Qatar Univ. Sci. Bull. (1984) 4: 45-55

A NEW LIQUID MEMBRANE ELECTRODE FOR SELECTIVE DETERMINATION OF CAFFEINE

By

SAAD S. M. HASSAN
Department of Chemistry,
Faculty of Science,
Qatar University,
Doha, Qatar

M. M. SAOUDI
Department of Chemistry,
Faculty of Science,
Ain Shams University,
Cairo, Egypt

Key words: Caffeine picrylsulfonate complex. Determination of caffeine. Liquid membrane electrode. Pharmaceutical analysis.

ABSTRACT

A new liquid membrane electrode for caffeine prepared from a solution of caffeine-picrylsulfonate ion-pair complex in n-octanol is developed. It exhibits Nernstian response in the range of 10^{-2} to 10^{-6}M caffeine with a cationic slope of 59 mV/concentration decade. The electrode has a wide working pH range (5.5 - 9.5), fast response time (20 seconds - 1.5 minutes), stable response for at least 30 days and high selectivity for caffeine in the presence of many organic bases. The results obtained for quantitation of 1 - 1000 μg ml^{-1} of caffeine show an average recovery of 99.5% and a mean standard deviation of 1.3%.

INTRODUCTION

Caffeine is one of the most important alkaloids consumed in our daily life. It is a mild central nervous system stimulant, analeptic, restores mental alertness in fatigued patients and improves psychomotor coordination. It is present in coffee, tea, cola beverages and chocolates and used alone or in combination with analgesics in many pharmaceutical preparations for the treatment of headache (Osol, 1980). Determination of caffeine in these preparations, however, is commonly beset with many difficulties. The United States Pharmacopoeia (USP, 1963), British Pharmaceutical Codex (BPC, 1973), and European Pharmacopoeia (EP, 1971) recommended three methods for the determination of caffeine after prior separation. These are potentiometric titration with perchloric acid in non-aqueous solvents, extraction from strong alkaline media with chloroform, drying and weighing as free base, and spectrophotometric measurement at 276.5 nm. These methods are time consuming, non-selective and inapplicable to low levels of caffeine.

On the other hand, ion selective electrodes with liquid and poly(vinyl chloride) membranes have been developed for direct potentiometric determination of some alkaloides (Hassan and Elsayes, 1979, Ma and Hassan, 1982, Hassan and Tadros, 1984). These monitoring systems have many advantages in terms of simplicity, selectivity, applicability to samples of different nature and possible interfacing with automated systems. However, no membrane electrode is, so far, available for the determination of caffeine. The present work thus, describes the first electrode introduced for caffeine determination based on the use of caffeine-picrylsulfonate ion

pair complex in n- octanol as a liquid membrane. The electrode exhibits high sensitivity, reasonable selectivity and long term stability. It has satisfactorily been used for the determination of caffeine in some pharmaceutical preparations. The obtained results match with those obtained by the official methods.

EXPERIMENTAL

Apparatus. Potentiometric measurements were made at a constant temperature in the range of 25 - 30°C with an Orion Microprocessor Ionalyzer (Model 901). Caffeine-picrylsulfonate liquid membrane electrode in conjunction with Orion double junction Ag/AgCl reference electrode (Model 90-02) with 10% KNO_3 in the outer compartment was employed. An Orion combined glass calomel electrode (Model 91-00) was used for pH adjustment. The infrared (IR), mass (MS) and nuclear magnetic resonance (NMR) spectra were recorded with Unicam 200G IR spectrometer, Varian CH-7 mass spectrometer and Varian EM 390 90MHz NMR spectrometer, respectively.

Reagents. All solutions were prepared with deionized twice-distilled water and analytical reagent grade substances, unless otherwise stated. The organic solvents were twice-distilled reagent grade. Caffeine and picrylsulfonic acid were obtained from Sigma Chemical Co., (St. Louis, MO). A 10^{-2} M caffeine stock solution was prepared by dissolving 1.942 g of pure anhydrous caffeine base in 500 ml 10^{-1} M hydrochloric acid solution, the pH adjusted to 1.5 and the solution was diluted to exactly 1 liter with twice-distilled water. Dilute solutions (10^{-3} - 10^{-6} M) were prepared by appropriate dilution and kept in air tight containers. Pharmaceutical preparations containing caffeine were obtained from local drugstores. Picrylsulfonic acid should be handled with care due to its corrosive nature.

