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Bromhexine-Selective PVC Membrane Electrode Based on Bromhexinium Tetraphenylborate

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A bromhexine ion-selective PVC membrane electrode based on bromhexinium tetraphenylborate has been prepared with dioctyl phthalate as plasticizer. The electrode showed a linear response with a slope factor of 57.5 mV/concentration decade at 20°C over the concentration range from 4×10^{-4} to 10^{-1} M bromhexine. The effects of membrane composition, pH of the test solution, and the time of soaking on the electrode performance were studied. The electrode exhibited good selectivity for bromhexine with respect to a large number of inorganic cations and organic substances of biological importance. The standard addition method and potentiometric titrations were used to determine bromhexine concentrations in pure solutions and in a pharmaceutical preparation, with satisfactory results.

Key Words: bromhexine-selective electrode; response characteristics; selectivity coefficients.

INTRODUCTION

Ion-selective electrodes based on lipophilic salts of tetraphenylborate (TPB) with various organic cations of pharmaceutical importance have been investigated (*1–5*). Bromhexine hydrochloride (BHX HCl, *N*-(2-amino-3,5-dibromobenzyl)-*N*-cyclohexylmethylamine hydrochloride) is an important pharmaceutical compound and is widely used as a muculytic drug in conjunction with antibiotics such as penicillins for treatment of congestive respiratory diseases.

There are a variety of methods for the determination of BHX, although few of them can readily be adapted to routine analysis as automated monitoring methods for the in-line process control during production of BHX dosage forms. Gas–liquid chromatography (GLC) with electron capture (*6, 7*) with mass spectrometric (*8*) detection allows the determination of BHX in biological fluids at the ng/ml level after extraction and formation of its trifluoracetyl derivative. GLC with flame ionization detection (*9*) has also been used to determine BHX in the presence of other active ingredients in cough-cold syrups; however, the detection limit is very high (60 μg/ml) and the retention time is ca. 10 min. Kumar *et al.* (*10*) reported an HPLC determination for BHX in pharmaceutical preparations with an analysis time of 15 min. The formation and extraction in organic solvents of the ion pair formed between BHX and $[Co(SCN)_4]^{2-}$ has been used to determine BHX in pharmaceutical preparations by molecular (*11*) and atomic (*12*) absorption spectrometry. Although the selectivity of these methods is quite good, the quantification limit is very high.

The presence of a para aromatic amine group in the BHX molecule allowed the

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TABLE 1
Composition and Response Characteristics of PVC-Matrix Membranes

Membrane	Ion pair content (%)	Slope (mV/decade)	Potential response: Linear detection region (M)	Potential response: Response time (sec)	Potential response: Intercept at $p = 0$ (mV)
a	2.44	48.0	8.0×10^{-4}–6.3×10^{-2}	10–2	140
b	6.98	43.5	4.0×10^{-4}–6.3×10^{-2}	10–15	163
c	4.76	57.5	4.0×10^{-4}–1.0×10^{-1}	10–15	164
d	9.09	44.0	1.6×10^{-3}–5.0×10^{-2}	15–20	132

development of several photometric methods for its determination based on the coupling of the diazotized BHX derivative with *N*-(1-naphthyl)-ethylenediamine (NED) (*13*, *14*), 2-naphthol (*15*), orcinol (*16*), resorcinol (*17*), and phloroglucinol (*18*). All these methods feature a very similar dynamic range for the calibration graph (μg/ml level) and entail waiting for 5–10 min to ensure maximum reaction development.

The foregoing methods suffer from poor throughputs and are difficult to adapt to BHX routine determinations. The automatic determination of BHX has been addressed in two ways. One involves nitrite (*19*) and has been used for content uniformity testing. The sampling rate, however, is very low as the titration time is ca. 15 min. The other involves spectrophotometric measurement of the chloroform extract of the ion pair formed between BHX and Bromocresol Purple (*20*). The method thus developed, with a sampling frequency of 30 h^{-1}, was applied to binary mixtures of BHX with cephalexin, cefaclor, and oxytetracycline by using complex instrumentation including sophisticated extraction equipment and two spectrophotometers, one encompassing the visible region for BHX measurement and the other the UV region for the antibiotic measurement. However, BHX interfered with the determination of penicillins such as ampicillin and amoxycillin, which are present in many pharmaceutical preparations of BHX. Gala *et al.* (*21*) described a direct kinetic method for the determination of BHX in pharmaceutical formulations.

