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Ion-selective electrodes in medicinal drug determination

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Abstract. Data published in the past 10 years on the use of ion-selective electrodes in direct potentiometry and potentiometric titration for the determination of organic medicinal drugs are analysed. In the vast majority of cases, ion-sensitive membranes contain associates of drug cations or anions with appropriate counter-ions. The theoretical approaches to optimisation of the characteristics of ion-selective electrodes are discussed. The mechanism of electrode response generation for neutral and charged carriers of organic ions is considered. The bibliography includes 314 references.

I. Introduction

The advance of the pharmaceutical science is marked by the appearance of 30 – 40 new medicinal drugs annually. At present, there are more than 10 000 medicinal drugs (MD) and over 100 000 drug preparations registered all over the world.[1, 2]

According to the data issued by the Ministry of Health and Social Development, since 1997, the number of MD registered in the Russian Federation has increased almost 1.5-fold (Fig. 1), of which ~80% pertains to reproduced preparations.[2] Figure 2 illustrates the dynamics in the development of original Russian MD in the period from 1997 to 2003. The average number of new MD introduced into the national health protection practice amounted to 40 – 60 items per year.

In line with the progressively increasing number of new MD, the problem of their identification and determination in both individual samples (*in vitro*) and living organisms (*in vivo*) becomes urgent. The demand for the accumulation, generalisation and systematisation of data on the MD monitoring and analysis resulted in the appearance of specialised scientific periodicals. Since 1983, the international *Journal of Pharmaceutical and Biomedical Analysis* (*J. Pharm. Biomed. Anal.*), which deals with the studies in the field of the MD analysis, analytical biochemistry, pharmacokinetics, forensic toxicology and other related fields, has been published. *Fresenius' Journal of Analytical Chemistry* has been published under a new title, *viz.*, *Analytical and Bioanalytical Chemistry* since 2002. Among the other international issues that publish the results of studies in the field of MD analysis, mention should be made of journals *American Journal of Pharmaceutical Education*, *Archiv der Pharmazie*, *Drug Information Journal*, *European Journal of Pharmaceutical Sciences*, *Il Pharmaco*, *International Journal of Pharmaceutics*, *Journal of Chromatography B: Biomedical Sciences and Applications*, *etc*. The main Russian journal devoted to this field is the *Khimiko-farmatsevticheskii Zhurnal* [*Pharm. Chem. J.* (*Engl. Transl.*)], which has been published since 1967.

Considering the data published in original papers in *J. Pharm. Biomed. Anal.*, it can be stated with confidence that the chromatographic methods of analysis still occupy the leading position (more than 1500 publications in 10 years). They amount more than 50% of all methods of MD determination (Fig. 3), of which 45% fall on HPLC, 23% correspond to liquid chromatography, 14% are devoted to liquid chroma-

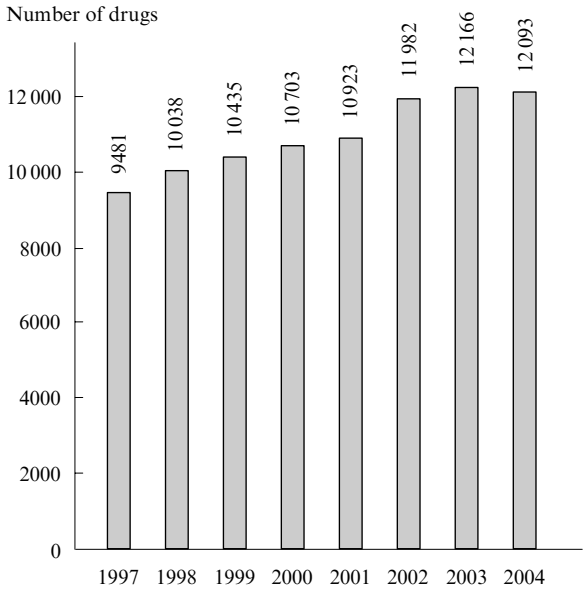


Figure 1. Increase in the number of registered medicinal drugs in Russia in 1997 – 2004 (according to the Ministry of Health and Social Development of the Russian Federation).

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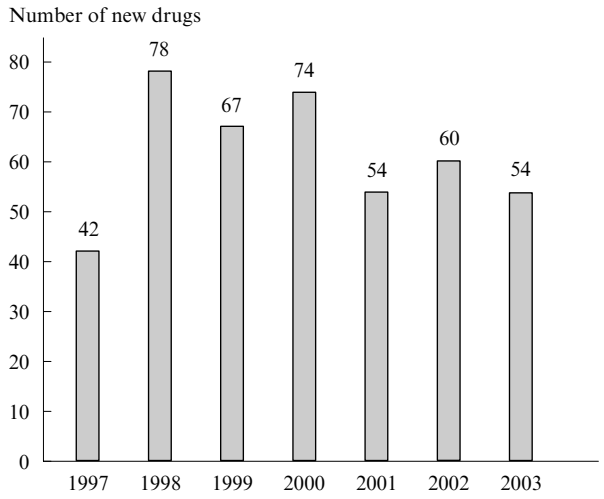


Figure 2. Dynamics in the development of new medicinal drugs in Russia in 1997 – 2003 (according to the data issued by the Ministry of Health and Social Development of the Russian Federation).

tography with mass spectrometric detection, 7% deal with gas chromatography and 11% fall on the rest chromatographic techniques.

According to the number of publications in *J. Pharm. Biomed. Anal.*, the electrochemical methods of the MD analysis occupy the third place after photometry and spectrophotometry, ~20% of publications being devoted to the potentiometric determination of MD.

Equilibrium electrochemical methods of the MD analysis, which include direct potentiometry (ionometry) and potentiometric titration, are extremely convenient, simple and make it possible to determine those MD that can be converted into the corresponding ionic forms. As a rule, they combine sufficient selectivity with the precision of determination, which can substantially be enhanced even in the direct determination by operating the sensors *via* the mechanism of super-Nernstian response. Moreover, potentiometric detectors are capable of operation under the conditions of on-line analysis and can sufficiently easily be miniaturised to serve as micro- and ultramicroelectrodes.

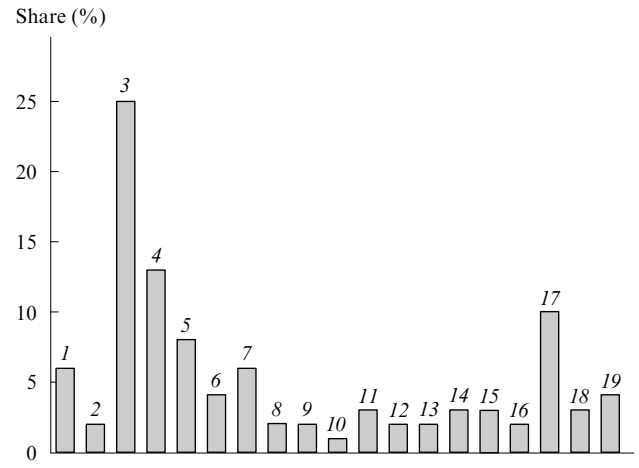


Figure 3. Distribution (%) of different instrumental methods for quantitative determination of MD (according to publications in *J. Pharm. Biomed. Anal.* in 1995 – 2005).
(*1*) Capillary (including zone) electrophoresis (6%); (*2*) bioanalysis and biosensors (2%); (*3*) HPLC (25%); (*4*) liquid chromatography (13%); (*5*) liquid chromatography with mass spectrometric detection (8%); (*6*) gas chromatography (4%); (*7*) other chromatographic methods (6%); (*8*) mass spectrometry (2%); (*9*) immunoassay and radioimmunoassay (2%); (*10*) IR spectroscopy and Raman spectroscopy (1%); (*11*) voltammetry (3%); (*12*) inversion voltammetry (2%); (*13*) ionometry (2%); (*14*) miscellaneous electrochemical methods (3%); (*15*) fluorimetry (3%); (*16*) NMR (2%); (*17*) spectrophotometry and photocolourimetry (10%); (*18*) flow-injection analysis (3%); (*19*) miscellaneous analytical methods (4%).

In 1980 – 1990, many reviews were devoted to the use of ion-selective electrodes (ISE) in the pharmacological, clinical and biomedical assay. The biomedical aspects of the use of ISE and microelectrodes,[3,4] the application of ISE in the medicinal practice and the potentiometric determinations *in vivo* [5,6] were considered. The peculiarities of the use of ISE, including the application of potentiometric measurements with ISE and transducers in the clinical chemistry, were discussed. [7–14]. The data on the use of various ISE (with liquid and film membranes, 'coated wire' ISE, heterogeneous ISE with matrix-incorporated ion exchangers, pseudoliquid ISE, *etc.*) in pharmacy and pharmacological analysis were systematised.[15–25]

However, in the past decade, a vast number of new MD appeared and different ISE types were elaborated for their determination, which necessitates the systematisation of the corresponding literature data.

II. Principles of operation of membrane ion-selective electrodes

An ion-selective electrode can be defined as an electrochemical sensor with a membrane the potential of which serves as the measure of the activity of a certain ion.[26] An ISE membrane may represent a crystalline or non-crystalline, homogeneous or heterogeneous phase, which, as a rule, exhibits high ionic conductivity. Crystalline membranes are based on single crystals (*e.g.*, LaF_3 for F^--ISE), polycryalline compounds (*e.g.*, Ag_2S for Ag^+- and S^{2-}-ISE), heterogeneous mixtures pressed into pellets or incorporated into an inert binding material (matrix) (the Pungor electrodes). Glass, liquid and plasticised membranes are classified with non-crystalline membranes. The latter are used most extensively. The main requirement to a membrane is the ability to exchange ions of only one type. For an ISE to be selective with respect to a single type of ions, its membrane should contain a substance that can reversibly bind the ion under determination and at the same time exhibit the minimum solubility in aqueous solutions. Substances with such properties are called electroactive compounds (EAC). According to the mechanism of EAC reactions with the determined ion, the EAC are divided into charge carriers or ion-exchangers (the ion is transferred by an active ion-exchange site due to electrostatic interactions), neutral carriers or ionophores (the ion transfer follows the mechanism of selective complexation) and chelate-forming carriers (the ion transfer proceeds due to both electrostatic interactions and the complexation).[26]

Ion-selective electrodes are classified according to the type of membranes used. Solid-phase, liquid-phase and film ISE are distinguished, which can be divided further to various groups depending on the nature of EAC used and the design of the ISE itself. Thus gas electrodes, enzyme electrodes, solid-contact electrodes and microelectrodes are often singled out into individual groups. Figure 4 shows the designs of most popular ISE types.

In addition to EAC, other components are often introduced into membranes to improve the functional properties of ISE. These can be additives that affect the electrophysical characteristics of membranes or substances capable of additional specific or non-specific interactions with the membrane or solution components.

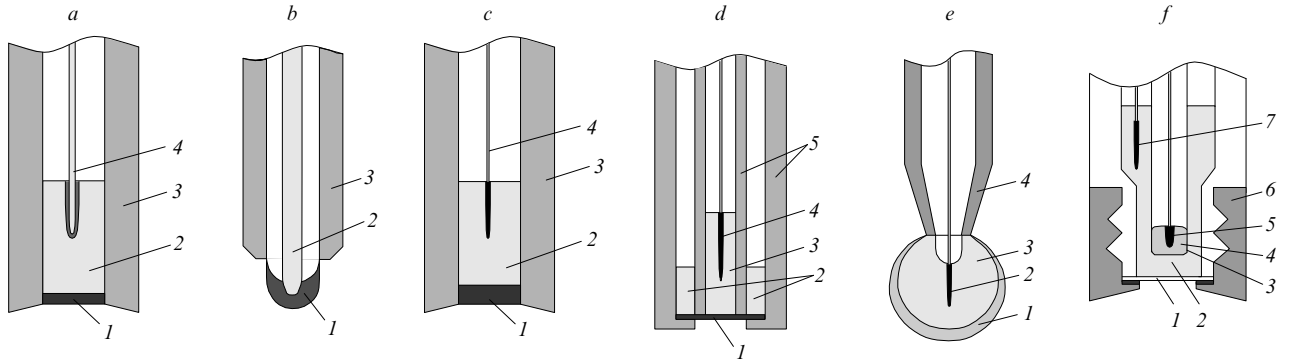


Figure 4. Designs of main types of ion-selective electrodes.
(*a*) Solid-phase ISE with crystalline or heterogeneous membranes: (*1*) ion-selective membrane, (*2*) hydrophobic graphite layer, (*3*) case (a PVC or PTFE tube), (*4*) electron conductor (steel wire).
(*b*) Solid-contact electrodes of the 'coated wire' type: (*1*) ion-selective membrane, (*2*) electron conductor (Au, Pt or Cu wire), (*3*) case (usually glass).
(*c*) ISE with a polymeric membrane and an internal liquid contact: (*1*) ion-selective membrane, (*2*) internal standard solution, (*3*) case, (*4*) internal reference electrode (Ag/AgCl).
(*d*) ISE with a liquid membrane: (*1*) porous plate impregnated with EAC solution, (*2*) EAC solution in an organic solvent, (*3*) internal standard solution, (*4*) internal reference electrode (Ag/AgCl), (*5*) case.
(*e*) Glass ISE: (*1*) ion-selective glass membrane, (*2*) internal reference electrode (Ag/AgCl), (*3*) internal standard solution, (*4*) case.
(*f*) Gas-sensitive ISE: (*1*) gas-permeable membrane, (*2*) internal solution, (*3*) ISE with (*4*) standard solution and (*5*) reference electrode, (*6*) case, (*7*) internal reference electrode

Ion-selective electrodes can be used in the determination of both organic and inorganic ions and certain neutral molecules. As will be shown below, the vast majority of studies dealing with the ISE for medicinal drugs were associated with the development of procedures for the quantitative determination of MD in model solutions, drug preparations, more rarely, in biological fluids and raw materials used in chemical and pharmaceutical industries. Much fewer studies were aimed at relating the physicochemical, electrochemical and transport properties of selective membranes to the potentiometric characteristics of the relevant ISE.[27–38]

In the majority of cases, the charged carriers, *i.e.*, ion associates (IA) formed by MD cations or anions with the corresponding counter-ions, are introduced into selective membranes as the EAC. In addition to ion-exchange properties and the minimum solubility in water, an EAC should be compatible with the other components of the ion-sensitive membrane. The mechanism of operation of such ISE is described by a model of charged carriers.[39]

Pungor[40,41] has considered the processes that occur on the membrane surface and in its bulk and assessed the contributions of individual components to the membrane potential. In discussing the anomalies that arise in the interpretation of the mechanism of ISE operation, he took into account[40] the Donnan effect, the response time, the surface morphology, *etc*. The modified electrodes the chemical reaction on which involves the potential-determining ion were found to demonstrate a surface response. For IA-based ISE, the lyotropic series rule is valid; the surface reactions are also possible; however, such electrodes not always demonstrate the Nernstian response. Such aspects as the energy of the transfer of charged species across the electrode–solution interface were also considered.

