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A New Liquid Membrane Electrode for Selective Determination of Ephedrine

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ABSTRACT. A new liquid membrane electrode based on an ion-association extraction system responding to ephedrine is described. It incorporates ephedrine-5-nitrobarbiturate ion pair complex in octan-1-ol as a noval electroactive component. The electrode exhibits Nernstian response over the concentration range of 10^{-2} to 10^{-6} M ephedrine in solutions of pH 4-9. The response time varies from 20 to 90 seconds and interferences from many organic bases and some common inorganic cations are negligible. Determination of 0.1 to 2000 μg/ml ephedrine in both pure and pharmaceutical samples gives results with an average recovery of 99.2% and a mean standard deviation of 1.5%.

Ephedrine is a sympathomimetic drug stimulating both α and β adrenergic receptors. It is used in therapeutic doses at the level of 15-60 mg to produce peripheral vasoconstriction, to raise blood pressure, to prevent hypotension and to treat allergic states, catalepsy and myasthenia gravis. It is also utilized as antidote for poisoning by central nervous system depressants. Official methods used for determination of ephedrine in various pharmaceutical preparations are mainly based on extraction followed by spectrophotometric measurement at 241 nm (BPC 1973). Many organic compounds, drug excipients and various organic bases, however, absorb at the same wavelength and thus significantly interfere. Membrane electrodes responsive to the cations of ephedrine and methylephedrine based on the use of the tetraphenylborate derivatives of these compounds have been described for selective determination of these drugs (Fukamachi *et al.* 1975).

In previous studies, we described new liquid membrane electrodes for selective determination of strychnine (Hassan and Elsayes 1979), atropine (Hassan

and Tadros 1984), caffeine (Hassan *et al.* 1985) and xylocaine (Hassan and Ahmed 1985) in various pharmaceutical preparations. These electrodes are based on the use of picrolonate, reineckate and picrylsulfonate derivatives of these alkaloids as membrane materials. In the present work, a liquid membrane electrode with significantly improved characteristics for ephedrine is developed. It is based on the use of ephedrine-5-nitrobarbiturate in octan-1-ol as a novel electroactive material. The electrode is satisfactorily used for determination of ephedrine in simple and complex matrices.

Experimental

Reagents

All solutions were prepared with deionized twice-distilled water and reagent grade substances, except where otherwise stated. 5-Nitrobarbituric acid, ephedrine hydrochloride and all other alkaloids were obtained from Sigma Chemical Co. (St. Louis, MO). Pharmaceutical preparations containing ephedrine were obtained from local drug stores.

Membrane Preparation

Ephedrine-5-nitrobarbiturate complex was prepared by mixing and stirring a 20 ml aliquot of 10^{-2}M ephedrine hydrochloride solution with a 30 ml aliquot of 10^{-2}M 5-nitrobarbituric acid solution. The precipitate was filtered with a G-3 sintered glass crucible, washed with twice-distilled water followed by ethanol, dried at 100°C for 1 hour and ground to fine powder. A 10^{-2}M solution of ephedrine-5-nitrobarbiturate in octan-1-ol was used as a liquid membrane.

Electrode Assembly

An Orion liquid membrane electrode body (Model 92) equipped with an Orion 92-05-04 porous membrane was assembled as previously described (Ma and Hassan 1982). A 10^{-2}M solution of ephedrine-5-nitrobarbiturate in octan-1-o1 as liquid membrane and an aqueous solution containing 10^{-2}M of both ephedrine hydrochloride and potassium chloride as internal reference solution were used. The electrode was conditioned for 24 hours by soaking in 10^{-2}M aqueous ephedrine hydrochloride solution and stored in the same solution when not in use.

Potential Measurement

Potential measurement was made with ephedrine-5-nitrobarbiturate liquid membrane electrode in conjunction with a double junction Ag/AgCl reference electrode (Orion Model 90-02-00) containing 10% KNO_3 in the outer compartment. The electrode cell used was as follows: 10^{-2}M ephedrine hydrochloride + 10^{-2}M KCl/10^{-2}M ephedrine-5-nitrobarbiturate in octan-1-ol// porous membrane/ ephedrine test solution/Ag/AgCl double junction reference electrode. The cell

potential was measured at 25 ± 0.5°C with an Orion microprocessor ionalyzer (Model 901). Adjustment of pH to 4-8 was carried out using Orion combined glass-calomel electrode system (Model 90-00).

