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USE OF PLASTIC MEMBRANE
ION-SELECTIVE ELECTRODES
FOR THE ANALYSIS OF DRUG SUBSTANCES*

Adel F. SHOUKRY
Department of Analytical Chemistry
Faculty of Science, Cairo University, Giza, Egypt

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An overview is given on plastic membrane ion-selective electrodes of the conventional and/or coated-wire type constructed for 23 drug compounds. These are based on incorporation of ion-pairs or ion-associates in poly(vinyl chloride) network in the presence of dioctyl phthalate as a plasticizer. The electrodes are very selective to their respective drugs; a comparative study proved that stereospecificity is a major factor affecting their selectivity. They have a relatively large working pH-ranges (more than 4 pH units for most cases). The isothermal temperature coefficients (dE°/dT) of the electrodes range from 2.5×10^5 to 32.0×10^4 V/°C over a wide temperature limits. The electrodes can be employed successfully for assaying the investigated drugs in many of their pharmaceutical preparations.

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Introduction

Most of electroanalytical methods depend on the use of chemical sensors, the sensing in this case is part of an information acquisition process in which some insight is obtained into the chemical composition of the system in real time. Ion-selective electrodes, as a broad category of indicator electrodes, occupy a very prospecting position among the sensors being developed recently. The fundamental characteristic of such electrodes is the reproducible correlation between the potential of the electrode membrane and the activity of the chemical species. Also the electrode should be selective, easily constructed and handled, durable and not fragile. In addition, it should have fast response.

Plastic Membrane Electrodes

In the plastic membrane-containing ion-selective electrodes (ISEs), the active ingredient which is dispersed into the polymer network with the help of a solvent mediator (plasticizer) may be neutral sequestering substance (e.g. cyclic polyether), ion-exchanger, complex species, ion-pair or ion-associate. During the last decade numerous research works in the field of drug analysis have been published employing plastic membrane electrodes as potentiometric sensors. In this respect, the contribution of the analytical chemistry school, Faculty of Science, Cairo University, to the field¹⁻¹⁸ is listed in Table I.

Table I List of pharmaceutical compounds analyzed using ISEs in Chemistry Department, Faculty of Science, Cairo University (1986 - 1994)

Substance	Abb.	Year	Ref.
Metoclopramide	MCP	1986	1
Tetracycline	TC	1987	2
Doxycycline	DC		2
Oxytetracycline	OTC		2
Diphenhydramine	DPH		3
Antazoline	An	1988	4
Hydralazine	HL		6
Lignocaine	LC		5
Procaine	PC		5
Benzocaine	BC		5
Thioredazine	Tr		7
Phenylephrine	PE	1989	8
Adiphenine	Ad	1990	9

Table I - Continued

Substance	Abb.	Year	Ref.
Bupivacaine	BpC	1991	10
Oxybuprocaine	ObC		10
Papaverine	Pv		11
Propylhexedrine	PX	1992	12
Ephedrine	Ep	1993	13
Ampicilin	Amp	1994	14
Metformin	Mf		15
Amoxycilin	Amox		17
Trimethoprim	TM		18
Tetramisole	Tm		16

The potentiometric determination of the pharmaceutical compounds listed is based on the use of poly(vinyl chloride) (PVC) membranes containing either ion-pair or ion-associate as the exchanger. The membrane is made by mixing a solution of PVC of high molecular weight in tetrahydrofuran with an ion-pair or ion-associate composed of the compound under investigation in its cationic form and tetraphenylborate (TPB^-) or phosphotungstate (PT^{3-}) anion, respectively. To this solution mixture, appropriate amount of the plasticizer (dioctyl phthalate, DOP) is added with vigorous stirring. The mixture is then poured into a Petri-dish of 5.0 - 7.5 cm diameter and the solvent is left to evaporate. A disc of the membrane formed is cut out and glued to a tube containing a reference electrolyte solution into which an internal reference Ag/AgCl electrode is immersed (conventional type electrode). To prepare the coated-wire type electrode, a terminal part (1 - 2 cm) of a metallic wire or rod is dipped into the above solution mixture and left to dry in air for few minutes, the process is then repeated several times till a membrane of proper thickness covers the metallic part.¹⁹⁻²¹

