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A quinidine-responsive plastic membrane electrode

V. V. COSOFRET† and R. P. BUCK*

Department of Chemistry, University of North Carolina, Chapel Hill, NC 27514, USA

Abstract: A membrane electrode based on quinidine tetraphenylborate in a PVC matrix is described. The electrode exhibits a rapid and near-Nernstian response in the range 3.5 $\times 10^{-5}$–1 $\times 10^{-2}$M quinidine sulphate at pH 6–8. In an acidic medium the electrode responds to diprotonated quinidine. In sodium tetraphenylboron (Na TPB) solutions the response is linear in respect of log (TPB^-) over the range 10^{-4}–10^{-2}M. Direct potentiometry and potentiometric titrations are used to determine quinidine in pharmaceutical preparations.

Keywords: *Quinidine; quinidine membrane electrode; potentiometry; standard addition method.*

Introduction

Several ion-selective electrodes sensitive to some organic bases and alkaloids of pharmaceutical interest have been reviewed recently [1–4]. In the last three years electrodes sensitive to propranolol [5], nicotine [6], atropine and novatropine [7], cocaine, protriptyline, methylamphetamine and methadone [8], and scopolamine and *N*-butyl scopolammonium [9] were reported.

Quinidine has the same actions and potency as those of quinine in malaria, but is rarely used for this purpose mainly because of its cost. It prolongs the refractory period of cardiac muscle and therefore reduces the rate at which successive contractions can take place. It is commonly used in cardiac arrhythmias in which it is far superior to quinine [10]. The content of quinidine in pharmaceutical preparations (usually in tablet form) is conventionally assayed by spectrophotometric methods after solvent extraction of the active principle [11]. Potentiometric methods are usually simple and rapid for the analysis of pharmaceutical preparations when a suitable sensor is available; since the excipients are mostly inactive, less clean-up is needed.

In this paper, the performance characteristics of a quinidine-selective membrane electrode are described. The electroactive material of the membrane is quinidine tetraphenylborate in a PVC matrix. This electrode exhibits useful analytical characteristics for the direct or indirect determination of protonated quinidine either in pure form

* To whom correspondence should be addressed.
† On leave from Institute of Chemical and Pharmaceutical Research, Bucharest, Romania.

or in pharmaceutical preparations. It is sufficiently selective for the determination of quinidine in tablets without prior separation from excipients.

Experimental

Apparatus

The quinidine plastic membrane electrode was used with an Orion 91-01 double junction reference electrode with 10% Na_2SO_4 solution in the outer compartment; pH measurements were performed with an Orion glass electrode (Model 91-02). E.m.f. values were measured with an Orion digital pH/mV-meter (Model 701A). All readings were recorded at room temperature; constant magnetic stirring was used.

Reagents and materials

Solutions of reagent-grade chemicals were prepared with distilled water. The materials were quinidine sulphate (Aldrich), sodium tetraphenylboron (Aldrich), 2-nitro-phenyl-octyl ether (Fluka), nitrobenzene (Aldrich), dibutyl sebacate (Eastman) and PVC-high molecular weight (Aldrich). Pharmaceutical preparations were purchased from local pharmacies.

Standard 5×10^{-3}M *quinidine sulphate*

A 3.9148 g sample of quinidine sulphate (2 H_2O) was dissolved in 50 ml methanol; the volume was adjusted to 1 l with TRIS–HCl buffer solution (pH 7.0). Solutions (5×10^{-6} to 5×10^{-4}M) were obtained by successive dilutions of the standard solution using the same buffer solution. All solutions contained 5% v/v of methanol.

Standard 10^{-1}M *sodium tetraphenylboron*

A 34.223 g sample of sodium tetraphenylboron was dissolved in TRIS–HCl buffer solution (pH 8.0) and the volume was adjusted to 1 l with this solution. Solutions (10^{-5} to 10^{-2}M) were obtained by successive dilutions of the standard solution using the same buffer solution (pH 8.0).

Quinidine electrode ion-exchange

Quinidine tetraphenylborate was precipitated by mixing 20 ml of 5×10^{-3}M quinidine sulphate with 20 ml of 10^{-2}M sodium tetraphenylboron. The mixture was filtered through a G4 sintered Gooch filter, and the white precipitate was washed with distilled water and dried at room temperature.