The low cost and ease of operation of potentiometric instrumentation make its use for the determination of BHX a useful alternative. For these reasons we have investigated the performance characteristics of a BHX-selective membrane electrode based on incorporation of bromhexinium tetraphenylborate (BHX-TPB) into a poly(vinyl chloride) (PVC) matrix and used this electrode for the determination of BHX in pure solutions and in pharmaceutical preparations such as Bisolvon tablets.

EXPERIMENTAL METHODS

Reagents

All reagents were of the highest purity available. The TPB solution was standardized as previously described (*22*). The BHX-TPB was prepared by a method similar to that described previously (*3*).

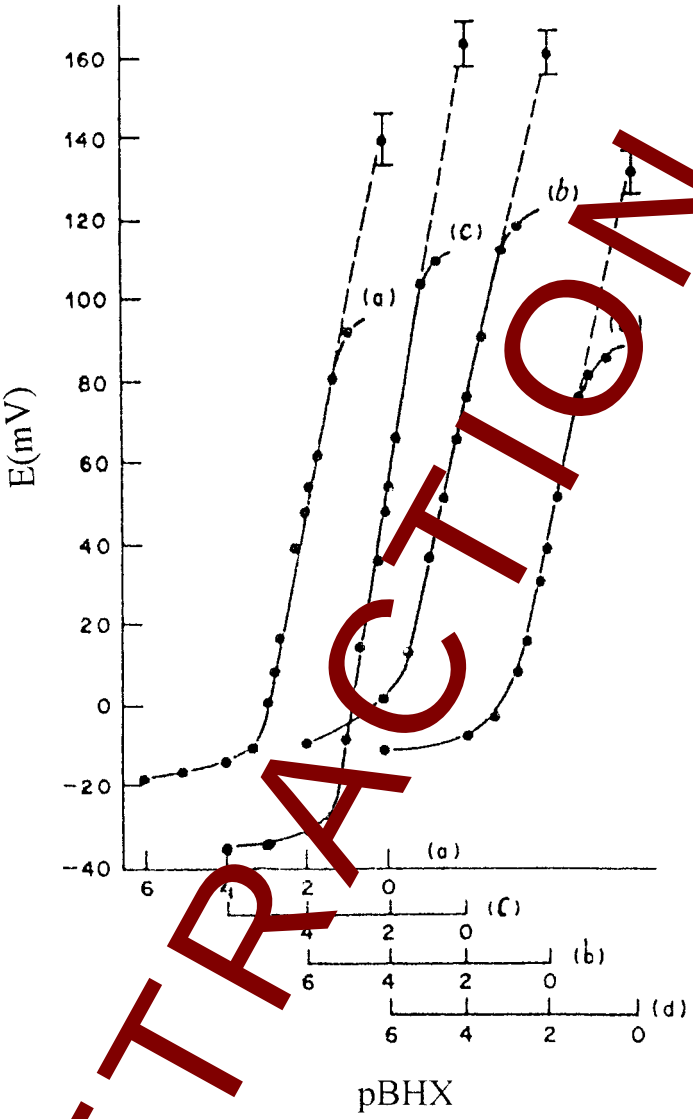

FIG. 1. Calibration plots of the BHX electrodes.

Membrane Preparation

Four membranes were prepared in which the concentration of BHX-TPB was varied to find the optimum composition. A selected amount (25, 50, 75, or 100 mg) of the salt was dissolved in a mixture of 15 ml of tetrahydrofuran (THF), 0.5 g of PVC, and 0.5 g of dioctyl phthalate. The resulting solution was poured into a Petri dish (9.5 cm in diameter) and left at room temperature for the THF to evaporate. A transparent membrane about 0.2

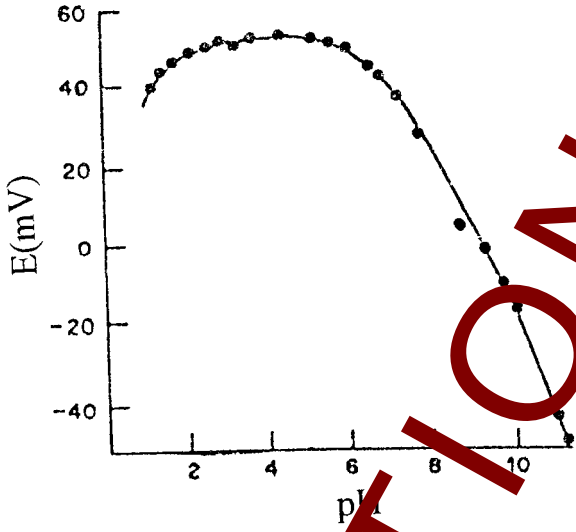

FIG. 2. Effect of pH on the potential of electrode c.

