Anal Bioanal Chem (2005) 382: 1642–1651
DOI 10.1007/s00216-005-3351-9

ORIGINAL PAPER

Sergey V. Kharitonov

Transport properties and electroanalytical response characteristics of drotaverine ion-selective sensors

Received: 4 April 2005 / Revised: 16 May 2005 / Accepted: 23 May 2005 / Published online: 9 July 2005

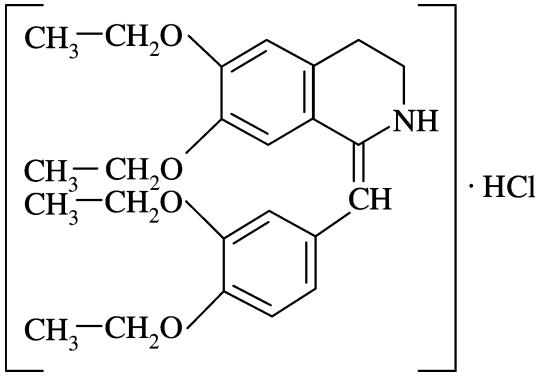
Abstract The construction and electroanalytical response characteristics of poly(vinyl chloride) matrix ion-selective sensors (ISSs) for drotaverine hydrochloride are described. The membranes incorporate ion-association complexes of drotaverine with tetraphenylborate, picrate, tetraiodomercurate, tetraiodobismuthate, Reinecke salt, and heteropolycompounds of Keggin structure—molybdophosphoric acid, tungstophosphoric acid, molybdosiliconic acid and tungstosiliconic acid as electroactive materials for ionometric sensor controls. These ISSs have a linear response to drotaverine hydrochloride over the range 8×10^{-6} to 5×10^{-2} mol L^{-1} with cationic slopes from 51 to 58 mV per concentration decade. These ISSs have a fast response time (up to 1 min), a low determination limit (down to 4.3×10^{-6} mol L^{-1}), good stability (3–5 weeks), and reasonable selectivity. Permeabilities and ion fluxes through a membrane were calculated for major and interfering ions. Dependences of the transport properties of the membranes on the concentrations of the ion exchanger and near-membrane solution and their electrochemical characteristics are presented. The ISSs were used for direct potentiometry and potentiometric titration (sodium tetraphenylborate) of drotaverine hydrochloride. Results with mean accuracy of $99.1 \pm 1.0\%$ of nominal were obtained which corresponded well to data obtained by use of high-performance liquid chromatography.

Keywords Drotaverine hydrochloride · Ion-selective electrodes · Permeability coefficient · Ion flux

S. V. Kharitonov
Department of Analytical Chemistry,
Saint-Petersburg State Institute of Technology,
Moskovsky pr. 26, Saint-Petersburg 190013,
Russian Federation
E-mail: kharitonov@hotmail.ru

Introduction

Drotaverine (1-(3,4-diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline) hydrochloride, is an isoquinoline derivative. It is a highly potent spasmolytic agent [1]. This drug is capable of relieving spasms of various organs, regardless of their function and innervation. Drotaverine hydrochloride has been proved to be superior in its efficiency to papaverine hydrochloride and its absorption after oral administration is more reliable [2].



Str. 1

For qualitative and quantitative determination of drotaverine hydrochloride in biological fluids and in pharmaceutical preparations high-performance liquid chromatography has been reported [3]. However, this method needs expensive equipment.

Ion-selective sensors (ISSs) are useful in pharmaceutical analysis because of their low cost, ease of use and maintenance, and the simplicity and speed of the assay procedures [4–6]. Although ISSs have been widely used in pharmaceutical analysis no electrodes responsive to drotaverine have so far been described.

To reveal regularities in the optimum selection of ionophores for ion-exchange membranes with given properties, it is necessary to study transport processes at the surface of the membrane and in the membrane phase. Usually these studies receive insufficient attention, although a knowledge of these processes and the ability to control them will enable optimization of the electrochemical characteristics of potentiometric devices.

This paper reports the use of simple potentiometric sensors for determination of drotaverine hydrochloride in pharmaceutical formulations. The sensors are based on the use of tetraphenylborate, picrate, tetraiodomercurate, tetraiodobismuthate, Reinecke salts, and heteropolycompounds of Keggin structure for formation of ion-association species. These species, which are characterized by different lipophilicities and stabilities, were used as electroactive substances (EAS) in plasticized poly(vinyl chloride) matrix membranes. The ISSs based on these membranes were prepared, characterized, compared, and used for rapid and accurate selective determination of drotaverine hydrochloride. We studied the effect of some factors on the transport characteristics of ion-exchange membranes (based on ion-associative complex drotaverine with tetraphenylborate) to determine their main electrochemical properties—the permeability coefficient and ion flux through the surface.

Experimental

Equipment

Potentiometric measurements at 20 ± 1°C were made with an I-130 high-impedance pX-meter (Russia) using membrane sensors in conjunction with the Radelkis OP-0820P Ag/AgCl double-junction reference electrode containing 1 mol L^{-1} KNO_3 solution in the outer compartment. Adjustment of pH was monitored with an combination glass electrode. EAS composition was determined by potentiometric or amperometric titration. For the latter we used a polarograph and a rotating platinum electrode. Analysis to determine the drotaverine ion concentration was performed with a Varian Model 5029 HPLC system.

