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Salbutamol plastic membrane electrodes based on individual and mixed ion-exchangers of salbutamolium phosphotungstate and phosphomolybdate

Nour T. Abdel-Ghani,* Mahmoud S. Rizk and Rasha M. El-Nashar

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

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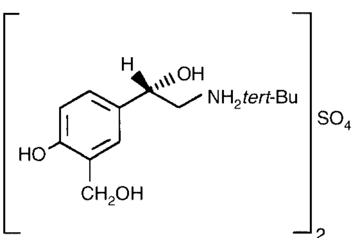
Salbutamol (Sl), also known as albuterol, selective PVC membranes based on ion associates of salbutamolium phosphotungstate (Sl-PTA), salbutamolium phosphomolybdate (Sl-PMA) or a mixture of both (Sl-PTA/PMA) were prepared. The electrodes displayed a linear response over the concentration range 6.3×10^{-6}–1.0×10^{-1} mol dm^{-3} salbutamol sulfate (Sl_2SO_4). The working pH ranges of the above electrodes were 2.5–11.0, 3.0–11.0 and 2.5–10.5 and their isothermal temperature coefficients were 0.00095, 0.00105 and 0.00136 V °C^{-1}, respectively. The electrodes showed good selectivity to salbutamolium ion with respect to many inorganic cations, sugars and amino acids. The standard additions method was used to determine Sl_2SO_4 in pure solutions and pharmaceutical preparations with high accuracy and precision.

Introduction

Salbutamol sulfate (Sl_2SO_4), 1-(4-hydroxy-3-hydroxyphenyl)-2-*tert*-butyl aminoethanol sulfate (18559-94-9),[1] is a bronchodilator without cardiovascular side effects; thus, it can be used safely for patients suffering from heart diseases or hypertension.[1]



$[C_{13}H_{22}NO_3]_2 \cdot SO_4$

Sl_2SO_4 has been determined by several techniques, including HPLC,[2,3] HPLC-MS,[4,5] GC-MS,[6,7] electrokinetic chromatography,[8] MS,[9,10] LC,[11] immunoassay,[12,13] capillary electrophoresis,[14,15] spectrophotometry,[16] voltammetry,[17,18] and polarography.[19] Although potentiometry has the advantage over other techniques, being easy, precise, accurate and of low expense, no salbutamol ion-selective electrode (ISE) has yet been constructed.

In the present study, plastic membrane electrodes for the Sl cation have been constructed based on the incorporation of salbutamolium phosphotungstate (Sl-PTA), salbutamolium phosphomolybdate (Sl-PMA) or Sl-PTA/PMA ion-exchanger(s) in PVC membranes plasticized with dioctylphthalate (DOP). The results showed that, although each individual ion-exchanger can be used to prepare an ISE for the drug, the incorporation of two ion-exchangers in the membrane increases to a large extent the lifespan of the electrode.

Experimental

Reagents and materials

All chemicals used were of analytical grade. Pure grade Sl_2SO_4 and the pharmaceutical preparations (Salbovent Forte tablets, 4 mg per tablet; Salbovent syrup, 2 mg per 5 ml of syrup) were provided by Alexandria Company for Pharmaceuticals, Alexandria, Egypt.

The ion-exchangers, salbutamolium phosphotungstate (Sl-PTA) (faint yellow powder) and salbutamolium phosphomolybdate (Sl-PMA) (yellowish green crystals), were prepared by the addition of 150 cm^3 of 10^{-2} mol dm^{-3} salbutamol sulfate solution to 100 cm^3 of 10^{-2} mol dm^{-3} of each of phosphotungstic acid or phosphomolybdic acid, respectively. The precipitates were filtered, washed thoroughly with distilled water until sulfate free and air dried. The chemical composition of the precipitates was identified and confirmed by (C, H, N) elemental analysis (Table 1).