For polymeric membranes that contain charged ion-exchangers and neutral carriers as the ionophores, it was proposed[42–45] to quantitatively describe the ISE response based on the consideration of the ion-exchange equilibrium at the membrane–solution interface. The validity range of the Nikolskii–Eisenman equation used in the calculation of the selectivity coefficient of ISE was discussed. It was shown that the derived mathematical relationships allow more accurate calculations of ISE selectivity coefficients in the presence of interfering ions with different charges. It was concluded that this approach can be applied in assessing the selectivity of most ISE with polymeric membranes.

The studies aimed at the optimisation of electroanalytical properties of membrane ISE were largely developed in two directions, namely, the optimisation of the internal near-membrane solution and the introduction of different ions and molecules into the membrane.

The first direction was developed in the studies by Pretsch and Bakker. In 1997, Pretsch and co-workers[46] demonstrated that the introduction of hydrophilic (thus, incapable of penetrating into the membrane) complexing agents that can form stable complexes with the determined ion, into the intramembrane solution intensifies the ion fluxes from the external solution to the membrane phase and dramatically lowers the detection limit. The development of these ideas made it possible to create a new model describing the detection limit of ISE and to elaborate new sensors with superhigh sensitivity.

The processes that lead to lowering of the detection limits of ionophore-based ISE are described by a steady-state model of ion fluxes.[47,48] It was found that the ion-exchange and extraction equilibria at both sides of a membrane stimulate the appearance of concentration gradients in the membrane phase and can affect the detection limit through the ion fluxes. The concentration variations in the near-membrane internal solution can change the ISE detection limits by more than five orders of magnitude. However, it is necessary to produce high gradients of concentration to achieve adequate ISE characteristics. It was shown that the appearance of a superlow detection limit of ISE (10^{-9}–10^{-12} mol litre^{-1}) cannot be defined according to the IUPAC rules. The impurities present in minor concentrations in the membrane phase can have a strong effect on the ISE characteristics when the electrodes operate at the concentrations of determined substances below 1 μmol litre^{-1}.

Mention should be made of studies[42,49–53] on the effect of different parameters on the ISE characteristics, which were based on the steady-state model.[47,48] The effect of interfering ions, the composition of near-membrane and intramembrane solutions, the selectivity coefficients, the analyte lipophilicity, the concentrations of ionophore and lipophilic additives in the membrane, the thicknesses of the Nernstian diffusion layer and

the membrane and the diffusion coefficients of ions in both phases were studied. Based on the results obtained, it was concluded that all these factors might contribute to the lowering of the detection limit of potentiometric sensors.[53]

The most general theoretical description of the stationary potentiometric response of ISE membranes was presented.[54–56] Membrane systems that contain any number of ionophores with ion-exchange centres fixed on a polymeric matrix were considered. The thermodynamic model explains the characteristics of ISE selectivity based on different diffusion-induced effects associated with trans-membrane ion fluxes at zero emf. The appearance of super- and sub-Nernstian responses and the upper and lower limits of the determined concentrations were discussed; the temporal characteristics of ISE were considered. The approach developed allows one to considerably improve the selectivity coefficients and detection limits of ionophore-containing ISE. These studies open up new possibilities and prospects for the wide application of ISE techniques, which can compete with the most sensitive analytical methods.

A non-classical interpretation of the electrode response of sensors based on ionophores was discussed.[57] Several new concepts on the development of ionophore-based ISE were considered. Various long-known ISE for simple cations and anions are widely used in the industry and clinical chemistry. However, further studies that would allow the optimisation of ISE properties for analytical purposes are necessary. These studies should be carried out in the following directions:

– reduction of the lower limit of determined concentrations by governing the analyte ion fluxes through the membrane;

– development of methods for the determination of ion concentrations using sensors that exhibit the effect of the intensification of ion fluxes to the internal near-membrane solution;

– targeted search for ionophores that can provide the super-Nernstian response to the ions determined;

– development of ion-exchange membranes sensitive to polyions according to a non-equilibrium mechanism of electrode response;

– development of membranes selective to molecules of non-ionogenic surfactants;

– development of ISE with the electrode response formed due to redox reactions between the ionophore and the detected ion.

Insofar as the current practice consists of the incorporation of membrane-active complexones (ionophores) synthesised for this purpose[58–106] into the ISE, the results of studies mentioned above[42–57] are of fundamental importance for the development of ionometry of MD.

The second direction in the optimisation of ISE properties dates back to the pioneering studies of 1970s in which polymeric matrices with fixed charges were used for the improvement of electrode characteristics of membranes.[39] Later, this idea gave impetus to the development of mobile anionic sites in the membrane by the introduction of highly lipophilic ions such as tetraphenylborate anions.[39,107–109] It is believed that due to the poor solubility in water, these species indeed reside in the organic phase of a membrane. Lipophilic ions should remove the analyte anions to one extent or another from the membrane rather than compete with the ionophore for the formation of complexes with cations. As a result, the effect of the anion permeability that deforms the cationic response of the ISE is diminished or totally eliminated. Such compounds proved to be promising for ISE based on dissociating ion exchangers.[110] This made it possible not only to extend the interval of the ISE electrode response, but also to considerably enhance the electrode selectivity.

The mechanism of operation of ISE based on liquid ion-exchangers, which are incorporated in the membrane in a mixed form, *viz*., preferentially as a salt with an ion modifier and partially as a salt with the determined ions, was considered.[111] The ion modifier should be much more lipophilic than the determined ion to ensure the virtually constant concentrations of both salts in the membrane surface layer in the course of an ion exchange reaction that occurs once the membrane is brought into contact with the aqueous solution containing ions to be determined. The boundary conditions for the linearity of the electrode function for ISE of such a kind in solutions of determined ions were formulated. It was proved theoretically and demonstrated experimentally that for electrodes under consideration, the extraction selectivity of the ion-exchanger with respect to the determined ion can be adequately converted into the potentiometric form.

At present, almost all electrodes (including ISE based on ion associates) for the determination of both cations and anions employ membranes modified with lipophilic additives, which considerably improve their characteristics. The incorporation of ionic components into ISE membranes based on neutral carriers also proved to be advantageous due to the substantial reduction of the Ohmic resistance in the membrane.

The operation limits of ISE are the important characteristics. The dynamic range of the ISE operation can be substantially extended by either modifying the membrane or introducing a special buffer into the internal solution of the ISE. In the first case,[110] the ISE membrane will operate by the mixed mechanism, namely, the addition of a lipophilic salt will increase the ISE selectivity (due to the stabilisation of counterions in the membrane) and also decrease the negative effect of co-ions that cause degeneration of the ISE electrode function.

The studies on the effect of the intramembrane buffer on the detection limit have shown[42,46,49,50,112–114] that the buffer can affect the ion fluxes and thus change the detection limit of conventional ISE. Such parameters as the composition of the internal electrolyte, the membrane thickness, the nature and concentration of the ion exchanger were studied with the aim of achieving the lower detection limits of ISE. The experimental data were explained based on the fundamental concepts of theoretical models of the diffusion transfer.

Reliable information on the effect of the membrane composition and the ion-exchanger properties on the electrochemical and analytical characteristics of ISE retrieved by studying the transfer of potential-determining species across interfaces under both equilibrium and non-equilibrium conditions. The state of EAC based on MD ion associates in the membrane phase,[27–36] the nature and physicochemical properties of ion exchangers in the membrane solvent[27–29,33] and the processes associated with the effect of water on the properties of interfaces[37] were considered.

Studies on the kinetics of the ion-exchange sorption of MD cations on the surface of ion-selective membranes have shown that the degree of ion exchange is determined by the lipophilicity of the eluting ion, while the time of the establishment of the equilibrium state is controlled by the diffusion. A mechanism of the exchange of hydrophobic organic ions on the surface of liquid membranes with strongly associating active sites was proposed.[38]

The effect of the nature of the polymeric matrix on the electroanalytical properties of ISE was discussed.[115] The studies on the transport of organic cations through membranes involved the determination of their transport numbers. The dependences of the selectivity coefficients on the transport properties of polymeric matrices and on the coefficients of MD distribution between aqueous and membrane phases were obtained.

III. Mechanism of electrode selectivity of ionophore-based membranes

Neutral carriers (ionophores) were used as EAC in the ISE for different MD, namely, protonated amines, quaternary ammonium compounds, amino acids, peptides, nucleotides.[58–106] The use of neutral carriers as the receptors for organic ions is based on their specific reactions and the formation of 'host–guest' complexes. In the formation of such complexes, the hydrophobic effects, van der Waals forces, hydrogen bonds and π-cationic interactions play the great role.[116] The stability of complexes formed is determined by the following factors:[117]

– the correspondence between the geometrical sizes of the molecule-guest and the cavity of the molecule-host,

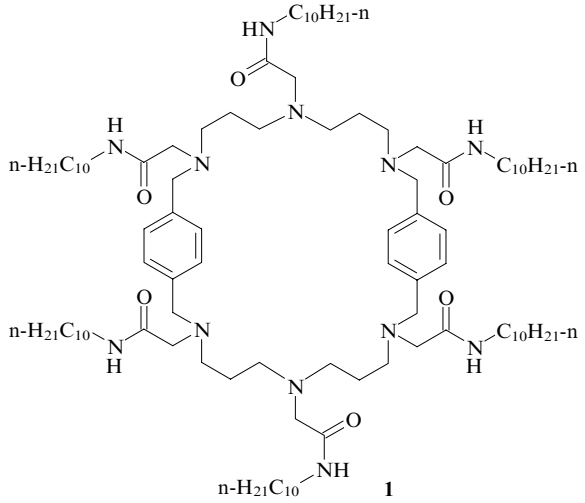
– the conformational flexibility of the ligand,

– the presence of functional groups in ionophore molecules,

– the nature of the solvent.

The membrane potential in a cell with an ISE based on a neutral carrier is formed as a result of processes of selective molecular recognition between the ionophore and the potential-determining ion, which occur at the interface.

To find the principles of potentiometric selectivity of ionophores with respect to organic ions and molecules, it is expedient to consider the effect of the polarity of structural fragments in organic compounds.[118] For polar organic ions, the appearance of a specific membrane potential was associated with the electrostatic interaction and(or) the formation of hydrogen bonds between the functional groups of the ionophore and the polar fragments of the organic molecule (ion). Such a mechanism of selective recognition is typical of macrocyclic polyamines with long-chain hydrocarbon substituents, which can form multicharged cations upon protonation. These ionophores are selective with respect to multicharged organic anions such as adenine nucleotides and anions of certain dicarboxylic acids.[119–121] Moreover, the potentiometric selectivity of ionophores depends on the charge of organic ions (the potentiometric response decreases in the sequence $ATP^{4-} \gg ADP^{3-} \gg AMP^{2-}$)[119,121] or on the localisation of the negative charge on the organic anion [the potentiometric response decreases in the sequences *cis*-$^-$OOC–CH=CH–COO$^-$ > *trans*-$^-$OOC–CH=CH–COO$^-$; *o*-$C_6H_4(COO^-)_2$ > *m*-$C_6H_4(COO^-)_2$ > *p*-C_6H_4.$(COO^-)_2$] (Refs 120, 121). Thus macrocyclic hexamine **1** was used as the neutral carrier in the benzoate-ISE.[58] The selectivity of an electrode based on amine **1** with respect to anions decreased in the sequence $PhCOO^- \approx Cl^- \approx SO_4^{2-} \approx PO_4^{3-} > AcO^- > NO_3^-$ > citrate.



1

Macrocyclic hexamine **1** exhibits a pronounced anionic receptor function at the pH from 4 to 6 due to the presence of amide groups in the β-positions relative to the nitrogen atoms of the polyamine ring, which enhance the affinity of the ionophore for hydrogen ions and improve its receptor function with respect to anions.[122] The same ionophore was used as the EAC in an ion-selective electrode sensitive with respect to anions of adenosine diphosphate and adenosine monophosphate; moreover, the electrode function slope proved to be close to the theoretical slope.[59]

The effect of positively charged nitrogen atoms formed upon protonation of ionophores on their complexation properties was demonstrated by the example of cyclic and acyclic polyamines.[121]

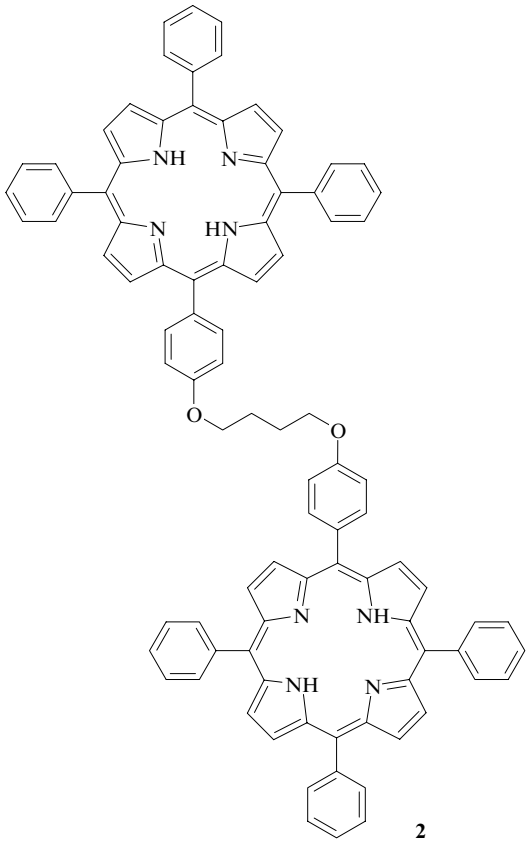
Porphyrine and its derivatives represent typical cyclic polyamines (azacrown compounds) with donating nitrogen atoms, which are softer bases as compared with oxygen atoms. They were used in ISE sensitive with respect to salicylate and valproate anions.[60,63–65] 5-*n*-{[4-(10,15,20-Triphenyl-5-porphynato)phenoxy]-1-butoxy}phenyl-10,15,20-triphenylporphyrine (**2**) and 5,10,15,20-tetrakis[2-(2,3,4,6-tetraacetyl-β-D-glucopyranosyloxyphenyl]porphyrine (**3**) served as specific ionophores in ISE for alkaloid berberine.[61,62]

The studies on the reaction of ionophores **2** and **3** with berberine cations involved the analysis of electron absorption spectra of their solutions in chloroform and nitromethane, which were measured before and after these solutions were brought into contact with an aqueous solution of berberine cations.[62] The absorption peaks of porphyrin **3** at 418, 516, 588 and 654 nm observed upon the contact with the solution of a berberine salt shifted to the long-wave region on average by 4 nm and the peak at 544.5 nm disappeared. This was also observed for ionophore **2**. At the same time, the absorption spectra of a manganese(II) complex with porphyrin **3** remained unchanged both before and after its contact with the berberine salt.