Procedure. For the preparation of caffeine-picrylsulfonate ion pair complex, a 30 ml aliquot of 10^{-1} M aqueous caffeine hydrochloride solution and 50 ml aliquot of 10^{-1} M aqueous picrylsulfonic acid solution were mixed and stirred for 20 minutes. The yellow precipitate of caffeine-picrylsulfonate complex was filtered with a G-3 sintered glass crucible, washed with twice-distilled water followed by ethanol, dried at 100°C for 1 hour, ground to fine powder and stored.

For preparing caffeine-picrylsulfonate liquid membrane electrode, an Orion liquid membrane electrode barrel (Model 92) was used as the electrode assembly with an Orion 92-05-04 porous membrane. The internal reference solution was a mixture of equal volumes of 10^{-2} M caffeine hydrochloride and potassium chloride. The liquid ion-exchanger was 10^{-2} M caffeine picrylsulfonate ion pair in n-octanol. The electrode was conditioned by soaking in 10^{-2} M caffeine hydrochloride solution for 3 days before use and was also stored in the same solution when not in use. The operative life time of the electrode was 4 weeks with daily usage of at least 6 hours.

For electrode calibration, 15 ml aliquots of 10^{-2} to 10^{-6} M caffeine hydrochloride solutions were transferred to 100-ml beakers, the pH was adjusted to 6-8.5 by addition of sodium hydroxide solution. The caffeine-picrylsulfonate liquid membrane electrode was immersed in conjunction with a double junction reference electrode (Orion 90-02) into the solutions. The potentials of the stirred solutions were recorded when becoming stable and were plotted as a function of logarithm of caffeine concentration. The graph was used for subsequent determination of caffeine containing smples.

For determination of caffeine in drugs, the contents of 5 tablets or 2 ampoles were homogenized and a weighed quantity equivalent to one tablet or one suppository was treated with 50 ml

aliquot of 10^{-2} M hydrochloric acid. After gentle heating to about 60°C for 10 minutes and cooling, the solid paraffin wax in suppository was scimmed from the top of the sample solution. The solution was then transferred to a 100-ml volumetric flask and completed to the mark with twice-distilled water. A 15 ml aliquot of the solution was transferred to 10-ml beaker and the pH adjusted to 6-8.5 with sodium hydroxide. The caffeine-picrylsulfonate liquid membrane electrode was immersed in conjunction with a double junction reference electrode into the solution, the potential was measured after stable reading and compared with the calibration graph.

RESULTS AND DISCUSSION

Nature and Composition of the Membrane. Caffeine readily reacts with picrylsulfonic acid to form a stable 1:1 ion pair complex. The elemental analysis data and the signals appear in the mass spectrum (MS) of the reaction product at m/z corresponding to $(M-1)^+$, M^+ and $(M+1)^+$ agree with the composition $C_{14}H_{13}N_7O_{11}S$. The most significant and prominent absorption bands appear in the infrared spectrum (IR) of this compound, but not displayed in the spectra of the reactants, are those at 2720 cm^{-1} and 1150 cm^{-1} due to stretching vibrations of protonated imino group (=N−H) and sulfonate salt (SO_3), respectively. The nuclear magnetic resonance spectra (NMR) of pure caffeine and its picrylsulfonate ion pair complex show that the 4 singlet signals displayed at δ = 3.2, 3.4, 3.9 and 8.0 ppm due to three N-CH_3 and olefinic hydrogen atoms of caffeine, appear without splitting at almost the same position in the spectrum of the complex beside two additional singlets at δ 4 8.9 and 3.7 ppm due to aromatic and NH hydrogen atoms, respectively. This indicates that the unalkylated nitrogen in the caffeine molecule is the proton acceptor center in the ion pairing reaction. The structure of the complex may thus be represented as shown in Figure 1.

