Journal of Pharmaceutical & Biomedical Analysis
Vol. 10, Nos 10–12, pp. 757–761, 1992
Printed in Great Britain

0731–7085/92 $5.00 + 0.00

PVC membrane electrode without inner reference solution for the direct determination of ephedrine in pharmaceutical preparations*

MANUEL N.M.P. ALÇADA, JOSÉ L.F.C. LIMA† and M. CONCEIÇÃO B.S.M. MONTENEGRO

Physical Chemistry Department, Faculty of Pharmacy, 4000 Porto-Portugal

Abstract: A PVC membrane electrode, without inner reference solution, based on an ion association extraction system responding to ephedrine is described. It incorporates an ephedrine-tetrakis (4-chlorophenyl)borate ion-pair complex in 2-nitrophenyloctyl ether. The prepared electrode exhibits a near Nernstian response (57.5 mV per decade) over the concentration range of 2×10^{-5}–10^{-1} M ephedrine in solutions of pH 2.5–9. The reproducibility of the electrode potentials were ±1 mV by day during at least 6 months. Response time was about 6 s for ephedrine concentrations between 10^{-5} and 10^{-1} M. Determinations of ephedrine in pharmaceutical preparations (tablets, nasal drops and syrups) by direct potentiometry gave an average recovery of 99.1% (w/w) and a mean standard deviation of 1.9% (w/w).

Keywords: *Ion selective electrode; pharmaceutical preparations; ephedrine determination.*

Introduction

Ephedrine hydrochloride is widely used as a sympathomimetic drug that stimulates both α- and β-adrenergic receptors. The official pharmacopoeias describe a nonaqueous titration [1, 2] for the compound analysis. Many organic substances, drug excipients and various organic bases interfere significantly, thereby resulting in a method which are not in good agreement with the ephedrine content. This fact justified the development of other analytical techniques involving, for example, UV spectrophotometry [3, 4], conventional titration [5], polarography [6], colorimetry with colour reagents such as picryl chloride [7] or thymol blue [8], chromatography [9] and potentiometry with ion selective electrodes [10–16].

Although potentiometry presents advantages over the other methods above mentioned, especially as regards the speed and ease of determination, the characteristics of the electrodes used, principally the selectivity and reproducibility of the potentials, resulted in rather inexact results in the majority of cases. The most significant drawbacks of the several types of electrodes constructed so far [10–16] are due to the use of tetraphenylborate as an ion extractor [10, 13, 16] or to the use of a liquid sensor [11, 14–16]. In effect, the electrodes whose construction and evaluation was referred to earlier, have a short life-time in addition to their reduced reproducibility and selectivity.

In previous studies we described different electrodes, with a PVC membrane and without inner reference solution for the selective determination of several anionic organic compounds, such as benzoate [17], salicylate [18], 5,5-diethylbarbiturate [19, 20], 5-ethyl-5-phenylbarbiturate [21]. This type of construction provided electrodes with good stability and life-time.

With a view to obtaining an electrode with better operating characteristics than the aforementioned ephedrine electrodes [10–16] tetrakis (4-chlorophenyl)borate was used as ionic extractor dissolved in 2-nitrophenyloctyl ether. The ion sensor, immobilized in PVC, was applied directly to an epoxy resin support with dispersed graphite as a conductor.

In order to assess the extent of the improvements thus obtained a detailed study of the operating characteristics was performed and determinations of the primary ion in pharma-

*Presented at the "Fourth International Symposium on Drug Analysis", May 1992, Liège, Belgium.
†Author to whom correspondence should be addressed.

ceutical preparations commonly available on the Portuguese market were conducted.

Experimental

Apparatus and electrodes

A Crison 2002 (sensitivity ±0.1 mV) potentiometer coupled to an electrode switcher of the same brand was used for measuring the electrode potentials.

All determinations were performed at 25.0 ± 0.2°C, using a silver chloride–silver Orion 900200 double-junction reference electrode with 0.1 M sodium chloride solution in the outer compartment. An Ingold 10/402/3092 electrode was used for the pH measurements.

