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Direct determination of triamterene by potentiometry using a coated wire selective electrode

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Abstract

A coated wire triamterene-selective electrode based on the incorporation of a triamterene–tetraphenylborate ion-pair in a poly(vinylchloride) coating membrane was constructed. The influence of membrane composition, temperature, pH of the test solution, and foreign ions on the electrode performance were investigated. The electrode showed a Nernstian response over a triamterene concentration range from 1.0×10^{-6} to 3.5×10^{-2} M, at 25 °C, and was found to be very selective, precise, and usable within the pH range 4.5–7.5. The standard electrode potentials, E°, were determined at 15, 20, 25, 30, 35, 40 and 45 °C and used to calculate the isothermal temperature coefficient (dE°/dt) of the electrode. Temperatures higher than 45 °C seriously affected the electrode performance. The electrode was successfully applied to the potentiometric determination of triamterene hydrochloride both in pure solutions and in pharmaceutical preparations.

Keywords: Coated wire electrode; Ion pair; Triamterene; Isothermal temperature coefficient; Pharmaceutical preparations

1. Introduction

Triamterene (6-phenylpteridine-2,4,7-triamine), is a natriuretic agent used to treat various types of diseases. It may be used in the treatment of oedema associated with congestive heart failure, cirrhosis of the liver, nephritic syndrome, and idiopathic and drug-induced oedema [1]. In recent years, diuretics have been abused in sports with two main purposes, namely, to rapidly lower body weight (basically in sports where competitors are classified into weight categories) and to reduce the concentration of medical drugs in urine though dilution, which hinders detection of other doping substances. No medical reason can justify a rapid loss of weight in any sport [2]; in fact, abusing the drugs used for this purpose can pose serious health risks through adverse secondary effects such as hyperkalemia, nausea, vomiting, leg cramps, and dizziness [3]. A folic acid deficiency has been reported to occur occasionally following the use of triamterene. Triamterene causes a modest (2–

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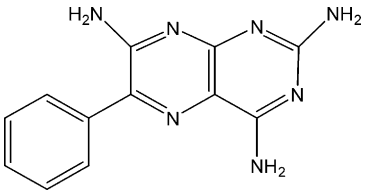
3%) increase in Na^+ and HCO_3^- excretion, a reduction in K^+ and H^+ loss, and a variable effect on Cl^- elimination [4].



Several methods have been reported for the determination of triamterene, including spectroscopy [5–7], high performance liquid chromatography [8–10], gas chromatography–mass spectrometry [11], liquid chromatography [12], micellar liquid chromatography [13], isopotential fluorometry [14], fluorescence spectrometry using partial-least squares calibration [2], column-switching chromatography [15], capillary zone electrophoresis using fluorescence detection [16], and flow injection analysis-liquid chromatography [17]. However, some of these methods involve several manipulation steps before the final result of the analysis is obtained. For instance, the developed method by Li et al. [11] to determine amiloride, triamterene, canrenone, and spironolactone in urine based on gas chromatography and mass spectrometry, is very complex, as it requires prior extraction with ethyl acetate followed by centrifugation. Then the extract is evaporated to dryness and the residue is dissolved in ethyl acetate and dried under nitrogen. The resulting residue is derivatized with bis(trimethsilyl) trifluoroacetamide containing 1% trimethylchlorosilane with heating.

Although potentiometric methods of analysis using ion-selective electrodes are simple, cheap and applicable to samples, no selective electrode is so far available for the determination of triamterene. This work describes a new selective membrane electrode, of the coated wire type, for the determination of triamterene in pure solutions and in pharmaceutical preparations. This electrode is based on incorporation of an ion-pair complex of the tetraphenylborate anion (TPB^-) with triamterene cation (TAH^+) in a poly(vinylchloride) matrix.

It is noteworthy that most previously reported works using poly(vinylchloride) membrane selective electrodes for the determination of species of pharmaceutical and/or medical importance have been carried out at only one temperature, mainly 20 or 25 °C. Less attention has been paid to the higher temperature ranges (e.g. 25–50 °C), although many potentiometric measurements concerning biological media and fluids are made at such temperatures [18]. Here, the effect of the temperature of the test solution on the performance characteristics of the proposed coated wire electrode (CWE) is reported. The work also includes methods for the regeneration of the exhausted electrodes.