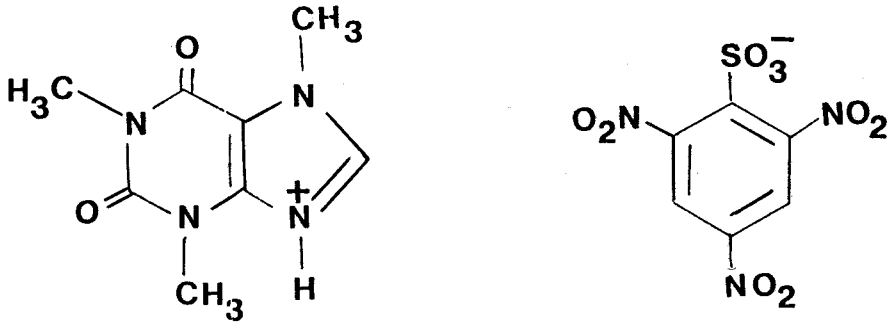

Fig. (1) *Caffeine-picrylsulfonate ion-pair complex.*

Caffeine-picrylsulfonate ion pair complex is sparingly soluble in water but dissolves easily in some water-immiscible organic solvents such as n-octanol, nitrobenzene and benzyl alcohol. Solutions of the complex in these solvents are examined as liquid membranes for potentiometric determination of caffeine using the electrochemical cell represented by equation 1. The emf is measured as a function of logarithm caffeine concentration according to equation 2.

Ag/AgCl 10^{-2}M KCl 10^{-2}M Caffeine	10^{-2}M Caffeine picryl-sulfonate in organic solvent	Caffeine in test solution	SCE (1)

$$E = E_o + 0.059 \log | a_{caffeine} + K_{ij}(a_j)^z | \quad (2)$$

Where E_o is the conditional standard potential of the electrode under the conditions used in the cell, K_{ij} is the selectivity coefficient, $a_{caffeine}$ and a_j are the activities or concentrations of protonated caffeine species and the foreign interfering substance having a charge z and present in the test solution, respectively.

Response Characteristics of the Membrane. The response characteristics of electrodes incorporating 10^{-2}M caffeine-picrylsulfonate complex as an electroactive material in n-octanol, benzyl alcohol, and nitrobenzene solvents are evaluated at 25±0.5°C. The least squares analysis of the data is given in Table 1. These data demonstrate the suitability and sensitivity of these membranes for the determination of caffeine and the significant role of the solvent on both the slope of the calibration graph and the limit of detection. The lower limit of usable range for each electrode shown in Table 1 is based on the detection limit recommended by IUPAC 1976. The reproducibility cited represents data collected over a period of 6 months from 15 different electrodes. It can be seen that, n-octanol gives a fairly stable and sensitive membrane with Nernstian response for caffeine in pure aqueous solutions over 4 orders of magnitude of concentration (Fig. 2). No change in the response behavior of the electrode is noticed either by measuring caffeine in 0.1 M potassium nitrate background or changing the concentration of the complex in n-octanol over the range of 10^{-2} to 10^{-3}M. This electrode is used for subsequent investigation.

Table 1.

Response Characteristics of Caffeine-Picrylsulfonate Liquid Membrane Electrode at 25°C in Some Organic Solvents

Parameter	Nitrobenzene	Benzyl alcohol	n-Octanol
Slope, (mV/log C)	35.5	41.7	59.0
St. Dev., (mV)	1.5	1.3	0.7
Corr. Coff., (r)	0.998	0.997	1.000
Intercept, (mV)	62.1	60.2	70.1
Lower limit of linear range, (M)	5×10^{-5}	3×10^{-5}	2×10^{-6}
Detection limit, (M)	10^{-5}	10^{-5}	10^{-6}