Reagents and solutions

The water used in the preparation of all the reagents and standard solutions was doubly de-ionized. All chemicals were of analytical-reagent grade.

The standard 0.01 or 0.1 M aqueous ephedrine hydrochloride solutions were prepared daily by weighing, and when not in use stored away from light.

The buffer used for the potentiometric determination of ephedrine in pharmaceutical preparations was an acetic acid–sodium acetate solution at pH 5.2 and an ionic strength of about 0.1 M, prepared in 1 l flask, by adding 100 ml of a 1 M sodium hydroxide solution to 120 ml of acetic acid and completing the volume with de-ionized water.

Membrane preparation and electrode assembly

For the preparation of the membranes, 5 ml of 0.11 M aqueous ephedrine hydrochloride was added to 10 ml of 0.05 M solution of potassium tetrakis (4-chlorophenyl) borate in acetone. The precipitate resulting after evaporating the acetone, was filtered and washed with de-ionized water and dried, protected from the light, in a desiccator at room temperature.

Approximately 0.04 g of precipitate were dissolved in 0.56 g of 2-nitrophenyloctyl ether. About 0.4 ml of this solution was mixed with 0.18 g of PVC previously dissolved in about 6 ml of tetrahydrofuran, resulting in a membrane whose composition of the ion pair complex was about 5% (w/w).

The prepared membrane was applied directly to a support composed of a mixture of epoxy resin and graphite as previously described [22].

The constructed electrodes were conditioned by soaking in 5×10^{-3} M ephedrine hydrochloride solution. The same solution was used for conditioning the electrodes whilst stabilizing the internal potential during the first three days after construction (for details, see Lifetime and Reproducibility).

Determination of ephedrine in pharmaceutical preparations

For ephedrine hydrochloride determinations in tablets, about 10 tablets were finely powdered and approximately 20 mg of this powder were placed in a 50 ml volumetric flask and diluted with water.

For liquids a volume equivalent to 4 mg of ephedrine hydrochloride was diluted to 50 ml with water.

The potentiometric determinations were performed on these solutions by mixing equal volumes with acetic acid–sodium acetate buffer (pH 5.2 and ionic strength 0.1 M). These measurements were preceded by the calibration of the electrode with solutions of several concentrations of ephedrine hydrochloride standard with the same amount of buffer.

The accuracy of the potentiometric determinations was checked by evaluating the recovery. For this, a small amount of 10^{-2} M ephedrine hydrochloride (500 µl) was added to one sample prepared as previously described. The variation reading was recorded and used to calculate the percentage recovery of the amount added.

Results and Discussion

Electrode behaviour

The overall electrode operating characteristics were assessed on the basis of the calibration curves obtained by measuring the e.m.f. values of a series of ephedrine hydrochloride solutions. The experiments were performed over the concentration range 10^{-1}–10^{-6} M in solutions with (sodium chloride 0.1 M) and without the ionic strength adjusted and in acetic acid–sodium acetate buffer solutions with a pH of 5.2 (Fig. 1).

Table 1 shows the values obtained for the general operating characteristics of the ephedrine electrode under the aforementioned experimental conditions. The data presented

Table 1
Working characteristics for the ephedrine selective electrode

Characteristics	I*	II†	III§
Slope (mV dec.$^{-1}$)	55 ± 1	57.2 ± 0.5	57.5 ± 0.4
LLLR (M)	8×10^{-6}	2×10^{-5}	8×10^{-5}
LLD (M)	4×10^{-6}	1×10^{-5}	1×10^{-5}
Range of pH‖	2.5–9	2.5–9	—
Response time (s)	<20	~6	~6
Reproducibility (mV day^{-1})	±1.5	±1.0	±0.9
Lifetime (months)	>6	>6	>6

*Obtained in pure solutions without the ionic strength adjusted.
†Obtained in solutions with I = 0.1 M adjusted with NaCl.
§Obtained in acetic acid–sodium acetate buffer solutions (pH 5.2 and i = 0.1 M).
‖Obtained in 5×10^{-3} M ephedrine hydrochloride solutions.