Evaluation of Selectivity of ISEs

Selectivity is the ability of a sensor to respond primarily to only one species in the presence of others. In living organisms, selectivity strategy is, mainly, to involve shape recognition, i.e. stereospecificity. For ISE based on ion-exchanger, selectivity depends on both stereospecificity and electrostatic environment of the exchanged species providing that the process is thermodynamically possible on the basis of entropy and/or enthalpy considerations. If the process is not associated with increase in entropy, the enthalpy change should be enough to

compensate this hindering factor. In nature this is the case in the process of formation of hydrogen bonds, ionic bonds, charge transfer complexes, etc. In the case of ion-exchange at the surface of ISE in aqueous solutions, the entropy, most probably, increases as a result of the disturbance of water molecules arrangements around each of the binding site and the mobile species. Moreover, the process is greatly affected by the nature of the attacking species, thus if certain region on the molecule is hydrophobic, then again it must be matched by the hydrophobic region in the ion-pair or ion-associate. Any other interaction will have positive free energy change, which means repulsion. It is evident that the matching in nature of the two exchangeable species will contribute to the free energy of interaction only if the two species fit geometrically and eliminate some hydration water from binding cleft and its vicinity. The mobility of ionic species which affects the kinetics of the process is also one of major factors determining the selectivity.

Generally, the membrane output (R_{out}) results from the contribution of different species present in the sample solution. If the contribution from the primary species i^z dominates while that from other species j^y is minimal, it is said that the membrane (the electrode) is highly selective to i . R_{out} is a response function of the type

$$R_{out} = f[a_i^z, K_{ij} a_j^{z/y}] \quad (1)$$

K_{ij} is called the selectivity coefficient. For ISE it has been customary to study and evaluate K_{ij} by using the specific form of equation (1), the so-called Nikolskii-Eisenman equation:

$$E = E_o + \frac{RT}{zF} \ln[a_i + K_{ij} a_j^{z/y}] \quad (2)$$

Experimentally, K_{ij} can be evaluated using various methods, the most common of which are separate solutions and the mixed solutions methods²²⁻²⁵

Separate Solution Method

This is based on two e.m.f. measurements performed by introducing the i^z ion-selective electrode into each of two solutions, one for i with activity (a_i) and the second for j with activity (a_j) and recording the electrode potentials E_1 and E_2 , respectively; then by substituting in equation (2), K_{ij} can be obtained:

$$\log K_{ij} = \frac{E_2 - E_1}{S} + \left(1 - \frac{z}{y}\right) \log a_j \quad (3)$$

$$a_i = K_{ij} a_j^{z/y} \quad (4)$$

Equation (3) is valid for the case $a_i = a_j$, and equation (4) for the case $E_1 = E_2$, and S is the slope of the calibration graph. The method has been applied successfully to investigate the selectivity of ISE's for the compounds listed in Table I toward large number of cationic species. Representative results are given in Table II. The results show that K_{ij} values for K^+ and phenylalanine are generally higher than the corresponding values for Na^+ and alanine, respectively. This may be explained in light of the stereospecificity factor determining the selectivity, since the ionic volume of K^+ and phenylalanine are greater than those of Na^+ and alanine, respectively, and consequently having higher degree of lipophilicity.

Table II Selectivity coefficient values of plastic membrane electrodes for their respective species

Primary Cation	- $\log K_{ij}$				
	Interferent, j				
	Na^+	K^+	Glycine	Alanine	Phenylalanine
MCP	3.12	2.87	3.26	3.29	3.10
TC	2.43	2.39	2.47	2.57	2.44
DC	2.05	2.03	2.49	2.58	2.45
OTC	3.11	2.57	3.28	3.35	3.19
DPH	3.11	2.99	2.23	2.18	2.01
An	2.86	2.88	2.96	3.03	2.97
HL	1.64	1.46	2.13	2.19	2.00
Tr	3.60	3.55	4.48	4.17	4.05
Ad	3.14	3.07	3.21	3.19	3.21
BpC	1.77	1.92	1.62	2.08	1.86
ObC	1.80	1.89	2.35	2.35	2.04
Pv	3.20	3.21	4.22	4.02	4.05
PX	1.55	1.60	1.45	1.41	
EP	1.04	1.09	1.60	1.54	
TM	2.70	2.41	2.85	2.96	
Tm	3.18	3.09	2.38	3.19	

For abbreviations, see Table I.

Mixed Solutions Method

The e.m.f. is measured in a solution containing a fixed quantity of the interfering ion and a variable activity of the primary ion.

$$K_{ij} = \frac{a_i}{a_j^{z_j/y}} \quad (5)$$

a_i and a_j being the values corresponding to the intersection of that part of the calibration curve (of approximately zero slope) which corresponds to complete interference by ion j , with the Nernstian or approximately Nernstian part corresponding to the electrode functioning to the primary ion i . An example is shown in Fig.1 where K_{ij} is calculated for an OH^- responsive electrode²⁶ in the presence of F^- , Cl^- , Br^- , I^- and NO_3^- anions as foreign ions.