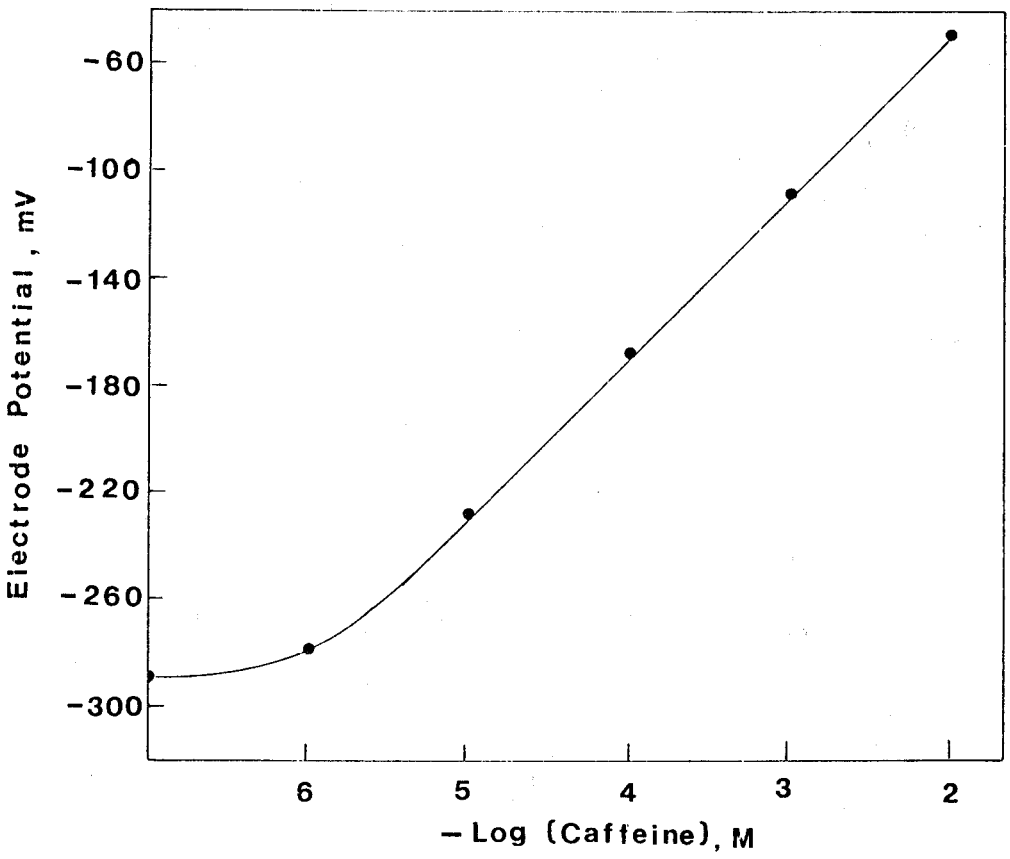

Fig. (2) *Calibration curve for caffeine at pH 6-8 using caffeine-picrylsulfonate liquid membrane electrode.*

Response Time and Stability of the Membrane. The time required for caffeine-picrylsulfonate membrane electrode to reach a value ±1 mV from the final equilibrium potential after successive immersion in different caffeine solutions each having a 10-fold difference in concentration is measured. The time required to achieve ±1 mV of the steady potential by rapid 10-fold increase of caffeine concentration to the same solution is also monitored. Both results indicate an average response time of 20 seconds for solutions $> 10^{-3}$M and 1.5 minutes for solutions $< 10^{-4}$M (Fig. 3). Electrode aging has no effect on the response time. On the other hand, the electrode exhibits a day-to-day reproducibility within ±2 mV for caffeine concentrations in the range of 10^{-2} -10^{-5}M. The potential reading increases ~ 10 mV after one month. The average slope of the calibration graph in the first, second, and third days after preparation are 55.7, 57.7, and 59 mV/concentration decade, respectively. The slope remains constant after the third day for at least 3 weeks, then declined to 57 mV/concentration decade. After 4 and 6 weeks, the slopes become 56.7 and 53.2 mV/concentration decade, respectively. The electrode can be used for at least one month before renewal of the liquid membrane.