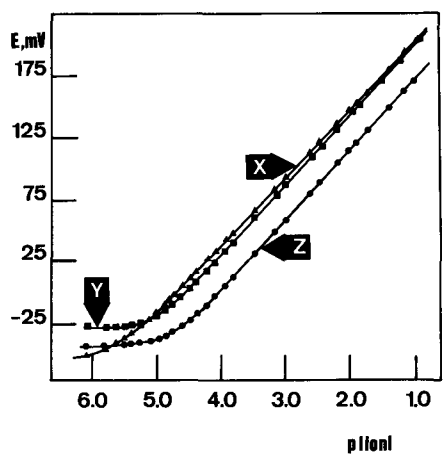

Figure 1
Calibration curves for ephedrine electrode obtained in solutions: (X) — without ionic strength adjusted; (Y) — with ionic strength adjusted (NaCl 0.1 M); (Z) — in acetic acid–sodium acetate buffer (pH 5.2).

correspond to the average of six values obtained in two determinations with three electrodes. Comparing the results obtained with those presented by other authors for electrodes sensitive to the same cationic species using tetraphenylborate as the ionic extractor [10, 13, 16] a significant increase in the linear response range (of about 1 decade of concentration) was noted.

The response time of the electrode was fast, being nearly instantaneous in solutions with the pH and the ionic strength adjusted with the setting of a value of ±0.2 mV for the stabilization of the electrode. When the ionic strength was not adjusted the response of the electrode did not exceed the 20 s, when the criterion for its stability was the same.

The values obtained for this parameter are considerably shorter than those referred in the literature for other ephedrine electrodes [11, 14, 15], for which response times of about 30 s for concentrations greater than 10^{-3} M and of 90 s for lower values have been claimed.

Effect of pH

The effect of pH on the potential of the ephedrine electrode was checked by recording the e.m.f. of the ion-selective electrode in 5×10^{-3} M ephedrine hydrochloride solutions (pK_a = 9.958 [23]). The pH of the initial solution was modified by adding very small volumes of concentrated hydrochloride acid or sodium hydroxide solutions. The diagrams presented in Fig. 2 show that the electrode potentials in 5×10^{-3} M ephedrine solutions were not affected by the pH in the 2.5–9 range. The significant decrease of the potential observed above pH 9 is probably due to the increased concentration of the unprotonated amine.

Selectivity

The interference of various cations was studied by a separated solution method [24] at two concentration levels without ionic strength adjusted (Table 2).

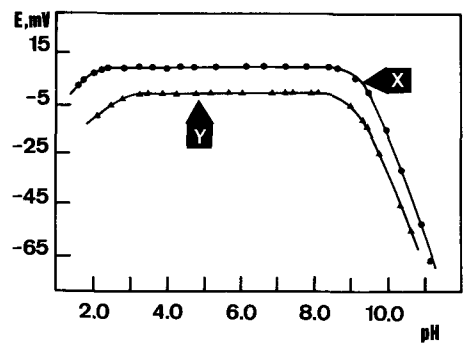

Figure 2
Effect of pH on the potential of ephedrine electrode in 5×10^{-3} M ephedrine solutions: (X) — with ionic strength adjusted to 0.1 M; (Y) — without ionic strength adjusted.

Table 2
Potentiometric selectivity coefficients (log K^{pot}) for ephedrine selective electrode*

Inferent	Concentration (M)	
	1×10^{-4}	1×10^{-3}
Calcium	−3.42 ± 0.07	−3.95 ± 0.07
Sodium	−1.42 ± 0.04	−2.50 ± 0.04
Ammonium	−1.32 ± 0.05	−2.25 ± 0.04
Potassium	−1.35 ± 0.05	−2.23 ± 0.05
Atropine	+0.05 ± 0.04	+0.64 ± 0.08
Quinidine	+0.21 ± 0.04	+2.16 ± 0.03
Pilocarpine	+0.12 ± 0.04	+0.38 ± 0.03
Strychnine	+0.07 ± 0.11	+1.67 ± 0.04

*Mean and standard deviation of four values obtained with three electrodes.

