Chem. Pharm. Bull.
33(1) 236-241 (1985)

Fabrication of Quinine-Sensitive Membrane Electrodes and Their Properties

JUN-ICHI ANZAI, CHIEMI ISOMURA,
and TETSUO OSA*

Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

(Received April 14, 1984)

The fabrication and performance characteristics of quinine-sensitive membrane electrodes based on the ion-association complex of quinine with tetraphenylborate are described. The electrodes showed a near-Nernstian response over the range of about 5×10^{-5}—1×10^{-1} M quinine concentration. The potentiometric response of the electrodes was satisfactorily fast above a concentration of 1×10^{-5} M, though below this level a longer time was required to attain the steady state-potential. The effects of ion-association complex concentration in the membrane and the membrane thickness on the potentiometric response were small. The electrodes showed good selectivity for quinine relative to several inorganic and organic ions, though the response was interfered with alkaloids. The electrodes can be used in the pH range of 5.3—7.3. Direct potentiometry and potentiometric titration were applicable for the determination of quinine concentration.

Keywords——membrane electrode; direct potentiometry; potentiometric titration; quinine; quinine-tetraphenylborate complex

Much effort has been directed to the selective determination of organic substances of pharmaceutical importance by means of spectroscopic, chromatographic, and electrochemical methods.[1] Recently, ion-selective electrodes (ISEs) equipped with a sensitive membrane have been investigated extensively because of their low cost and ease of fabrication as well as their possible application, in principle, to any kind of ionic species. To date, many drugs such as ephedrine,[2] novocaine,[3] strychnine,[4] nicotine,[5] and codeine,[6] have been determined by the use of ISEs.

We report here the fabrication and performance characteristics of quinine-sensitive membrane electrodes based on the ion-association complex of quinine with tetraphenylborate (**1**). Quinine is one of the most important alkaloids of chinchona bark and is used as an antimalarial and antipyretic. The Japanese Pharmacopoeia recommends a titration method with 0.1 N perchloric acid and methylrosaniline chloride as a titrant and an indicator, respectively, to determine pure quinine hydrochloride.[7] For the purpose of estimating the quality of pharmaceutical preparations, however, rather time-consuming pretreatment are required before titration. A simple, rapid and accurate procedure for determining quinine hydrochloride in pharmaceutical preparations is described in this paper.

Experimental

Reagents——Poly(vinyl chloride) (PVC) with a molecular weight of 68000 was used as a membrane matrix. Quinine hydrochloride, sodium tetraphenylborate (TPB), and di-*n*-butyl phthalate (DBP) were purchased from Tokyo Kasei Co., Ltd. All chemicals used were of reagent grade.

Fabrication of Membrane Electrodes——An ion-association complex of quinine with TPB (**1**) was prepared by mixing 0.02 M quinine hydrochloride solution with an appropriate volume of TPB. The resulting precipitate was

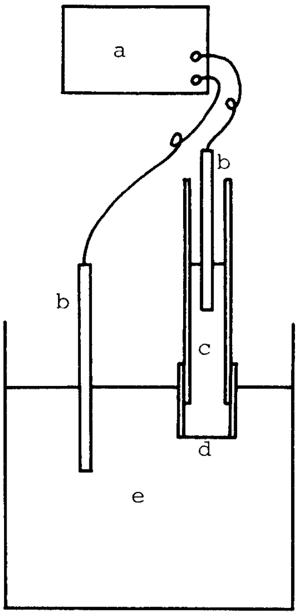


Fig. 1. Schematic Representation of the Quinine Sensitive Membrane Electrode

a, potentiometer; b, S.C.E.; c, internal solution; d, membrane; e, sample solution.

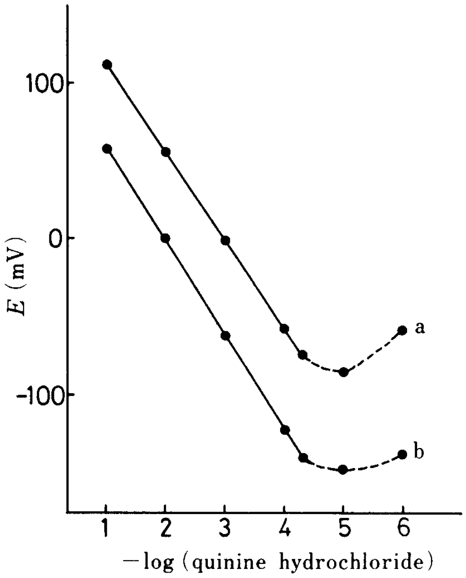
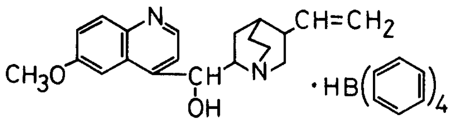


Fig. 2. Potentiometric Response of the Electrodes

Internal solution: a, 1×10^{-3}; b, 1×10^{-2} M.

filtered off, washed with distilled water, and dried at 40 °C for 12 h. The composition of **1** was ascertained to be 1 : 1 (quinine : TPB) by elemental analysis. *Anal.* Calcd for $C_{44}H_{45}BN_2O_2$: C, 77.63; H, 7.25; N, 4.11. Found: C, 77.22; H, 7.00; N, 4.69.