2. Experimental

2.1. Reagents and materials

All chemicals used were of analytical or pharmacopeial grade (i.e. can be used for manufacturing pharmaceutical preparations). Doubly distilled water was used throughout the experiments. Chloroform ($CHCl_3$), acetone (C_3H_6O), tetrahydrofuran (THF), and hydrochloric acid (HCl) were supplied by Merck Chemical Company and sodium tetraphenylborate (NaTPB), dibuthylphthalate (DBP), PVC of relatively high molecular weight by Fluka. The pharmaceutical preparations containing triamterene (Dyrenium, Dyazide and Maxzide) were obtained from local drug stores. The pure form of these drugs were supplied by Sobhan pharmaceutical company (Rasht, Iran). The ion-pair associate was prepared by mixing 50 ml 10^{-2} M TAH^+ and 50 ml 10^{-2} M TPB^- solutions. The resulting white precipitate was filtered, washed with water till found to be chloride free and dried at room temperature. The product was subjected to elemental analysis for C, H, N and O (Table 1). As seen, the results are in good agreement with the required values for a 1:1 (TAH:TPB) molar ratio stoichiometry.

Stock triamterene hydrochloride solution (1.0×10^{-2} M) was prepared daily by dissolving an appropriate amount of the drug in double distilled water. More dilute solutions were prepared by

Table 1
Elemental analysis of the ion-associate TAH–TPB

Element	TAH–TPB (1:1)	
	Calculated (%)	Found (%)
C	75.4	73.8
N	17.1	18.3
H	5.4	5.1

appropriate dilution. All triamterene hydrochloride solutions were kept in dark brown bottles.

2.2. Construction of electrodes

Pure aluminum wires of 4.0 cm length were tightly insulated by polyethylene tubes leaving 1.0 cm at one end for the coating and 0.5 cm at the other end for connection. The coating solutions were prepared by dissolving varying amounts of powdered PVC, dibuthylphthalate (as plasticizer) and ion-exchanger TAH–TPB in the minimum amount of tetrahydrofuran possible (3–4 ml) (Table 2). Prior to coating, the polished aluminum surface was washed with a detergent and water, thoroughly rinsed with water, and dried with acetone. Then the wire was rinsed with chloroform and allowed to dry. Afterwards, the aluminum wire was coated by quickly dipping it into the coating solutions (a), (b), (c), (d), or (e) (Table 2) several times and allowing the film left on the wire to dry for about 3 min. The process was repeated several times until a plastic membrane of approximately 1.0 mm thickness was formed. The prepared electrodes were conditioned by soaking them for 3 h in a 1.0×10^{-3} M TAHCl solution daily.

2.3. Apparatus

Potentiometric and pH measurements were carried out using a Corning pH/mV meter ion Analyzer (Corning GmbH, Kaiserslautern, Germany) in stirred solutions. In all instances, an Ag–AgCl/KCl (sat.) electrode (Azar electrode company, Urmia, Iran) was used in conjunction with the respective indicator electrode. A Haake Model FK2 circulation water bath (Hamburg, Germany) was used to control the temperature of the test solution. The electrochemical system was as follows:

Al/membrane/test solution||KCl salt bridge||KCl (sat.)/AgCl–Ag

2.4. Recommended procedures

2.4.1. Construction of the calibration graphs

Suitable increments of standard TAHCl solution were added to 50 ml of 1×10^{-7} M TAHCl solution so as to cover the concentration range from 1.0×10^{-7} to 1.0×10^{-1} M. In the case of concentrated solutions, separate solutions were used. In this solution, the sensor and the reference electrode were immersed and the emf was recorded after 10 s, at 25 °C, after each addition. The

Table 2
Composition of the coating membranes and slopes of the corresponding calibration graphs at 25 °C

Membrane	Coating solution (mg)[a]			Membrane composition (%, m/m)			Linear range (M)	Slope (mV/decade)	R.S.D. (%)[b]
	PVC	DBP	Ion-pair	PVC	DBP	Ion-pair			
(a)	63	55	7	50.4	44	5.6	4.8×10^{-6}–1.2×10^{-2}	54.2	1.3
(b)	60	55	10	48	44	8	7.2×10^{-6}–2.4×10^{-2}	56.0	1.0
(c)	60	50	15	48	40	12	3.9×10^{-6}–3.5×10^{-2}	62.5	1.4
(d)	60	53	12	48	42.4	9.6	1.2×10^{-6}–1.5×10^{-2}	57.1	1.1
(e)	53	60	12	42.4	48	9.6	2.7×10^{-6}–1.6×10^{-2}	54.6	1.2

[a] Dissolved in the least amount of tetrahydrofuran possible (3–4 ml).
[b] Relative standard deviation values of slopes (five determinations).

unknown concentration was determined from the calibration graph.