Reagents and preparation of solutions

All solutions were prepared with deionized water. The chemicals used were all of analytical grade. Sodium tetraphenylborate ($Na[B(C_6H_5)_4]$), sodium picrate ($Na[C_6H_2(NO_2)_3O]$), sodium tetraiodobismuthate ($Na[BiI_4]$), potassium tetraiodomercurate ($K_2[HgI_4]$), Reinecke salt ($NH_4[Cr(NH_3)_2(SCN)_4]$) and heteropolycompounds of Keggin structure—molybdophosphoric acid ($H_3[PMo_{12}O_{40}]$), tungstophosphoric acid ($H_3[PW_{12}O_{40}]$), molybdosiliconic acid ($H_4[SiMo_{12}O_{40}]$), and tungstosiliconic acid ($H_4[SiW_{12}O_{40}]$)—were obtained from Aldrich; poly(vinyl chloride) (PVC, high molecular weight) was from Fluka. We used low-permittivity membrane solvents (MS) ($\epsilon < 10$), such as dioctyl phthalate (DOP), dibutyl phthalate (DBP), bis(2-ethylhexyl)sebacate (EHS), and heptyl benzoate (HB) from Reakhim (Russia). 1-(3,4-diethoxybenzilyden)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (drotaverine hydrochloride, hereafter $[C_{24}H_{32}O_4N]^+Cl^-$), 6,7-dimethoxy-1-(3,4-dimethoxybenzyl)isoquinoline hydrochloride (papaverine hydrochloride, $[C_{20}H_{22}O_4N]^+[Cl]^-$), benzhydrol hydrochloride β-dimethylaminoethyl ether (diphenhydramine hydrochloride $[C_{17}H_{22}ON]^+[Cl]^-$), 2-benzylbenzimidazole hydrochloride (bendazole hydrochloride $[C_{14}H_{12}N_2]^+[Cl]^-$), 10-(2-dimethylaminopropyl)-phenothiazine hydrochloride (promethazine hydrochloride, $[C_{17}H_{21}SN_2]^+[Cl]^-$), diethylaminoethyl *p*-aminobenzoate hydrochloride (procaine hydrochloride, $[C_{13}H_{21}O_2N_2]^+[Cl]^-$), piperazine dihydrochloride ($[C_4H_{12}N_2]^{2+}2[Cl]^-$), and *N*-cetylpyridinium chloride ($[C_{16}H_{33}N]^+[Cl]^-$), purity 99.5%, were obtained from the Nanjing Pharmaceutical Factory (China). Tablets and injections of drotaverine hydrochloride were purchased from a local drug store.

Procedures

Preparation of ion exchangers

The ion-association complexes were prepared by mixing stoichiometric amounts of 0.05 mol L^{-1} solution of sodium tetraphenylborate (and also $Na[C_6H_2(NO_2)_3O]$, $K_2[HgI_4]$, $Na[BiI_4]$, $NH_4[Cr(NH_3)_2(CNS)_4]$, $H_3[PW_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, and $H_4[SiMo_{12}O_{40}]$) with an equimolar solution of drotaverine hydrochloride. The precipitates were filtered and washed with deionized water several times until there was no white precipitate when a drop of $AgNO_3$ was added to the washing solution. The precipitates were then dried at 25°C under vacuum for at least 48 h. The ion-association complexes should be stored in a desiccator.

PVC membrane sensors

The ion-selective membranes were prepared as described elsewhere [7]. In a glass Petri dish (5 cm diameter), drotaverine ion exchangers were thoroughly mixed with plasticizers and PVC in amounts depending on the structure of a membrane. The mixture was dissolved in 5 mL cyclohexanone. The Petri dish was covered with a filter paper and left to stand overnight to enable solvent evaporation at room temperature. Membranes of thickness 0.3 mm were obtained.

Sensor assembly and calibration

Punched circular membranes (ca. 8 mm diameter) were used to assemble the sensors. The ISSs bodies were filled with an inner filling solution containing 0.01 mol L^{-1}

drotaverine hydrochloride and 0.1 mol L^{-1} KCl. ISSs were conditioned by soaking in 1×10^{-2} mol L^{-1} aqueous drotaverine hydrochloride solutions for 24 h and stored in the same solution when not in use.

Membrane ISSs were calibrated by immersion in 1×10^{-2}–1×10^{-6} mol L^{-1} drotaverine hydrochloride solutions and left to equilibrate with constant stirring in conjunction with an Ag/AgCl reference electrode. The ISSs were stored in bidistilled deionized water between measurements. The electrode potential was recorded as a function of drotaverine hydrochloride concentration in an electrochemical cell:

Ag	AgCl	1×10^{-2} mol/l sol. $[C_{24}H_{32}O_4N]^+Cl^-$ + 1×10^{-1} mol/l sol. KCl	Ion-selective membrane	Calibration or test solution	KCl (Sat. sol.)	AgCl	Ag

Radelkis double junction reference electrode

Str. 2

The calibration plots obtained were used for subsequent measurement of unknown drotaverine hydrochloride concentrations.

Potentiometric selectivity coefficients: ($K^{Pot}_{DrotH^+,J^+}$) were determined by the separate solutions method.

Membrane-transport experiment

The transport properties of membranes were studied using a cell consisting of two sections of equal volumes separated by an ion-exchange membrane (Fig. 1). The area of the membrane between two aqueous solutions was 2×10^{-3} m^2. A drotaverine hydrochloride solution of the required concentration was placed in section 1, and doubly distilled water was placed in section 2. Both phases were stirred. At regular intervals, samples were taken from the reservoirs with a glass pipette with a volume of 2–5 mL and diluted with doubly distilled water. The concentrations of drotaverine hydrochloride were determined by spectrophotometric method.

Solubility product of drotaverine ion-exchangers

Because drotaverine hydrochloride has absorption peaks in the UV range (molar extinction coefficient approx. 20,000 L mol^{-1} cm^{-1}, $\lambda_{max}=260$ nm), the solubility products (SP) of EAS were calculated from spectrophotometry data (Specord M-40), using equilibrium concentrations of drotaverine cations in the solution above the solid, after construction of a calibration plot.

Direct potentiometric determination of drotaverine hydrochloride in tablets

The contents of one tablet were mixed with deionised water and transferred to a 100-mL volumetric flask and diluted to volume, to give a ca. 1×10^{-3} mol L^{-1} solution of drotaverine hydrochloride. Aliquots of this solution were separately transferred to 100-mL volumetric flasks

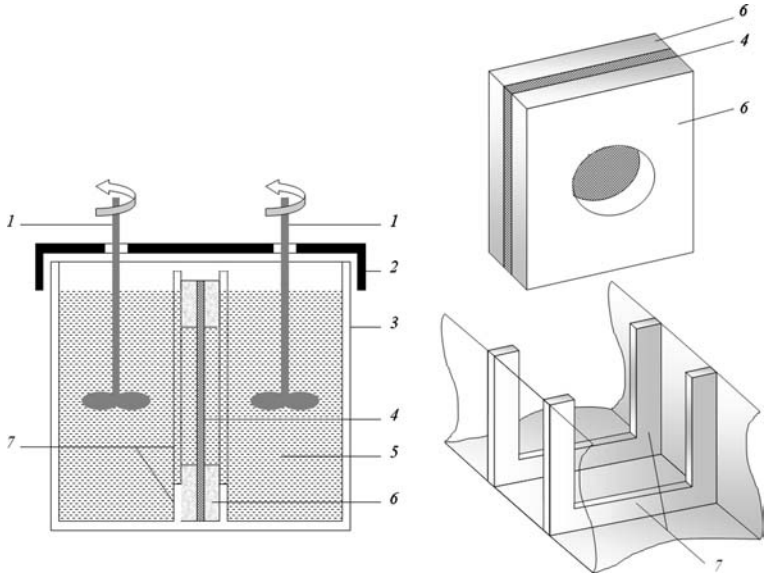


Fig. 1 Diagram of the set-up for studying ion transport through selective membranes: (*1*) glass arm stirrer, (*2*) cover, (*3*) Plexiglas vessel, (*4*) ion-exchange membrane containing the neutral complex of the ion exchanger IS, (*5*) solution (section 1, $[C_{24}H_{32}O_4N]^+Cl^-$, concentration c_1; section 2, doubly distilled water gradually enriched with $[C_{24}H_{32}O_4N]^+Cl^-$ because of the migration of ions from section 1), (*6*) fixing plates, and (*7*) holding frames