A membrane of *ca.* 0.2 mm thickness was prepared by pouring a solution, which contained 330 mg of PVC, 0.75 ml of DBP, 171 mg of **1**, and 20 ml of tetrahydrofuran (THF), onto a flat Petri dish (7.7 cm diameter) and



1

allowing the solvent to evaporate at ambient temperature. A piece of the membrane was glued to a PVC tube with THF as an adhesive and the other end of the tube was connected to the electrode body (Fig. 1). Saturated calomel electrodes were employed as internal and external reference electrodes for all measurements. The internal reference solution of the membrane electrode was 10^{-3} or 10^{-2} M quinine hydrochloride solution. All measurements were conducted at 23 °C. The composition of the electrochemical cell for the electromotive force (e.m.f.) measurements was as follows; Hg_2Cl_2 (s), Hg | KCl (sat.) | internal reference solution | membrane | sample solution | KCl (sat.) | Hg_2Cl_2 (s), Hg. The potential readings were corrected so as to be zero when the ionic concentrations in the internal and external solutions were equal.

Direct Potentiometry——The quinine and reference electrodes were put into a stirred solution of quinine hydrochloride (10^{-1}—10^{-6} M). The e.m.f. of the electrode (membrane potential, E) was measured and plotted as a function of the logarithm of quinine hydrochloride concentration.

Potentiometric Titration——A gently stirred solution of quinine hydrochloride was titrated with a TPB solution. The membrane potential was plotted against the volume of the titrant.

Results and Discussion

Figure 2 illustrates a typical potentiometric response of the quinine electrode for 1×10^{-1}—1×10^{-6} M quinine hydrochloride solutions. Over the range of 1×10^{-1}—1×10^{-5} M, the electrode exhibited a linear response with the slope of 56.7 mV/decade and 56.3 mV/decade for 1×10^{-2} M and 1×10^{-3} M internal solutions, respectively. The electrode reached a steady-state potential within 10 s above a concentration of 1×10^{-5} M, though below this level the potentiometric response was slow. After attainment of the steady-state potential, no further change in the potential (and also no potential drift) was observed. The potentiometric response of the electrode was fairly reproducible (Fig. 3).

Effects of the Membrane Thickness and 1 Content in the Membrane

The nature of the sensing membranes, *i.e.*, material, thickness, and ion-exchanger contents, *etc.*, should be a crucially important factor governing the performance characteristics of the electrodes, but little detailed works has been done previously. We, therefore, examined the effects of the membrane thickness and **1** content in the membrane on the potentiometric response. Table I shows the slopes of the calibration graphs obtained by using electrodes with sensing membranes of 0.10, 0.15, 0.21, and 0.31 mm thickness. The 0.10 mm membrane gave the maximum responses of 63.7 mV/decade and 64.8 mV/decade, which deviated from the expected value of 59.1 mV/decade, for 1×10^{-3} and 1×10^{-2} M internal solutions, respectively. A slightly reduced response were observed with the thicker mem-

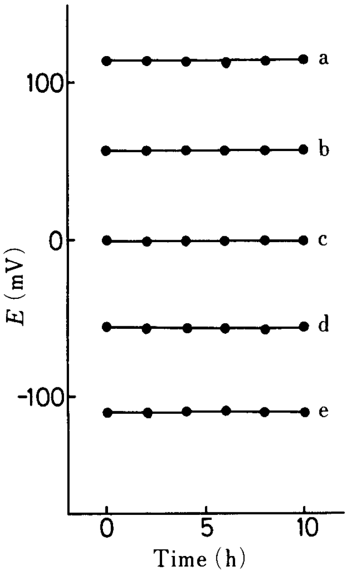


Fig. 3. Reproducibility of the Electrode Potentials

Internal solution: 1×10^{-3} M. The concentrations of the samples were: a, 1×10^{-1}; b, 1×10^{-2}; c, 1×10^{-3}; d, 1×10^{-4}; e, 1×10^{-5} M.