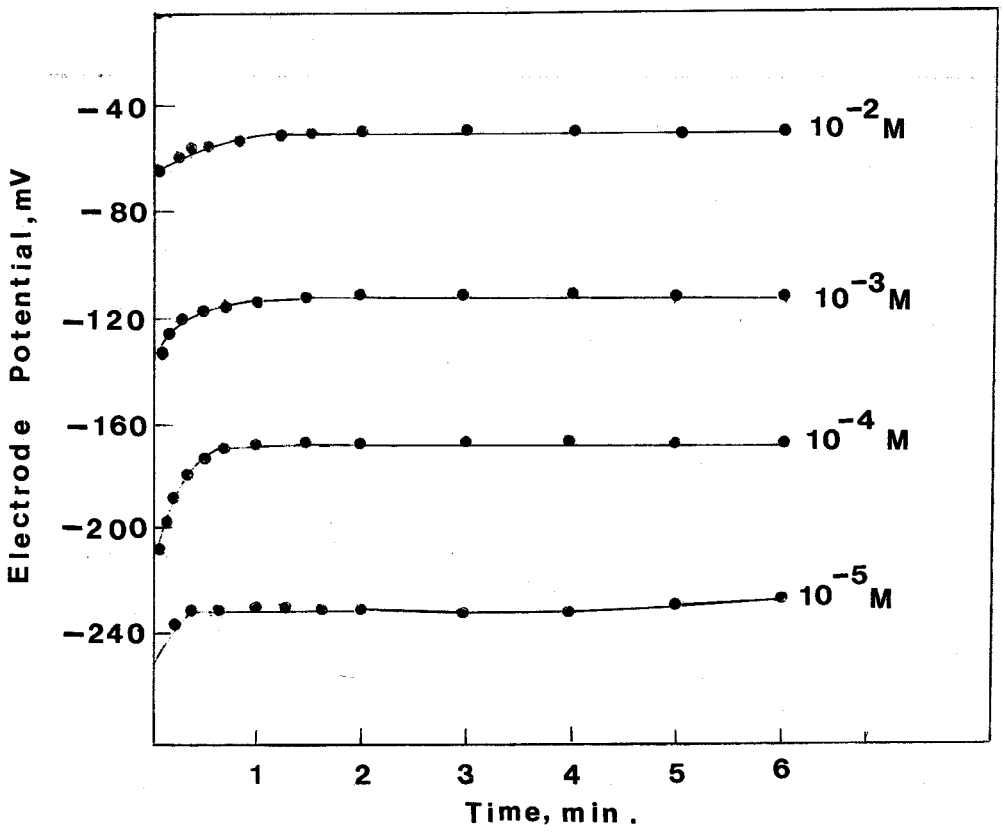

Fig. (3) *Response time of caffeine-picrylsulfonate liquid membrane electrode for different caffeine concentrations at pH 6-8.*

Effect of pH and Diverse Compounds. The effect of pH on the response of the electrode for different caffeine concentrations is shown in Fig. 4. The pH of the initial caffeine solutions is altered by addition of sodium hydroxide and hydrochloric acid solutions. No change of the electrode potential is observed over the pH range of 5.5-9.5. The potential difference does not exceed 2 mV within the entire range of pH over the concentration range of 10^{-2} - 10^{-5}M. During the operative life of the electrode, no significant change in the potential-pH behavior is noticed.

The response of the electrode for caffeine is also examined in the presence of some cationic and anionic organic compounds. The potential of solutions each containing 10^{-2}M of the foreign compound with variable caffeine concentrations in the range of 10^{-2} - 10^{-5}M is measured. The selectivity coefficients are calculated using the mixed method (Hassan and Tadros, 1984) equation 4.