Table 1 Results from amperometric titrations of drotaverine hydrochloride by various compounds

$H_3[PMo_{12}O_{40}]$	$H_3[PW_{12}O_{40}]$	$H_4[SiMo_{12}O_{40}]$	$H_4[SiW_{12}O_{40}]$
2.8 ± 0.3	2.7 ± 0.1	4.1 ± 0.1	4.0 ± 0.2
2.9 ± 0.1	2.7 ± 0.2	4.2 ± 0.1	4.1 ± 0.3
2.8 ± 0.2	2.6 ± 0.3	4.3 ± 0.1	4.1 ± 0.3
3.0 ± 0.2	2.8 ± 0.2	4.0 ± 0.2	3.8 ± 0.2
3.1 ± 0.3	3.0 ± 0.3	4.1 ± 0.1	4.1 ± 0.3
2.9 ± 0.2	3.2 ± 0.2	4.3 ± 0.2	4.0 ± 0.2

and diluted to volume with water. Aliquots (25 mL) of each of these solutions were transferred to 100-mL beakers. The electrode system was immersed in each solution and the reading was recorded and compared with the calibration plot.

Potentiometric titration of drotaverine hydrochloride

Solutions of drotaverine hydrochloride were transferred to 50-mL beakers. A membrane ISS in conjunction with an Ag/AgCl reference electrode was immersed in the solution which was titrated with 1×10^{-2} mol L^{-1} sodium tetraphenylborate solution. The mV reading was recorded after each addition of titrant.

Results and discussion

Structure of electroactive substances

The picrate, tetraphenylborate, $[BiI_4]^-$, and $[Cr(NH_3)_2(CNS)_4]^-$ anions react with the drotaverine cation to form stable 1:1 ion-association complexes. It is known [8] that a metal atom forming the heteropolyanions used in our experiments can be reduced from an oxidation state of +5 to +3. This property was used in amperometric titrations and to establish the composition of the associates. The half-wave potential was −0.74 V for heteropolycompounds containing molybdenum ($H_3PMo_{12}O_{40}$ and $H_4SiMo_{12}O_{40}$) and −0.54 V for heteropolycompounds containing tungsten ($H_3PW_{12}O_{40}$ and $H_4SiW_{12}O_{40}$). The results of the amperometric titrations are listed in Table 1. The drotaverine-to-heteropoly anions ratio was found to be 1:3 and 1:4, which corresponds to the following stoichiometry of reaction:

$$n[C_{24}H_{32}O_4N]^+Cl^- + H_n[P(Si)Me_{12}O_{40}] \rightarrow ([C_{24}H_{32}O_4N]^+)_n[P(Si)Me_{12}O_{40}]^{n-} \downarrow + n\ HCl$$

Table 2 Solubility product (K_s) of some drotaverine ion-exchangers

Lipophilic anion	K_s
$[B(C_6H_5)_4]^-$	$(3.7 \pm 0.3)\times10^{-12}$
$[C_6H_2(NO_2)_3O]^-$	$(2.5 \pm 0.4)\times10^{-9}$
$[HgI_4]^{2-}$	$(7.6 \pm 0.3)\times10^{-15}$
$[BiI_4]^-$	$(5.6 \pm 0.2)\times10^{-9}$
$[Cr(NH_3)_2(SCN)_4]^-$	$(2.2 \pm 0.2)\times10^{-11}$
$[PMo_{12}O_{40}]^{3-}$	$(4.2 \pm 0.4)\times10^{-25}$

The SP (K_s) of the ion-exchangers are listed in Table 2. The lowest SP are for ion-associates of the drotaverine cation with anions of high molecular weight and high lipophilicity.

Transport properties of $[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^-$ - selective membranes

For description of diffusive mass transfer through an ion-exchange membrane, we use the equation [9]:

$$\ln\left\{1-\left(1+\frac{V_2}{V_1}\right)\frac{c_2^\tau}{c_1^\circ}\right\} = -PS\left[\frac{1}{V_1}+\frac{1}{V_2}\right]\tau, \quad (1)$$

where P is the permeability coefficient, m s^{-1}; c_2^τ is the average molar concentrations of the solution in section 2 at time τ, and c_1^0 is the initial molar concentration of the solution in section 1 (Fig. 1); V_1, V_2, and S are the volume of section 1, volume of section 2, and the area of the membrane surface in contact with the solution, respectively.

Generally, solvent transfer does not significantly affect the change in solution volumes in sections 1 and 2; therefore, in first approximation these changes can be ignored in calculations of membrane permeability and the initial values of volumes V_1^0 and V_2^0 can be used.

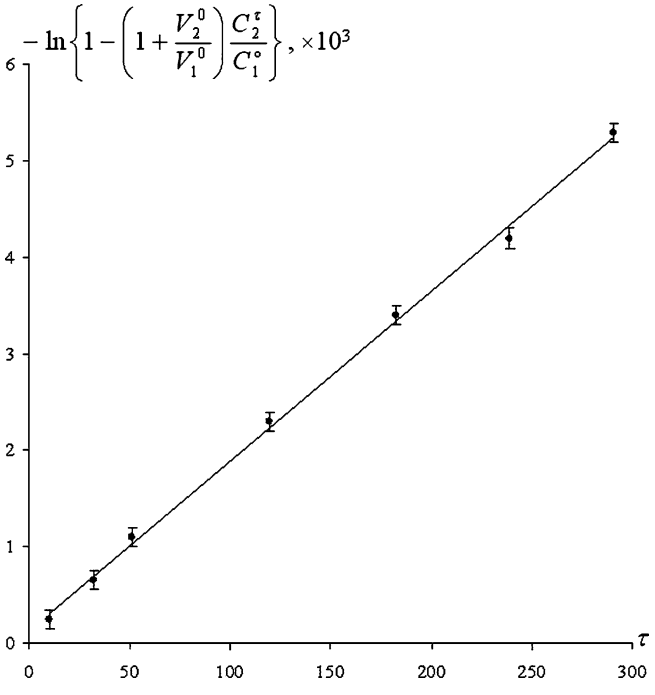


Fig. 2 Dependence of $\ln\left\{1-\left(1+\frac{V_2^0}{V_1^0}\right)\frac{c_2^\tau}{c_1^\circ}\right\}$ on time (τ, h) for a membrane based on $[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^+$