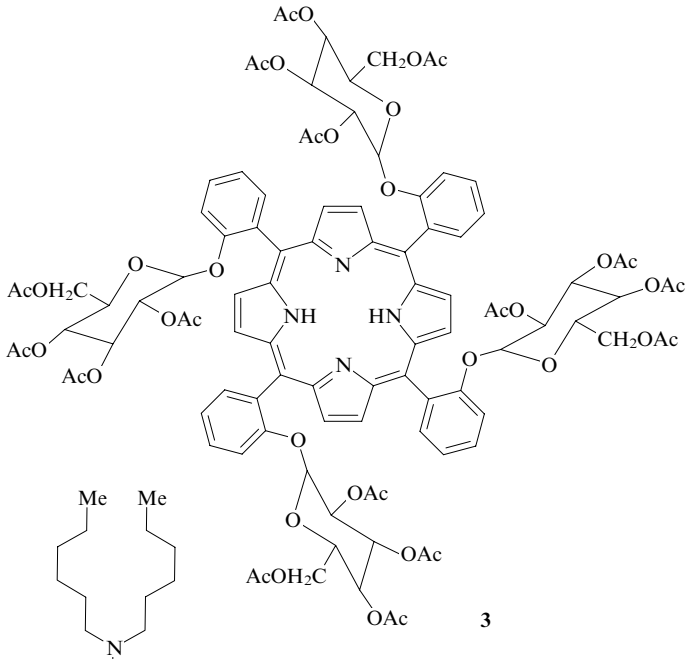
A comparison of IR spectra of PVC membranes based on ionophore **3** before and after their contact with a berberine salt revealed the shifts of absorption bands at 1643.9, 1218.7 and 707.9 cm^{-1} to 1647.1, 1221.9 and 720.0 cm^{-1}, respectively, and the appearance of a new characteristics peak at 1046.5 cm^{-1} associated with the valence vibrations of the amino group in the berberine molecule. This made it possible to assume[62] the reversible complexation of ionophores with the berberine cation.

A more complicated process that accompanies the complexation is the formation of hydrogen bonds between the 'guest' and 'host' molecules. In this case, the potentiometric selectivity was demonstrated for liquid membranes that contained ionophore **4** with a dual receptor function and were capable of recognising guanine- and adenine-containing nucleotides with high selectivity with respect to the former.[123]

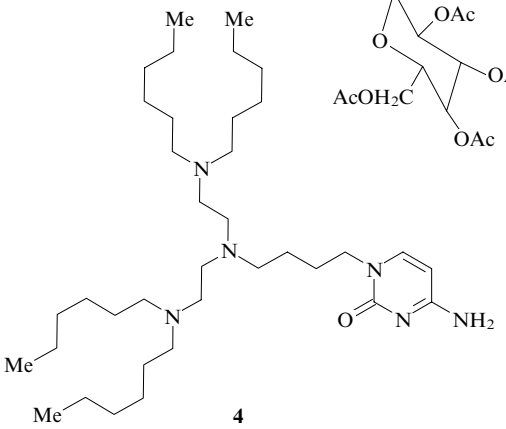
The selectivity of ionophores with respect to organic compounds depends on the presence of non-polar fragments of different nature and structure and, in the general case, is determined by the hydrophilic–lipophilic balance in the organic molecule as a whole. Although the ability for the incorporation of organic molecules into the hydrophobic cavities of the matrices of molecules-hosts is one of the key factors in the molecular recognition, for example, for cyclodextrins and cyclophans in aqueous solutions, the membrane systems pose certain difficulties in the realisation of this selectivity mechanism due to the presence of competitive interactions between ionophores, organic molecules and membrane components. This is why the potentiometric selectivity of ionophores is associated with such properties of organic molecules as lipophilicity and chirality.[118,124–126]



2



3

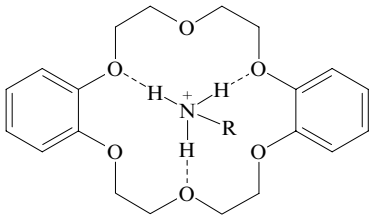


4

The enantiomeric potentiometric selectivity of ionophores with respect to protonated amines and esters of amino acids was demonstrated for PVC membranes based on crown ethers,[127, 128] natural ionophores [129] and cyclodextrins.[130] Due to the peculiarities of their three-dimensional structure, calix[*n*]arene derivatives exhibited selectivity with respect to primary amines and catecholamines.[131]

Cyclic coronands (crown ethers) such as 18-crown-6, dibenzo-15-crown-5, dibenzo-18-crown-6, dibenzo-21-crown-7, dibenzo-24-crown-8, dibenzo-30-crown-10, dicyclohexano-18-crown-6, 4′,4″(5″)-di-*tert*-butylcyclohexano-18-crown-6 and dicyclohexano-24-crown-8 were used in the ISE sensitive with respect to chlorophenoxamine,[66] mexitil [67] and amphetamine stimulators.[68, 69]

Potentiometric selectivity of crown ethers is associated with the lipophilicity of organic ions. The formation of complexes between 'guest' and 'host' molecules is accompanied by the formation of hydrogen bonds, which is typical of, *e.g.*, any protonated primary amines. Thus the selectivity of dibenzo-18-crown-6 with respect to primary ammonium cations correlates with the log *P* and decreases in the following sequence: octylammonium $(3.06 \pm 0.18) \approx$ adamantylammonium $(2.22 \pm 0.24) >$ phenetylammonium $(1.46 \pm 0.19) >$ benzylammonium $(1.09 \pm 0.21) \approx$ *tert*-butylammonium (0.56 ± 0.21). Its selectivity with respect to catecholamines decreases in the sequence dopamine $(0.12 \pm 0.22) >$ adrenaline $(-0.63 \pm 0.28) >$ noradrenaline (-0.88 ± 0.27) (Ref. 70).† The structure of resulting complexes is as follows.



In certain cases, the lipophilicity of an organic cation is not the key factor for the potentiometric selectivity of crowns. It was assumed that an ISE based on dibenzo-18-crown-6 should be more selective with respect to the hydrophobic cations of phentermine $(\log P = 2.16 \pm 0.21)$ as compared with less hydrophobic cations of amphetamine $(\log P = 1.81 \pm 0.20)$ and phenetylamine $(\log P = 1.46 \pm 0.19)$. However, its selectivity turned out to be approximately the same with respect to all mentioned cations.[68] Here, the key role is played by the steric factor that directly affects the stability of complexes formed. In the phentermine molecule, steric accessibility of the positively charged nitrogen atom for complexation is restricted by two α-methyl groups. The use of an acyclic ionophore with carboxamide fragments made it possible to develop an ISE with the higher selectivity with respect to phentermine. The ISE selectivity decreased with the decrease in the lipophilicity of the organic cation in the series phentermine > amphetamine > phenetylamine. This suggests that the stability of complexes of a series of (phenylalkyl)amines with an acyclic ionophore is independent of the steric accessibility of the NH_3^+ group. The peculiarities of the complexation of crown ethers with nitrogen-containing organic compounds were discussed.[117]

Acyclic oxygen-, nitrogen- and phosphorus-containing podands, namely, *N*,*N*-bisoctadecyl-*N*′,*N*′-dipropyl-3,6-

† Logarithms of coefficients of distribution in the water – n-octanol system were calculated using the ACD Labs software with a *C* log *P* predictor for the deprotonated amine form.

dioxaoctanediamide (Pb^{2+}-ionophore I, ETH 322); bisdodecyl ether of triethylene glycol; *N*,*N*,*N*′,*N*′-tetrakis(cyclohexyl)-oxybis(*o*-phenyleneoxy)diacetamide (Ba^{2+}-ionophore I); *N*,*N*,*N*′,*N*′-tetrakis(cyclohexyl)diglycolamide (Ca^{2+}-ionophore II, ETH 129); *N*,*N*,*N*′,*N*′-tetrakis(cyclohexyl)-1,2-phenylenedioxydiacetamide (Na^{+}-ionophore III, ETH 2120) and tris[(2-(2-diphenylphosphinylmethyl)phenoxy)ethyl]amine, which are traditionally used in the ISE reversible with respect to metal ions, turned out to be selective ionophores with respect to amphetamine preparations,[68,69] β-lactam antibiotics,[71] anions of hydroxy-, mono- and dicarboxylic acids and surfactants.[72]

Calix[*n*]arenes can form π-complexes due to the presence of aromatic rings. Such complexes are formed with organylammonium, -iminium and tropylium cations; their stability depends first of all on the conformational peculiarities of the calix[*n*]arene molecule.[132] Thus complexes of amino acids, aliphatic amines, guanidine, creatinine with methyl, ethyl and propyl ethers of calix[6]arene proved to be more stable than the complexes of amino acids with cyclodextrins and crown ethers.[133]

Theoretical calculations and the results of computer simulations have confirmed that the complexing ability of a calix[*n*]arene directly depends on the size and conformational peculiarities of its macrocycle and the presence of functional groups.[134–137]

It was assumed that the reaction of calix[*n*]arenes with amines in solutions can be described[138] by the following sequence of reactions:

$$ArOH + R_3N \rightleftharpoons ArO^- + R_3NH^+ \rightleftharpoons ArO^- \cdots {}^+HNR_3.$$

In the first stage, a mobile proton is transferred from the calix[*n*]arene molecule to the amine molecule. In the second stage, complexation with association of ions occurs, where the ammonium cation can be incorporated into the conical hollow in the ionophore matrix due to the π-cationic interaction.[139–141]

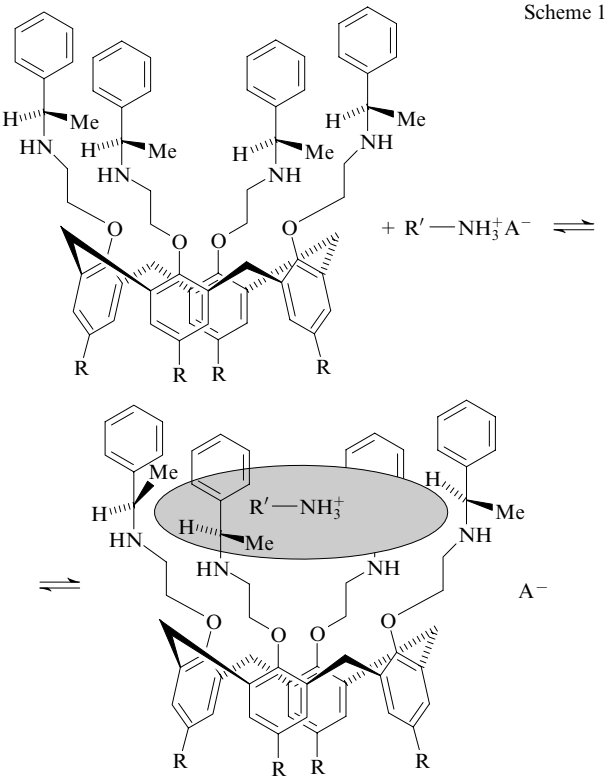
For example, Scheme 1 illustrates the reaction of 25,26,27,28-tetrakis[(*S*)-(−)-(1)-phenylethylaminoethoxy]calix[4]arene with anions of amino acids or aliphatic amines in water–organic media.[142]

Complexes with the different composition (other than 1 : 1) are formed if the reaction proceeds by the following mechanism: encapsulation of the amine molecule by a macrocycle, formation of a coordination bond between the 'host' molecule and another amine molecule.

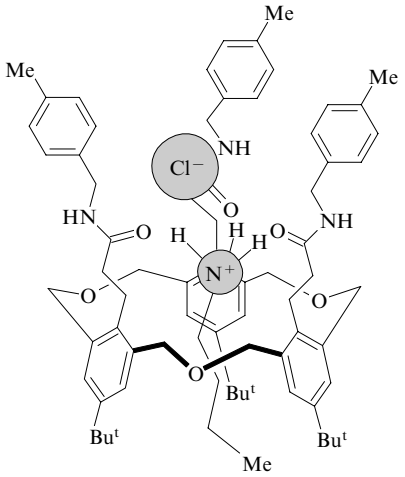
As a rule, the arrangement of amine molecules is such that hydrocarbon radicals are located in the intramolecular cavities of the calixarene matrix.[143]

Chemical modification of calix[*n*]arenes is a sufficiently simple, effective and versatile approach to the synthesis of receptors highly selective with respect to both cations and anions.[144] The introduction of different functional groups into calix[*n*]arene molecules makes it possible to change the selectivity of ionophores with respect to organic ions. Thus *N*,*N*-diethylamide of hexahomotrioxacalix[3]arene extracts 97.8% of $Bu^nNH_3^+$, 48.1% of $Bu^iNH_3^+$ and 35.4% of $Bu^tNH_3^+$ from the salt mixture. The introduction of a (4-methylbenzyl)aminocarbonyl group into the same calix[3]arene results in the total loss of its specificity with respect to metal ions, whereas the selectivity with respect to nitrogen-containing organic cations such as tetrabutylammonium and trimethylphenylammonium appears as a result of higher electron density on the oxygen atom of the carbonyl group due to the conjugation in the $N-C=O \leftrightarrow N^+=C-O^-$ fragment.[145–149] As the result of the formation of hydrogen bonds between the neighbouring NH and CO groups, the calixarene molecule looses its affinity for 'soft' and 'hard' metal cations.[150] In the formation of a complex with the $Bu^nNH_3^+$ cation, the alkyl substituent travels through the ligand π-cavity thus causing changes in the calixarene conformation; moreover, no intramolecular hydrogen bonds are formed in this conformation. The anion (Cl^-) is located within the complex and does not leave it due to the formation of an intramolecular hydrogen bond with the NH group.

Scheme 1

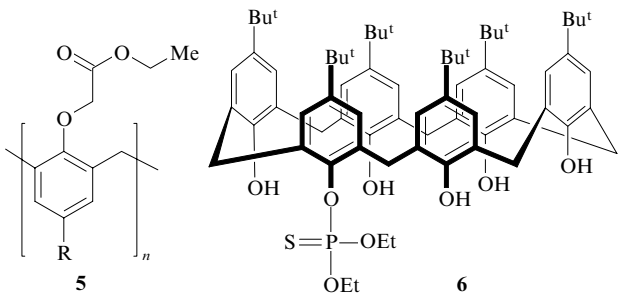


R = H, Bu^t; R′ = (+)- and (−)-$CH_3CH(Ph)$, (+)- and (−)-$Me(CO_2Me)CH$, (+)- and (−)-$PhCH_2(CO_2Me)CH$.



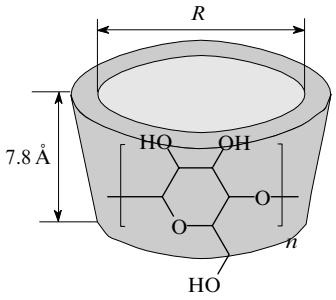
The peculiarities of complexation of calix[*n*]arenes with nitrogen-containing organic compounds (amines, quaternary ammonium cations, iminium ions, amino acids, peptides) were discussed in several reviews.[116,151]

Derivatives of calix[6]- and calix[8]arenes (**5** and **6**, respectively) with specific complexing properties with respect to histamine, dopamine, norephedrine, serotonin[73] and chlorphenoxamine[66] were synthesised and used as the specific receptors in ISE membranes.



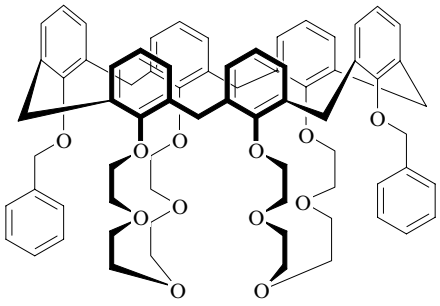
5 **6**

R = H, Bu^t; n = 6, 8.