Electrode Calibration

The ephedrine-5-nitrobarbiturate liquid membrane electrode in conjunction with the reference electrode was immersed in 15 ml aliquots of $10^{-2} - 10^{-6}$M ephedrine solutions. The potential readings were recorded after stabilization to ± 0.3 mv and plotted as a function of the logarithm of ephedrine concentration. The graph was used for subsequent determination of ephedrine in unknown samples.

Electrode Selectivity

The selectivity coefficients were evaluated based on the potential measurement in mixed solutions which contained 10^{-3}M ephedrine hydrochloride solution and $10^{-2} - 10^{-5}$M of the interfering compounds (Ma and Hassan 1982). The selectivity coefficients $K^{pot}_{A,B}$ were calculated according to the relation:

$K^{pot}_{A,B} = (10^{\triangle E/S} - 1)\ a_A/(a_B)^{1/z}$ where $\triangle E$ is the change in potential in the presence of the diverse compound $B^{z\pm}$. S is the slope of the calibration graph for ephedrine and a_A and a_B are the concentrations of protonated ephedrine and the diverse compound, respectively.

Determination of Ephedrine in Drugs

The contents of one vial (1-2 ml) or 10 ml portion of eye drops or tincture or one powdered tablet were homogenized. A weighed quantity equivalent to 20-50 mg ephedrine was treated with 5 ml of 10^{-2}M hydrochloric acid, gently heated to about 60°C for 5 minutes and cooled. The solution was transferred to a 25 ml volumetric flask, diluted to the mark with twice-distilled water and shaken well. A 20 ml aliquot of the solution was transferred to 100 ml beaker, the pH adjusted to 4-8 with dilute sodium hydroxide solution and ephedrine-5-nitrobarbiturate liquid membrane electrode in conjunction with a double junction Ag/AgCl reference electrode immersed in the solution. The solution was stirred well, the steady potential recorded after a stable reading and compared with the calibration graph.

Results and Discussion

Membrane Material and Characteristics

It has been reported that some organic bases can be identified by examining the photomicrographs or measuring the melting points of their 5-nitrobarbiturate derivatives (Chatten and Barry 1968). In this study, ephedrine-5-nitrobarbiturate was prepared, characterized and tested as a novel ion exchanger site in a liquid membrane electrode responsive for ephedrine. The elemental analysis data of the

product obtained by reaction of ephedrine with 5-nitrobarbituric acid agree with the composition $C_{14}H_{18}N_4O_6$. The infrared spectrum of this product displays almost all the absorption bands which appear in the spectra of both reactants besides a stretching vibration band at 2460 cm^{-1} assigned to the imino group (= N^+H). These results indicate the formation of 1:1 (ephedrine: 5-nitrobarbiturate) ion pair complex (Fig. 1).

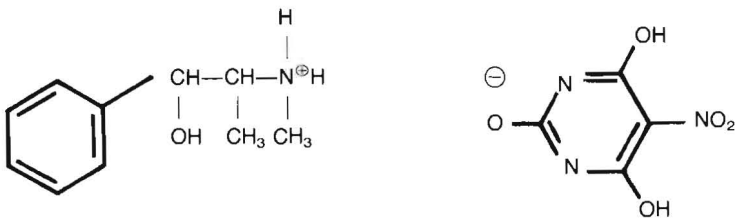

Fig. 1. Ephedrine-5-nitrobarbiturate ion-pair complex.

Liquid membrane electrodes consisting of ephedrine-5-nitrobarbiturate as an ion exchanger dissolved in some lipophilic solvents such as octan-1-ol, decan-1-ol and nitrobenzene have been prepared. The response characteristics of these electrodes are evaluated at 25 ± 0.5°C over the course of 30 days for standard solutions of ephedrine hydrochloride. Linear regression analysis of the obtained data is given in Table. 1.

Table 1. Response characteristics of ephedrine-5-nitrobarbiturate liquid membrane electrode at 25°C in some lipophilic solvents.

Parameter	octan-1-ol	Decan-1-ol	Nitrobenzene
Slope, (mv/log C)	55.2	46.5	55.0
St.dev., (mv)	0.7	0.9	0.9
Corr. coff., (r)	0.9996	0.9997	0.9992
Intercept, (mv)	208.2	131.0	157.5
Lower limit of linear range, (M)	10^{-6}	10^{-5}	10^{-5}
Detection limit, (M)*	9.9×10^{-7}	8×10^{-6}	9×10^{-6}

* The concentration of ephedrine at which the electrode potential deviates by 18 mv from the extrapolated linear part of the calibration plot.