Table 3 Dependence of permeability and ion flux on the concentration of drotaverine hydrochloride solution for a membrane based on $[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^-$ with a ion exchanger concentration of 1×10^{-2} mol kg^{-1} (MS) plasticized with DBP

Concentration of on $[C_{24}H_{32}O_4N]^+$ in section 1 (mol L^{-1})	Permeability coefficient P (m/s)	Ion flux J (mol m^{-2} s^{-1})	Correlation coefficient (r)
2.5×10^{-2}	1.1×10^{-9}	3.2×10^{-8}	0.96
1.0×10^{-2}	2.3×10^{-9}	3.0×10^{-8}	0.95
7.3×10^{-3}	5.1×10^{-8}	3.3×10^{-8}	0.98
5.0×10^{-3}	1.8×10^{-8}	8.9×10^{-8}	0.98
1.0×10^{-3}	4.2×10^{-8}	9.6×10^{-8}	0.99
2.5×10^{-4}	3.4×10^{-7}	1.4×10^{-7}	0.98

The permeability coefficient of an ion-exchange membrane P can be calculated from the slope of the plot constructed in $\ln\left\{1-\left(1+\frac{V_2^0}{V_1^0}\right)\frac{c_2^\tau}{c_1^\circ}\right\}$ versus τ coordinates.

Figure 2 shows a typical relationship of this type for a membrane based on $[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^+$. As seen in Fig. 2, the plot is a straight line passing through the origin of slope $PS\left[\frac{1}{V_1^0}+\frac{1}{V_2^0}\right]$.

The values of permeabilities and ion fluxes for membranes of constant composition with different concentrations of $[C_{24}H_{32}O_4N]^+[Cl]^-$ solution in section 1 (Table 3) demonstrate that there is no clear linear correlation between the concentration of $[C_{24}H_{32}O_4N]^+[Cl]^-$ in section 1 and the permeability coefficients of the ion-exchange membrane at its fixed thickness and cross-sectional area. However, we can generally state that the permeability of membranes decreases with increasing concentration of $[C_{24}H_{32}O_4N]^+[Cl]^-$ in section 1. Evidently, this is related to rapid saturation of the membrane and, as a consequence, to the existence of difference of potentials in the system between the surface and the membrane phase, which, in turn, leads to a decrease in ion transfer through the phase surface. The value of the flux typically approaches a constant value on increasing the concentration of $[C_{24}H_{32}O_4N]^+[Cl]^-$ in section 1. This supports the theory that transfer is limited by diffusion through the aqueous boundary layer which forms at the surface of the membrane on contact with the solution.

The absence of correlation is because even the most strongly associated ion exchanger has a dissociation constant in the membrane solvent (DOP) larger by an order of magnitude than its solubility product (K_s) in water. Evidently, the smaller the dissociation constant of the ion exchanger, the faster the aqueous phase is saturated with the ion exchanger. Leaching of the ion exchanger, which must occur to some extent, has a detrimental effect on the electrochemical and performance characteristics of ion-selective electrodes because it inevitably leads to their degradation.

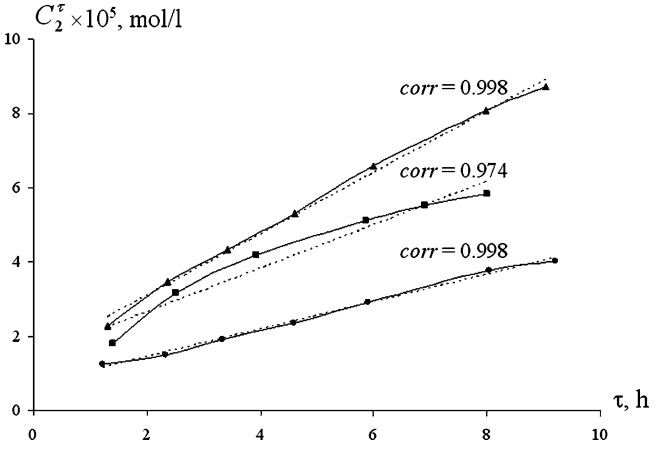


Fig. 3 Effect of membrane composition and the concentration of the near-membrane solution on the time dependence of the concentration of $[C_{24}H_{32}O_4N]^+Cl^-$ in the enriched solution: (*filled triangles*) $c_{IS}=5.0\times10^{-3}$ mol L^{-1}, near-membrane solution was $[C_{24}H_{32}O_4N]^+Cl^-$ with $c=1.0\times10^{-2}$ mol L^{-1}; (*filled squares*) $c_{IS}=7.5\times10^{-3}$ mol L^{-1}, near-membrane solution was $[C_{24}H_{32}O_4N]^+Cl^-$ with $c=2.5\times10^{-4}$ mol L^{-1}; and (*filled circles*) $c_{IS}=1.0\times10^{-2}$ mol L^{-1}, near-membrane solution was $[C_{24}H_{32}O_4N]^+Cl^-$ with $c=1.0\times10^{-3}$ mol L^{-1}

Permeability and ion flux depend on the concentration of the ion exchanger in the membrane phase (Table 4, Fig. 3). Figure 3 shows the dependence of the concentration of $[C_{24}H_{32}O_4N]^+[Cl]^-$ in the enriched solution on the composition of the membrane and the concentration of the near-membrane solution. The nearly linear form of the time dependence of concentration c_2^τ in Fig. 3 can be explained by analyzing Eq. (1). According to Fig. 2, $\ln\left\{1-\left(1+\frac{V_2^0}{V_1^0}\right)\frac{c_2^\tau}{c_1^\circ}\right\}<1$,

Table 4 Dependence of permeability and ion flux on the concentration of the ion exchanger $[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^-$ in the membrane phase