Construction of the electrode

The PVC membrane and the electrode were constructed as described elsewhere [12]. The electro-active material (20 mg) was well mixed with the plasticizer (dibutyl sebacate, nitrobenzene or 2-nitro-phenyl-octyl ether) (400 mg) and then with 200 mg PVC powder dissolved in about 5 ml of tetrahydrofuran. The clear mixture was poured into a 28-mm i.d. glass ring on a sheet of plate glass. A pad of filter paper on top of the ring was kept in place by a heavy metallic weight and the assembly was left for at least 48 h to allow the solvent to evaporate slowly. A disc (0.9 cm diameter) was cut from this membrane and fixed to the end of a 10-mm Tygon tube by means of a PVC–tetrahydrofuran solution as adhesive. The other end of the Tygon tube was fitted into a glass tube to form the electrode body. A silver/silver chloride wire was then inserted and the electrode body

was filled with 5×10^{-4}M quinidine sulphate (pH 7.0; TRIS–HCl buffer). The electrode was preconditioned for 10 min by soaking in 5×10^{-3}M quinidine sulphate and was stored in the same solution between use.

Electrode characteristics

The performance of the electrode was investigated by measuring the e.m.f. values of 1×10^{-2} to 5×10^{-6}M quinidine sulphate solutions. Potentials were recorded when stable readings were obtained, usually within 30 s.

Direct potentiometric measurement of quinidine

The quinidine electrode and the Orion double junction reference electrode were immersed in the aqueous solutions (50 ml) or pH 7.0 (TRIS–HCl buffer). After the solution had been stirred until equilibrium was attained, the e.m.f. values were compared with the calibration graph. The values were checked by the standard addition method.

Potentiometric titration of quinidine

A 10-ml aliquot of the quinidine sulphate solution (containing 2–20 mg of quinidine sulphate) was transferred by pipette into a 100-ml beaker. About 30 ml of TRIS–HCl buffer solution (pH 7.0) was added. The solution was titrated with 1×10^{-2}M NaTPB using the quinidine electrode and the Orion double junction reference electrode.

Direct potentiometric assay of tablets

Five tablets of quinidine (as sulphate or gluconate) were finely powdered and exactly one-fifth of the powder was transferred with 25 ml of methanol and TRIS–HCl buffer (pH 7.0) to a 500-ml volumetric flask. The solution was diluted to 500 ml with TRIS–HCl buffer solution (pH 7.0) (solution A). A 10-ml aliquot of solution A was transferred by pipette into a 50-ml volumetric flask containing 2.0 ml of methanol. The solution was diluted to 50 ml with TRIS–HCl buffer (pH 7.0). The contents were shaken and transferred into a 100-ml beaker. The quinidine electrode and the Orion double junction reference electrode were immersed in the solution. After the solution had been stirred until equilibrium was attained, the e.m.f. value was recorded and compared with the calibration graph. The value was checked using the standard addition method. For this purpose 5.0 ml of the standard solution of 5×10^{-3}M quinidine sulphate was added. The change in the reading in mV was recorded and used to calculate the concentration of quinidine (as sulphate or gluconate).

Potentiometric titration assay of tablets

Aliquots of 10–50 ml of solution A were transferred by pipette to a 100-ml beaker and the potentiometric titrations carried out as described for the potentiometric titration of quinidine.

Results and Discussion

Membrane material

Like other alkaloids, quinidine is known to react with sodium tetraphenylboron to form a stable, insoluble ion-pair complex (QdTPB). The complex, precipitated at pH 7.0, was used as electroactive material for the PVC membrane. Dibutyl sebacate, nitrobenzene and 2-nitro-phenyl-octyl ether (2-NPOE) were tested as plasticizers; 2-

NPOE showed good behaviour in respect to response time and reproducibility of e.m.f. values of the electrode. The membrane composition was QdTPB 3.2%, 2-NPOE 64.5% and PVC 32.3%. A membrane with the composition $Qd(TPB)_2$ 3.2%, 2-NPOE 64.5% and PVC 32.3% exhibits a near-Nernstian response to diprotonated quinidine (QdH_2^{2+}) in the range 5×10^{-5} to 5×10^{-3}M at pH 2.0 (adjusted with 1N sulphuric acid); the electroactive material was obtained by precipitation of quinidine sulphate solution with NaTPB solution at pH 2.0.

Electrode function

Typical calibration curves for the quinidine electrode under various experimental conditions are shown in Fig. 1.