The electrodes

The electrodes were constructed as previously described.[20] The membrane composition was studied by varying the percentages (w/w) of the ion-exchanger(s), PVC and DOP until an optimum composition exhibiting the best performance characteristics was reached. The membranes were prepared by dissolving the required amounts of PVC, ion-exchanger(s) and the plasticizer (DOP) in a 5.0 cm diameter Petri dish containing 10.0 cm^3 of tetrahydrofuran (THF) (the total weight of the ingredients is 0.35 g). The Petri dish was then covered with a filter paper and left to dry in air. To obtain a uniform membrane thickness, the amount of THF was kept constant and its evaporation was fixed for 24 h.

A 12 mm diameter disc was cut out from the prepared membrane and glued using PVC–THF paste to the polished end of a plastic cap attached to a glass tube. The electrode body was filled with a solution that was 10^{-2} mol dm^{-3} with respect to

Table 1 Elemental analysis of the salbutamol ion-associates

Ion-associate	C(%)		H(%)		N(%)	
	Found	Calculated	Found	Calculated	Found	Calculated
I[a]	12.98	13.01	1.80	1.83	1.09	1.16
II[b]	20.01	19.90	2.76	2.80	1.75	1.78

[a] **I**, $[C_{13}H_{22}NO_3]_3\ [P(W_3O_{10})_4]$. [b] **II**, $[C_{13}H_{22}NO_3]_3\ [PO_4.12MoO_2]$.

both NaCl and Sl_2SO_4 and preconditioned by soaking in 10^{-3} mol dm^{-3} Sl_2SO_4 solution.

The electrochemical system

The potentiometric measurements were carried out with a Schott-Gerate CG 820 pH-meter (Hofheim, Germany) and WTW microprocessor pH/ion meter pMX 2000 (Weilheim, Germany). A Techne circulator (Cambridge, UK) thermostat Model C-100 was used to control the temperature of the test solutions. A WTW packed saturated calomel electrode (SCE) was used as an external reference electrode. The electrochemical system may be represented as follows: Ag/AgCl/filling solution/membrane/test solution//KCl salt bridge//SCE.

Selectivity

The selectivity coefficients, $K^{pot}_{Sl,J^{z+}}$, of the electrodes towards different cationic species (J^{z+}) were determined by the separate solution method,[21] in which the following equation is used:

$$\log K^{pot}_{Sl,J^{z+}} = \frac{E_2 - E_1}{S} + \log[Sl] - \log[J^{z+}]^{1/z}$$

where E_1 and E_2 are the electrode potentials in 10^{-2} mol dm^{-3} solution of Sl_2SO_4 and interferent, J^{z+}, respectively, and S is the slope of the calibration graph in mV.

In some cases, when the selectivity coefficients were not very high, both matched potential[22] and mixed solution[23,24] methods were used.

Potentiometric determination of Sl_2SO_4

Sl_2SO_4 has been determined potentiometrically using the investigated electrodes by the standard additions method.[25] This was achieved by adding small portions (0.1 cm^3) of standard 10^{-1} mol dm^{-3} Sl_2SO_4 solution to 50 cm^3 of water containing 1, 5, 10, 15, 20, 25, 30, 40 and 50 mg of pure compound or the equivalent from pharmaceutical preparations. The change in mV readings was recorded after each addition and used to calculate the concentration of Sl_2SO_4 sample solution.

For sampling of tablets (Salbovent Forte, 4 mg per tablet), 100 tablets were ground together and appropriate weights of each were taken as samples; the required amount (10–100 mg) was dissolved in 0.01 mol dm^{-3} H_2SO_4 (about 0.1 cm^3 per mg of Sl_2SO_4 tablet) and made up to 50 cm^3 with distilled water. For the syrup (Salbovent syrup, 2 mg per 5 ml), the contents of 10 bottles were mixed and volumes equivalent to the required weights were taken and then used for the determination of the drug content by the standard additions method.