mm in thickness was obtained, from which a disk of about 12-mm diameter was cut. The disk was glued to the polished end of a PVC tube by means of PVC solution in THF. The electrode body was then filled with 0.1 M sodium chloride/0.001 M BHX as the internal solution.

Potential Measurements

The electrochemical system was as follows: Ag, AgCl/internal filling solution/membrane/test solution//saturated KCl salt bridge//saturated calomel electrode. The potential was measured at a constant temperature of 20°C with an Orion Model 701 A digital pH/mV meter, the test solution being continuously stirred.

TABLE 2
Selectivity Coefficients for the Bromhexine Electrode

Interferent	$K^{pot}_{BHX,J_{z^+}}$	Interferent	$K^{pot}_{BHX,J_{z^+}}$
NH_4^+	2.7×10^{-2}	Phenylalanine	1.0×10^{-2}
Na^+	2.3×10^{-2}	Et_3NH^+	5.5×10^{-2}
K^+	3.5×10^{-2}	$Et_2NH_2^+$	3.5×10^{-1}
Ca^{2+}	7.9×10^{-4}	$Me_2NH_2^+$	2.4×10^{-1}
Mg^{2+}	8.5×10^{-3}	Me_4N^+	4.3×10^{-2}
Fe^{2+}	6.6×10^{-3}	Maltose	4.2×10^{-2}
Fe^{3+}	4.8×10^{-3}	Lactose	2.4×10^{-2}
Glycine	7.4×10^{-3}	Sucrose	2.7×10^{-2}
Alanine	6.5×10^{-3}		

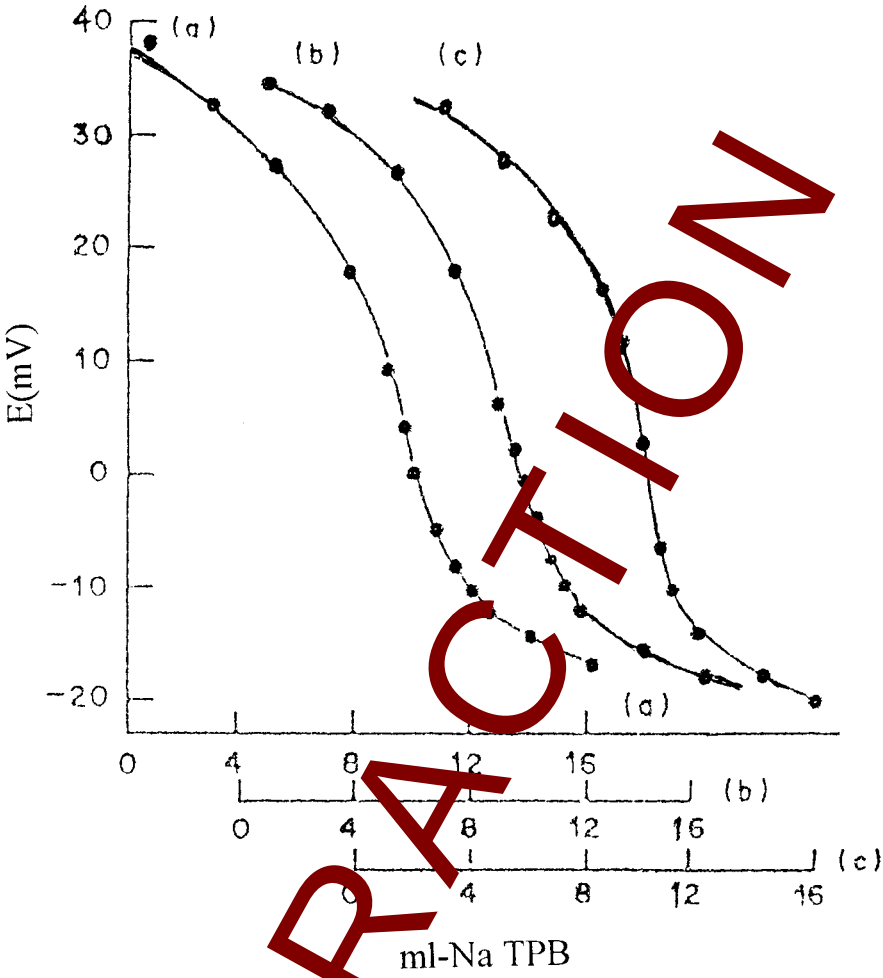

FIG. 3. Potentiometric titration of solutions containing powdered Bisolvon tablets (10 mg of BHX) with 5×10^{-3} NaTPB.