The electrode potentials, $E_{elec.}$, were calculated from the emf values and plotted versus pTAHCl ($-\log$[TAHCl]). The process was repeated at 20, 30, 35, 40, 45 °C. The electrode was repeatedly calibrated over a period of 3 months.

2.4.2. Standard addition method

Small increments of a standard triamterene hydrochloride solution (1.0×10^{-2} M) were added to 50 ml aliquot samples of various drug concentrations (3.0×10^{-4}–1.5×10^{-3} M). The change in potential reading (at a constant temperature of 25 °C) was recorded for each increment and used to calculate the concentration of TAHCl sample solution.

For the analysis of triamterene formulations, Dyrenium, Dyazide or Maxzide, one tablet of each was dissolved in 50 ml of distilled water and the standard addition technique was applied as described above.

2.4.3. Selectivity of the electrode

Selectivity coefficients were determined by the separate solution method [19] in which the following equation was applied:

$$\log K^{Pot}_{TA,J^{z+}} = (E_2 - E_1)/S + \log[TA] - \log[J^{z+}]^{1/z}$$

where E_1 is the electrode potential in a 1.0×10^{-3} M TAHCl solution; E_2, the potential of the electrode in a 1.0×10^{-3} M solution of the interferent ion J^{z+} and S is the slope of the calibration plot. The selectivity of the electrodes towards sugars and amino acids was studied by adding small increments of a 1.0×10^{-1} M solution of the interfering species to a 50 ml of 1.0×10^{-5} M TAHCl solution. The extent of interference was determined by calculating the tolerance values imparting a 2 mV drift in potential value.

2.4.4. Content uniformity assay of triamterene tablets

Ten individual tablets were placed in separate 100 ml beakers and dissolved in 90–100 ml of distilled water. Concentration of the solutions was determined by the standard addition method, as described above.

2.4.5. Dissolution test

The test was carried out according to the USP XXV method [20], with the use of a standard equipment for this purpose (Pharmatest Model PTWS600, Germany). One tablet was placed in the basket, and the dissolution medium (900 ml 1.0×10^{-1} M hydrochloric acid) was maintained at 37 ± 0.5 °C. The basket was rotated at 100 rpm. For the potentiometric determination, after an appropriate time interval (0.5–5 min), the potential values were recorded, and the amount of the triamterene was calculated from the calibration graph. In order to investigate all the important physical processes during the dissolution period, the release profiles were numerically simulated by a typical equation.

3. Results and discussion

3.1. Composition of the coating membrane

Five coating membrane compositions were investigated as given in Table 2. CWE made by using coating solution (d) exhibited a calibration plot of near Nernstian slope (57.1 mV per concentration decade, at 25 °C, Table 2) over a wide TAH^+ concentration range (1.0×10^{-6}–3.5×10^{-2} M) with a detection limit of 5.8×10^{-7} M and a relative standard deviation of 1.1%. Consequently, the electrode made by using coating solution (d) was selected for carrying out all further studies.

3.2. Effect of soaking and lifetime of the electrode

The performance characteristics of the TAHCl CWE were studied as a function of soaking time. For this purpose the electrode was soaked in a 1×10^{-3} M solution of TAHCl and the calibration graphs (E_{elec}, mV vs. pTAH) were plotted after 10 min and 0.5, 1.0, 2, 3, 5, 6 and 24 h. The optimum soaking time was found to be 2.5–3.0 h, at which the slopes of the calibration curves were 56.2–57.1 mV per pTAH decade, at 25 °C. The electrodes should be kept dry in an opaque closed vessel and stored in a refrigerator while not in use. The

reproducibility of ten repeated measurements on the same solutions was ±1 mV.