Results and discussion

Composition of the membranes

In the plastic membrane of an ion-selective electrode, the amount of lipophilic salt should be sufficient to obtain reasonable ionic exchange at the gel layer/test solution interface, which is responsible for the membrane potential. Also, the amount of plasticizer should be such that a membrane with good physical properties is produced, which at the same time efficiently acts as a solvent mediator for the ion-exchanger(s) lipophilic salts. An increase in the amount of plasticizer improves to a large extent the adhesive properties of the membrane but, on the other hand, aids in the deterioration of the membrane depending on the properties of both the ion-exchanger(s) and the matrix.[26,27] In this work, the ratio of the plasticizer (DOP) to polymer (PVC) was kept constant at 1 : 1, while the amount of ion-exchanger was varied.

Several compositions for the electrodes were investigated in which the ion-exchanger percentage ranged from 1 to 20% for Sl-PTA and Sl-PMA and from 5 to 15% (of each ion-exchanger) for Sl-PTA/PMA. For each composition, the electrodes were repeatedly prepared four times. The preparation process was highly reproducible as revealed by the low relative standard deviation values of the slopes obtained employing the prepared membranes (mean RSD was about 0.6%).

The best performances were obtained using compositions of 10% Sl-PTA, 45% PVC and 45% DOP for Sl-PTA, 12% Sl-PMA, 44% PVC and 44% DOP for Sl-PMA) and 10% Sl-PTA, 10% Sl-PMA, 40% PVC and 40% DOP for Sl-PTA/PMA. The above optimum compositions were used to prepare membrane electrodes for all further investigations.

Effect of soaking

Freshly prepared electrodes must be soaked to activate the surface of the membrane to form an infinitesimally thin gel layer at which ion exchange occurs. This preconditioning process requires different times depending on diffusion and equilibration at the electrode test solution interface; a fast establishment of equilibrium is certainly a condition for a fast potential response.[28] For the present electrodes, the presoak times were 2, 1 and 1 h with slopes of 57.0, 57.0 and 58.5 mV per concentration decade and a usable concentration range of 6.3×10^{-6}–1.0×10^{-1} mol dm^{-3} for Sl-PTA, Sl-PMA and Sl-PTA/PMA, respectively.

Nevertheless, continuous soaking of the electrodes in 10^{-3} mol dm^{-3} Sl_2SO_4 solution affects negatively their response to the salbutamolium cation; this is attributed to leaching of the active ingredients (ion-exchanger(s) and plasticizer) to the bathing solution. It was noticed that the slopes of the calibration graphs obtained by the preconditioned electrodes were nearly constant for the first 10 days; they then started to decrease gradually to about 50.0 mV per concentration decade after 21, 28 and 42 days, reaching about 45.0 mV per decade after 28, 35 and 49 days for Sl-PTA, Sl-PMA and Sl-PTA/PMA, respectively. Fig. 1, shows the effect of soaking on the Sl-PTA/PMA electrode.

It is noteworthy that the lifespan of the membrane containing the mixed ion-exchangers is much longer than that of the membrane containing an individual ion-exchanger. This can be correlated with some sort of physical interaction between the two ion-exchangers within the PVC network. It may also be due to the diffusion and partition coefficients of both the ion-exchangers and the plasticizer; there is a relatively large amount of ion-exchanger (~ 20%) in the mixed membrane electrode compared to that present in the individual exchanger membrane electrodes.[29,30] However, it was noted that, in all cases, electrodes which had been kept dry in a closed vessel and stored in a refrigerator showed a good preservation of the slope values and response properties extending to several months. Thus, it is recommended that unused electrodes should be kept dry in closed vessels in a refrigerator.

Regeneration of the electrodes

The above discussion reveals that soaking of the electrodes in the drug solution for a long time has a negative effect on the response of the membranes towards the salbutamolium ion. The same effect appears after working with the electrode for a long time.

The regeneration of the electrodes was tried simply by re-formation of the ion-exchanger(s) on the external gel layer of the membrane.[31] The regeneration of Sl-PTA/PMA was successfully achieved by soaking the exhausted electrode for 24 h in a solution that was 10^{-2} mol dm^{-3} in both PTA and PMA, followed by soaking for 3 h in 10^{-2} mol dm^{-3} Sl_2SO_4 solution. Fig. 2, shows the calibration graphs for an exhausted electrode (slope 45.0 mV per decade) and for the same electrode after regeneration (slope 56.3 mV per decade).