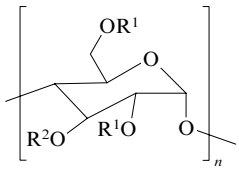
Cyclo-dextrin	n	Cavity diameter R /Å
α	6	5.7
β	7	7.8
γ	8	9.5

Calix[6]crown ethers were tested as the ISE ionophores in the determination of catecholamines (epinephrine, norepinephrine, dopamine).[74] ISE based on compound **7** exhibited the best potentiometric characteristics. The selectivity of such an electrode doped with a lipophilic compound decreased in the sequence epinephrine > K^+ ≈ dopamine > NH_4^+ > norepinephrine > Na^+. The detection limit for epinephrine was 1.86×10^{-5} mol litre^{-1}. The calculated values of log P were −0.17, −0.39, −0.97 for dopamine, epinephrine and norepinephrine, respectively. The inversed order of the extraction selectivity for catecholamines suggests that the complexation of ionophores with the epinephrine cation makes the main contribution in the formation of the potentiometric response of an ISE.



7

Cyclodextrins (CD) are cyclic oligosaccharides that consist of D-glucopyranose residues linked with one another with α-1,4-glycosidic bonds. Their lipophilic derivatives **8** were incorporated into selective membranes for the determination of diclofenac sodium,[75] protonated physiologically active amines, namely, dopamine,[76] (*S*)-enalapril,[77] tricyclic antidepressants (desipramine, imipramine, trimipramine),[78] local anaesthetics (bupivacaine, lidocaine, procaine, prilocaine),[79] propranolol, acetylcholine, methacholine, metformin, norephedrine, phenformin, choline, ephedrine.[80–83]



8

n = 6: R^1 = n-C_8H_{17}, R^2 = H (50% or 57%) + n-C_8H_{17} (50% or 43%);
n = 7: R^1 = n-$C_{12}H_{25}$, R^2 = H;
R^1 = n-C_8H_{17}, R^2 = H (48%) + n-C_8H_{17} (52%).

α-, β-, γ-Cyclodextins differ from one another in the number of glucopyranose residues in the molecule and, correspondingly, in the diameter of the inner cavity:[152]

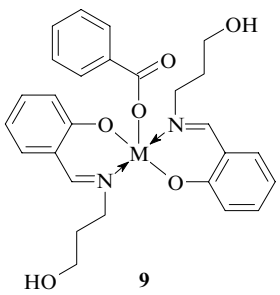
The presence of an inner cavity makes it possible for cyclodextrin molecules to form inclusion compounds with both inorganic and organic molecules and ions.

Cyclodextrin derivatives that exhibit enantiomeric selectivity can be used in ISE for the determination of organic compounds.[81] Thus ISE based on lipophilic 2,6-dioctyl-α-cyclodextrin and 2,6-bisdodecyl-α-cyclodextrin allow the selective determination of the (−)-(1*R*,2*S*)-ephedrine cation in the presence of its three stereoisomers, even though the free energies of the formation of isomer complexes differed by merely 2.5 kJ mol^{-1}. The method of proton magnetic relaxation, which was used in the studies of diastereomeric complexes of ephedrine and its analogues with lipophilic cyclodexrins, has demonstrated the difference in the degree of hydrogen bond formation between the structural fragments $NH^+ \cdots O$ in the complex compounds.[84] As a result of stereo-differentiation in the formation of cyclodextrin complexes with ephedrine cations, a more stable complex of the corresponding stereoisomer was formed.[81]

A guanidinium ion and 2,6-bisdodecyl-β-cyclodextrin form a 1 : 1 complex, and the ISE on its basis exhibited approximately equal sensitivity with respect to organic cations with the structures close to that of guanidine.[81] The occasional independence of the ISE electrode response on the cyclodextrin structure (α-, β-, OH- and alkylcyclodexrins) was associated with the formation of a primary hydrogen bond between the positively charged nitrogen atom and the oxygen atom of the cyclodextrin molecule.[80]

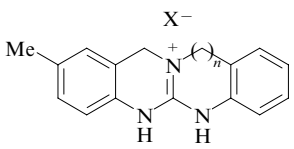
Certain cyclodextrin derivatives can form supramolecular polymers, intramolecular inclusion complexes and more intricate supramolecular systems, which extends the possibilities of their practical application as specific receptors.[153]

Complexes of aluminium, tin(IV) and copper(II) with tetra(*tert*-butyl)phthalocyanine and oxo(phthalocyaninato)-vanadium(IV) and -molybdenum(IV) were used as ionophores in liquid[85–89] and solid-contact[90] membranes of salicylate-selective electrodes. Metallocenes [bis(cyclopentadienyl Co(II), Fe(II), Ni(II), Hf(IV), Nb(V), Tl(I) and Zr(IV)], tribenzyltin(IV), phenolates and carboxylates, phenylboronic acid derivatives, heptyl 4-(trifluoroacetyl)benzoate, complexes of Al(III) and Sn(IV) with *N*,*N*′-bis(salicylidene)-*o*-phenylenediamine, complexes of Schiff base **9**, guanidine derivatives **10** and tetraazo[14]annulene copper(II) also proved to be suitable



9

M = Co(III), Mn(III)



10

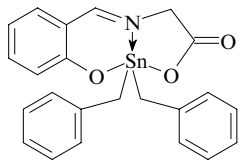
n = 2, X = ClO_4; n = 3, X = BF_4

ionophores for the ISE selective with respect to salicylate anions (Sal^-).[91–95]

Spectrophotometry,[63,88,89,96] IR spectroscopy[63] and the electrochemical impedance method[97] were used for the elucidation of the mechanism of the potentiometric response of ISE to salicylate anions. Spectral methods provided information on the mechanism of complex formation, while the electrochemical impedance method afforded data on the kinetic characteristics and limiting stages of the transfer processes.

Based on experimental data, it was shown that the reaction of tetra(*tert*-butyl)phthalocyaninato(iodo)cobalt(III) with salycilate anions proceeds *via* the substitution of a salicylate ion for the axial iodide ion. This was not the case for tetra(*tert*-butyl)phthalocyaninato(chloro)rhodium(III) due to the very strong Rh—Cl bond and the hindered coordination through the free sixth axial position on the metal, because the radius of the Rh(III) ion substantially exceeds the size of the phthalocyanine cavity so that the metal ion 'leaves' the plane in the direction of the axial chloride ion. An ion-selective electrode based on tetra(*tert*-butyl)phthalocyaninato(chloro)rhodium(III) does not respond to salicilate anions, whereas an ISE based on tetra(*tert*-butyl)phthalocyaninato(iodo)cobalt(III) demonstrates an electrode function with a slope S of 50 ± 2 mV $(pC)^{-1}$ and a detection limit of 6.3×10^{-5} mol litre^{-1} of Sal^- (Ref. 88).

An ion-selective electrode based on complex **11** formed by dibenzyltin with a Schiff base produced a super-Nernstian response [$S = 65.5 \pm 1.8$ mV $(pC)^{-1}$] to salicylate anions in the range of 1.0×10^{-1}–4.0×10^{-6} mol litre^{-1} of Sal^- (Ref. 97).



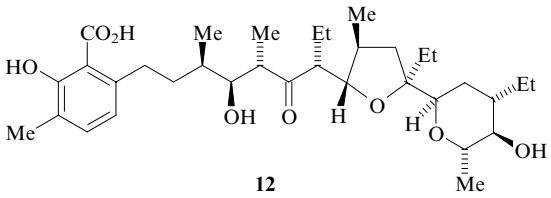
11

The appearance of the super-Nernstian response was associated with the ability of the ionophore to form dimers and more complex aggregates in the organic phase of the membrane, while the increase in the electrode function slope is the consequence of the changes in the stoichiometry of the ionophore reaction with the salicylate anion (2 : 1 in place of 1 : 1). Based on the analysis of electron absorption spectra of ionophore solutions in chloroform measured before and after their contact with the NaSal solution, the potentiometric selectivity of a membrane with respect to Sal^- was associated with the thermodynamically preferential coordination of the Sal^- anion at the central metal atom of the ionophore. The results of impedance measurements made it possible to assume the diffusion-controlled transfer of salicylate anions.[97]

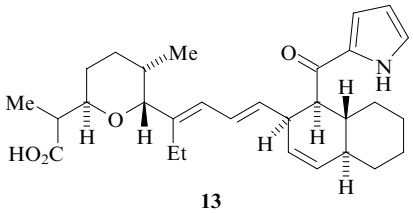
The mechanism of the potentiometric response of an ISE with a membrane based on μ-oxobis[5-(*p*-hydroxyphenyl)-10,15,20-triphenylporphyrinato]manganese(III) {$[Mn(5\text{-}HP).TPP]_2O$} was studied by IR and UV spectroscopic techniques.[63] The selectivity of the ISE electrode with respect to Sal^- was associated with the formation of charged carriers in the membrane as a result of the following reaction:

$$2(Sal^-)_{solution} + \{[Mn(5\text{-}HP)TPP]_2O\}_{membrane} \rightleftharpoons$$
$$\rightleftharpoons 2\{[Mn(5\text{-}HP)TPP]^+Sal^-\}_{membrane} + 2(OH^-)_{solution}.$$

Acyclic polyether antibiotics lasalocid (**12**) and omomycin (**13**) were shown to exhibit enantiometric selectivity with respect to optical isomers of methyl esters of amino acids.[98]



12



13

The electrode function of ISE in solutions of L-isomers had a slope close to theoretical. The coefficient of enantiometric selectivity for L- and D-isomers of methyl phenylalaninate was 2.38 for lasalocid-based membranes and 1.85 for membranes containing omomycin. According to the transport tests, it was shown that lasalocid can transfer protonated cations of methyl phenylalaninate across the liquid mebrane – solution interface according to the antiport principle at a rate close to that of the transfer of cations by other ionophore antibiotics.

Phenylboronic acid derivatives and complexes of hydroxamic acids with boric acid were used as ionophores for ISE membranes sensitive to protonated forms of catecholamines (adrenaline, dobutamine, dopamine, noradrenaline),[95,99] phenolic acids (gallic, homoprotocatechuic, caffeic and salicylic acids).[94,99] The electrode response of ISE membranes was associated with the trend of polyhydroxycompounds for the fast and reversible formation of covalent ester bonds with boric acid derivatives.[94,95,99]

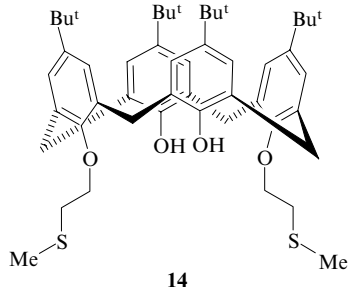
Of other ionophores, 2,3,5-triphenyl-2*H*-tetrazolium tungstophosphate was used in the ISE for ascorbic acid,[100] a complex of iron(II) with 2,4,6-tri(piperidino)-1,3,5-triazine was used in ISE for diclofenac sodium,[101] *O*-(2,4-dichlorophenyl) *O*-ethyl *S*-propyl dithiophosphate was employed in ISE for histamine,[102] heptyl 4-(trifluoroacetyl)benzoate was used as the ionophore in salicylate-ISE.[103]

Studies were carried out devoted to the development and optimisation of characteristics of ISE for polyions (heparin and protamine).[154–164] The equilibrium response of sensors to polyions of different structure was compared for ISE based on tri(dodecyl)methylammonium chloride and tetra(dodecyl)ammonium chloride. The deviations in the emf changes were used as the basis for stating a correlation between the energy of interaction of ionic pairs and the polyion charge. A threshold mass of polyion molecules was required for reaching the maximum emf value. The effect of lipophilic additions on the ISE response was studied. It was shown that the ISE may be used in the monitoring of the enzymatic hydrolysis of protaozoline with tripsin.

A modernised ISE for protamine, which was based on its associate with dinonylnaphthalinesulfonate, was developed for the whole blood analysis.[163] The electrode operates by the mechanism of non-equilibrium response in the concentration range of 0.5–20 mg litre^{-1} and can be used in both direct potentiometry and potentiometric titration of heparin with protamine. The results of ISE determinations agreed with the data of other (independent) analytical techniques. It was shown that the procedure of potentiometric titration of heparin using this ISE allows complete automation.

The development and optimisation of solid-contact ISE for heparin was discussed.[164] The temporal instability of the potential is the main drawback of solid-contact ISE. To

remove this drawback, silver(I) complexes with a lipophilic derivative of *tert*-butylcalix[4]arene **14** were incorporated into the membrane in addition to EAC [tri(dodecyl)methylammonium chloride].



14

This complex serves as the reversible electron carrier between the polymeric membrane and the current lead and favours the stabilisation of the potential of the solid-contact sensor.

IV. Components of ion-selective electrode membranes and methods of potentiometric determination of medicinal drugs

As was mentioned above, IA formed by MD cations and anions with the corresponding counter-ions are used most often as the EAC in selective membranes. Table 1 presents different EAC types, which are incorporated into the composition of ISE membranes both directly and in the form of ion associates with MD. Tetraphenylborate and its derivatives are used most extensively in EAC for cation-selective electrodes, while the cations of quaternary ammonium bases (QAB) are employed in EAC for anion-selective electrodes.

Nitrobenzene derivatives (in ISE with liquid membranes), nitrophenol ethers, esters of *o*-phthalic, adipic, sebacic, phosphonic and phosphoric acids are used most often as the solvents-plasticisers. Table 2 shows membrane solvents used in ion-selective membranes. *o*-Nitrophenyl octyl ether, dibutyl phthalate and dioctyl phthalate are the most common plasticisers of the polymeric binder, *i.e.*, polyvinyl chloride (PVC). Depending on the particular case, one or another membrane

Table 1. Electroactive compounds incorporated into the selective membrane either directly or as ion associates with medicinal drugs.