The influence of prolonged soaking on the lifetime of TAH–TPB CWE was followed by constructing calibration plots. The electrode was soaked continuously in 10^{-3} M solution of TAHCl for 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60 and 65 days.

The calibration plot slopes decreased slightly to 53.6 mV/decade after 20 days and continued to decrease reaching 46.5 mV/decade after 65 days (Table 3). This is due to leaching, though minimal, of the electroactive species into the bathing solution.

3.3. Regeneration of the electrodes

A regeneration process for the exhausted CWEs has been developed by dipping alternately in 10^{-2} M TAHCl and NaTPB solutions for 1 h at three alternative times. The process succeeded in reactivating the electrodes (Table 3).

3.4. Effect of pH

The effect of pH of the TAHCl solution (10^{-4} and 10^{-3} M TAHCl) on the electrode potential was investigated. The solutions were acidified by the addition of very small volumes of HCl then the pH value was increased gradually using NaOH (0.1 or 1.0 M). For each pH value, the potential was recorded and thus the potential–pH curves for two TAHCl concentrations were constructed (Fig. 1). As is obvious, within the pH range 4.5–7.5, the electrode potential is practically independent of pH, and in this range, the electrode can be safely used for triamterene determination. The increase in mV readings at pH less than 4.5 may be due to penetration of H^+ into the membrane surface [21] or a gradual increase of protonated species and

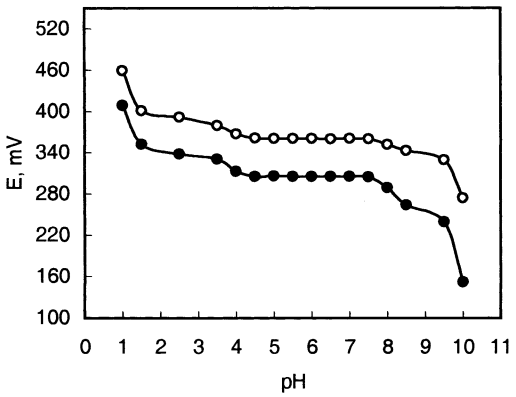


Fig. 1. Effect of pH of the test solution on the potential reading: (●) 1.0×10^{-4} M TAHCl, (○) 1.0×10^{-3} M TAHCl solution at 25 °C, using electrode (d).

Table 3
Effect of prolonged soaking time and performance characteristics of TAH–TPB electrode before and after regeneration, (d), days

Number	Soaking time (days)	Before regeneration		After regeneration	
		Slope (mV/decade)	Usable concentration range (mol/dm^3)	Slope (mV/decade)	Usable concentration range (mol/dm^3)
1	2	54.2	2.5×10^{-6}–4.0×10^{-4}	56.3	3.1×10^{-6}–1.1×10^{-2}
2	3	55.1	4.0×10^{-6}–3.0×10^{-4}	56.4	4.8×10^{-6}–5.5×10^{-3}
3	5	52.9	3.0×10^{-6}–2.0×10^{-4}	55.9	3.7×10^{-6}–4.3×10^{-3}
4	10	54.1	1.0×10^{-5}–4.0×10^{-4}	53.8	8.3×10^{-6}–1.2×10^{-2}
5	15	53.9	3.0×10^{-5}–7.0×10^{-4}	56.2	3.4×10^{-5}–1.0×10^{-2}
6	20	53.6	2.0×10^{-5}–4.0×10^{-4}	56.3	4.3×10^{-5}–1.0×10^{-2}
7	25	50.8	5.0×10^{-5}–6.0×10^{-4}	54.8	6.1×10^{-5}–7.1×10^{-3}
8	30	51.3	4.0×10^{-5}–8.0×10^{-4}	52.1	4.3×10^{-5}–6.2×10^{-3}
9	35	49.3	6.0×10^{-5}–8.0×10^{-4}	56.7	2.0×10^{-5}–1.0×10^{-3}
10	40	49.1	4.0×10^{-5}–6.0×10^{-4}	54.0	5.0×10^{-5}–1.0×10^{-2}
11	50	47.6	6.0×10^{-5}–5.0×10^{-4}	52.9	3.1×10^{-5}–7.3×10^{-3}
12	60	46.8	3.0×10^{-5}–2.0×10^{-4}	53.4	4.3×10^{-5}–6.6×10^{-3}
13	65	46.5	8.0×10^{-5}–3.0×10^{-4}	54.0	3.8×10^{-5}–8.4×10^{-3}

dependence of the emf on the pH of the solution [22]. At higher pH values (pH > 7.5), free base precipitates in the test solution and consequently, the concentration of unprotonated species gradually increased. As a result, lower emf readings were recorded [22]. The decrease in potential readings at pH > 7.5, on the other hand, can be probably attributed to penetration of OH^- ions into the gel layer of the membrane [23].