It was found that the lifespan of the regenerated electrode is limited to 2 h due to the ease of leaching of the lipophilic salts from the gel layer at the electrode surface compared with those that are attached homogeneously to the PVC network through the solvent mediator.

With regard to Sl-PTA and Sl-PMA, they are not affected by soaking for intervals reaching 24 h. This can be attributed to the formation constants of these ion-exchangers and the high rigidity of the membranes which prevents the penetration of anions into the external surface during the regeneration process.

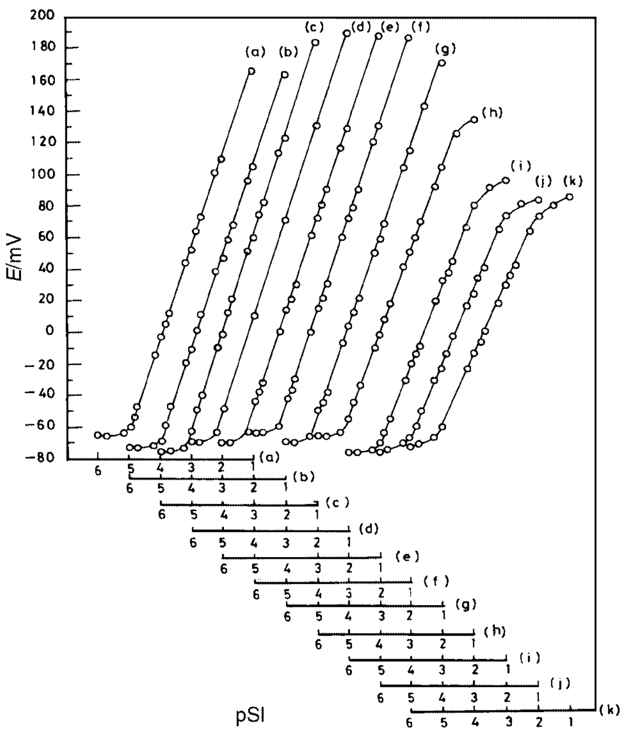


Fig. 1 Calibration graphs obtained at 25 ± 1 °C after soaking the Sl-PTA/PMA electrode for 0.5 h (a), 1 h (b), 24 h (c), 7 days (d), 14 days (e), 21 days (f), 28 days (g), 35 days (h), 42 days (i), 45 days (j) and 49 days (k).

Effect of temperature of the test solution

Calibration graphs [electrode potential (E_{elec}) *versus* pSl] were constructed at different test solution temperatures (25, 30, 35, 40, 50, 60 and 70 °C) for all electrodes. The slopes, usable concentration ranges and the standard electrode potentials ($E°$) of the electrodes at each temperature are given in Table 2.

For the determination of the isothermal coefficients ($dE°/dt$) of the electrodes, the standard electrode potentials ($E°$) against the normal hydrogen electrode at the different temperatures were obtained from the calibration graphs as the intercepts at pSl = 0 (after subtracting the values of the standard electrode potential of the calomel electrode at these temperatures) and were plotted *versus* ($t - 25$), where t is the temperature of the

