropov, Theoretical Electrochemistry, Mir, Moscow, 1977.
[22] M.S. Bahbouh, A.A. Salem, Y.M. Issa, Mikrochim. Acta 128 (1998) 57.
[23] J.C. Miller, J.N. Miller, Statistics for Analytical Chemistry, Ellis Horwood, Chichester, 1984.
[24] British Pharmacopoeia, vol. II, Her Majesty's Stationary Office, London, 1993, p. 584.
[25] J.E.F. Reynolds (Ed.), Martindale, The Extra Pharmacopoeia, 30th ed., The Pharmaceutical Press, London, 1993, p. 1294.
[26] J.E.F. Reynolds (Ed.) Martindale, The Extra Pharmacopoeia, 30th ed., The Pharmaceutical Press, London, 1993, p. 1183.
[27] A.F. Shoukry, Analyst 113 (1988) 1305.
[28] H.M. Irving, R.J.P. Williams, Analyst 77 (1952) 813.