Concentration of the ion exchanger [mol kg^{-1} (MS)]	Permeability coefficient P (m s^{-1})	Ion flux J (mol m^{-2} s^{-1})
5.1×10^{-2}	5.3×10^{-7}	3.2×10^{-7}
1.2×10^{-2}	2.4×10^{-7}	1.0×10^{-7}
6.5×10^{-3}	7.0×10^{-8}	8.3×10^{-8}
3.5×10^{-3}	5.1×10^{-8}	6.4×10^{-8}
1.3×10^{-3}	2.3×10^{-8}	3.1×10^{-8}

Table 5 Permeability coefficient and ion flux through the membrane|solution boundary for membranes based on $[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^-$ for different counterions

Dissolved compound	Permeability coefficient P (m s^{-1})	Ion flux J (mol m^{-2} s^{-1})
$[C_{16}H_{33}N]^+[Cl]^-$	4.1×10^{-7}	2.7×10^{-6}
$[C_{17}H_{21}SN_2]^+[Cl]^-$	3.4×10^{-8}	2.4×10^{-7}
$[C_{20}H_{22}O_4N]^+[Cl]^-$	1.5×10^{-8}	1.0×10^{-7}
$[C_{14}H_{12}N_2]^+[Cl]^-$	8.7×10^{-9}	5.8×10^{-8}
$[C_{17}H_{22}ON]^+[Cl]^-$	4.3×10^{-9}	2.7×10^{-8}
$[C_{13}H_{21}O_2N_2]^+[Cl]^-$	3.9×10^{-9}	2.5×10^{-8}
$[C_4H_{12}N_2]^{2+}$ 2[Cl]$^-$	1.8×10^{-9}	1.2×10^{-8}

and, consequently, the product $\frac{c_2^\tau}{c_1^\circ} \times \left(1 + \frac{V_2^0}{V_1^0}\right)$ is also less than unity; then Eq. (1) can be written in the form:

$$\left(1 + \frac{V_2^0}{V_1^0}\right) \frac{c_2^\tau}{c_1^\circ} = PS\left[\frac{1}{V_1} + \frac{1}{V_2}\right]\tau. \quad (2)$$

To a first approximation, the ratio of volumes $\frac{V_2^0}{V_1^0}$ is a constant value; therefore, introducing designations $\left(1 + \frac{V_2^0}{V_1^0}\right) = a$ and $PS\left[\frac{1}{V_1} + \frac{1}{V_2}\right] = b$, we obtain

$$c_2^\tau = \frac{b}{a} c_1^\circ \tau. \quad (3)$$

According to Eq. (3), the dependence of on t is, to a first approximation, described by a straight line, which also follows from Fig. (3).

The dependence of P and J on the nature and concentration of interfering ions for the membrane on the basis of $[C_{17}H_{22}ON]^+[B(C_6H_5)_4]^-$ is presented in Table 5. It is seen that the permeability of the membrane with respect to counterions increases in the order $[C_4H_{12}N_2]^{2+}2[Cl]^- < [C_{13}H_{21}O_2N_2]^+[Cl]^- < [C_{17}H_{22}ON]^+[Cl]^- < [C_{14}H_{12}N_2]^+[Cl]^- < [C_{20}H_{22}O_4N]^+[Cl]^- < [C_{17}H_{21}SN_2]^+[Cl]^- < [C_{16}H_{33}N]^+[Cl]^-$, which corresponds both to the order of extractability of compounds to the membrane solvent phase and to the order of ion-exchange affinity. This fact supports the theory of a conjugated transfer mechanism with the predominance of at least two determining factors—extraction distribution of charged particles to the membrane and their transfer, because of preferable binding with the lipophilic anion, as a result of the ion-exchange reaction

$$L^+ + \bar{I}\bar{S} \rightleftarrows \bar{L}\bar{S} + I^+.$$

where L^+ denotes the lipophilic counterion.

As a result of ion exchange, the aqueous phase is gradually enriched with I^+ cations, which initially enter into the composition of the ion exchanger IS, and the membrane becomes sensitive to both I^+ and L^+ cations because a thermodynamically controlled mixture of IS and LS capable of ion-exchange with solution components is formed at the surface of the membrane and in the bulk. An important consequence from the above discussion is presented in Fig. 4. In Fig. 4, the selectivity coefficient of the ISS membrane is related to the ratio of the permeabilities of the membrane to the counterion, which increases on changing from less lipophilic to more lipophilic counterions, which, in turn, associate to a greater extent on binding with a lipophilic anion in the membrane phase. This proves once more that the selectivity of membranes in which active centers and counterions are nearly fully associated depends both on the extraction selectivity of the membrane solvent–plasticizer and on the specificity of the bond formed by active centers with counterions.

Electroanalytical characteristics of the electrode

Electrode response

The critical response characteristics of drotaverine ISSs at 20°C are given in Table 6. Calibrations were performed at constant pH and ionic strength. The response of the sensors was linearly dependent on the concentration of aqueous drotaverine hydrochloride solutions over a wide range. The characteristics of ISSs strongly depend on the nature of the electroactive substance. The ISSs had a Nernstian response with very good linearity for drotaverine hydrochloride. The lower detection limit observed for the drotaverine ISSs based on drotaverine–

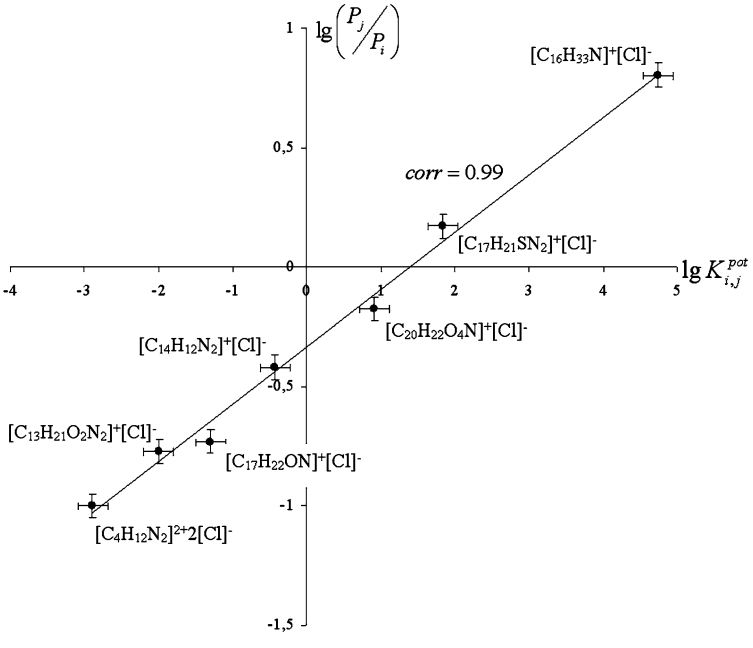


Fig. 4 Correlation between the potentiometric selectivity coefficients and the ratio of the permeabilities of the membrane based on $[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^-$

