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Polymeric membrane electrodes for drug analysis*

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Abstract: Two new polymeric membrane electrodes selective to cholate and to benzylpenicillinate, based respectively on PVC membranes containing polybenzylpropargilamine as conductor polymer and benzyldimethylcethylammonium-cholate, or -benzylpenicillinate as exchangers, have been prepared, and applied to the determination of cholic acids, anionic surfactants and antibiotics. Results are compared with those ones obtained by analogous PVC sensors and liquid membrane sensors, previously described.

Keywords: *PVC membrane sensor; conducting polymer; drugs and surfactants analysis.*

Introduction

Previous research in the field of potentiometric sensors, both on PVC (polyvinylchloride) membrane sensors containing specific exchangers [1, 2] and on polymeric membrane sensors with conducting polymers [3, 4], prompted an investigation of the possibility of constructing new polymeric membrane sensors based on PVC and using polybenzylpropargylamine (PBPA) as conductor, sebacate as plasticising agent and benzyldimethylcethylammonium-chlolate, or -benzylpenicillinate as selective exchanger. In this paper the full characterisation of two sensors so assembled, and their application to real matrices, such as drugs containing cheno- or urso-deoxycholic acids, sodium salts of antibiotics of the penicillin, or cephalosporin groups, and anionic surfactants, are described. The quantitative analysis of these substances is performed and a detailed comparison of the results, with those given by analogous liquid membrane sensors [5, 6, 7], or PVC sensors [1, 2], described during recent years, is included.

Experimental

Reagents

All the reagents were of analytical reagent grade: cholate sodium salt and lauryl bisulphate were supplied by Merck; deoxycholate, chenodeoxycholate sodium salts by

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Sigma; ursodeoxycholic acid by Giuliani, Italy; benzylpenicillin potassium salt was supplied by Squibb S.p.A., Rome, Italy; laurylbenzensulphonate by Farmitalia-Carlo Erba, Milano, Italy; piperacillin sodium salt by Cyanamid S.p.A., Catania, Italy; cephalothin sodium salt by Istituto Biochimico Italiano, Pomezia, Italy; benzyldimethyl-cetylammonium chloride, 1-decanol, high molecular polyvinylchloride (PVC) and bis (2-ethylhexyl) sebacate by Fluka, Switzerland; other reagents by Merck, Darmstadt, FRG.

The analysed drugs, commercially available, were injectable preparations, or pellets, each containing an antibiotic (piperacillin, or cephalotin), or an antilithogenic compound [8] (cheno-, or urso-deoxycholic acid). Further details about these drugs have been reported previously [5–7].

Polybenzylpropargylamine (PBPA) was synthesised according to Furlani *et al.* [9]. The measured conductivity of this polymer was 1.5×10^{-5} ohm^{-1} cm^{-1}.

The exchangers salts, benzyldimethylcethylammoniumcholate (BDMCACh), or -benzylpenicillinate (BDMCABP), were prepared and purified as described previously [5, 7].

Apparatus and measurements

Potentiometric measurements were performed by means of an Orion research potentiometer Model 901 with a Radiometer REC 61 Servograph recorder. An automatic burette (Scott-Gerate TA 50) coupled to the potentiometer-recorder system and a saturated calomel electrode, as reference, were used to obtain calibration curves. The solutions to be analysed were magnetically stirred and thermostatted at 20°C. In the potentiometric measurements, both for the calibration plot and for the standard addition measurements, the initial volume was 25.0 ml.

The determination of the critical micellar concentrations (CMC), of the different cholanic acids, was performed by graphical analysis of the potentiometric curves [1] as illustrated in Fig. 1.

The aqueous standard cholate, or benzylpenicillinate solutions and those of the other cholanic acids, antibiotics, anionic surfactants and analysed drugs, were prepared by the procedure extensively described in previous papers [1, 2].