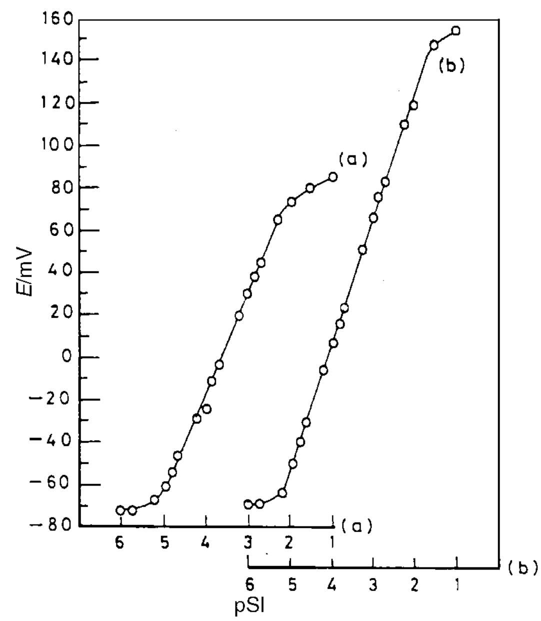


Fig. 2 Regeneration of Sl-PTA/PMA electrode: (a) calibration graph of an exhausted electrode; (b) calibration graph of the electrode after regeneration.

Table 2 Performance characteristics of Sl electrodes at different temperatures

Electrode	Temperature/°C	Slope/mV per decade	Usable concentration range/mol dm^{-3}	$E°^{a}$/mV
Sl-PTA	25	57.0	6.3×10^{-6}–1.0×10^{-1}	74
	30	58.5	6.3×10^{-6}–1.0×10^{-1}	78
	40	61.0	6.3×10^{-6}–1.0×10^{-1}	91
	50	63.0	6.3×10^{-6}–1.0×10^{-1}	99
	60	64.8	6.3×10^{-6}–1.0×10^{-1}	107
	70	66.2	1.0×10^{-5}–1.0×10^{-1}	107
Sl-PMA	25	57.0	6.3×10^{-6}–1.0×10^{-1}	31
	30	58.3	6.3×10^{-6}–1.0×10^{-1}	43
	40	61.0	6.3×10^{-6}–1.0×10^{-1}	54
	50	63.5	6.3×10^{-6}–1.0×10^{-1}	65
	60	66.0	1.0×10^{-5}–1.0×10^{-1}	75
	70	68.3	1.0×10^{-5}–1.0×10^{-1}	82
Sl-PTA/PMA	25	58.5	1.0×10^{-5}–1.0×10^{-1}	−21
	30	59.5	6.3×10^{-6}–1.0×10^{-1}	−4
	40	61.0	6.3×10^{-6}–1.0×10^{-1}	8
	50	62.5	6.3×10^{-6}–1.0×10^{-1}	20
	60	64.0	7.9×10^{-6}–1.0×10^{-1}	34
	70	66.3	1.0×10^{-5}–1.0×10^{-1}	34

[a] $E°$ is the standard electrode potential against the normal hydrogen electrode (NHE).

test solution in °C. A straight line plot is obtained according to the following equation:[32]

$$E° = E°(25) + (dE°/dt)\ (t - 25)$$

The slopes of the straight lines obtained represent the isothermal coefficients of the electrodes (0.00095, 0.00105 and 0.00136 V $°C^{-1}$ for Sl-PTA, Sl-PMA and Sl-PTA/PMA, respectively); these slopes were compared with the theoretical values at the given temperature and were found to be in good agreement, revealing a fairly high thermal stability of the electrodes within the temperature ranges investigated. The investigated electrodes were found to be usable up to temperatures reaching 70 °C without any deviation from the theoretical Nernstian behaviour.

Effect of pH

The effect of the pH of the test solution (10^{-2}, 10^{-3} and 10^{-4} mol dm^{-3} Sl_2SO_4) on the electrode potentials was investigated. The variation in potential with pH change was followed by the addition of small volumes of HCl and NaOH (0.1–1.0 mol dm^{-3}). Representative curves are given in Fig. 3, showing the variation in potentials of the three electrodes with pH change using a test solution of 10^{-3} mol dm^{-3} Sl_2SO_4. It is evident that the electrodes do not respond to pH changes in the range 2.5–11.0, 3.0–11.0 and 2.5–10.5 for Sl-PTA (a), Sl-PMA (b) and Sl-PTA/PMA (c), respectively. At pH values lower than these values, the potential decreases gradually and this can be related to the interference of the hydronium ion; the decrease occurring at higher pH values is most probably attributed to the formation of the free salbutamol base in the solution or the ionization of the hydroxy group, leading to a decrease in the concentration of the salbutamolium cation.