Class of compounds	Compound	Ref.
Tetraphenylborate derivatives	sodium tetraphenylborate	86, 87, 106, 165–219
	sodium tetrakis(4-methylphenyl)borate	37, 170
	potassium tetrakis(4-chlorophenyl)borate	37, 66, 68, 73, 74, 76, 80, 83, 86, 170, 171, 191, 192, 211, 220–226
	potassium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate	37, 67, 78–82, 192, 227, 228
	sodium tetrakis[3,5-bis(1,1,1,3,3,3-hexafluoro2-methoxy-isopropyl)phenyl]borate $Na[B(C_{14}H_9O_2F_{12})_4]$	64, 67, 102, 229
Heteropoly compounds	molybdophosphoric acid $H_3[PMo_{12}O_{40}]$	32, 34, 36, 165, 170, 172, 175, 184, 189, 198, 230–246
	molybdosilicic acid $H_4[SiMo_{12}O_{40}]$	32, 34, 36, 170, 172, 231, 239, 240, 246
	tungstophosphoric acid $H_3[PW_{12}O_{40}]$	32, 34, 36, 100, 170–172, 177, 184, 195, 196, 208, 212, 233–235, 238–241, 243–261
	tungstosilicic acid $H_4[SiW_{12}O_{40}]$	32, 34, 36, 170, 172, 195, 202, 232, 240, 262–266
1,10-Phenanthroline and its derivatives	1,10-phenanthroline	267, 268
	4,7-diphenyl-1,10-phenanthroline (batophenanthroline)	267, 269–271
Quaternary ammonium and phosphonium cations	*N*,*N*,*N*,*N*-tetraoctylammonium	272–274
	N,*N*,*N*,*N*-tetrakis(decyl)ammonium	31, 170, 275, 276
	N-methyl-*N*,*N*,*N*-trioctylammonium	71, 87, 220, 277–280
	N,*N*,*N*,*N*-tetradodecylammonium	75
	N-hexadecylpyridinium	281
	N,*N*,*N*-tridodecyl-*N*-methylammonium	58, 103
	N,*N*,*N*-tributyl-*N*-hexadecylphosphonium	71
	bis(triphenylphosphoranilidene)ammonium $[Ph_3P{=}N^+{=}PPh_3]$	64, 273, 282, 283
Nitroaromatic compounds	2,2′,4,4′,6,6′-hexanitrodiphenylamine (dipicrylamine)	271, 284–286
	2,4,6-trinirophenol (picric acid)	34, 100, 204
	3-methyl-4-nitro-1-*p*-nitrophenylpyrazol-5-one (picrolonic acid)	100, 287, 288
Miscellaneous salts (anions) and acids	sodium dodecyl sulfate	285, 288, 289
	Reinecke salt anion $[Cr(NH_3)_2(NCS)_4]^-$	32, 34, 197–199, 201, 210, 214–216, 225, 242, 253, 255, 261
	tetraiodobismuthate	32, 34, 183, 204
	tetraiodomercurate	32, 34, 197, 204, 290, 291
	tetraiodocadmate	292
	trioctyloxybenzenesulfonic acid	293
	hexathiocyanoferrate(III) anion	294
	tetrathiocyanocobaltate(II) anion	242
	5-nitropyrimidine-2,3,6-trione (5-nitrobarbituric acid)	295

Table 2. Solvents-plasticisers used in membranes of liquid and polymeric ion-selective electrodes.

Plasticiser type	Name of compound	Ref.
Plasticisers with high permittivity		
Nitro compounds	nitrobenzene	284
	2-nitrotoluene	100
	1-isopropyl-4-nitrobenzene	222, 274
	2-nitrophenyl octyl ether (NPOE)	35, 61–63, 67, 71, 73–75, 78–83, 85, 91–96, 103, 104, 171, 174, 180, 182, 189, 192, 197, 207, 208, 221–225, 227, 233, 234, 243, 261, 263, 266, 269–273, 279, 281–283, 296
	2-nitrophenyl dodecyl ether	227
	2-nitrophenyl phenyl ether	213, 222, 233
	2-nitrophenyl 2-fluorophenyl ether	67, 76, 192, 229
Plasticisers with low permittivity		
Esters of *o*-phthalic acid	dibutyl phthalate (DBP)	31, 32, 34, 36, 37, 61, 105, 169, 170, 177, 179, 182, 184–186, 188, 195–197, 204, 206, 228, 239, 240, 244, 254, 262, 275–277, 281, 293
	bis(2-ethylhexyl) phthalate	65, 90
	dioctyl phthalate (DOP)	32, 34, 36, 61, 62, 66, 67, 85, 172–174, 177, 186, 187, 190, 191, 193, 195–199, 201, 202, 204, 212, 214–216, 218, 230–232, 235, 238, 239, 243, 245, 246, 256–260, 266–268, 275, 276, 279, 281, 284, 290, 291, 294, 297
	diisooctyl phthalate	62
	bis(2-ethyloctyl) phthalate	96
	dinonyl phthalate (DNP)	58, 192, 278
	diisononyl phthalate (DiNP)	36, 202, 262
Esters of adipic acid	bis(2-ethylhexyl) adipate	91, 226
	bis(1-butylpentyl) adipate	80, 83, 86, 91
Esters of sebacic acid	diethyl sebacate (DES)	85, 94, 95
	dibutyl sebacate (DBS)	197, 214, 225, 266, 281
	bis(2-ethylhexyl) sebacate (EHS)	32, 61, 66, 68, 104, 182, 192, 205, 222, 225, 227, 273, 275, 276
	dioctyl sebacate (DOS)	36, 62, 74, 202, 224
	dinonyl sebacate	86
Esters of phosphoric and phosphonic acids	tributyl phosphate	85
	dioctyl phenyl phosphonate (DOPP)	51, 277
	tritolyl phosphate (mixture of isomers) (TTP)	36, 67, 202, 230, 239
	bis(2-ethylhexyl) phosphate	225
	tris(2-ethylhexyl) phosphate	67, 69, 192, 225
	trioctyl phosphate	226
Esters of miscellaneous acids and non-ester plasticisers	chlorobenzene	181
	n-octanol	292
	heptyl benzoate	32, 34, 275
	bis(1-butylpentyl)decan-1,10-diyl diglutarate	64
	tetrakis(2-ethylhexyl) pyromellitate	192

solvent may prove to be more suitable for the achievement of optimum electroanalytical characteristics of ISE for MD.

In the organic analysis, arrays of sensors (multisensor systems of the 'electronic tongue' type) are used. A multisensor system has been developed for the determination of lysine in foodstuffs.[298] The array of sensors comprised an enzyme electrode based on lysine oxidase with NH_4^+-ISE and a set of solid-contact ISE for H^+, NH_4^+, K^+, Na^+, Ca^{2+}, Mg^{2+} and Li^+ cations. The response of the enzyme electrode was associated with the enzymatic reaction

$$H_2N(CH_2)_4CH(NH_2)CO_2H + H_2O + O_2 \xrightarrow{\text{lysine oxidase}} H_2N(CH_2)_4C(O)CO_2H$$

Insofar as the selectivity of the enzyme electrode with respect to other cations is low, the cross-selectivity-based potentiometric response of a multisensor system can be determined using the multiversion regression analysis. Among the methods for mathematical processing of potentiometric data, the least-squares technique with partial regression, which provides the smallest prediction errors, has shown the best results.[298]

An ISE-based method of precipitation potentiometric titration was also used for the determination of MD and drug preparations. Sodium tetraphenylborate commonly used as the titrant in the cationic MD determination proved to be suitable for determination of both individual MD[266, 268, 291] and multicomponent MD mixtures.[299]

The method of preciptation potentiometric titration was also used in the flow analysis. In the determination of ephedrine by potentiometric titration, a flow-injection cell with a tubular indicator electrode containing tetrapentylammonium tetraphenylborate dissolved in *o*-nitrophenyl pentyl ether has been developed.[213] An ISE-containing individual channel in the cell was provided for the ephedrine determination. The

Table 3. Composition of membranes and characteristics and electroanalytical properties of ion-selective electrodes for determination of medicinal drugs.

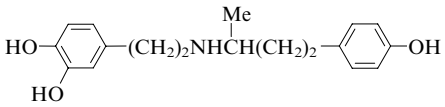
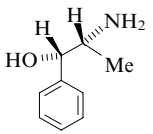
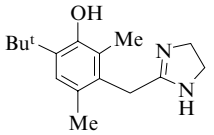
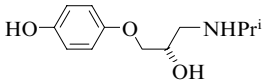
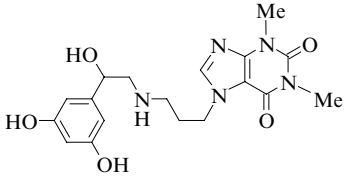
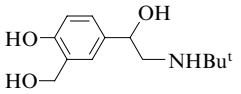
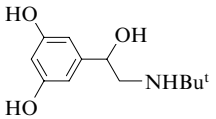
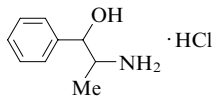
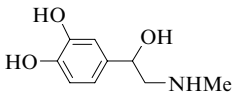
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Adrenomimetics and sympathomimetics				
Dobutamine		PPVCM (NPOE or DES) with phenylboronic acid derivatives	LR $1.0\times10^{-2}-5.0\times10^{-4}$, DL $= 1.7\times10^{-5}$, $S = 58$, pH 6.3–8.0	95
Norephedrine		PPVCM [bis(1-butylpentyl) adipate] with a lipophilic derivative of β-CD and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	DL $= 7.9\times10^{-6}$, $S = 58$	82
		PPVCM (NPOE) with derivatives of calix[*n*]arenes ($n = 6, 8$) and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	LR $1.0\times10^{-2}-n\times10^{-6}$, $S = 50-57$	73
Oxymetazoline		PPVCM (DOP) based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-2.0\times10^{-5}$, $S = 57.2$, pH 1.0–9.4	260
Prenalterol		PPVCM (DOP) based on IA of MD cations with BPh_4^-	LR $3.2\times10^{-2}-1.2\times10^{-5}$, $S = 56.3$, pH 2.2–7.5	187
Reproterol		PPVCM with individual IA of MD cations with $[PW_{12}O_{40}]^{3-}$ and $[PMo_{12}O_{40}]^{3-}$ or their mixture	LR $1.0\times10^{-1}-6.3\times10^{-6}$, pH 2.0–9.0	241
Salbutamol		ISE for FIA with PPVCM (DOP) based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$ and $[PMo_{12}O_{40}]^{3-}$	LR $1.0\times10^{-1}-6.3\times10^{-6}$, $S = 57-67$, pH 2.0–11.0	235, 238
		SC-ISE (glassy carbon substrate) with an ion-electron transducer (polyaniline), PPVCM based on IA of MD cations with BPh_4^-	LR $1.0\times10^{-1}-4.0\times10^{-5}$, DL $= 1.2\times10^{-5}$, $S = 60.4$, pH 3.9–7.8	194
Terbutaline		PPVCM based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$	–	250
Phenylpropanolamine hydrochloride		PPVCM (DBP or DOP) based on IA of MD cations with BPh_4^- and $[PW_{12}O_{40}]^{3-}$	LR $8.9\times10^{-3}-1.0\times10^{-5}$	177
Epinephrine		PPVCM (DOS) with calix[6]crowns and addition of lipophilic $K[B(C_6H_4Cl\text{-}4)_4]$	LR $1.0\times10^{-2}-1.0\times10^{-4}$, DL $= 1.9\times10^{-5}$, $S = 45$, pH 7.2	74

Table 3 (continued).

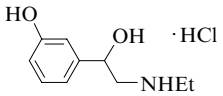
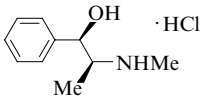
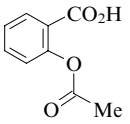
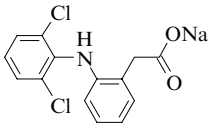
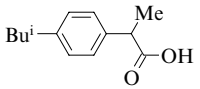
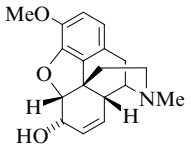
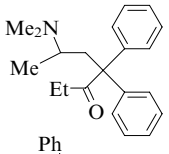
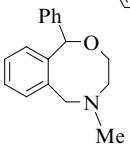
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Adrenomimetics and sympathomimetics				
Etilefrine		PPVCM (DOP) based on IA of MD cation with BPh_4^- and $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-1}-6.3\times10^{-5}$,	212
Ephedrine		microsensor based on a field transistor and a sensitive membrane modified with β-cyclodextrin	LR $1.0\times10^{-1}-3.0\times10^{-6}$, $S = 58$, pH 3.0–8.0	303
		PPVCM [bis(1-butylpentyl) adipate] with a lipophilic derivative of β-CD and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	DL $= 2.5\times10^{-7}$, $S = 60$	80, 83
		tubular ISE for FIA with PPVCM based on IA $[(n\text{-}C_5H_{11})_4N]^+[BPh_4]^-$	LR $1.0\times10^{-1}-3.8\times10^{-6}$, $S = 56.4$, pH 2.5–11.5	213
		PPVCM with a mixture of IA formed by ephedrine cations with BPh_4^-, $[Cr(NH_3)_2(NCS)_4]^-$ and by phenylephedrine cations with $[Cr(NH_3)_2(NCS)_4]^-$	LR $1.0\times10^{-1}-1.0\times10^{-5}$, DL $= 4.0\times10^{-6}$, $S = 50-55$, pH 2.0–9.0	215
Analgesic drugs (narcotic and non-narcotic analgesics)				
Acetylsalicylic acid (AcSA)		tubular flow ISE for salicylate anions formed upon alkaline hydrolysis of AcSA	LR $4.0\times10^{-2}-4.0\times10^{-3}$, pH 8	304
		flow ISE, PPVCM (NPOE) with addition of tetraoctylammonium salicylate and *p*-(*tert*-octyl)phenol for the determination of AcSA after its preliminary hydrolysis	LR $1.0\times10^{-2}-5.0\times10^{-5}$, DL $= 5.0\times10^{-5}$, $S = 56$	272
		tubular flow SC-ISE based on ethylene–vinyl acetate co-polymer, trioctylmethylammonium salicylate and addition of $K[B(C_6H_4Cl\text{-}4)_4]$, sensitive to salicylate anions formed upon hydrolysis of AcSA	LR $5.0\times10^{-1}-5.0\times10^{-3}$, DL $= 2.5\times10^{-3}$, $S = 58.3$, pH 6–10	220
Diclofenac sodium		PPVCM (NPOE) with addition of α-CD and $[(n\text{-}C_{12}H_{25})_4N]Br$	LR $1.0\times10^{-2}-5.0\times10^{-6}$, DL $= 1.0\times10^{-6}$, $S = 57.5$, pH 8.2–12.7	75
		PPVCM based of IA of diclofenac with a Fe(II) complex with 2,4,6-tris(2-pyridyl)-1,3,5-triazine	LR $n\times10^{-2}-n\times10^{-6}$, pH 5.5–9.5	101
Ibuprofen		PPVCM based on IA of MD anions with cations of different QAB	–	305
		PPVCM (DOP) with IA formed by MD anions with a Fe(II) complex with phenanthroline	LR $1.0\times10^{-2}-2.0\times10^{-5}$, DL $= 0.8-1.3$ μg ml^{-1}, $S = 59-60$	268
Codeine		PPVCM (DOP) with IA of MD cations with BPh_4^- and $[Cr(NH_3)_2(NCS)_4]^-$	LR $1.0\times10^{-2}-n\times10^{-5}$, DL $= 3.5\times10^{-5}$, $S = 50-60$, pH 2.5–8.0	199, 214
Methadone		PPVCM (NPOE) with IA of MD cations with $[B(C_6H_4Cl\text{-}4)_4]^-$	LR $1.0\times10^{-1}-2.5\times10^{-5}$, $S = 59.5$, pH 2.0–9.0	221
Nefopam		PPVCM with a nefopam–picrolonate complex	LR $5.0\times10^{-2}-5.0\times10^{-4}$, DL $= 7.9\times10^{-5}$, $S = 56$	287

Table 3 (continued).