Some of the ions were chosen because they represent potentially low-level contaminants in pharmaceutical preparations of ephedrine.

The more common inorganic cations do not interfere with the normal performance of the ephedrine electrode. Soluble drug excipients and diluents such as maltose, glucose, lactose, starch and gelatin binders that are present in some tablets also do not interfere with the electrode response.

As regards the alkaloids studied, the electrode is more selective than other units sensitive to the same species [10–16], and is adequate for the determinations of the pharmaceutical formulations tested herein.

Life-time and reproducibility

Various units which were constructed and subjected to periodic evaluations, remained operational without altering their response characteristics for at least 6 months. This value was obtained by repeating the calibration curves in ephedrine hydrochloride solutions with the ionic strength adjusted to 0.1 M.

During this time the reproducibility of the potential readings was about ±1 mV each day, over the entire concentration range. In the first 3 days after the electrode preparation, however, the potential varied from 5 to 10 mV and should not be used for analytical purpose during this period. This time corresponds to the stabilization of the inner reference system [25].

In previous studies on the construction of ephedrine electrodes [10–16] life-times not exceeding four weeks are given for optimum behaviour. The value given in this paper is exceptionally high due, on the one hand, to the use of 2-nitrophenyloctyl ether as a plasticizing agent and on the other hand, to the elimination of hydrostatic pressure resulting from the absence of an inner reference solution [26].

Analytical applications

The assessment of the analytical usefulness of the electrodes constructed and of the advantages of the new improvements was complemented with a study of how they could be applied to the determination of ephedrine in pharmaceutical preparations currently available on the Portuguese market.

The determinations were made on various types of samples (tablets, nasal drops and syrups), prepared as described herein. Table 3 gives the mean results obtained with two electrodes on three independent preparations of each lot (mean of six values).

The solid residues resulting from the preparation of the tablets did not affect the measurements, hence one can dispense with their elimination by filtration.

Table 3
Determination of ephedrine in some pharmaceutical preparations using ephedrine electrode

Preparation*	Labelled active ingredients (%w/w)	Ephedrine found (%)†	Ephedrine recovery (%)†
Antiasmático (tablet)	9.98	9.26 ± 0.07	96.4 ± 1.6
Argotone (nasal drop)	0.90	0.93 ± 0.02	99.3 ± 1.5
Nasocalma (nasal drop)	1.0	1.00 ± 0.02	99.7 ± 2.7
Codeisan (syrup)	0.16	0.17 ± 0.02	98.6 ± 3.4
Efedril (syrup)	0.13	0.09 ± 0.01	101.7 ± 2.0

*Commercially available dosage forms with names written in Portuguese.
†Mean and standard deviation of six determinations with two electrodes.

As it was not possible to apply pharmacopoeial procedures [1, 2] for determinations of the pure drug or its preparations recoveries were determined to assess the accuracy of the potentiometric results. The values obtained varied between 96.4 and 101.7%, which corresponds to an average recovery of 99.1% and a mean standard deviation of 1.9%.

Conclusions

The results presented herein led us to conclude that the use of tetrakis (4-chlorophenyl)-borate as an ion extractor provides electrodes with good operating characteristics, particularly as regards linear range, selectivity, and stability.

The elimination of the inner reference solution and the use of 2-nitrophenyloctyl ether as a mediator solvent contributed to the greater reproducibility of the units as compared to others described [10–16] and most especially to a considerably significant increase in the lifetime of the electrodes.

It is inferred that the electrode based on ephedrine-tetrakis (4-chlorophenyl) borate as an ion exchanger and 2-nitrophenyloctyl ether as mediator, without an inner reference solution, provides a rapid, sensitive, inexpensive and reliable method for ephedrine determinations in pharmaceutical analysis with minimal sample pre-treatment.

Acknowledgements — The authors gratefully acknowledge the financial support granted them by the Instituto Nacional de Investigação Científica (Project 89/SAD/1). One of us (MNMPA) was supported by a grant from JNICT (Lisbon, Portugal). We thank Mrs Belmira Pereira for carrying out routine work.