Table 6 The average response characteristics for drotaverine hydrochloride PVC membranes using the proposed sensors (the membrane solvent was DBP)

Ion-exchanger	Concentration range (mol L^{-1})	Slope (mV per decade)	Detection limit (mol L^{-1})
$[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^-$	5.0×10^{-2} – 7.9×10^{-6}	58 ± 2	$(4.3\pm0.2)\times10^{-6}$
$[C_{24}H_{32}O_4N]^+[C_6H_2(NO_2)_3O]^-$	2.7×10^{-2} – 1.2×10^{-4}	51 ± 4	$(7.2\pm0.4)\times10^{-5}$
$[C_{24}H_{32}O_4N]^+[BiI_4]^-$	2.6×10^{-2} – 1.6×10^{-4}	51 ± 2	$(3.3\pm0.4)\times10^{-5}$
$[C_{24}H_{32}O_4N]^+[Cr(NH_3)_2(SCN)_4]^-$	2.5×10^{-2} – 1.7×10^{-5}	54 ± 3	$(8.7\pm0.4)\times10^{-6}$
$[C_{24}H_{32}O_4N]_{2+}$ $[HgI_4]^{2-}$	2.5×10^{-2} – 6.3×10^{-5}	55 ± 2	$(2.0\pm0.4)\times10^{-5}$
$[C_{24}H_{32}O_4N]_{3+}$ $[PW_{12}O_{40}]^{3-}$	1.0×10^{-2} – 3.9×10^{-5}	55 ± 2	$(1.3\pm0.4)\times10^{-5}$
$[C_{24}H_{32}O_4N]_{3+}$ $[PMo_{12}O_{40}]^{3-}$	3.0×10^{-2} – 1.0×10^{-5}	56 ± 2	$(5.5\pm0.4)\times10^{-6}$
$[C_{24}H_{32}O_4N]_{4+}$ $[SiW_{12}O_{40}]^{4-}$	3.1×10^{-2} – 3.8×10^{-5}	54 ± 2	$(1.1\pm0.4)\times10^{-5}$
$[C_{24}H_{32}O_4N]_{4+}$ $[SiMo_{12}O_{40}]^{4-}$	2.5×10^{-2} – 4.4×10^{-5}	52 ± 2	$(1.2\pm0.4)\times10^{-5}$

tetraphenylborate and drotaverine–molybdophosphate was determined in accordance with IUPAC recommendations and was found to be $(4.3\pm0.2)\times10^{-6}$ mol L^{-1} and $(5.5\pm0.4)\times10^{-6}$ mol L^{-1} drotaverine hydrochloride, respectively. The potential readings were stable and consistent to ±5 mV within the same day and were reproducible to within ±2 mV in a 1×10^{-2} mol L^{-1} drotaverine hydrochloride solution for 4 h continuous use. The time required for the ISSs to reach 90% of final response was less than 60 s. The stability and reproducibility of the response of the ISSs was good. The electrodes were sufficiently stable to give satisfactory responses after 3 weeks of storage in distilled water with no noticeable degradation.

Studies of the linear concentration ranges of the ISSs showed that linear concentration ranges correlated with the solubility in water of the EAS (Fig. 5). As the solubility of ionophores in water decreased, the linear concentration ranges extended. This interesting effect demands further research.

Effect of pH

The effect of pH on the potential of the ISSs was checked by recording the e.m.f. of a standard cell and varying the acidity by addition of small volumes of hydrochloric acid and/or potassium hydroxide solution (1.0 mol L^{-1} each). It was found that the drotaverine-sensitive ISSs based of drotaverine ion-association complexes had virtually no pH response over the range 2.0-7.0 pH units (Fig. 6). That means the protonated form of drotaverine could be maintained in the range of 2.0-7.0 pH units. Decrease in the potentials at pH > 7 is presumably because of the formation of the deprotonated drotaverine species and precipitation of free drotaverine base in the test solutions, which were not sensed by the electrode.

Selectivity of the electrodes

The potentiometric selectivity coefficient defines the ability of an ISS to distinguish a particular ion from others. It is one of the most important characteristics of an ISS, because it often determines whether reliable measurement in the target sample is possible. Considering possible utilization of the drotaverine-selective sensors for analysis of biological samples, for example urine and blood, some substances which might be present after sample preparation were selected. Interferences of common organic and inorganic cations with

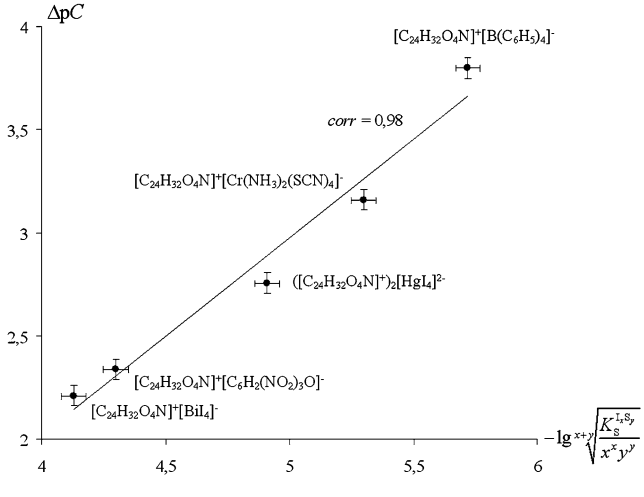


Fig. 5 Correlation of linear concentration ranges of ISSs (ΔpC) with solubility in water of drotaverine EAS $\left(-\lg\sqrt{[x+y]\frac{K_S^{I_xS_y}}{x^x y^y}}\right)$