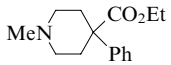
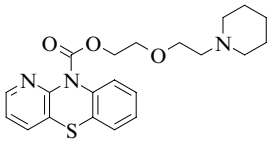
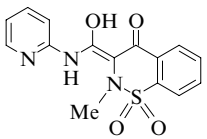
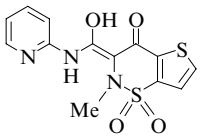
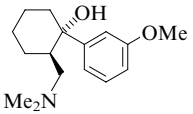
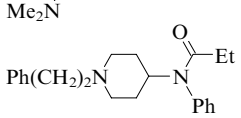
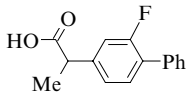
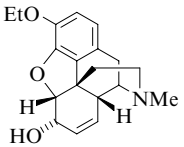
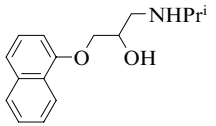
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Analgesic drugs (narcotic and non-narcotic analgesics)				
Pethidine		PPVCM (DBP) with IA of MD cations with BPh_4^- and $[SiW_{12}O_{40}]^{4-}$	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL $= 2.2\times10^{-6}$, $S = 51.8$, pH 2.0–8.0	206, 265
Pipazetate		PPVCM (DOP) with IA of MD cations with $[PMo_{12}O_{40}]^{3-}$ and $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-1}-6.3\times10^{-5}$, $S = 45-50$, pH 2.0–9.0	245
Piroxicam		PPVCM (DNP) with IA of MD anions with trioctylmethyl ammonium cations (Aliquat 336S)	LR $1.0\times10^{-2}-n\times10^{-5}$, DL $= (2.4-6.0)\times10^{-6}$, $S = 54-56$, pH 4.0–7.5	278
Tenoxicam		the same	the same	278
Tramadol		SC-ISE with PM (DOP or DBPhos) and IA of MD cations with $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-n\times10^{-5}$, DL $= 2.3\times10^{-6}$, $S = 55.9\pm0.4$, pH 1.0–7.0	249, 257
Fentanyl		PPVCM with IA of MD cations with $[B\{(C_6H_3(CF_3)_2\text{-}3,5\}_4]^-$	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL $= 6.29\times10^{-6}$, $S = 57.9$	228
Flurbiprofen		PPVCM with IA of MD anions with Aliquat 336S	LR $1.0\times10^{-2}-7.0\times10^{-5}$	280
Ethylmorphine		SC-Sensor (Si/Si_3N_4 substrate) with PPVCM based on IA of MD cations with BPh_4^- and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	LR $1.0\times10^{-2}-2.5\times10^{-5}$, DL $= 1.0$ μg ml^{-1}, pH 2.5–6.5	211
Antiadrenergics and dopamine mimetics				
Propranolol		PPVCM (DiNP or DOP) with IA of MD cations with $[SiW_{12}O_{40}]^{4-}$, $[PMo_{12}O_{40}]^{3-}$ or $[SiMo_{12}O_{40}]^{4-}$ PPVCM (NPOE) with a lipophilic derivative of β-CD and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	LR $2\times10^{-2}-n\times10^{-6}$, DL $= (1.0-10.0)\times10^{-7}$, $S = 30.0-54.7$, pH 4.0–8.0 DL $= 1.0\times10^{-5}$, $S = 60$	231, 262 83

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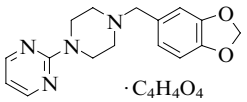
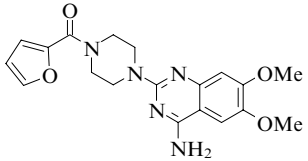
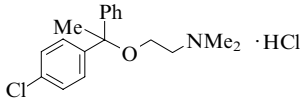
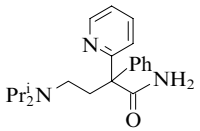
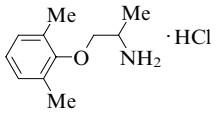
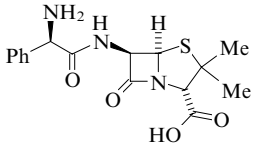
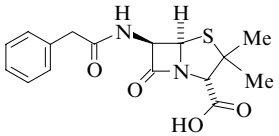
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Antiadrenergics and dopamine mimetics				
Piribedil		PPVCM (DBP and DOP) based on IA of MD cations with BPh_4^-, BiI_4^- or HgI_4^{2-}	LR $n \times 10^{-2} - n \times 10^{-6}$, $S = 30-57$, pH 3.0–6.4	186, 204
Prazosin		PPVCM based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$	LR $1.0 \times 10^{-2} - 2.7 \times 10^{-6}$, pH 1.5–6.4	248
Chlorphenoxamine		PPVCM containing a mixture of ionophores (18-crown-6, dibenzo-18-crown-6 or 37,38,39,40,41-pentakis[(diethoxythiophosphoryl)oxy]-5,11,17,23,29,35-hexakis(1,1-dimethylethyl)calix[6]arene-42-ol) with $K[B(C_6H_4Cl\text{-}4)_4]$	LR $5.0 \times 10^{-2} - 6.3 \times 10^{-6}$, DL $= 5.9 \times 10^{-6}$, $S = 35-55$, pH 3–8	66
Antiarrhithmic drugs				
Disopyramide		PPVCM (2-nitro-2′-fluorodiphenyl ether) with $Na[B(C_{14}H_9O_2F_{12})_4]$	LR $1.0 \times 10^{-4} - 6.0 \times 10^{-6}$, DL $= 8.0 \times 10^{-7}$, $S = 55-63$, pH 7.4 (buffer)	229
		PPVCM with IA of MD cations with dodecyl sulfate	LR $n \times 10^{-2} - n \times 10^{-5}$, DL $= 7.1 \times 10^{-8}$, pH 2.0–6.5	289
Mexitil		PPVCM based on 4′,4″(5″)-di(*tert*-butyl)cyclohexano-18-crown-6 and $Na[B(C_{14}H_9O_2F_{12})_4]$	LR $1.0 \times 10^{-2} - 1.0 \times 10^{-5}$, DL $= 3.0 \times 10^{-6}$, $S = 54-59$, pH 7.4 (buffer)	67
Antibiotics				
Ampicillin		PPVCM (NPOE) containing tris{[2-(2-diphenylphosphonylmethyl)phenoxy]ethyl}amine	LR $10^{-3} - 10^{-4}$, DL $= 3.1 \times 10^{-5}$, $S = 58 \pm 1$	71
		PPVCM (DMP) based on IA of MD anions with $[(n\text{-}C_{10}H_{21})_4N]^+$	LR $n \times 10^{-1} - n \times 10^{-6}$, DL up to 6.3×10^{-6}, $S = 58-62$, pH 5.0–9.2	31
Penicillin G		the same	the same	31
		PPVCM (NPOE) containing $[Bu_3^n(n\text{-}C_{16}H_{33})P]Br$ or $[(n\text{-}C_8H_{17})_3MeN]Cl$	LR $1.0 \times 10^{-1} - 2.5 \times 10^{-5}$, DL $= 1.0 \times 10^{-5}$, $S = 49-57$, pH 4.5–8.0	71
		ISFT (Ta_2O_5 substrate) with immobilised enzyme penicillinase (β-lactamase)	LR $1.0 \times 10^{-3} - 5 \times 10^{-5}$, DL $= 5.0 \times 10^{-6}$, $S = 120 \pm 10$	306
		microsensor for FIA based on $Si-SiO_2-Ta_2O_5$	LR $5.0 \times 10^{-3} - 1 \times 10^{-4}$, $S = 135$	307
		PM (NPOE) based on PVC and ethyl vinyl ether and containing manganese(III) 5,10,15,20-tetraphenylporphyrinate and lipophilic additives	LR $1.0 \times 10^{-1} - 2.0 \times 10^{-5}$, $S = 59-61$	296

Table 3 (continued).

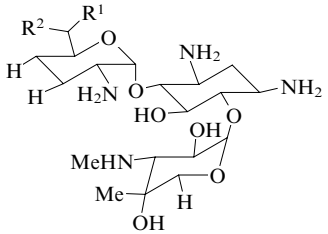
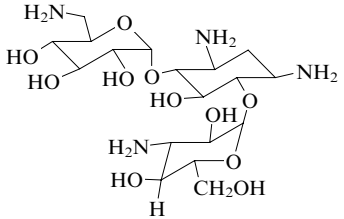
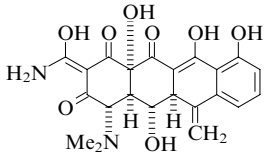
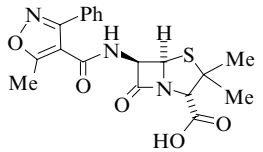
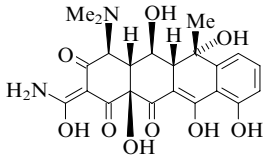
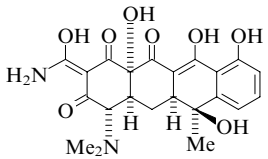
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Antibiotics				
Gentamycin	 $R^1 = H$, $R^2 = NH_2$; $R^1 = Me$: $R^2 = NH_2$, NHMe	PPVCM (DBP) with IA of MD cations with BPh_4^-	LR $1.0 \times 10^{-1} - 1.0 \times 10^{-6}$, DL $= 1.0 \times 10^{-6}$, $S = 26 \pm 2$, pH 5.5–6.0	169, 188
Kanamycin		the same	the same	169, 188
Metacyclin		PPVCM (DOP) with IA of MD cations and BPh_4^-	LR $3.0 \times 10^{-2} - 6.0 \times 10^{-6}$, DL $= 3.4 \times 10^{-6}$, $S = 52.9$, pH 2.6	195
Oxacillin		PPVCM (NPOE) containing copper tetra(*tert*-butyl)phthalocyaninate or $[Bu^n_3(n\text{-}C_{16}H_{33})P]Br$ PPVCM(DBP) with IA of MD anions with $[(n\text{-}C_{10}H_{21})N]^+$	LR $1.0 \times 10^{-1} - 2.0 \times 10^{-5}$, DL $= 8.0 \times 10^{-6}$, $S = 57 \pm 2$, pH 4.5–8.0 LR $1.0 \times 10^{-2} - 3.2 \times 10^{-6}$, DL $= 3.1 \times 10^{-6}$, $S = 65 \pm 3$, pH 5.0–6.0	71 31
Oxytetracycline		SC-ISE with PPVCM (DBP) with IA of the cationic form of MD with BPh_4^-, $[PMo_{12}O_{40}]^{3-}$ or $[PW_{12}O_{40}]^{3-}$	LR $n \times 10^{-2} - n \times 10^{-7}$, $S = 59 - 62$, DL up to 1.0×10^{-7}, pH 4.0–11.0	184, 185
Tetracycline		PM (NPOE or EHS) based on a mixture of PVC and ethylene–vinyl acetate co-polymer with addition of $K[B(C_6H_4Cl\text{-}4)_4]$	LR $1.0 \times 10^{-2} - 1.2 \times 10^{-4}$, $S = 57.4$, pH 2.0–3.8	223

Table 3 (continued).

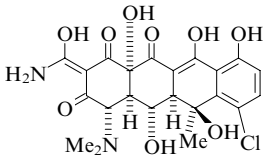
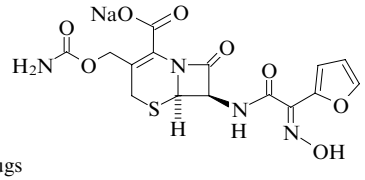
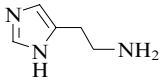
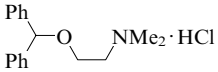
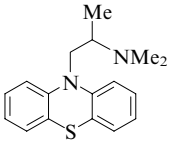
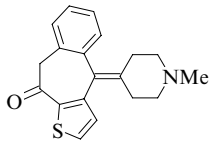
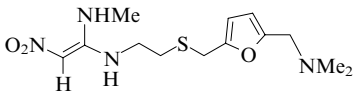
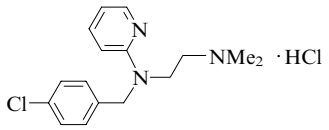
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Antibiotics				
Chlortetracycline		PPVCM based on IA of MD cations with $[PMo_{12}O_{40}]^{3-}$ and $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-1.0\times10^{-6}$, $S = 60-67$, pH 5.5–11.5	252
Cefuroxime		PPVCM (NPOE or EHS) (including those for FIA) with IA of MD anions with $[(n\text{-}C_8H_{17})_4N]^+$ and bis(triphenylphosphoranylidene)ammonium cations and addition of *p*-(*tert*-octyl)phenol	DL = 1.3×10^{-4}, $S = 50-55$, pH 3.5 ($H_3PO_4-NaH_2PO_4$ buffer)	273
Antihistamine drugs				
Histamine		PPVCM with *O*-(2,4-dichlorophenyl) *O*-ethyl *S*-propyl dithiophosphate and $Na[B(C_{14}H_9O_2F_{12})_4]$	LR $1.0\times10^{-2}-5.0\times10^{-5}$, DL = 2.0×10^{-5}, $S = 56$	102
		PPVCM (NPOE) with derivatives of calix[*n*]arenes ($n = 6, 8$) and $K[B(C_6H_4Cl\text{-}4)_4]$	–	73
Diphenhydramine hydrochloride		PPVCM based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$, BPh_4^- and $[Cr(NH_3)_2(NCS)_4]^-$	LR $n\times10^{-2}-3.5\times10^{-5}$, $S = 57.5$, pH 2.0–7.5	253
		SC-ISE with PPVCM (DOP) based on IA of MD with $H_3[PMo_{12}O_{40}]$ and $H_4[SiW_{12}O_{40}]$ and poly(α-naphthylamine) as the transducer	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL = 3.0×10^{-6}, $S = 57.5$, pH 2–6	232
Promethazine		PPVCM (DOP) based on IA of MD cations with organic and inorganic anions	LR $3.2\times10^{-2}-1.0\times10^{-5}$, DL = 3.5×10^{-6}, $S = 41-55$, pH 2.5–6.0	172
		PPVCM (NPOE or EHS) (including those for FIA) with IA of MD cations with BPh_4^-	LR $1.0\times10^{-2}-5.0\times10^{-5}$, DL = 2.0×10^{-5}, pH 6.0 (phosphate buffer)	207
Ketotifen		PPVCM based of IA of MD cations with $[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]^-$	–	227
Ranitidine		Ag/AgCl SC-ISE with PPVCM (DNP) and IA of MD cations and BPh_4^-	LR $1.0\times10^{-1}-5.0\times10^{-4}$, DL = 2.8×10^{-4}, $S = 59.7$, pH 8.2 (phosphate buffer)	192
Chloropyramine		PPVCM based on IA of MD cations with anions $[B(C_6H_4Cl\text{-}4)_4]^-$, $[Cr(NH_3)_2(NCS)_4]^-$, $[PW_{12}O_{40}]^{3-}$, $[PMo_{12}O_{40}]^{3-}$ and $[SiMo_{12}O_{40}]^{4-}$	LR $1.0\times10^{-2}-2.3\times10^{-5}$, DL = 1.1×10^{-5}, $S = 48-55$, pH 2.6–5.5	225, 246

Table 3 (continued).