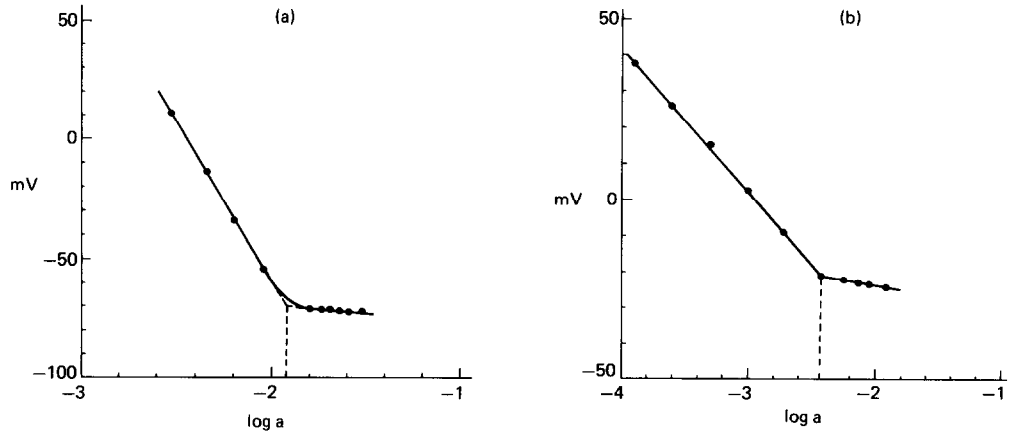

Figure 1
CMC determination by polymeric (PVC + PBPA) cholate electrode: (a) cholate, (b) deoxycholate.

The evaluation of the calibration curves and the calculation of the selectivity coefficients, were carried out with the aid of a HP 86 personal computer using the software developed by the authors [10].

Polymeric and liquid membranes electrode assembly

The assembly of liquid membrane electrodes using 1.0 mM solutions of the exchanger salt in 1-decanol was performed according to the procedure adopted by previous workers [5–7].

The polymeric membranes were obtained by dissolving 165 mg of PVC in 3 ml of tetrahydrofuran, then adding 330 mg of bis (2-ethylexyl) sebacate, as plasticising agent, and 5% w/w of BDMCACh or BDMCABP. In the new polymeric membranes, containing a conductor polymer, studied in this paper, 5% w/w of PBPA also was added

Table 1
Characterisation of the polymeric (PVC + PBPA) membrane cholate sensor in standard solutions of sodium cholate. Selectivity coefficients according to the Moody-Thomas method

j^{n-}	$K_{chol,j^{n-}}$	Background level of interference (mol l^{-1})
Citrate	1.02×10^{-2}	1.00×10^{-2}
Oxalate	4.91×10^{-3}	1.00×10^{-1}
Nitrate	4.67×10^{-2}	1.00×10^{-2}
Sulphate	2.15×10^{-3}	1.00×10^{-1}
Chloride	6.27×10^{-2}	1.20×10^{-2}
Hydroxyl	4.38	1.60×10^{-3}

Response time: <10 s.
Slope: −0.0584 (±0.0009) ΔV/Δ log a.
Linearity range: 5.0×10^{-4}–1.9×10^{-2} (mol l^{-1}).
Repeatability of measurements (as % pooled standard deviation) in the linearity range: 1.1%.
Inaccuracy in the linearity range: direct method −0.8% (RSD = 0.5). Standard addition method −0.8% (RSD = 0.6).