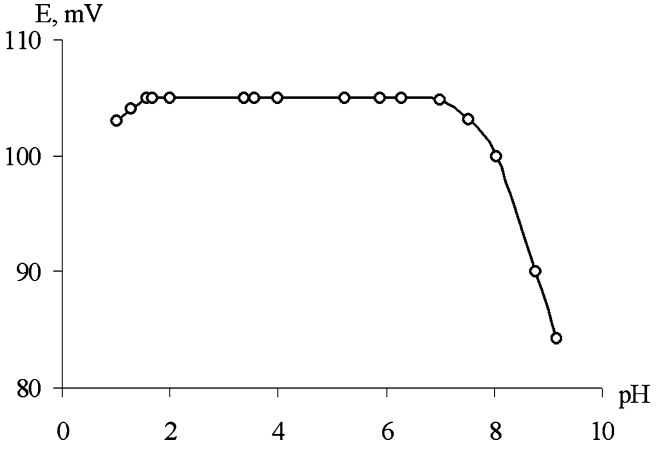


Fig. 6 Effect of pH on the response of the $[C_{24}H_{32}O_4N]^+$ $[B(C_6H_5)_4]^-$ selective membrane electrode at 25°C (1×10^{-2} mol L^{-1} drotaverine hydrochloride solution)

Table 7 Potentiometric selectivity coefficients of the proposed sensors using the separate solution method (SSM)

Ion-exchanger	lg $K_{i,j}^{pot}$									
	K^+	Na^+	NH_4^+	$[C_4H_{12}N_2]^{2+}$ 2[Cl]$^-$	$[C_{13}H_{21}O_2N_2]^+$ [Cl]$^-$	$[C_{17}H_{21}SN_2]^+$ [Cl]$^-$	$[C_{14}H_{12}N_2]^+$ [Cl]$^-$	$[C_{17}H_{22}ON]^+$ [Cl]$^-$	$[C_{20}H_{22}O_4N]^+$ [Cl]$^-$	$[C_{16}H_{33}N]^+$ [Cl]$^-$
$[C_{24}H_{32}O_4N]^+[B(C_6H_5)_4]^-$	−3.3	−3.1	−3.5	−2.9	−2.0	−1.5	−0.4	0.9	1.8	4.7
$[C_{24}H_{32}O_4N]^+[C_6H_2(NO_2)_3O]^-$	−2.3	−2.2	−2.7	−2.1	−1.8	−1.2	−0.3	1.0	2.1	5.6
$[C_{24}H_{32}O_4N]^+[BiI_4]^-$	−2.9	−3.5	−3.1	−2.1	−1.7	−1.2	−0.2	0.8	2.3	4.4
$[C_{24}H_{32}O_4N]^+[Cr(NH_3)_2(SCN)_4]^-$	−3.1	−2.7	−3.2	−2.6	−2.1	−1.3	−0.4	1.1	2.3	5.0
$[C_{24}H_{32}O_4N]_2^{2+}[HgI_4]^{2-}$	−2.3	−2.9	−3.0	−3.0	−2.0	−1.6	−0.5	1.2	1.8	5.4
$[C_{24}H_{32}O_4N]_3^{3+}[PW_{12}O_{40}]^{3-}$	−3.3	−4.1	−4.5	−3.2	−1.7	−1.1	−0.2	1.1	2.0	4.8
$[C_{24}H_{32}O_4N]_3^{3+}[PMo_{12}O_{40}]^{3-}$	−3.7	−3.1	−3.3	−3.2	−2.1	−1.2	−0.3	1.3	1.7	4.7
$[C_{24}H_{32}O_4N]_4^{4+}[SiW_{12}O_{40}]^{4-}$	−1.8	−2.2	−2.0	−2.6	−2.1	−1.2	−0.3	1.4	2.0	5.2
$[C_{24}H_{32}O_4N]_4^{4+}[SiMo_{12}O_{40}]^{4-}$	−2.8	−3.1	−3.0	−2.8	−1.8	−1.1	−0.2	1.2	2.0	5.1

selectivity of the proposed electrodes were studied by the separated solution method (SSM) recommended by the IUPAC [10]. The concentrations of drotaverine hydrochloride and the interferents were kept at a level of 1×10^{-2} mol L^{-1} in solutions of the same pH at 20 ± 2°C. The potentiometric selectivity coefficients ($K_{i,j}^{pot}$) listed in Table 7 show that the proposed electrode had reasonable selectivity toward drotaverine hydrochloride. There was no significant interference from most of the tested substances, with the exception of cetylpyridinium chloride, which caused slight interference. Apparently with this compound a membrane potential is formed as a result of electrostatic interaction of the ion with a surface of a membrane and the characteristics of sensors are determined by the hydrophobicity of interfering ion which has an adverse effect on electrode response owing to sorption on the membrane surface.

Effect of ionophore concentration and the nature of the membrane solvent on the sensitivity of ISSs

Drotaverine sensors prepared with different amounts of ionophore were evaluated for their potential response as a function of the different activities of the drotaverine cations. The working range and the sensitivity of the ISSs for drotaverine cations improved appreciably on increasing the amount of the ionophore in the membrane matrix up to a limit of 1×10^{-2} mol kg^{-1} MS. The sensors with low amounts of the ionophore (below 10^{-4} mol kg^{-1} MS) are not suitable for detection of drotaverine cations owing to poor sensitivity. Sensors prepared with more ionophore (concentration higher than 5×10^{-2} mol kg^{-1} MS had improved lower and upper detection limits. ISSs prepared with 1×10^{-2} mol kg^{-1} MS of ionophore have the highest working range of 1.5×10^{-5} to 5.0×10^{-2} mol L^{-1} and high slope of 58 mV per decade activity of the drotaverine cations. On further increasing the amount of the ionophore beyond 1×10^{-2} mol kg^{-1} MS, sensor response was not improved and interference from other cations was clearly observed.