It can be seen that these electrodes display logarithmic response of nearly Nernstian character in ephedrine solutions of concentrations down to approximately 10^{-6}M ephedrine. This indicates the feasibility of using these electrodes for the

determination of low levels of ephedrine. The lower limit of linear response and slope of the calibration plots are affected by the nature of the solvent. Octan-1-ol provides a wide linear response, stable potential readings and low limit of detection. All the results shown below are obtained with this electrode. The slope of the linear part of the response curve is 56.4 ± 0.6 mv/concentration decade (Fig. 2). The slope is stable within ± 2 mv/log [ephedrine] up to a period of 4 weeks. During one day's use, the potential readings vary by not more than ± 1 mv and the drift over a period of one week is about ± 3 mv.

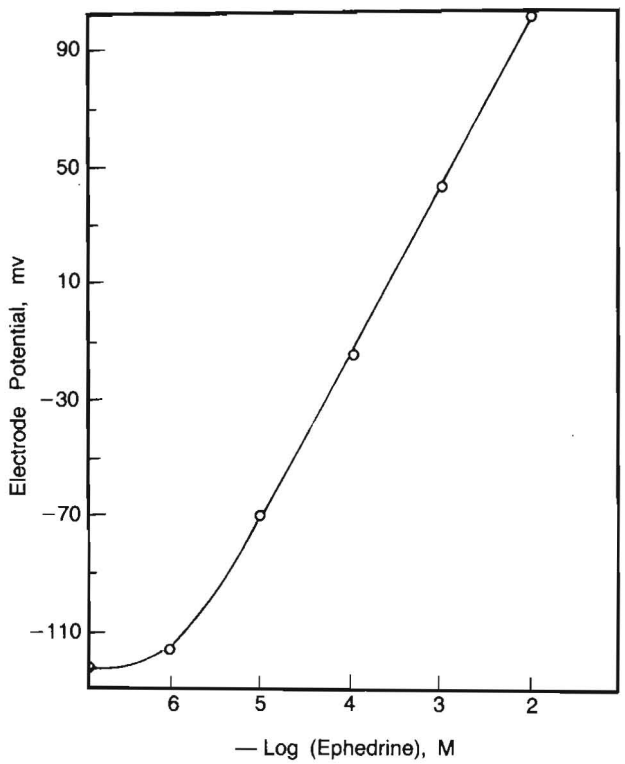

Fig. 2. Calibration curve for ephedrine at pH 4-8 using ephedrine-5-nitrobarbiturate liquid membrane electrode.

Response Time

The time required for ephedrine-5-nitrobarbiturate liquid membrane electrode to provide stable emf readings within ± 1 mv of the steady potential by either tenfold increase of ephedrine concentration to the same solution or after successive immersion of the electrode in a series of ephedrine solutions each having a 10-fold difference in concentration are measured. Both results show short response time; normally 20-30 seconds for solutions $> 10^{-3}$M and 90 seconds for solutions <

10^{-4}M ephedrine (Fig. 3). Electrode age of up to 20 days has no effect on the response time. The electrode can be used for 25 days before renewing the membrane and without any noteciable deterioration in the response.

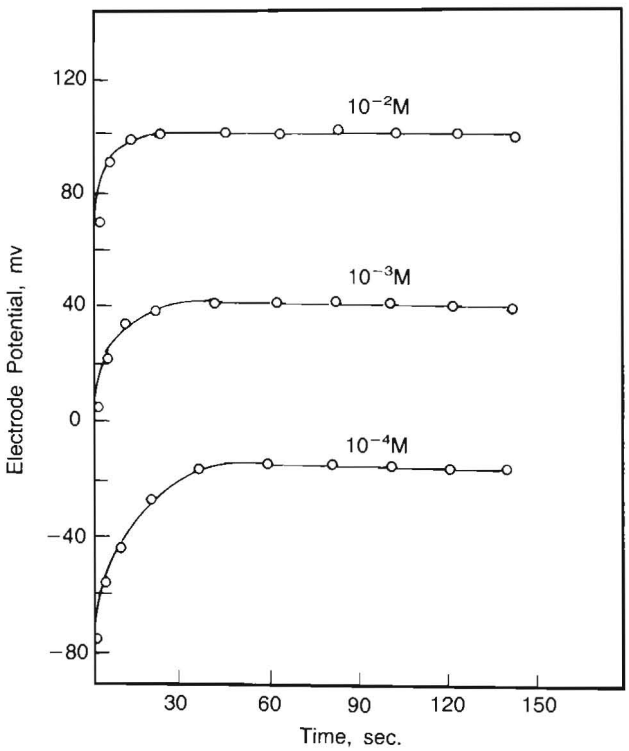

Fig. 3. Response time of ephedrine-5-nitrobarbiturate liquid membrane electrode for different ephedrine concentrations at pH 4-8.