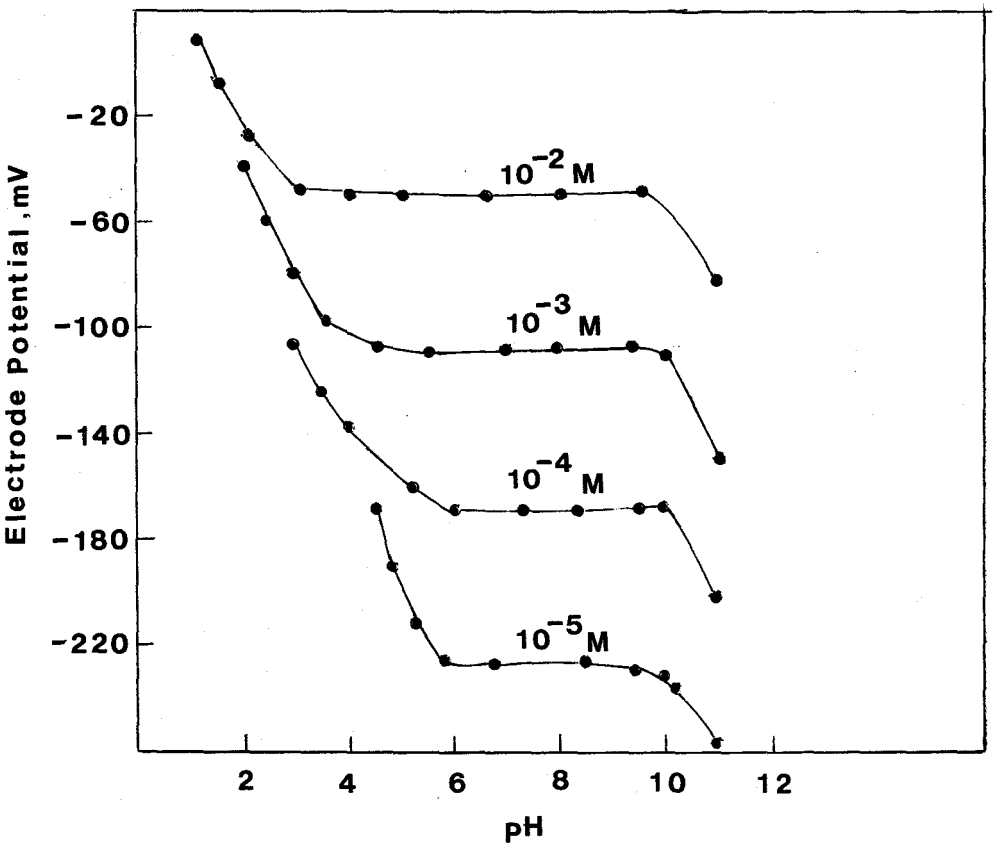

Fig. (4) *Effect of pH on the potential of caffeine-picrylsulfonate liquid membrane electrode.*

$$K_{ij} = a_i/(a_j)^{1/z} \pm | 10^{\Delta E/S} - 1 | \quad (4)$$

Where ΔE is the change in potential in the presence of the foreign compound $j^z\pm$, S is the slope of the calibration curve for caffeine, a_i and a_j are the concentrations of caffeine and the foreign compounds, respectively. The results obtained (Table 2) show that no significant effect is caused by many organic bases and inorganic salts. The electrode, however, suffers lack of selectivity for ephedrine, quinine, brucine and strychnine. These compounds interfere only when present at concentration levels of at least 10 times greater than caffeine.

Determination of Caffeine. Caffeine solutions at the concentration range of 0.6-1000 μg ml are prepared from pharmaceutical grade and determined by direct potentiometry using caffeine-picrylsulfonate liquid membrane electrode. The potentials displayed by these solutions are compared with a calibration graph to assess the accuracy and reproducibility. The results

Table 2.

Selectivity Coefficients for Caffeine-Picrylsulfonate Liquid Membrane in n-Octanol

Interfering compound, (j)	Selectivity coefficient, (K_{ij})
Glycine	7.2×10^{-2}
Diethylamine	1.2×10^{-1}
Triethanolamine	2.0×10^{-1}
Urea	1.3×10^{-2}
Piperidine	3.2×10^{-3}
Ammonium acetate	2.7×10^{-3}
Sodium chloride	2.8×10^{-3}
Potassium chloride	4.4×10^{-3}
Barium chloride	2.8×10^{-1}
Nicotinic acid	4.1×10^{-1}
Nicotine	3.4×10^{-1}
Ephedrine	1.5
Quinine	1.3
Brucine	1.6
Strychnine	3.5

obtained (Table 3) for 15 samples, each in triplicate, show an average recovery of 99.6% and a mean standard deviation of 1.4%. Similar results (average recovery 99.5%, mean standard deviation 1.2%) are obtained using the known addition (spiking) technique. A number of pharmaceutical diluents, excipients and analgesics commonly used in drug formulations have also been examined for their effect on the electrode response. No interference is caused by aspirin, phenacetin, accacia, sucrose, tween-80, carboxymethylcellulose, lactose, cocoa butter, ethylene glycol, and paraffin oil at levels far in greater excess than normally found in drugs (~ 200 mg).