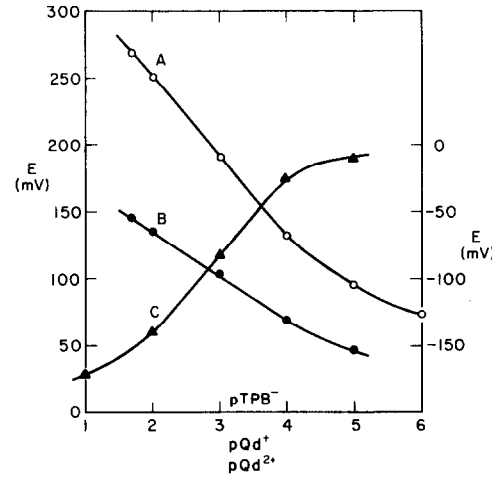

Figure 1
Electrode response to quinidine cations and tetraphenylborate anion (A) Quinidine sulphate solutions at pH 7.0 (TRIS–HCl buffer). The scale pQd^+ applies. (B) Quinidine sulphate solutions at pH 2.5 (borate–citrate–phosphate–HCl buffer). The scale pQd^{2+} applies. (C) Sodium tetraphenylborate solutions at pH 8.0 (TRIS–HCl buffer). The e.m.f. values in the graph are negative. The $pTPB^-$ scale applies.

The e.m.f. measurements were made using the following electrochemical cells:

$$\text{Qd} \mid \text{Quinidine sulphate } 5 \times 10^{-6} \text{ to } 1 \times 10^{-2}\text{M} \mid \text{Rf} \quad \text{pH} = 7.0 \text{ (TRIS–HCl buffer)} \tag{I}$$

$$\text{Qd} \mid \text{Quinidine sulphate } 5 \times 10^{-6} \text{ to } 1 \times 10^{-2}\text{M} \mid \text{Rf} \quad \text{pH} = 2.5 \text{ (citrate–borate–phosphate–HCl buffer)} \tag{II}$$

$$\text{Qd} \mid \text{Sodium tetraphenylboron } 1 \times 10^{-5} \text{ to } 1 \times 10^{-1}\text{M} \mid \text{Rf} \quad \text{pH} = 8.0 \text{ (TRIS–HCl buffer)} \tag{III}$$

where Qd = quinidine electrode and Rf = Orion double junction reference electrode with 10% Na_2SO_4 in the outer compartment. The respective potentials are given by:

$$E_I = E_{o(I)} + 0.058 \log [QdH^+] \tag{1}$$

$$E_{II} = E_{o(II)} + 0.033 \log [QdH_2^{2+}] \tag{2}$$

$$E_{III} = E_{o(III)} - 0.057 \log [TPB^-] \tag{3}$$

The response of quinidine electrode is linear in the range 3.5×10^{-5} to 1×10^{-2}M quinidine sulphate with near-Nernstian slopes for a monovalent cation (QdH^+) at pH 7.0 and for a divalent cation (QdH_2^{2+}) at pH 2.5, respectively. The response of the electrode to TPB^- anions is nearly Nernstian in the range 1×10^{-4}–1×10^{-2}M. Similar behaviour has been reported by Campbell *et al.* [13] in plastic electrodes for organic ions, prepared by coating a plasticized PVC film on to a graphite support.

Effect of pH

The effect of pH on the potential of the quinidine electrode was checked by recording the e.m.f. of the cell(I) in quinidine sulphate solutions with varying acidity. The pH of the initial solution was modified by addition of very small volumes of sulphuric acid and/or sodium hydroxide solutions. The graphs presented in Fig. 2 show that the potentials are not affected by pH in the range 6–8; this result is in accordance with the response of the electrode to monoprotonated quinidine (QdH^+). A linear graph of E(mV) against pH was also observed in the pH range 2–2.8. At higher pH values (pH>8) quinidine base in the test solutions is precipitated, and consequently the concentration of unprotonated quinidine gradually increases. As a result, lower e.m.f. readings were recorded. At lower pH values (3.0–5.5) the electrode becomes progressively sensitive to diprotonated quinidine (QdH_2^{2+}) and the e.m.f. readings decrease as the pH is reduced. At pH <3 most of the quinidine in solution is diprotonated. In addition, the electrode exhibits a near-Nernstian response to QdH_2^{2+} species (see also curve B in Fig. 1).