Selectivity of the Electrode

The selectivity coefficients were evaluated by the separate solution method (*4*) with a 10^{-3} M solution of BHX and the interferent.

Potentiometric Determination of BHX

Small increments of 0.1 M BHX were added to 100-ml samples of various concentrations. The change in emf was recorded after each addition and used to calculate the concentration of the BHX sample solution.

For the analysis of BHX formulations, 20 tablets of Bisolvon were ground up and 140- to 250-mg portions of the powder were quantitatively transferred to 150-ml beakers

TABLE 3
Potentiometric Determination of Bromhexine

	Standard addition method			Potentiometric titration		
Solution	Taken (mg)	Mean recovery (%)	Standard deviation (%)	Taken (mg)	Mean recovery (%)	Standard deviation (%)
Pure BHX	9.83–29.79	99.6	1.5	5–20	99.9	0.9
Bisolvon[a]	12.03–21.49	101.1	2.4	10–25	98.0	1.0

[a] Chemical Industries Development, S.A.A., Giza, Egypt.

containing 100 ml of distilled water. The mixture was stirred vigorously until dissolution seemed complete, and the standard addition technique was applied as above.

Potentiometric Titration of BHX

An aliquot of solution containing 5–20 mg of BHX was transferred to a 150-ml beaker and the volume made up to 100 ml with distilled water. This solution was titrated with 5×10^{-3} M standard NaTPB solution, the BHX membrane electrode being used as the sensor. For BHX in Bisolvon tablets, 120- to 290-mg portions of the powdered tablets were transferred to 100-ml beakers containing 50 ml of water and titrated as above.

RESULTS AND DISCUSSION

The response characteristics of the membranes investigated are summarized in Table 1 and the calibration graphs are given in Fig. 1. It is clear that electrode c was the best, giving a calibration plot with an almost Nernstian slope over a relatively wide range of concentration and having a fast response. Electrode c was therefore used for all subsequent studies.

Effect of pH

The effect of pH of the test solution (10^{-2} M BHX, 0.1 M NaCl) on the electrode potential was investigated by following the variation in emf with change in pH produced by the addition of very small volumes of 0.01–0.1 M sodium hydroxide or hydrochloric acid. Figure 2 shows that the electrode can be used at pH 2.1–6.0 for BHX determination. At pH < 2.1 the potential decreases, presumably because of formation of the diprotonated species. At pH > 6.0 the decrease in potential can be attributed to the conversion of BHX^+ into BHX.

Effect of Soaking

Calibration graphs (pBHX vs E) were obtained by use of the electrode after it had been soaked in 10^{-3} M BHX for periods of 5 min and 0.5, 1.0, 1.5, 2.0, 3.0, 6.0, and 24 h.

The optimum soaking time was found to be 1–2 h, the slopes of the calibration curves being 57.5–55.5 mV/pBHX at 20°C. Soaking for longer than 2 h is not recommended and the electrode should be kept dry in an opaque closed vessel in a refrigerator when not in use.

Selectivity

None of the species (J) investigated interfered (Table 2), as indicated by the very small values of $K^{pot}_{BHX,\ J}{}^{z+}$. The inorganic cations did not interfere because of differences in ionic size, mobility, and permeability compared with BHX^+. In the case of sugars, amino acids, and amines, the high selectivity is mainly attributed to their different polarity and lipophilic nature compared with bromhexine.

Analytical Applications

The electrode was used successfully for the determination of BHX in pure solution and in Bisolvon tablets by the standard-addition method and potentiometric titration (Table 3). Representative replicate titration curves are given in Fig. 3. The standard deviations and recoveries in Table 3 reveal the reasonably good precision and accuracy of the proposed methods and indicate that the excipients in the Bisolvon tablets do not interfere.

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