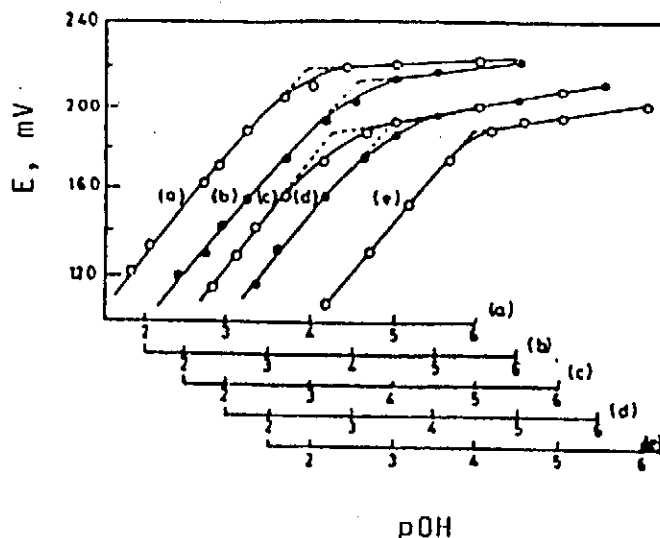


Fig. 1 Application of the mixed solutions method to the determination of selectivity coefficients of hydroxyl ion-selective electrode towards different anions: (a) F^- , (b) Cl^- , (c) Br^- , (d) I^- , (e) NO_3^-

Effect of pH

Generally, each ISE has, though variable, certain pH range within which the electrode potential is constant (working pH range). The ISE's for compounds listed in Table I exhibit the pH ranges shown in Table III. At pH values higher than the upper limits of the working pH ranges, most of the electrodes exhibit

a decrease in their potentials, representative potential - pH curves are shown in Fig. 2. This is attributed to the disappearance of the protonated species as a result of the formation of the free bases. In some cases, the decrease in potential in that part of the curve was in/or close to a Nernstian behaviour toward hydroxyl ions. This is because the free base, being lipophilic and capable of receiving hydronium ions on its surface, may act as an exchanger of the freely hanged OH^- ions with those of the bathing solution. A plastic membrane hydroxyl ion-selective electrode based on the use of chlorpromazine base has been successfully prepared²⁷.

At pH values lower than the acid limit of the working pH range of a plastic membrane, the hydronium ion may penetrate the membrane test solution interfacial junction causing a higher value in the potential reading than that expected by the primary ion. In many cases this process is opposed by the formation of the diprotonated species in solution leading to a decrease in the concentration of the primary cation and consequently to a decrease in potential. In most cases, the electrodes responsive to compounds listed in Table I showed a decrease in potential at low pH values indicating the predominance of the second process.

Table III Working pH ranges for the investigated electrodes

Pharmaceutical compound	pH range	Pharmaceutical compound	pH range
MCP	2.5 - 7.3	Ad	2.2 - 7.5
TC	7.0 - 11.5	BpC	2.3 - 6.3
DC	8.3 - 11.5	ObC	2.6 - 7.4
OTC	6.5 - 11.5	Pv	1.0 - 6.2
DPH	2.0 - 7.0	PX	2.5 - 9.5
An	2.3 - 9.0	Ep	2.0 - 8.0
HL	2.1 - 6.0	Amp	3.0 - 11.0
LC	1.9 - 7.7	Mf	4.0 - 11.0
PC	3.1 - 7.9	Amox	3.5 - 11.0
BC	6.9 - 9.0	TM	1.8 - 6.3
Tr	2.1 - 7.0	Tm	3.0 - 6.3
PE	2.9 - 8.0		

For abbreviations, see Table I.

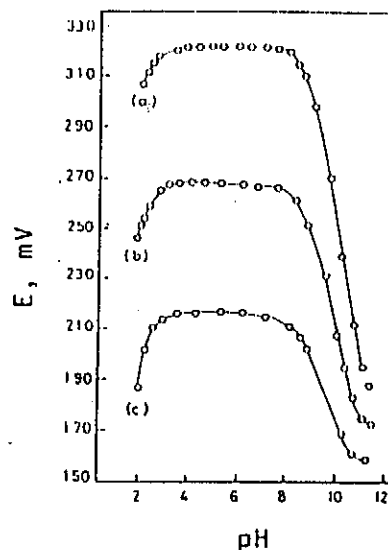


Fig. 2 Effect of pH on PC-electrode potential in solutions of procaine of different concentrations: (a) 10^{-2} , (b) 10^{-3} , (c) 10^{-4} mol dm⁻³

Effect of Temperature

It is very important to study the effect of temperature on the performance characteristics of plastic membrane ISE's because many potentiometric measurements concerning biological media and fluids are made at higher temperatures than the ambient temperature or the temperatures at which most of the investigations are carried out, namely 20 and 25 °C.