During the operating life of the electrode (3 months), no significant change in the potential–pH behavior was observed.

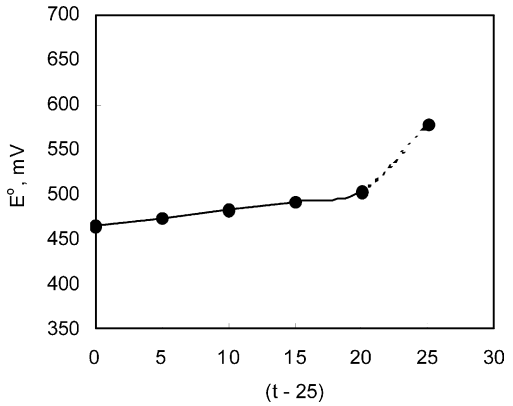


Fig. 2. Variation of $E^{\circ}_{elec.}$ (●) with changes of test solution temperature.

3.5. Effect of temperature of the test solution

Calibration graphs were constructed at different test solution temperatures (i.e. 25, 30, 35, 40 and 45 °C) for the TAH–TPB electrode. The slope, response time, usable concentration range and the standard electrode potentials ($E^{\circ}_{elec.}$) (obtained from the calibration plots as the intercepts at pTAH = 0) corresponding to each temperature are reported in Table 4.

It is clear that the electrode has a more or less good Nernstian response in the temperature range 25–45 °C. For the determination of the isothermal coefficients (dE°/dt) of the electrode, the standard electrode potentials ($E^{\circ}_{elec.}$) at different temperatures were plotted versus (t − 25) (Fig. 2), where t is the temperature of the test solution. A straight-line plot was obtained according to the following equation [24]:

$$E^{\circ} = E^{\circ}_{(25)} + (dE^{\circ}/dt)(t - 25)$$

The slope of the straight line obtained represent the isothermal coefficient of the electrode (amounting to $+1.88 \times 10^{-3}$ V/°C), reveals a fairly good thermal stability of the electrode within the investigated temperatures range.

3.6. Selectivity of the electrode

The selectivity of the ion-pair associates based membrane electrodes depends on the selectivity of the ion-exchange process at the membrane–test solution interface and the mobilities of the respective ions within the membrane. The selectivity coefficients obtained by the separate solution method [19] (Table 5) showed that the proposed CWE is highly selective toward TAH^+ ion. The inorganic cations did not interfere due to the differences in their mobilities and permeabilities as compared with TAH^+. For natural species, the tolerance ratios of their concentration to that of TAHCl were as follows: 1600 for D(+)glucose, 1920 for lactose, 1780 for maltose, 1360 for alanine and 1140 for glycine. In the case of sugars and amino acids, the high selectivity is mainly attributed to the difference in polarity and lipophilic

Table 4
Performance characteristics of triamterene, selective electrode at different temperatures

Temperature (°C)	Slope (mV/decade)	Usable concentration range (mol/dm^3)	$E^{\circ}_{elec.}$ (mV)
25	57.1	1.2×10^{-6}–1.5×10^{-2}	458
30	57.8	6.2×10^{-6}–1.5×10^{-2}	470
35	58.4	8.2×10^{-6}–1.5×10^{-2}	483
40	59.1	4.3×10^{-5}–8.1×10^{-3}	496
45	59.9	7.2×10^{-5}–7.5×10^{-3}	503

Table 5
Selectivity coefficients of the triamterene CWE calculated by the separate solution method (1.0×10^{-3} M of both TAHCl and the interferent) at 25 °C