Effect of pH

The potential output of the electrode in ephedrine hydrochloride solutions of concentrations ranging from 10^{-2} to 10^{-5}M is recorded at various pH values. The potential of the electrode is practically independent of the pH in the range of 4-8 (Fig. 4). Over this range, the potential difference does not exceed ± 2 mv. The significant increase of the potential below pH 4 may be due to interference by H^+ and the decrease of the potential above pH 9 is presumably due to precipitation of ephedrine base.

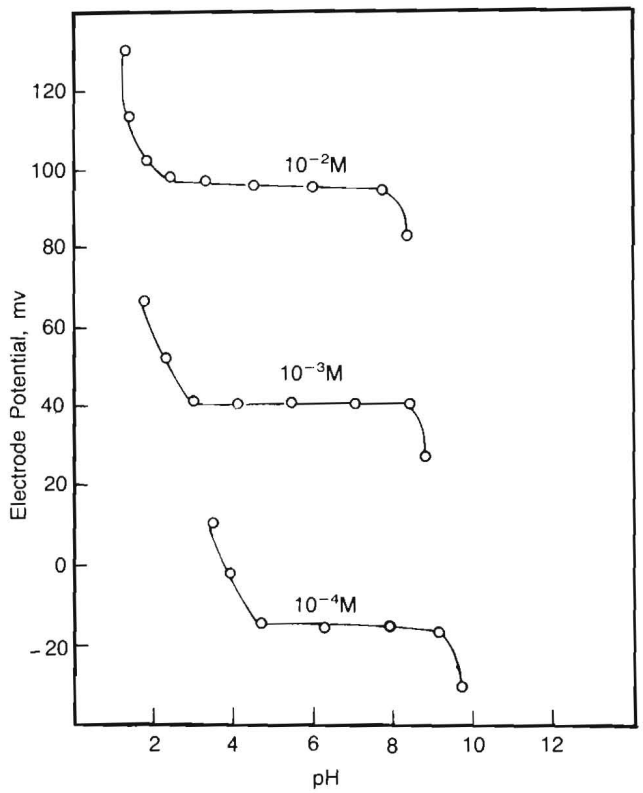

Fig. 4. Effect of pH on the potential of ephedrine-5-nitrobarbiturate liquid membrane electrode.

Effect of Foreign Compounds

The effect of high background levels of some basic, acidic and neutral compounds as well as inorganic anions and cations are assessed. Selectivity coefficients ($K^{pot}_{A,B}$) determined by the standard mixed solution method (Ma and Hassan 1982) are listed in Table 2. These results show that ephedrine-5-nitrobarbiturate liquid membrane electrode exerts a reasonable selectivity for ephedrine and exhibits negligible interferences from amines, amides, amino acids, carboxylic acids and common inorganic cations. Some pharmaceutical diluents and excipients normally used in drugs are also examined for their effect on the electrode response. No interference is measurable for maltose, glucose, lactose, Tween-80 and starch at levels as high as 10^{-2}M. However, the electrode is not really selective for ephedrine over nicotine and some alkaloids such as strychnine, quinine and cinchonine interfere.

Table 2. Selectivity coefficients for ephedrine-5-nitrobarbiturate liquid membrane in octan-1-ol.

Interfering compound, (B)	Selectivity coefficient, ($K^{pot}_{A,B}$)
Methyl urea	4.0×10^{-2}
Piperidine	4.2×10^{-2}
Glycine	1.1×10^{-2}
Diethylamine	1.5×10^{-2}
Triethanolamine	3.8×10^{-2}
Tetramethylammonium chloride	1.3×10^{-2}
Nicotine	9.9×10^{-1}
Nicotinic acid	9.7×10^{-2}
Sodium chloride	9.0×10^{-3}
Potassium chloride	7.0×10^{-3}
Barium chloride	8.0×10^{-3}
Ammonium acetate	1.1×10^{-4}
Strychnine	2.98
Cinchonine	1.51
Quinine	1.62