References

[1] *U.S. Pharmacopeia*, 19th rev., p. 276. U.S. Pharmacopeial Convention, Rockville, MD (1975).
[2] British Pharmacopoeia, p. 170. Her Majesty's Stationery Office, London (1980).
[3] H. Abdine, M. El-Sayed and S.A. Ibrahim, *Planta Med.* **23**, 398–400 (1973).
[4] M.A. Mohamed, A.M. Taha, S.R. El-Shabouri and P.Y. Khashaba, *J. Assoc. Off. Anal. Chem.* **65**, 894–898 (1982).
[5] S. Klosowsk and H. Zudwicki, *Acta Pol. Pharm.* **26**, 537–539 (1969).
[6] Kh.P. Ibragimov and Kh.R. Rustamov, *Dokl. Akad. Nank. Uzb., SSR* **27**, 30–31 (1970); *Chem. Abstr.* **74**, 83848 (1971).
[7] L.G. Chatten and L.I. Pugshey, *J. Am. Pharm. Assoc.* **41**, 108–110 (1952).
[8] S.K. Srivatova, P.C. Base, G.K. Ray and B. Mukerji, *J. Sci. Indian Res.* **20D**, 212–213 (1961).
[9] H.W. Schultz and C. Paveenbampen, *J. Pharm. Sci.* **12**, 1995–1997 (1973).
[10] K. Selinger and R. Staroscik, *Pharmazie* **33**, 208–212 (1978).
[11] S.S.M. Hassan, *Arab. Gulf. J. Sci. Res.* **4**, 127–137 (1986).
[12] R. Zeng, G. Li and J. Ma, *Yaoxue Tongbao* **22**, 736–738 (1987).
[13] J. Zeng, *Yaoxue Xuebao* **17**, 841–846 (1982).
[14] S.S.M. Hassan and G.A. Rechnitz, *Anal. Chem.* **58**, 1052–1054 (1986).
[15] S.S.M. Hassan and M.M. Saoudi, *Analyst* **111**, 1367–1370 (1986).
[16] K. Fukamachi, R. Nakagawa, M. Morimoto and N. Ishibashi, *Bunseki Kagaku* **24**, 428–432 (1975).
[17] J.L.F.C. Lima, M.C.B.S.M. Montenegro and A.M.R. Silva, *Ann. Pharm. Franc.* **49**, 76–83 (1991).
[18] J.L.F.C. Lima, M.C.B.S.M. Montenegro and A.M.R. Silva, *J. Flow Injection Anal.* **7**, 19–33 (1990).
[19] J.L.F.C. Lima, M.C.B.S.M. Montenegro and A.M.R. Silva, *Port. Electr. Acta* **6**, 69–76 (1988).
[20] J.L.F.C. Lima, M.C.B.S.M. Montenegro, J. Alonso, J. Bartroli and J.G. Raurich, *Anal. Chim. Acta* **234**, 221–225 (1990).
[21] J.L.F.C. Lima, M.C.B.S.M. Montenegro and A.M.R. Silva, *J. Pharm. Biomed. Anal.* **8**, 701–704 (1990).
[22] R.A.S. Lapa, J.L.F.C. Lima and A.M.R. da Silva, *Il Farmaco* **45**, 901–913 (1990).
[23] *Handbook of Chemistry and Physics*, 70th edn, p. 0–161. CRC Press, Boca Raton, FL (1989/1990).
[24] IUPAC Analytical Chemistry Division on Analytical Nomenclature, *Pure Appl. Chem.* **53**, 1913–1952 (1981).
[25] A. Hulanicki, M. Maj-Zurawska and R. Lewandowski, *Anal. Chim. Acta* **98**, 151–154 (1978).
[26] G.J. Moody, J.D.R. Thomas, J.L.F.C. Lima and A.A.S.C. Machado, *Analyst* **113**, 1023–1027 (1988).

[*Received for review 5 May 1992; revised manuscript received 17 June 1992*]