Table 2
Characterisation of the polymeric (PVC + PBPA) membrane benzylpenicillinate sensor in standard solutions of potassium benzylpenicillinate. Selectivity coefficients according to the Moody-Thomas method

j^{n-}	$K_{bp,j^{n-}}$	Background level of interference (mol l^{-1})
Citrate	8.25×10^{-3}	1.00×10^{-2}
Oxalate	4.77×10^{-3}	1.00×10^{-2}
Nitrate	6.38×10^{-1}	5.00×10^{-3}
Sulphate	1.24×10^{-2}	5.00×10^{-3}
Chloride	1.20×10^{-1}	5.00×10^{-3}
Hydroxyl	0.50	1.00×10^{-3}

Response time: <10 s.
Slope: −0.0536 (±0.0004) ΔV/Δ log a.
Linearity range: 1.2×10^{-4}–1.5×10^{-2} (mol l^{-1}).
Repeatability of measurements (as % pooled standard deviation) in the linearity range: 2.4%.
Inaccuracy in the linearity range: direct method −1.0% (RSD = 3.5). Standard addition method −2.0% (RSD = 3.0).

Table 3
Comparison of precision, accuracy and linearity range data, obtained in the analysis of standard solutions and of some real matrices, by liquid membrane, polymeric (PVC) membrane and polymeric (PVC + PBPA) membrane cholate sensors

	Liquid membrane electrode	Polymeric (PVC) membrane electrode	Polymeric (PVC + PBPA) membrane electrode
Standard cholate solution			
Linearity range (mol l^{-1})	4.0×10^{-5}–1.0×10^{-2}	8.0×10^{-5}–5.3×10^{-3}	5.0×10^{-4}–1.9×10^{-2}
Precision (as CV_{res})	0.5	1.3	1.1
Inaccuracy by direct method	+1.0% (RSD = 3.1)	−1.4% (RSD = 4.6)	−0.8% (RSD = 0.5)
Standard chenodeoxycholate solution			
Linearity range (mol l^{-1})	2.0×10^{-4}–3.2×10^{-3}	1.6×10^{-5}–2.0×10^{-4}	8.0×10^{-6}–4.0×10^{-4}
Precision (as CV_{res})	3.5	4.5	2.4
Inaccuracy by direct method	+3.3% (RSD = 3.5)	+2.3% (RSD = 3.0)	+3.2% (RSD = 1.5)
Standard ursodeoxycholate solution			
Linearity range (mol l^{-1})	1.0×10^{-4}–5.0×10^{-3}	1.6×10^{-5}–3.1×10^{-4}	8.0×10^{-6}–3.5×10^{-4}
Precision (as CV_{res})	1.0	1.1	1.8
Inaccuracy by direct method	+1.4% (RSD = 2.6)	+3.0% (RSD = 2.5)	+3.1% (RSD = 2.4)
Anionic surfactant solutions			
Linearity range (mol l^{-1})	1.6×10^{-5}–1.6×10^{-4}	2.2×10^{-5}–2.1×10^{-4}	6.2×10^{-6}–2.9×10^{-4}
Precision (as CV_{res})	4.6	3.3	4.1
Inaccuracy by direct method	+1.6% (RSD = 3.6)	+3.1% (RSD = 2.1)	+3.2% (RSD = 2.0)
Drug containing chenodeoxycholic acid			
Inaccuracy by direct method	+5.4% (RSD = 8.6)	+4.8% (RSD = 1.3)	+5.5% (RSD = 2.0)
Drug containing ursodeoxycholic acid			
Inaccuracy by direct method	+2.8% (RSD = 1.9)	+5.2% (RSD = 0.7)	+5.0% (RSD = 1.6)

to the tetrahydrofuran solution. The solution is evaporated in a Petri dish (5 cm diameter) to yield a membrane (≤0.1 mm thickness), which is cut in discs of 10 mm diameter. A disc is glued to the bottom of a PVC tube by an adhesive, obtained by dissolving PVC in cyclohexanone. The inner solution of the PVC tube is 10 mM sodium cholate and KCl, into which an Ag/AgCl reference electrode is dipped.