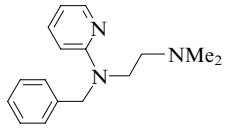
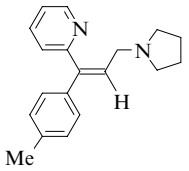
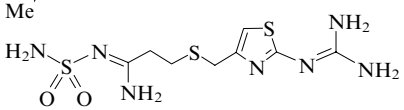
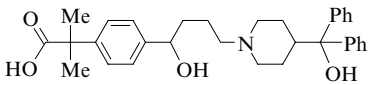
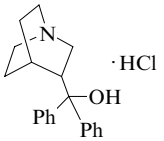
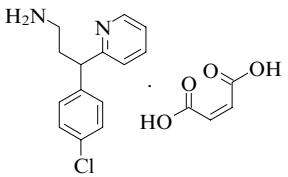
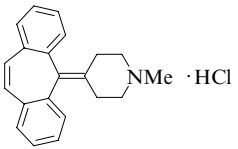
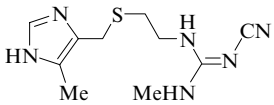
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Antihistamine drugs				
Tripelenamine		tubular and conventional ISE with PPVCM and IA of MD cations with BPh_4^-	LR $1.0\times10^{-1}-4.0\times10^{-5}$	182
Triprolidine		membrane ISE, carbon-paste and graphite-supported electrodes; PPVCM (DBP) and IA of MD cations with BPh_4^-	LR $1.0\times10^{-2}-2.0\times10^{-5}$, S = 54–56, pH 4.7–8.8	196
Famotidine		PPVCM based on IA of MD cations with BPh_4^-	LR $1.0\times10^{-3}-1.0\times10^{-5}$, pH 1.0–5.0	178
Fexofenadine		PPVCM, IA of MD cations with BPh_4^-, HgI_4^{2-} and $[Cr(NH_3)_2(NCS)_4]^-$	LR $1.0\times10^{-2}-2.5\times10^{-6}$, DL = 1.3×10^{-6}, S = 62, pH 2.0–4.5	197
Quifenadine		PPVCM based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$, $[PMo_{12}O_{40}]^{3-}$ and $[SiMo_{12}O_{40}]^{4-}$	LR $1.0\times10^{-2}-5.4\times10^{-5}$, DL = 3.6×10^{-5}, S = 43–50, pH 2.8–5.0	219
Chlorpheniramine maleate		ion-selective piezoelectric sensors with PVC membranes based on IA of MD cations with dipicrylamine, BiI_4^- and BPh_4^-	LR $1.0\times10^{-3}-1.0\times10^{-8}$, DL = 6.0×10^{-9}	183
		AgCl/Ag SC-ISE with membranes based on carbamide-formaldehyde resin with dispersed KCl and IA of MD cations with BPh_4^-	–	209
Cyproheptadine		PPVCM and IA of MD cations with $[B(C_6H_4Cl\text{-}4)_4]^-$ and dipicrylamine anions	LR $n\times10^{-2}-n\times10^{-7}$, pH 2.5–7.0	222
Cimetidine		PPVCM based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL = 5.0×10^{-6}, S = 58, pH 3.0–5.5	247

Table 3 (continued).

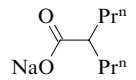
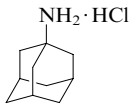
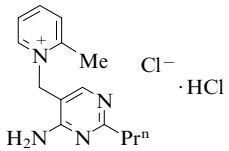
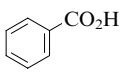
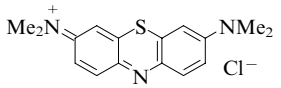
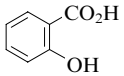
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Anticonvulsants				
Sodium valproate		PPVCM based on a Ga(III) complex with tetraphenylporphirine and bis(1-butylpentyl)decane-1,10-diyldiglutarate (ETH 469)	LR $1.0\times10^{-2}-5.0\times10^{-5}$, DL $= 2.0\times10^{-5}$, $S = 55$, pH 5.5 (buffer)	64
Antiseptics and viricides				
Amantadine		PPVCM (DOP) based on IA of MD cations with BPh_4^- and $[Cr(NH_3)_2(NCS)_4]^-$	–	173
Amprolium		PPVCM (DOP) based on IA of MD cations with BPh_4^- and $[Cr(NH_3)_2(NCS)_4]^-$	LR $1.0\times10^{-1}-1.0\times10^{-5}$, pH 7.0 – 11.0	216
Benzoic acid		PPVCM with a macrocyclic polyamine and a lipophilic additive	LR $1.0\times10^{-2}-1.0\times10^{-4}$, DL $= 1.0\times10^{-4}$, pH 5.0	58
		PPVCM based on heptyl 4-(trifluoroacetyl)benzoate	LR $5.0\times10^{-2}-2.0\times10^{-4}$, DL $= 1.0\times10^{-4}$	308
Methylene Blue		PM (DBP) with trioctyloxybenzenesulfonic acid as an ion exchanger	LR $1\times10^{-4}-1.0\times10^{-6}$, DL $= 6.2\times10^{-7}$, $S = 53.3\pm0.5$, pH 4.0 – 11.0	293
Salicylic acid		ISE based on complexes of Co(II) with bis(salicylaldehyde)diaminodipropylamine or Co(III) with Schiff bases as the carriers	LR $1.0\times10^{-1}-n\times10^{-6}$, DL up to 8.0×10^{-7}, $S = 66.8$, pH 4.0 or 5.5	96, 309
		PPVCM based on IA of 3-(4-tolylazo)phenylboronic acid with tetrahexylethylenediamine	LR $1.0\times10^{-1}-5.0\times10^{-5}$, DL $= 1.5\times10^{-5}$, $S = 54\pm1$	94
		PM based on Sn(IV) complexes with 8-hydroxyquinoline and tetra(*tert*-butyl)phthalocyanine	–	85
		PPVCM with μ-oxobis[5-(4-hydroxyphenyl)-10,15,20-triphenylporphyrinato]-manganese(III)] as the ionophore	LR $1.0\times10^{-1}-6.3\times10^{-7}$, $S = 57\pm3.5$, pH 6.0 (phosphate buffer)	63
		PPVCM with tribenzyltin phenolates or carboxylates as ionophores	LR $1.0\times10^{-1}-n\times10^{-6}$, DL up to 1.0×10^{-6}, $S = 57$, pH = 5.5 (phosphate buffer)	92, 93
		PPVCM (NPOE) with a guanidinium ionophore	LR $1.0\times10^{-1}-1.0\times10^{-3}$, DL $= 1.3\times10^{-4}$, pH 6.0	104
		PPVCM with different metallocenes as ionophores	LR $1.0\times10^{-1}-1.0\times10^{-3}$, $S = 58$, pH 5.5; 7.4	91
		PPVCM (dinonyl sebacate) with [2,9,16,23-tetra(*tert*-butyl)phthalocyaninato]tin(IV) and addition of $KBPh_4$	LR $1.0\times10^{-1}-1.0\times10^{-5}$, DL $= 6.3\times10^{-6}$, pH 5.5	86
		PPVCM with heptyl 4-(trifluoroacetyl)benzoate as the ionophore and addition of tri(dodecyl)methylammonium chloride	LR $1.0\times10^{-2}-2.0\times10^{-4}$, DL $= 4.0\times10^{-5}$, $S = 55$, pH 7.4	103
		PPVCM (DBP) with a neutral carrier	LR $1.0\times10^{-1}-2.5\times10^{-6}$, DL $= 1.0\times10^{-6}$, $S = 57\pm2$, pH 5.0	105
		SCE (graphite substrate), PPVCM containing Al(III) and Sn(IV) complexes with Salophen as ionophores with addition of $NaBPh_4$	LR $1.0\times10^{-1}-1.0\times10^{-6}$, DL $\sim 1.0\times10^{-6}$, $S = 57-59$, pH 3.0 – 8.0	106

Table 3 (continued).

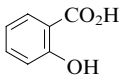
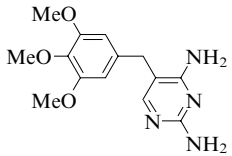
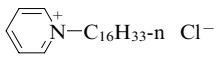
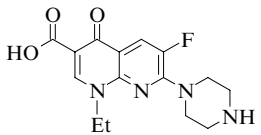
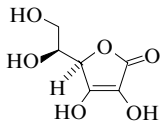
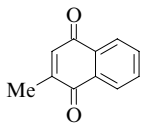
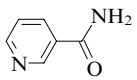
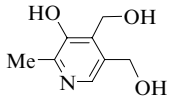
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Antiseptics and viricides				
Salicylic acid		PPVCM with chloro(tetraphenylporphyrinato)chromium(III)	LR $n\times10^{-1}-n\times10^{-6}$, pH 3.0–9.0	65
		PPVCM with oxo(phthalocyaninato)vanadium(IV) and -molybdenum(IV) as ionophores	LR $n\times10^{-1}-n\times10^{-7}$, pH 6.0–9.0	87
		SCE (graphite substrate), PPVCM with aluminium phthalocyaninate	LR $1.0\times10^{-1}-5.0\times10^{-6}$, $S=59\pm1$	90
Trimethoprim		PPVCM with IA of MD cations with $[PMo_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-2.3\times10^{-6}$, $S=56.5$, pH 1.6–6.2	237
		ion-selective piezoelectric sensor with PPVCM (DBP) based on IA of MD cations with $[PW_{12}O_{40}]^{3-}$	LR $2.0\times10^{-3}-2.0\times10^{-8}$, DL $=2.0\times10^{-8}$, pH 4.0	254
		PPVCM (DOP) with IA of MD cations with BPh_4^-, $[Cr(NH_3)_2(NCS)_4]^-$ or $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-n\times10^{-6}$, DL $=n\times10^{-6}$, $S=57-59$, pH 1.8–6.3	201, 256
Cetylpyridinium chloride		PPVCM (DOP) with IA of cetylpyridinium with iron(III) thiocyanate	LR $1.0\times10^{-3}-1.0\times10^{-6}$, DL $=8.0\times10^{-7}$, $S=57.5\pm0.4$, pH 1.0–6.0	294
		PPVCM (DOP) with IA of MD cations with HgI_4^{2-}	LR $1.0\times10^{-3}-2.0\times10^{-6}$, DL $=4.0\times10^{-7}$, $S=29.0\pm0.4$, pH 3.0–6.0	291
Enoxacin		PPVCM with IA of MD cations with BPh_4^- and an internal pin Ag/AgCl reference electrode	LR $1.0\times10^{-2}-7.9\times10^{-5}$, DL $=2.0\times10^{-5}$, $S=30.4$	176
Vitamins and their analogues				
Ascorbic acid		SC-ISE based on a PVC matrix modified with ionophores. A polymeric ISFT film based on MnO_2 nanoparticles immobilised on the transducer surface is fixed between the electrode and the PVC membrane	LR $5.0\times10^{-3}-5.0\times10^{-6}$, DL $=2.0\times10^{-6}$	310
			LR $1.3\times10^{-3}-2.0\times10^{-5}$, DL $=1.0\times10^{-5}$	167
		ISE with liquid membrane based on 2-nitrotoluene with dissolved IA of triphenyltetrazolium with $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-2.0\times10^{-4}$, $S=56-58$, pH 3.0–12.0	100
Menadione		PPVCM (NPOE) with IA of MD anions with complex cations of nickel(II) or iron(II) with batophenanthroline	LR $1.0\times10^{-1}-n\times10^{-5}$, DL $=2.0\times10^{-5}$, $S=51-58$, pH 1.0–5.0	270
Nicotinamide		ion-selective piezoelectric sensor with PVC membrane based on IA of MD cations with $[SiW_{12}O_{40}]^{4-}$	LR $1.0\times10^{-3}-1.0\times10^{-9}$, pH 7.0	264
Pyridoxine		PPVCM (NPOE) with IA of MD cations with $[PMo_{12}O_{40}]^{3-}$ or $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-6.0\times10^{-5}$, DL $=4.0\times10^{-5}$, $S=54$, pH 2–4	233, 234

Table 3 (continued).

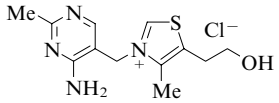
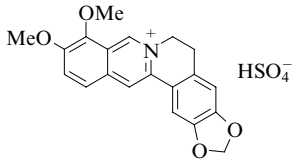
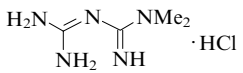
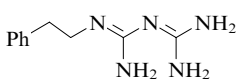
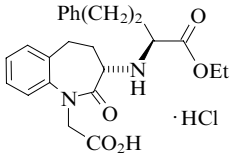
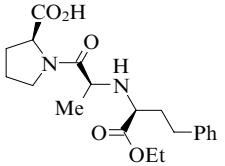
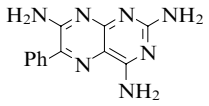
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Vitamins and their analogues				
Thiamine chloride		electrode represents a graphite disk covered with successive layers of conductive epoxy resin and ionophore-containing PVC membrane	LR $1.0\times10^{-1}-1.0\times10^{-6}$	311
Choline chloride	$Me_3\overset{+}{N}CH_2CH_2OH\ Cl^-$	PPVCM (NPOE) with lipophilic β-CD derivatives and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	DL up to 4.0×10^{-7}, $S = 61$, pH 7.0	80–82
Hepatotropic drugs				
Berberine bisulfate		PPVCM (different esters) based on porphyrins	LR $5.0\times10^{-3}-n\times10^{-7}$, $S = 60-66$, pH 3.7–11.2	61, 62
Hypoglycemic drugs				
Metformin		PPVCM with IA of MD cations with $[PMo_{12}O_{40}]^{3-}$ or $[PW_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-n\times10^{-5}$, $S = 58$, pH 3.0–11.0	236, 251
		PPVCM (DOP, NPOE or DBS) with IA of MD cations with $[Cr(NH_3)_2(NCS)_4]^-$ and $[SiW_{12}O_{40}]^{4-}$	LR $n\times10^{-1}-n\times10^{-5}$, pH 5.0–11.0	266
		PPVCM (NPOE) with lipophilic β-CD derivative and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	DL $= n\times10^{-6}$, $S = 56-61$	80, 81
Phenformin		the same	the same	80, 81
Hypotensive drugs				
Benazepril hydrochloride (Amlodipine)		'coated wire' electrode with PVC membrane based on benazepril–BPh_4^- associate	LR $5.8\times10^{-3}-1.3\times10^{-5}$, pH 2.5–9.2	217
Sodium nitroprusside	$Na_2[Fe(CN)_5NO]$	PPVCM with IA of MD anions with cetylpyridinium	LR $1.0\times10^{-2}-3.0\times10^{-5}$, DL $= 2.0\times10^{-5}$, $S = 27\pm1$, pH 2.0–10.0	281
Enalapril		ISE based on graphite paste (a mixture of graphite powder with kerosene) impregnated with a solution of 2-hydroxy-3-trimethylammoniopropyl-β-CD chloride	LR $6.4\times10^{-2}-3.6\times10^{-5}$, DL $= 1.0\times10^{-5}$, $S = 55\pm0.3$, pH 3.0–6.0	77
Diuretics				
Triamterene		'coated wire' electrode with PVC membrane and IA of MD cations with BPh_4^-	LR $3.5\times10^{-2}-1.0\times10^{-6}$, pH 4.5–7.5	179

Table 3 (continued).