Interferent	$K^{Pot}_{TAH,J^{z+}}$	Interferent	$K^{Pot}_{TAH,J^{z+}}$
Na^+	8.3×10^{-4}	Mn^{2+}	3.1×10^{-4}
NH_4^+	6.8×10^{-4}	Fe^{3+}	2.5×10^{-4}
Ca^{2+}	3.7×10^{-4}	Al^{3+}	7.3×10^{-4}
Sr^{2+}	1.3×10^{-3}	Hydrochlorothiazide	1.3×10^{-2}
Co^{2+}	4.8×10^{-4}	Primidone	2.3×10^{-1}
Ni^{2+}	2.0×10^{-4}	Chlordiazepoxide	3.4×10^{-1}
Zn^{2+}	2.4×10^{-4}	Sulfamethoxazole	1.1×10^{-2}

character of their molecules relative to TAHCl. Though primidone and chlordiazepoxide interfere, they are not found together with TAHCl in pharmaceutical preparations.

4. Analytical application

The present CWE has been successfully used for the determination of triamterene in aqueous solution and in pharmaceutical preparations (i.e. dyrenium, dyazide, and maxzide) by using the standard addition method described above, and the results are summarize in Table 6.

The recovery and relative standard deviation values given in Table 6 were calculated from eight determinations. Collective results, given in Table 6, indicate the high accuracy and precision of the present work as compared with those previously reported by spectroscopy [7] and HPLC [8] methods which require more complicated instrumentations or time-consuming pretreatment steps. The combination of sensitivity, selectivity and simplicity of the ion-selective electrode potentiometry makes it an excellent and versatile technique.

The performance of the method was assessed by calculation of the t- and F-values in comparison to the published method [14]. Mean values were obtained in a student's t- and F-test at 95% confidence limits for seven degrees of freedom [25], and the results showed that the calculated t- and F-values did not exceed the critical values.

The necessity for an in vitro test that adequately reflects the physiological availability of the solid-dosage forms of a drug is now recognized. The measurement of a parameter that is related to the rate of dissolution of a solid has been suggested as a more realistic variable and this has led to numerous papers describing different methods and equipments for monitoring the dissolution test [20,26].

The dissolution test was performed with a basket-stirrer USP-type apparatus operated at 100 rpm in 900 ml 1.0×10^{-1} M hydrochloric acid (simulated duodenum fluid), with the use of the potentiometric triamterene electrode. The simulated duodenum fluid was kept at 37.0 ± 0.5 °C. There are no degradation products in the in vitro test. The compression excipients do not interfere.

Taking into account the S shape of the dissolution curve obtained (Fig. 3) revealed that, the dissolution process involves two main steps: an initial step of about 7 min while the encapsulation layer is dissolved, followed by a relatively fast one of active-principle dissolution.

The method proved that the release of the active principle of the tablets in simulated duodenum fluid follows the Wagner model [27].

Table 6
Potentiometric determination of triamterene in aqueous solution and in pharmaceutical preparations with a triamterene electrode by the standard addition method, at 25 °C

Sample	Amount taken (mg)	Recovery (% of nominal value)	R.S.D. (%)
Pure TAHCl solution	15	100.4	0.9
Dyrenium tablets	30	98.7	1.1
Dyazide tablets	20	96.3	0.8
Maxzide tablets	20	99.2	1.2

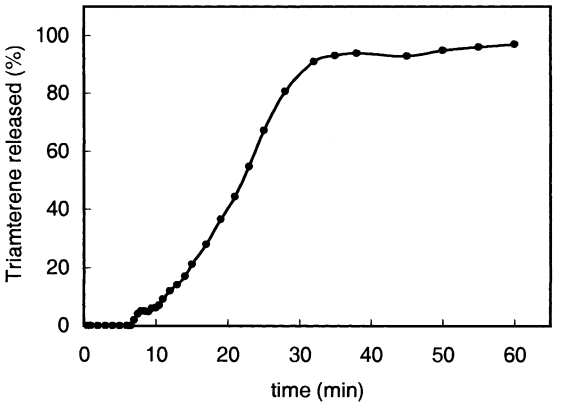


Fig. 3. Dissolution profile of triamterene capsules. All values are the average of four determinations.

5. Conclusion

The proposed method has some important advantages: the electrode proved to be successful, providing a rapid, simple and low cost potentiometric method for the determination of TAHCl in pure solutions and in pharmaceutical preparations; it ensures a good accuracy for the triamterene assay due to the possibility to control the ion activity continuously and also a fast assay of triamterene tablets. The present electrode is easily and simply regenerated.

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