Caffeine in some pharmaceutical analgesic preparations is determined. It is known that ergotamine tartrate in combination with caffeine is commonly used in some pharmaceutical preparations to abort vascular headaches such as migraine and cluster headaches (histamine cephalalgia). Some of these preparations have similarly been assayed by the present procedure. Tablets and suppositories are treated with hydrochloric acid, heated at 60°C, diluted with double distilled water and the potential of their solutions is measured after pH adjustment to 7-8. The results obtained show an average recovery of 100.2% and a mean standard deviation of 1.8% of the nominal values. The United States Pharmacopoeia method (USP, 1963) which

Table 3.

Microdetermination of Caffeine Using Caffeine-Picrylsulfonate Liquid Membrane Electrode

Weight added ($\mu g\ ml^{-1}$)	Calibration graph method		Known addition method	
	Recovery, (%)[a]	St. dev., (%)	Recovery, (%)[a]	St. dev., (%)
0.65	98.4	2.4	97.3	2.3
1.03	98.3	1.4	98.4	1.1
2.59	99.8	1.6	98.8	1.5
6.47	100.4	1.6	99.3	1.4
10.33	97.3	1.4	98.5	1.8
25.33	98.2	1.5	99.1	0.9
38.67	101.0	1.2	100.1	1.1
64.67	99.3	1.4	99.5	1.5
103.33	100.5	1.7	100.5	0.9
168.00	99.8	1.7	100.3	1.1
258.67	98.0	1.2	99.5	1.6
388.0	101.5	0.9	101.1	1.5
491.33	102.0	0.8	101.6	1.1
647.33	99.8	1.1	99.8	0.9
1035.33	99.9	0.9	98.9	0.9

a Average of 3 measurements

involves prior extraction followed by potentiometric titration with perchloric acid in benzene-acetic anhydride solvent is also used for comparison. A good agreement between the results obtained by both methods is obtained. The present method, however, offers several advantages in term of simplicity, selectivity and precision.

REFERENCES

British Pharmaceutical Codex, BPC. 1973. Pharmaceutical Press, London, pp. 667, 806.

European Pharmacopoeia, EP. 1971. Maisonneuve. S.A. Council of Europe, pp. 194-195.

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

Hassan, S.S.M. and **F.S. Tadros.** 1984. Liquid and poly(vinyl chloride) atropine-reineckate membrane

electrodes for determination of atropine. Analytical Chemistry 56: 542-546.

IUPAC Analytical Chemistry Division. 1976. Commission on Analytical Nomenclature, Recommendations for Nomenclature of Ion Selective Electrodes. Pure Appl. Chem. 48:127-129.

Ma, T.S. and **S.S.M. Hassan.** 1982. Organic Analysis Using Ion Selective Electrodes, Academic Press, London. pp. 150-164.

Osol, A. 1980. Remington's Pharmaceutical Sciences 16th Edition. Mack, Pennsylvania. pp. 1076-1077.

Pharmacopoeia of the United States of America. 1963. XVII Revision, U.S. Pharmaceutical Convention. Mack, Pennsylvania. pp. 85-86.

قطب جديد ذو غشاء سائل للتقدير الاختيارى للكافين

سعد السيد محمد حسن مشيرة مصطفى سعودى

أستحدث في هذا البحث قطب جديد للتقدير الاختياري للكافين يعتمد على إستخدام متراكب بيكريل سلفونيك الكافين مذابا فى كحول الأوكتانول كغشاء سائل . .ويستجيب هذا القطب إستجابة تتطابق مع معادلة نرنست في محاليل من الكافين يتراوح تركيزها المولارى بين $١٠^{-٢}$ و $١٠^{-٦}$ وأسها الايدروجينى بين ٥,٥ و ٩,٥ ووقت الإستجابة لهذا القطب يتراوح بين ٢٠ ثانية و $\frac{١}{٢}$ ١ دقيقة وهو يظهر ثباتاً ملحوظاً لمدة تصل إلى ٣٠ يوماً .

ولا تتداخل كثير من القواعد العضوية فى حساسية وسلوك هذا القطب الذي أمكن إستخدامه فى تقدير الكافين بكميات تتراوح بين ١ و ٢٠٠٠ ميكروجرام / سم^{٣} بدقة وصلت إلى ٩٩,٥ ٪ ومتوسط حيود قياسى مقداره ١,٣ ٪ .