Selectivity of the electrodes

The influence of some inorganic cations, sugars and amino acids on the Sl electrodes was investigated. The selectivity coefficients $K^{pot}_{Sl,J^{z+}}$ of the electrodes (Table 3) reflect a very high selectivity of the investigated electrodes for the salbutamolium cation. The mechanism of selectivity is mainly based on the stereospecificity and electrostatic environment, and is dependent on how much matching is present between the locations of the lipophilic sites in the two competing species in the bathing solution side and those present in the receptor of the ion-exchanger. The inorganic cations do not interfere because of differences in ionic size, mobility and permeability. Also, the smaller the energy of hydration of the cation, the greater the response of the membrane. The electrodes exhibit good tolerance towards sugars, amino acids and urea. Although there are many restrictions that must be taken into consideration on using the separate solution method in the determination of the selectivity coefficients, especially in the case of mixed ion solutions of different charges, it is still the simplest way to show whether interference takes place or not. It is used to perform measurements in important samples, such as blood;[33] a considerably higher concentration of the interferent ion is used (10^{-2} mol dm^{-3}) to ensure that there will be no interference when concentrations lower than this are used. The matched potential and mixed solution methods (rather time consuming due to the preparation of many solutions and the performance of many steps) were only used in cases when $-\log K^{pot}_{Sl,J^{z+}}$ was less than 3.5. It was demonstrated by these methods that the electrodes show high selectivity (Table 3).

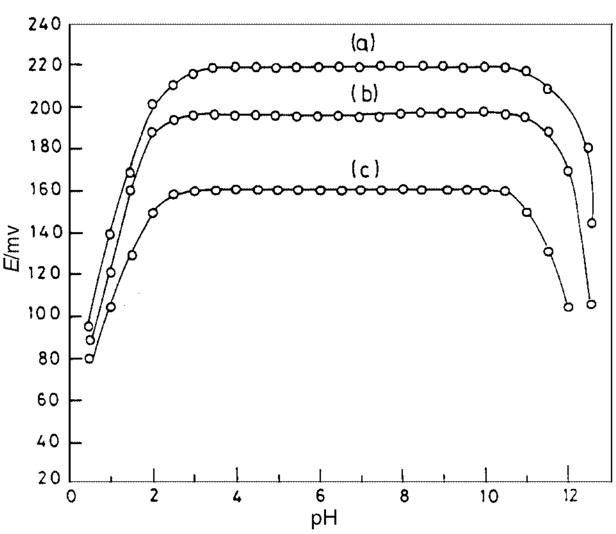


Fig. 3 Effect of pH of the test solution of concentration 10^{-3} mol dm^{-3} on the potential response of Sl-PTA (a), Sl-PMA (b) and Sl-PTA/PMA (c) electrodes.

Analytical applications

The investigated electrodes were found to be useful in the potentiometric determination of salbutamol sulfate in pure solutions by the extrapolation and standard additions method. The salbutamol-containing pharmaceutical preparations (tablets and syrup) have been assayed by the standard additions method using the investigated electrodes. In the case of tablets, better recovery was obtained by filtering the solution to remove the insoluble ingredients than without filtering; this may be attributed to some sort of interference of the ingredients contained in the tablets or to the adsorption of the standard solution on the surface of these insoluble ingredients.