Results

The analytical results in aqueous sodium cholate and potassium benzylpenicillinate solutions, obtained in order to characterise the new polymeric electrodes containing PBPA, are summarised in Tables 1 and 2. Also in these tables, the selectivity coefficients, relative to the most common interfering anions, are indicated. In Table 3, the new polymeric cholate sensor are given values of the linearity ranges, experimental precision and accuracy, obtained for solutions of cholate, chenodeoxycholate and ursodeoxycholate. These are compared with those obtained under the same experimental conditions, by the liquid cholate electrode and by a PVC electrode containing no conducting polymer. Also the results obtained for the analysis of real matrices (antilithogenic drugs, anionic surfactants), are reported in the same table. In Table 4, the critical micellar concentration values (CMC) of the most common unconjugated cholanic acids found by the two polymeric cholate electrodes are compared with data given by surface tension measurements. Finally, in Table 5 the analytical response of the polymeric benzylpenicillinate sensors, with or without PBPA, are compared with those given by the liquid membrane sensor based on the same exchanger. Measurements being made in standard benzylpenicillinate solutions and in commercial drug formulations.

Discussion and Conclusions

This study was intended to contribute to other efforts aiming to improve the efficiency of the membrane sensors. Thus, the use of a polymer in the membrane electrode assembly resulted in better robustness, longer lifetime, greater versatility and in lower memory effects when contacted with enough concentrated solutions of the ion to which they are selective compared with traditional liquid membrane electrodes. As a consequence some new applications are possible, such as CMC determination, (Table 4) while the other properties and characteristics are practically unaltered (response time, linearity range, quasi Nernstian slope, accuracy and precision) (Tables 1, 2, 3, 5 and data reported in previous comunications [1, 2, 6–7]). Among the polymeric electrodes, with

Table 4
Comparison of values of critical micellar concentrations (CMC), of the most important unconjugated cholanic acids, obtained by polymeric (PVC) membrane and by polymeric (PVC + PBPA) membrane cholate sensors, with literature reported data. All values obtained in 0.15 mol l^{-1} NaCl solution. Each value is the mean of at least three determinations

Cholanic salt	CMC by polymeric (PVC) membrane electrode (mmol l^{-1}, RSD = 3.0	CMC by polymeric (PVC + PBPA) membrane electrode (mmol l^{-1}) RSD = 3.0	Values of CMC (by surface, tension method). Reported in literature [10] (mmol l^{-1})
Cholate	11.1	11.7	11.0
Deoxycholate	4.2	3.8	3.0
Chenodeoxycholate	4.7	4.3	4.0

Table 5
Comparison of precision, accuracy and linearity range data, obtained in the analysis of standard solutions and of some real matrices, by liquid membrane, polymeric (PVC) membrane, and polymeric (PVC + PBPA) membrane benzylpenicillinate sensors

	Liquid membrane electrode	Polymeric (PVC) membrane electrode	Polymeric (PVC + PBPA) membrane electrode
Standard benzylpenicillinate solution			
Linearity range (mol l^{-1})	2.0×10^{-4}–3.1×10^{-3}	5.8×10^{-4}–7.1×10^{-3}	1.2×10^{-4}–1.5×10^{-2}
Precision (as CV_{res})	1.2	1.9	2.4
Inaccuracy by direct method	+2.2% (RSD = 3.9)	−1.0% (RSD = 1.5)	−1.0% (RSD = 3.5)
Drug containing penicillanic antibiotic sodium salt (piperacillin)			
Inaccuracy by direct method	+1.7% (RSD = 6.7)	+1.0% (RSD = 8.7)	+2.0% (RSD = 5.1)
Drug containing cephalosporamic antibiotic sodium salt (cephalothin)			
Inaccuracy by direct method	−1.2% (RSD = 2.1)	+1.0% (RSD = 4.0)	+1.5% (RSD = 3.5)

or without conductor polymer addition, even if no marked differences are observed, some improvements, following the introduction of the conducting polymer are found in terms of the linearity range and freedom from interferences, so enabling the possibility of optimising the choice of the sensor, depending on the matrix to be analysed and on the conditions to be adopted.

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