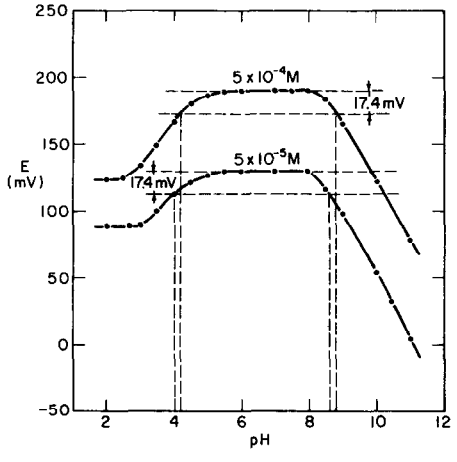

Figure 2
pH-effect on electrode response at two different concentrations of quinidine sulphate solutions.

The curves of e.m.f. against pH (Fig. 2) have been used to evaluate the basicity constants K_{b_1} and K_{b_2} of quinidine. Using the pH-dependent equilibria:

$$\underset{A}{QdH_2^{2+}} \overset{K_{a_2}}{\underset{H^+}{\rightleftharpoons}} \underset{B}{QdH^+} \overset{K_{a_1}}{\underset{H^+}{\rightleftharpoons}} \underset{C}{Qd} \qquad (4)$$

pK_{a_1} is the pH at which [B] = [C]; pK_{a_2} is the pH at which [A] = [B]. The pK_a values determined are: $pK_{a_1} = 8.73$ and $pK_{a_2} = 4.07$ (each represents the mean of two values

obtained from both curves in Fig. 2). The corresponding basicity constant values are: $K_{b_1} = 5.37 \times 10^{-6}$ and $K_{b_2} = 1.18 \times 10^{-10}$; these are in good agreement with the previously reported values of $K_{b_1} = 3.7 \times 10^{-6}$ and $K_{b_2} = 1.0 \times 10^{-10}$ [14]. The graphs of E(mV) against pH for different concentrations of sodium tetraphenylboron solution show that the electrode is affected by pH only at values higher than 9 and this is probably due to instability of the membrane electrode in alkaline solutions where QdH^+ from the membrane material can be converted into Qd free base.

Selectivity of the electrode

The response of the electrode toward different substances has been checked and the selectivity coefficients, $K_{QdH^+,J^{z+}}$, were used to evaluate the degree of interference. The values given in Table 1 were obtained using the separate solution method and the equation (4) below:

$$\log K_{QdH^+,J^{z+}} = \frac{E-E_I}{58} + \log[QdH^+] - \log[J^{z+}]^{1/z} \tag{5}$$

Table 1
Selectivity coefficients for the QdH^+–TPB^- membrane

Interferent, J	Selectivity coefficient, $K_{QdH^+,J^{z+}}$
K^+	1.15×10^{-2}
Ca^{2+}	5.25×10^{-4}
Zn^{2+}	4.37×10^{-4}
Isoniazid	1.41×10^{-2}
Glycine	1.45×10^{-2}
L-Arginine	1.45×10^{-2}
L-Histidine	1.45×10^{-2}
Acetylcholine	1.82×10^{-2}
Quinine	7.28×10^{-1}
Strychnine	3.55×10^{-1}
$(CH_3)_4N^+$	1.70×10^{-2}
$(C_2H_5)_4N^+$	2.09×10^{-1}
$(C_4H_9)_4N^+$	$10^{3.22}$

where E_I is the potential of the electrode in a quinidine solution of 5×10^{-4}M concentration (pH 7.0, adjusted with TRIS–HCl buffer; 5% v/v of methanol) and E is the potential of the same electrode in a solution containing $[QdH^+] = O$ and $[J^{z+}] = 5 \times 10^{-4}$M (pH 7.0, adjusted with TRIS–HCl buffer; 5% v/v of methanol).

The substances listed in Table 1 were chosen to represent potentially low-level contaminants in pharmaceutical preparations of quinidine. The bulk of the excipients, usually comprising lactose or glucose as diluent and maize starch or gelatin as binder, do not interfere. The same behaviour is shown for maltose, mannitol and sugar. The electrode potential is highly affected by quaternary ammonium compounds, mainly by those which contain more than four carbon atoms in each side chain.