Determination of Ephedrine

The results obtained for determination of 0.1 – 2000 μg/ml ephedrine using ephedrine liquid membrane electrode and the calibration graph method (Ma and Hassan 1982) are listed in Table 3. The average recovery is 99.2% and the mean standard deviation is 1.5%. Ephedrine in some pharmaceutical preparations is also determined after acid treatment of the drug, heating to 60°C, pH adjustment to 4–8 and dilution with water. The results obtained for some commercially available drugs are given in Table 4. The average recovery is 99% of the nominal values and the mean standard deviation is 1.5%. These results are within ± 3% of those obtained with the same drugs using the standard spectrophotometric method of the British Pharmaceutical Codex (BPC 1973).

Table 3. Direct potentiometric determination of ephedrine using ephedrine-5-nitrobarbiturate liquid membrane electrode and the calibration graph method.

Weight added, (μg/ml)	Recovery*, (%)	Standard deviation, (%)
1600.0	98.7	0.2
1000.0	99.0	0.2
600.0	101.6	2.4
400.0	97.5	1.7
100.0	98.0	1.2
60.0	99.0	1.2
10.0	98.0	1.2
4.0	97.5	1.7
1.0	101.0	1.8
0.10	102.0	2.8

* Average of 3 measurements.

Table 4. Determination of ephedrine in some pharmaceutical preparations using ephedrine-5-nitrobarbiturate liquid membrane electrode.

Preparation	Labeled active ingredients	Ephedrine recovery*, (%)	Standard deviation, (%)
Ephedrine sulfate (injection)	25 mg/ml	100.0	1.4
Ephedrine sulfate (injection)	50 mg/ml	99.4	1.3
Ephedrine hydrochloride (tablet)	25 mg/tablet	98.3	1.6
Ephedrine hydrochloride (tablet)	50 mg/tablet	98.6	1.3
Tepedrine (tablet)	25 mg/tablet	98.1	1.7
Coldal (syrup)	20 mg/7.5 ml	98.9	1.5
Asmasone (eye drop)	3 mg/ml	99.5	1.4

* Average of 5 measurements.

It is inferred that ephedrine-5-nitrobarbiturate liquid membrane electrode provides a rapid, sensitive, inexpensive and reliable method for ephedrine determination with minimal sample pretreatment compared to other methods. It should also be noted that the previously described electrode for ephedrine based on the use of ephedrine-tetraphenylborate is less sensitive (Fukamachi *et al.* 1975). The lower limit of detection reported for this electrode is 10^{-3}M. The low detection limit offered by the present electrode ($\sim 10^{-6}$M ephedrine) along with the reasonable selectivity and stability in various matrices further enhance its practicality in pharmaceutical analysis.

References

British Pharmaceutical Codex, BPC (1973), Pharmaceutical Press, London, pp. 178-179.

Chatten, L.G. and **Barry, P.J.** (1968) Identification and differentiation of organic medicinal agents, VI use of 5-nitrobarbituric acid as a differentiating reagent, *Can. J. Pharm. Sci.* **3**: 40-45.

Fukamachi, K., Nakagawa, R., Morimoto, M. and **Ishibashi, N.** (1975) Methylephedrine and ephedrine selective electrodes, *Bunseki Kagaku* **24**: 428-432.

Hassan, S.S.M. and **Elsayes, M.B.** (1979) Liquid membrane electrode for direct potentiometry and potentiometric titration of strychnine, *Analytical Chemistry* **51**: 1651-1654.

Hassan, S.S.M. and **Tadros, F.S.** (1984) Liquid and poly (vinyl chloride) atropine-reineckate membrane electrodes for determination of atropine. *Analytical Chemistry* **56**: 542-546.

Hassan, S.S.M., Ahmed, M.A. and **Saoudi, M.M.** (1985) Caffeine-picrylsulfonate liquid membrane electrode for selective determination of caffeine in analgesic preparations, *Analytical Chemistry* **57**: 1126-1130.

Hassan, S.S.M and **Ahmed, M.A.** (1985) A new liquid membrane electrode for determination of xylocaine (lidocaine) in local anaesthetic formulations, *J. Assoc. Offic. Anal. Chem.* in press.
Ma, T.S. and **Hassan, S.S.M.** (1982) *Organic Analysis Using Ion Selective Electrodes,* Academic Press, London, Vol. **1** and **2.**

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قطب جديد ذو غشاء سائل للتقدير الاختياري للأفيدرين

سعد السيد محمد حسن

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