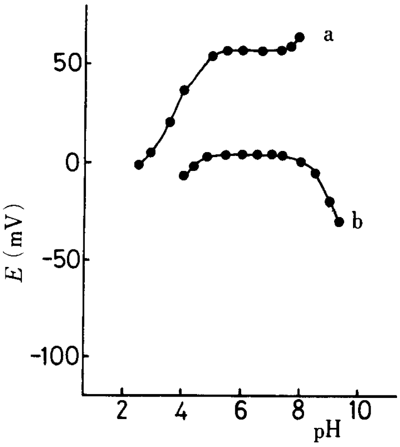


Fig. 4. pH-Dependence of the Electrode Potentials

The concentrations of the samples were: a, 1×10^{-2}; b, 1×10^{-3} M.

TABLE I. Effect of the Membrane Thickness on the Potentiometric Response of the Electrodes

Membrane thickness (mm)	Slope of the calibration graph (mV/decade) Concentration of the internal solution (M) 1×10^{-3}	 1×10^{-2}
0.10	63.7	64.8
0.15	60.3	55.0
0.21	56.3	56.7
0.31	51.8	54.1

The linear response ranges were always about 1×10^{-1}—5×10^{-5} M.

TABLE II. Effect of **1** Concentration in the Membranes on the Potentiometric Response of the Electrodes

1 content in the membranes (g/cm^2)	Slope of the calibration graph (mV/decade) Concentration of the internal solution (M)	
	1×10^{-3}	1×10^{-2}
3.67×10^{-4}	56.3	56.7
2.57×10^{-4}	54.5	52.5
1.84×10^{-4}	55.0	56.0
9.18×10^{-5}	53.6	55.0
2.29×10^{-5}	53.0	51.0

TABLE III. Potentiometric Selectivity Coefficients for Quinine Electrode[a]

Interference	a_j[b] (M)	Selectivity coefficient
Na^+	1.0×10^{-1}	1.0×10^{-4}
K^+	1.0×10^{-1}	1.0×10^{-4}
Ca^{2+}	1.0×10^{-1}	1.0×10^{-4}
NH_4^+	1.0×10^{-1}	1.0×10^{-4}
$(CH_3)_4N^+$	1.0×10^{-2}	1.0×10^{-3}
Phenylalanine methyl ester	1.0×10^{-2}	1.0×10^{-2}
Dopamine	5.0×10^{-3}	2.0×10^{-3}
Quinuclidine	5.0×10^{-3}	5.0×10^{-2}
Pilocarpine	1.0×10^{-3}	7.1×10^{-2}
Strychnine	1.0×10^{-3}	1.8×10^{-1}
Yohimbine	1.0×10^{-3}	5.6×10^{-1}
Quinidine	2.0×10^{-3}	1.1
Papaverine	1.0×10^{-4}	3.2

a) **1** content in the membranes, 3.67×10^{-4} g/cm^2; membrane thickness, 0.2 mm.
b) Concentration of the interfering ions.

branes. The electrodes with membranes thicker than 0.40 mm (not listed in Table I) showed relatively long response times. Considering both the response and the mechanical strength of the membrane, the 0.21 mm membrane was considered to be suitable for constructing the quinine sensitive membrane electrode.

Table II lists the slopes of the calibration graphs obtained by using electrodes with membranes containing 3.67×10^{-4}—2.29×10^{-5} g/cm^2 of **1**. The effect of **1** content in the membrane on the electrode functions seems to be small, irrespective of the concentration of the internal solution, suggesting that low **1** content membrane could be used for the sensing layer of a quinine electrode.

Effect of pH

To elucidate the pH-dependence of the electrode functions, potential-pH curves at 1×10^{-3} and 1×10^{-2} M quinine concentrations were constructed (Fig. 4). The pH of quinine solutions was regulated by addition of very small volume of NaOH or HCl solution. It is clear from Fig. 4 that the electrode potentials are little affected by pH in the range of pH 5.3—7.3 for 1×10^{-3} and 1×10^{-2} M solutions. The deterioration of the response in the higher and lower pH regions can be explained in terms of the formation of unprotonated and diprotonated forms of quinine, which are not major species contributing to the electrode

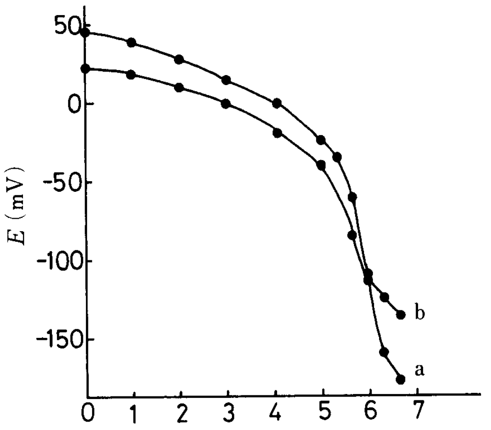


Fig. 5. Potentiometric Titration of Quinine Hydrochloride with TPB

a, 6×10^{-3} M quinine hydrochloride, 1×10^{-2} M TPB. b, 2×10^{-3} M quinine hydrochloride, 3.3×10^{-3} M TPB.