Response time and reproducibility

The response time of the electrode was fast, being nearly instantaneous at higher concentrations and less than 1 min with a 5×10^{-5}M quinidine solution. The

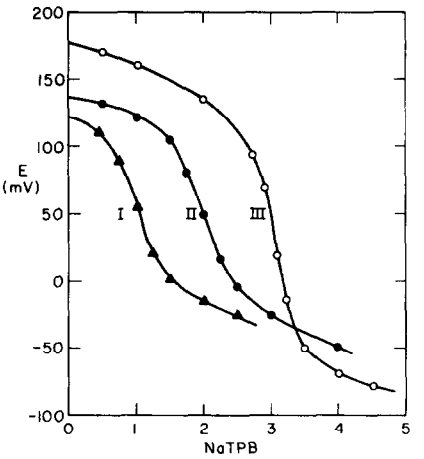

Figure 3
Potentiometric titrations of quinidine in different conditions. (I) 20 ml of 2.5×10^{-3}M quinidine sulphate at pH 7.0 (TRIS–HCl buffer); titrant: 1×10^{-2}M NaTPB. (II) 20 ml of 2.5×10^{-3}M quinidine sulphate at pH 2.5 (citrate–borate–phosphate–HCl buffer); titrant: 1×10^{-2}M NaTPB. (III) 30 ml of 5×10^{-3}M quinidine sulphate at pH 7.0 (TRIS–HCl buffer); titrant: 1×10^{-1}M NaTPB.

Table 2
Potentiometric determination of quinidine sulphate in solutions with quinidine electrode

	Found by potentiometric titration*		Found by standard addition method†	
Taken (mg)	mg	%	mg	%
1.87	1.90	101.6	1.83	97.9
3.74	3.77	100.8	3.81	101.9
5.61	5.53	98.6	5.72	102.0
7.48	7.39	98.8	7.36	98.7
11.22	11.13	99.2	11.02	98.4
14.96	15.02	100.4	14.84	99.2

* 10^{-2}M NaTPB solution as titrant; pH 7.0, adjusted with TRIS–HCl buffer.

† V_x = 50 ml (pH 7.0, TRIS–HCl buffer; 5% methanol); V_s = 10.0 ml; C_s = 5×10^{-3}M quinidine sulphate (pH 7.0).

Table 3
Potentiometric determination of quinidine in tablets with quinidine electrode*

		Result (% of nominal content ± S.D)	
Product	Sample	Potentiometric titration	Standard addition method
Quinidine sulphate	1	101.0 ± 0.74	103.6 ± 2.10
(Cin-Quin, Rowell;	2	99.2 ± 0.45	97.0 ± 1.92
300 mg/tablet)	3	99.9 ± 1.07	100.6 ± 2.41
Quinidine gluconate	1	100.1 ± 0.40	99.9 ± 1.43
(Rugby, 326 mg/tablet)	2	101.2 ± 0.24	101.5 ± 1.28
	3	99.6 ± 0.71	99.5 ± 1.75
	4	101.6 ± 1.26	103.3 ± 1.03

* All values are means of four determinations.

reproducibility of the readings of potential was better than ±1 mV over the entire range of concentrations, but in the first three days after electrode preparation the absolute potential varied from 5 to 10 mV, necessitating a one-point restandardization before each run.

Analytical applications

The electrode proved useful in the potentiometric determination of quinidine, both by direct potentiometry and by potentiometric titrations. From Fig. 3, which shows the potentiometric titration curves of quinidine sulphate, it is seen that at pH 7.0 a 1:1 complex (Qd:TPB) was formed, whereas at pH 2.5 the 1:2 complex (Qd:TPB) resulted. This is in agreement with the data presented in Fig. 2. In potentiometric titrations the most suitable reagent was sodium tetraphenylboron (usually 1×10^{-2}M); because of the good stability of this reagent it does not require to be restandardized until one month after preparation.

Table 2 shows the results of potentiometric determinations of quinidine sulphate in solutions with the quinidine electrode, both by the standard addition method and by potentiometric titrations with 1×10^{-2}M NaTPB. The results of the potentiometric analyses of quinidine sulphate tablets and quinidine gluconate tablets are presented in Table 3. In contrast to the time (about 2 h) required for assay by the official method, an electrode assay can be accomplished within 15 min. The rapidity of the method using the quinidine electrode makes it practical to perform the procedure on a single tablet so that tablet-to-tablet variation can be followed if desired.

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