Table 3 Selectivity coefficients and tolerance values for the Sl-responsive electrodes

	$-\log K^{pot}_{Sl,J^{z+}}$					
	Sl-PTA		Sl-PMA		Sl-PTA/PMA	
Interferent	SSM[a]	MSM[b]	SSM[a]	MSM[b]	SSM[a]	MSM[b]
Na^+	2.05	2.45	2.45	2.85	2.75	3.05
K^+	2.79	2.98	2.53	3.14	2.68	2.93
Li^+	3.41	3.75	2.98	3.42	3.24	3.87
NH_4^+	2.98	3.68	2.78	2.84	2.98	3.32
Mg^{2+}	3.45	3.97	3.01	3.53	3.12	3.65
Ca^{2+}	3.67	—	3.25	3.65	3.33	3.74
Sr^{2+}	3.89	—	3.54	—	3.67	—
Ba^{2+}	4.20	—	3.99	—	4.21	—
Mn^{2+}	4.44	—	4.02	—	4.25	—
Co^{2+}	3.01	3.52	3.21	4.12	3.35	3.64
Ni^{2+}	3.32	3.95	3.33	4.02	3.58	—
Cu^{2+}	3.74	—	3.54	—	3.78	—
Zn^{2+}	3.98	—	4.12	—	4.23	—
Pb^{2+}	4.24	—	4.58	—	4.68	—
Cd^{2+}	4.38	—	4.72	—	4.95	—
Cr^{3+}	4.21	—	4.31	—	4.42	—
Fe^{3+}	4.29	—	4.42	—	4.60	—
Al^{3+}	4.56	—	4.62	—	4.58	—
Glycine	4.05	—	4.25	—	4.65	—
L-Threonine	4.58	—	3.84	—	4.79	—
Alanine	5.32	—	4.75	—	5.75	—
Arginine	3.57	—	4.52	—	4.01	—
Glucose	3.87	—	4.00	—	4.01	—
Dextrose	3.65	—	3.94	—	4.32	—
Maltose	4.85	—	5.20	—	5.63	—
Lactose	5.21	—	4.88	—	5.35	—
Urea	2.85	3.12	3.01	3.24	3.78	—

[a] Separate solution method. [b] Mixed solution method.

Table 4 Statistical treatment of the data obtained for the Sl electrodes employing the standard additions method in comparison with the official method

	Official method	Sl-PTA	Sl-PMA	Sl-PTA/PMA
Pure solutions				
$x \pm$ SE	100.8 ± 0.045	101.30 ± 0.089	99.95 ± 0.065	100.5 ± 0.0074
Probability		< 0.05	> 0.01	> 0.01
Relative error (%)		1.00	0.97	0.88
$F^{3,3}$ value (9.27)[a]		5.01	4.85	3.75
Salbovent tablets (4 mg per tablet)				
$x \pm$ SE	100.9 ± 0.042	100.0 ± 0.075	99.9 ± 0.055	101.2 ± 0.053
Probability		< 0.05	> 0.01	> 0.01
Relative error (%)		1.22	1.02	0.95
$F^{3,3}$ value (9.27)[a]		6.05	6.42	5.98
Salbovent Syrup (2 mg per 5 cm^3)				
$x \pm$ SE	101.3 ± 0.051	101.7 ± 0.032	101.2 ± 0.037	100.3 ± 0.027
Probability		< 0.05	< 0.05	> 0.01
Relative error (%)		1.35	1.19	0.98
$F^{3,3}$ value (9.27)[a]		4.55	5.57	4.98

[a] One tail critical *F* value.

The results of the standard additions method are in good agreement with those obtained from the official method[1] (the latter depends on the measurement of the absorbance of the drug solution in 0.1 mol dm^{-3} HCl at 276 nm). The mean recovery of the amounts taken (1–50 mg) ranged from 96.8 to 100.7% with the relative standard deviation ranging from 0.09 to 0.38.

The results were subjected to linear regression analysis (found values *versus* taken), using the computer program Excel-5, in order to establish whether the investigated electrodes exhibit any fixed or proportional bias. The slopes and intercepts of the regression lines did not differ significantly from the ideal values, revealing the absence of systematic differences between the determined and expected concentrations within the investigated range. Also, they were compared with the results obtained from the official method[1] by applying *F*- and *t*-tests;[34] the results are shown in Table 4. Comparing the obtained *F* and *t* values with the theoretical values, it is clear that the applied methods do not exhibit significant differences in comparison with the official method, which reflects the accuracy and precision of the proposed method.

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