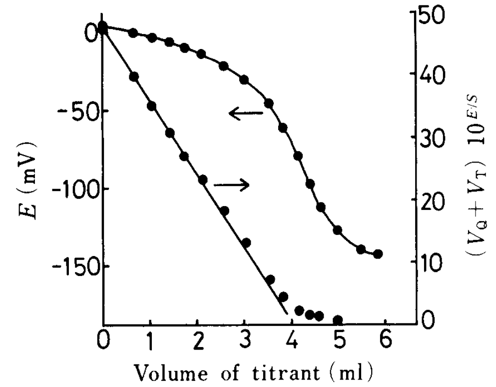


Fig. 6. Titration Curve and Its Gran's Plot

The concentration of the sample was 1×10^{-3} M.

potential. This is consistent with the fact that the pK values of quinine are 5.07 and 9.7 at 18 °C.[8] From these observations, we conclude that the electrode can be used in the neutral or slightly acidic pH region.

Selectivity of the Electrode

The potentiometric selectivity coefficients of ISEs can be estimated based on the two methods recommended by IUPAC.[9] We report here the selectivity coefficients of the quinine electrode based on the mixed solution method.[9] The results in Table III show high selectivity of the electrode in the presence of various potentially interfering inorganic and ammonium cations, though the interference by papaverine, quinidine and yohimbine was serious.

Potentiometric Titration

The electrode also functioned as an indicator electrode for the potentiometric titration of quinine with TPB. Figure 5 shows typical titration curves of 10 ml of 6×10^{-3} and 2×10^{-3} M quinine hydrochloride solutions with 1×10^{-2} and 3.3×10^{-3} M TPB solutions, respectively. The end point of the titration curves was conveniently determined from the intersection of the curves, and this method was applicable to sample solutions of mM level or more. In the case of lower-concentration samples, the direct determination of the end point from the intersection of the titration curves was difficult. In such cases, Gran's plots[10] of the titration curves appeared to be effective. Gran's plots were based on the following equation:

$$(V_Q+V_T)10^{E/S}=k(C_QV_Q-C_TV_T)$$

where V_Q, C_Q, V_T and C_T denote the volumes and concentrations of quinine hydrochloride and TPB, respectively. E and S represent the electrode potential and the slope of the calibration graph, respectively, and k is a constant. Figure 6 shows the titration curve of 40 ml of 1×10^{-3} M quinine hydrochloride with 1×10^{-2} M TPB and the Gran's plots. Extraporation of the linear part of the plots permitted the reasonably accurate determination of quinine.

It is thus clear that the electrodes are effective for the determination of the quinine concentration in pharmaceuticel preparations. We are now studying a coated-wire type quinine-sensitive electrode and the results will be reported elsewhere.

Acknowledgement The present work was supported in part by a Grant-in-Aid for Co-operative Research

(No. 58350048) from the Ministry of Education, Science and Culture of Japan.

References

1) R. K. Gilpin, L. A. Pachla, and J. S. Ranweiler, *Anal. Chem.*, **55**, 70R (1883).
2) K. Fukamachi, R. Nakagawa, M. Morimoto, and N. Ishibashi, *Bunseki Kagaku*, **24**, 428 (1975).
3) E. Hopirtean and F. Kormos, *Stud. Univ. Basbes-Bolyai Ser. Chem.*, **22**, 35 (1977).
4) S. M. S. Hassan and M. B. Elsayes, *Anal. Chem.*, **51**, 165 (1979).
5) C. E. Festathiou, E. P. Diamandis, and T. P. Hadjiioannou, *Anal. Chim. Acta*, **127**, 173 (1981).
6) T. Goina, S. Hobai, and L. Rosenberg, *Farmacia* (Bucharest), **26**, 141 (1978).
7) "Japanese Pharmacopoeia X Rev. (Commentary)," Hirokawa Shoten, Tokyo, 1981, p. C-405.
8) "The Merck Index," Tenth Edition, Merck Co., Inc., Rahway, NJ, 1983, p. 1165.
9) G. Guilbault, *Ion-sensitive Electrodes Rev.*, **1**, 139 (1979).
10) G. Gran, *Analyst*, **77**, 661 (1952).