Table 8 Sensitivities of drotaverine ISSs

Membrane			Detection limit (mol L^{-1})
EAS	$\bar{c}^{\circ}_{EAS}$ (mol/L)	MS	
$[C_{24}H_{32}O_4N]^+$ $[B(C_6H_5)_4]^-$	1.01×10^{-2}	DOP	$(8.9\pm0.5)\times10^{-6}$
	5.22×10^{-3}		$(7.5\pm0.4)\times10^{-6}$
	1.01×10^{-3}		$(5.1\pm0.4)\times10^{-6}$
	1.41×10^{-4}		$(1.9\pm0.4)\times10^{-6}$
	1.50×10^{-2}	DBP	$(4.3\pm0.3)\times10^{-6}$
$[C_{24}H_{32}O_4N]^+$ $[C_6H_2(NO_2)_3O]^-$	1.79×10^{-2}	DOP	$(8.3\pm0.2)\times10^{-5}$
	2.00×10^{-2}	EHS	$(5.0\pm0.3)\times10^{-5}$
$[C_{24}H_{32}O_4N]^+$ $[Cr(NH_3)_2(SCN)_4]^-$	1.85×10^{-2}	DOP	$(9.1\pm0.1)\times10^{-6}$
$[C_{24}H_{32}O_4N]^+$ $[BiI_4]^-$	5.17×10^{-3}	HB	$(4.0\pm0.5)\times10^{-5}$

Table 9 Comparison of mean values obtained from the potentiometric method (membrane electrode based on the drotaverine ion-associate complex with or tetraphenylboric acid) and the HPLC method for assay of drotaverine hydrochloride in tablets and injections

Sample	Potentiometric method				High-performance liquid chromatographic method [3]	
	Direct potentiometric method		Potentiometric titration			
	Recovery[a]	RSD (%)	Recovery[a]	RSD (%)	Recovery [a]	RSD (%)
1	98.32	1.04	98.37	0.97	98.23	0.71
2	98.61	0.87	99.25	0.88	99.11	0.93
3	99.44	1.07	99.54	0.89	98.54	0.84
4	98.70	1.03	98.98	0.90	98.60	0.81
5	100.37	1.01	99.52	0.95	99.84	0.91

[a]Percentage of nominal value. All values were averages from five determinations

Increasing the amount of the ionophore in the sensing membrane enhances the detection limits of the ISSs and interference of the interfering cations can be avoided by recording potential measurements in diluted solution.

As was shown earlier [11], the detection limit (DL) for liquid membranes is mainly governed by the association constant of an ion exchanger in a membrane solvent (k^{as}_{EAS}), the ionophore concentration in the membrane ($\bar{c}^{\circ}_{EAS}$), , and the distribution coefficient of the ionic form of compound (K_{ext}). Detection limit is described by the equation:

$$DL = \frac{\sqrt{2}\sqrt{2\bar{c}^{\circ}_{EAS}k^{as}_{EAS} + \sqrt{1 + 4\bar{c}^{\circ}_{EAS}k^{as}_{EAS}} + 1}}{2K_{ext}k^{as}_{EAS}}. \quad (4)$$

It is known that membrane solvents with low values of dielectric permittivity have weak solvating ability [12]. Association of most of the ions to form ion pairs is considered to be the main property of such solvents. In the explanation of electrolyte behavior in these media, assumptions are made about a small difference in solvation energies of ion pairs and single species and about the absence of specific interactions between a solute and a solvent. On the other hand, it is known that k^{as}_{EAS} of ionophores in such membrane solvents are rather high [13]. The transmembrane potential of ISSs is governed by the electrochemical properties of boundary layers formed at the membrane–aqueous solution interface. Hence, it may be assumed that, because of the penetration of water into the membrane medium, k^{as}_{EAS} of ionophores are close to the reciprocal of their SP [14]. This is confirmed by a correlation between linear concentration ranges of ISSs and the solubility in water of EAS, presented in Fig. 5. The values of solubility product of ionophores are presented in Table 2.

Table 8 shows the dependence on the concentration of ion exchangers and nature of membrane solvents of the DLs of ISSs. By analysing outcomes and comparing them with the equation for DL it is possible to draw a conclusion that the distribution constants of drotaverine hydrochloride for membrane solvents with low dielectric permeability are close and the DL are more dependent on the solubility product of ion exchangers. Smaller DL are characteristic of less water-soluble ion exchangers.

Analytical applications

The excellent characteristics of these ISSs enhance their potential usefulness for pharmaceutical and biochemical analysis. The proposed ISSs were used for assay of the drotaverine hydrochloride content of injections and tablets by the standard addition method and potentiometric titration method. Results from the potentiometric method are compared with those from the high-performance liquid chromatographic method [3] in Table 9. As can be seen, high precision was obtained (RSD < 1%) by use of the potentiometric method.

Conclusion

Simple potentiometric ISSs for determination of drotaverine hydrochloride are described. They are based on the use of tetraphenylborate, picrate, tetraiodomercurate, tetraiodobismuthate, Reinecke salts, and heteropolycompounds of Keggin structure ($H_3[PMo_{12}O_{40}]$), $H_3[PW_{12}O_{40}]$, $H_4[SiMo_{12}O_{40}]$, and $H_4[SiW_{12}O_{40}]$) in the formation of ion-association species. ISSs based on these membranes were prepared, characterized, compared, and used for rapid and accurate selective determination of drotaverine hydrochloride. The main transport properties were studied for selective membranes with low dielectric constants based on drotaverine–tetraphenylborate ion exchanger. Permeabilities and ion fluxes through a membrane were calculated for major and interfering ions. Dependences of the transport properties of the membranes on the concentrations of the ion exchanger and near-membrane solution, and their potentiometric characteristics, are presented.

References

1. Foye's Principles of Medicinal Chemistry/by Williams DA (2002) Williams& Wilkins, Lippincott
2. Mester L, Varga J, Kurmuczy SP, Szenci O (1999) 1st Middle-European Buiatrics Congress, Balatonfured, Hungary, pp 160–161
3. Bolaji OO, Onyeji CO, Ogungbamila FO, Ogunbona FA (1993) J Chromatogr 622:93–97

4. Cosofret VV (1982) Membrane electrodes in drug-substances analysis. Pergamon Press, New York
5. Cosofret VV, Buck RP (1992) Pharmaceutical applications of membrane sensors. CRC Press, Boca Raton, FL
6. Cosofret VV, Buck RP (1993) Crit Rev Anal Chem 24:1–58
7. Kharitonov SV, Gorelov IP (2000) Pharm Chem J 34:625–627
8. Pope MT (1983) Heteropoly and isopoly oxometalates. Springer-Verlag, Berlin
9. Kharitonov SV (2003) J Anal Chem 58:176–182
10. Buck RP, Cosofret VV (1993) Pure Appl Chem 65:1849–1858
11. Kharitonov SV, Gorelov IP (2001) Rus J Electrochem 37:823–826
12. Mishchenko KP, Poltoratskii GM (1969) Problems of thermodynamics and structure of aqueous and nonaqueous electrolyte solutions. Khimiya, Moscow
13. Morf WE (1981) The principles of ion-selective electrodes and of membrane transport. Akademiai Kiado, Budapest
14. Ion-selective electrodes/Ed. Durst RM (1969) National Bureau of Standards, Washington