The effect of temperature was first studied for a coated-wire Antazoline-selective electrode. The study comprises construction of calibration graphs in solution of different temperatures (Fig. 3) to record the effect of heat on the different characteristics of the electrode (usable concentration range, slope, etc.). As the temperature of the bathing solution exceeds certain value (50 - 70 °C), the electrode responds to the activity changes in a non-Nernstian way. This may be due to the following reason: At such high temperature the phase boundary equilibrium at the gel layer-test solution interface is distributed by the thermal agitation of the solution. Furthermore the failure of the electrode may be due to deformation effect on the membrane surface as a result of excessive heating.

The isothermal temperature coefficient (dE°/dT) of the electrode may be determined by aid of the equation¹⁶

$$E = E^{\circ} + \frac{dE^{\circ}}{dT}(t - 25) \quad (6)$$

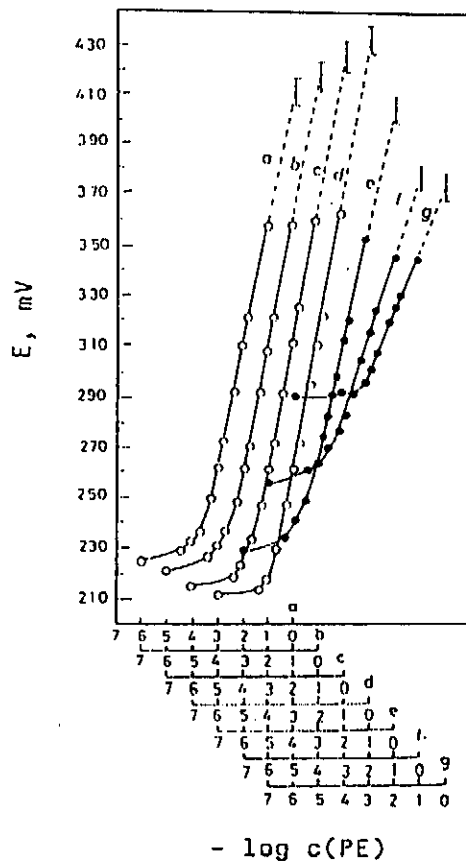


Fig.3 Calibration graphs for phenylephrine electrode soaked for 1 hour at different temperatures: (a) 25, (b) 35, (c) 45, (d) 65, (f) 75, (g) 85 °C

A plot of E^o vs $(t - 25)$ gives a straight line, the slope of which is dE^o/dT . E^o is simply determined as the intercept of the calibration graph at $\log c_i = \text{zero}$, where i is the investigated species. The isothermal temperature coefficients obtained were of comparable magnitude ranging from $2.5 \times 10^{-4} \text{ V/}^\circ\text{C}$ for pyrilhexedrine (PX) to $32.0 \times 10^{-4} \text{ V/}^\circ\text{C}$ for thioredoxine (Tr).

Analytical Applications

Plastic membrane ISE's proved, specially through the last two decades, to be very useful for the assay of pharmaceutical compounds in their preparations. Although many methods other than potentiometry have been reported for the

determination of such compounds, most of them are complicated and need sophisticated instrumentation such as HPLC or GLC. The low cost and ease of operation of potentiometric instrumentation make potentiometry using ISE's a highly desirable alternative (see a review²⁸).

Using plastic membrane ISE's for the pharmaceutical compounds listed in Table I, tens of pharmaceutical preparations containing these compound were assayed¹⁻¹⁸, representative results are given in Table IV. The techniques were standard additions method and/or potentiometric titration based on ion-pair formation (for more information about this kind of determinations see^{29,30}). The determinations were precise as the coefficient of variation was always very small, ranging from 0.15 to 2.40 %, and successful as the recovery values were close to 100 %.

Table IV Potentiometric determination of DPH drugs in syrups using PVC-DPH membrane electrodes

DPH-containing syrup	Standard addition method			Potentiometric titration		
	Taken mg	Found mg	RSD %	Taken mg	Found mg	RSD %
Isilin (The Nile Co. for Pharmaceuticals, Egypt). 270 mg DPH/100 ml		3.28			7.91	
	3.34	3.34	1.15	8.10	7.83	0.82
		3.27			7.96	
Sedaline (Kahira Pharmaceuticals, Egypt). 260 mg DPH/100 ml		3.76			7.80	
	3.76	3.77	0.15	7.80	7.98	1.30
		3.77			7.80	
Coldal (Cid Laboratories, Egypt) 266.7 mg DPH/100 ml		3.43				
	3.36	3.42	0.17			
		3.42				

^a The end points located in all titrations were shifted to higher values. This is due to the interference of ephedrine hydrochloride which is present in this syrup (66.7 mg/100 ml)

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