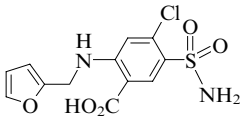
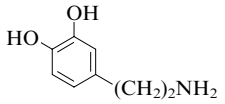
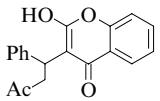
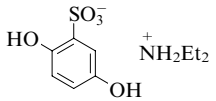
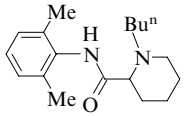
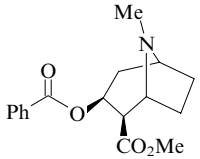
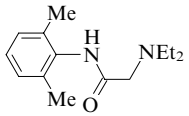
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Diuretics				
Furosemide		PPVCM (DBP or DOPP) with IA of MD anions with trioctylmethylammonium	LR $1.0\times10^{-2}-1.6\times10^{-4}$, DL $= 1.2\times10^{-4}$, $S = 58.9$, pH 7 – 10	277
Dopaminergic drugs				
Dopamine		Graphite-based SC-sensor with a membrane of carboxylated PVC with addition of β-CD, $K[B(C_6H_4Cl\text{-}4)_4]$ and 2-nitro-2′-fluorodiphenyl ether	LR $1.0\times10^{-1}-5.0\times10^{-5}$, DL $= 3.0\times10^{-6}$, $S = 59$, pH 2.0 – 7.5	76
		electrode for FIA, PPVCM (NPOE) with bis(triphenylphosphoranylidene)-ammonium periodate	LR $2.7\times10^{-1}-8.0\times10^{-3}$ g litre^{-1}, $S = 310.1\pm7.4$	283
		PPVCM (NPOE) with devivatives of calix[*n*]arenes ($n = 6$, 8) and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	–	73
Coagulants and anticoagulants				
Warfarin		PPVCM with IA of MD anions and complex cations of Ni(II) and Fe(II) with phenanthroline	LR $n\times10^{-1}-n\times10^{-5}$, DL $= 0.8-5.3$ μg ml^{-1}, $S = 51-60$	268, 271
Etamsylate (Dicinone)		the same	the same	268, 271
Local anesthetics				
Bupivacaine		PVC or polyuretane membranes (NPOE) with lipophilic derivatives of β-CD and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	LR $1.0\times10^{-2}-1.0\times10^{-4}$, DL $= 1.3\times10^{-5}$, $S = 54-62$, pH 6.84	79
Cocaine		PPVCM [tetrakis(2-ethylhexyl) pyromellitate] with IA of MD cations with $[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]^-$	LR $1.0\times10^{-2}-1.0\times10^{-6}$, DL $= 4.0\times10^{-7}$, $S = 56$, pH 1.0 – 8.0	192
Lidocaine		PPVCM (NPOE or DOS) modified with 2,6-disdodecyl-β-CD and $K[B(C_6H_4Cl\text{-}4)_4]$ (for FIA)	LR $1.0\times10^{-1}-n\times10^{-5}$, DL $= 1.6\times10^{-5}$, $S = 55$	224
		PVC or polyuretane membranes (NPOE) with lipophilic derivatives of β-CD and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	LR $1.0\times10^{-1}-1.0\times10^{-3}$, DL up to 1.5×10^{-4}, $S = 61-67$, pH 6.84	79
		PPVCM based in IA of MD cations with $[Co(SCN)_4]^{2-}$, $[PMo_{12}O_{40}]^{3-}$ and $[Cr(NH_3)_2(NCS)_4]^-$	LR $1.0\times10^{-1}-1.0\times10^{-5}$, pH 3.0 – 7.0	242

Table 3 (continued).

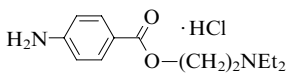
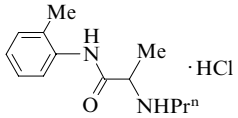
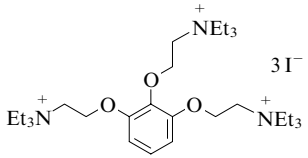
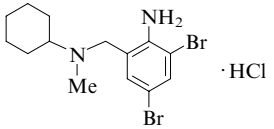
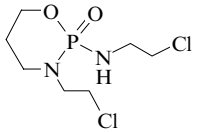
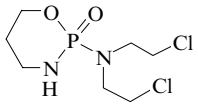
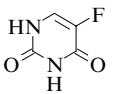
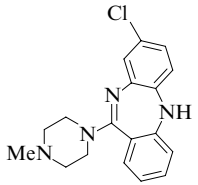
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Local anesthetics				
Procaine		piezoelectric sensor with selective PVC membrane based on IA of MD cations with BPh_4^-	LR $5.0\times10^{-3}-8.3\times10^{-8}$, DL $= 8.3\times10^{-8}$, pH 5.0	203
		PPVCM (NPOE) with lipophilic derivatives of β-CD and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	DL up to 1.0×10^{-5}, $S = 61$, pH 6.84	79
Prilocaine		the same	the same	79
Muscle relaxants				
Gallamine		carbon-paste electrode impregnated with IA gallamine – BPh_4^-	LR $1.0\times10^{-3}-2.0\times10^{-6}$, DL $= 1.0\times10^{-6}$, $S = 17.0\pm0.7$, pH 5.0–8.0	219
Mucolytic drugs				
Bromhexine		PPVCM (DOP) with IA of MD cations with BPh_4^-	LR $1.0\times10^{-1}-4.0\times10^{-4}$, $S = 57.5$	218
Antitumour drugs				
Iphosphamide		PPVCM (DOP) or a membrane based on carboxylated PVC (NPOE) with IA of MD cations with BPh_4^-	LR $n\times10^{-2}-n\times10^{-5}$, $S = 50-55$, pH 4–7	174
Cyclophosphan		the same	the same	174
Fluorouracil		PPVCM (DOP) based on IA of 5-fluorouracil with Ni(II) and Fe(II) complexes with batophenanthroline and Fe(II) complexes with phenanthroline	LR $1.0\times10^{-3}-1.0\times10^{-5}$, DL $= 1.0\times10^{-5}$, $S = 28-34$, pH 5–9	267
Psychotropic drugs				
Azaleptine		PPVCM (DOP or TTP) with IA of azaleptine cations with BPh_4^- or $[PMo_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL $= 2.8\times10^{-6}$, $S = 45-54$, pH 4.0–7.0	230

Table 3 (continued).

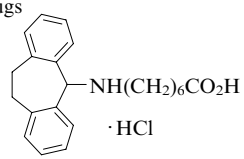
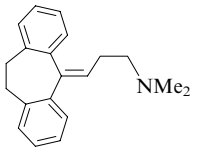
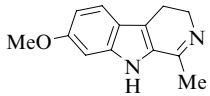
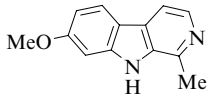
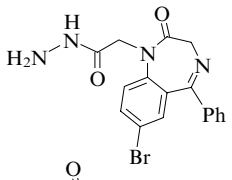
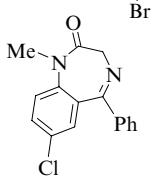
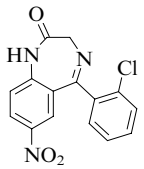
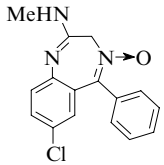
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Psychotropic drugs				
Amineptine		PPVCM (DOP or TTP) with IA of azaleptine cations with BPh_4^- or $[PMo_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-3.2\times10^{-6}$, $S = 54-58$, pH 2.0–3.9	165
Amitriptyline		PPVCM with IA clonidine–BPh_4^- against 10^{-3} M solution of NaCl and 10^{-3} M solution of clonidine	LR $1.0\times10^{-3}-1.0\times10^{-8}$, DL $= 5\times10^{-9}$, $S = 58.4$	166
Garmaline		sensors for FIA with PPVCM based on IA of MD cations with BPh_4^- and $[Cr(NH_3)_2(NCS)_4]^-$	LR $10^{-2}-10^{-6}$, DL up to 2 μg ml^{-1}, pH 3.0–8.0	210
Garmine		the same	the same	210
Hydazepam		PPVCM (DBP) with IA of MD cations with heteropolyanions and $[B(C_6H_4Cl\text{-}4)_4]^-$ and addition of a lipophilic compound	LR $n\times10^{-3}-n\times10^{-5}$, DL up to 4.8×10^{-6}, $S = 50-57$, pH 2.5–5.3	170
Diazepam (Relanium)		the same PPVCM (NPOE) based on IA of MD cations with BPh_4^- and $[PW_{12}O_{40}]^{3-}$	the same LR 31.57–0.29 mg ml^{-1}, DL up to 0.7 mg ml^{-1}, $S = 50-65$, pH 4.0–7.0	170 171, 208
Clonazepam		the same PPVCM (DBP) with IA of MD cations with hereropolyanions and $[B(C_6H_4Cl\text{-}4)_4]^-$ and addition of a lipophilic compound	the same LR $n\times10^{-3}-n\times10^{-6}$, DL up to 6.6×10^{-7}, $S = 48-60$, pH 2.5–5.3	171, 208 170
Chlordiazepoxide (Elenium)		the same SC-ISE (DOP) with ion-selective transducer [poly(*o*-aminophenol)] and IA of MD cations with $[PW_{12}O_{40}]^{3-}$ SC-ISE (DBP) with IA of MD cations with $[PMo_{12}O_{40}]^{3-}$ and $[PW_{12}O_{40}]^{3-}$	the same DL $= 6.7\times10^{-6}$, $S = 55.6$, pH 2.4–6.3 LR $1.0\times10^{-2}-3.2\times10^{-6}$, $S = 59-61$, pH 2.0–4.5	170 259 244

Table 3 (continued).

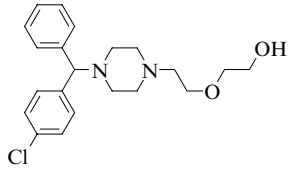
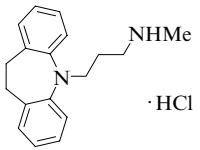
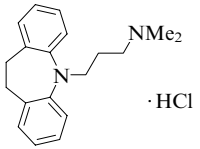
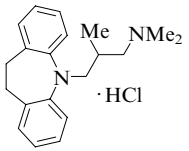
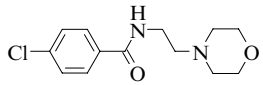
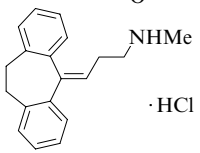
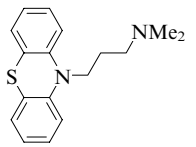
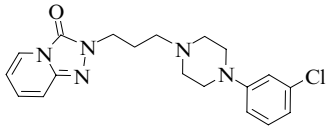
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Psychotropic drugs				
Hydroxyzine		PPVCM (NPOE) with IA of MD cations with $[SiW_{12}O_{40}]^{4-}$	LR $1.0\times10^{-2}-6.0\times10^{-7}$, DL $= 2.5\times10^{-7}$, $S = 57$, pH 2.8–6.9	263
Desipramine		PPVCM (NPOE) with alkylated CD and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	DL up to 2.5×10^{-6}, $S = 56-62$, pH 7.0	78
Imipramine		the same	the same	78
Trimipramine		the same	the same	78
Moclobemide		PPVCM with IA of MD cations with dodecyl sulfate	LR $10^{-2}-10^{-5}$, DL $= 1.1\times10^{-10}$, pH 2.0–6.5	289
Nortriptyline		PPVCM (DOP) with IA of MD cations with BPh_4^- and $[B(C_6H_4Cl\text{-}4)_4]^-$	LR $n\times10^{-2}-n\times10^{-5}$, DL $= (8.0-9.0)\times10^{-5}$, $S = 52-54$, pH 6.0–7.0	191
Promazine		ISE with liquid membrane based on IA of MD cations with CdI_4^{2-} in n-octanol	LR $1.0\times10^{-3}-5.0\times10^{-6}$, $S = 61$, pH 4.0–7.0	292
		PPVCM (EHS) with IA of MD cations with BPh_4^-	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL $= 1.0\times10^{-5}$, $S = 58.0\pm1.5$, pH 2.0–6.0	205
Trazodone		'coated wire' electrode (Cu) based on PPVCM (DOP) with IA trazodone–BPh_4^-	LR $8.9\times10^{-3}-1.4\times10^{-5}$, DL $= 1.0\times10^{-5}$, $S = 59$, pH 2.4–9.0	193

Table 3 (continued).

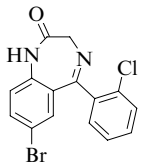
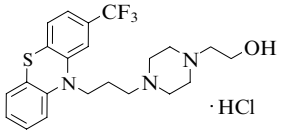
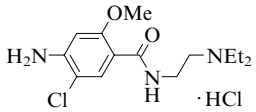
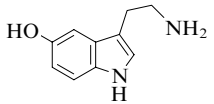
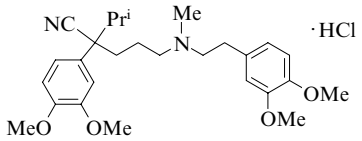
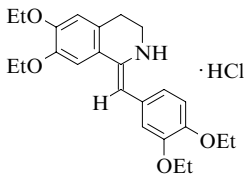
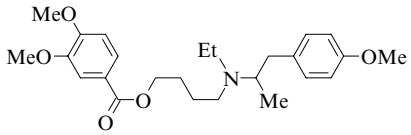
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Psychotropic drugs				
Phenazepam		PPVCM (DBP or DOP) with IA of MD cations with $[PMo_{12}O_{40}]^{3-}$, $[PW_{12}O_{40}]^{3-}$ and $[SiMo_{12}O_{40}]^{4-}$	LR $1.0\times10^{-2}-1.0\times10^{-5}$, $S = 43-54$, pH 1.0–3.0	239
Fluphenazine		PPVCM (DOP) with IA of MD cations with BPh_4^- and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	LR $n\times10^{-3}-n\times10^{-5}$, DL $= (4.5-5.5)\times10^{-5}$, $S = 59$, pH 6–7	191
Antiemetic drugs				
Metoclo-pramide		PPVCM (DOP) based on IA of MD cations with HgI_4^{2-} or $[PW_{12}O_{40}]^{3-}$	LR $1\times10^{-2}-6.0\times10^{-5}$, DL $= 4.0\times10^{-5}$, $S = 53\pm0.5$, pH 3.0–7.0	258, 290
Serotonergic drugs				
Serotonin		PPVCM (NPOE) with derivatives of calix[*n*]arenes ($n = 6, 8$) and addition of $K[B(C_6H_4Cl\text{-}4)_4]$	–	73
Spasmolytics				
Verapamil		microsensor based carboxylated PVC and Nafion on a graphite substrate	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL $= 4.1\times10^{-6}$, $S = 56-57$, pH 2.0–8.0	297
Drotaverine (No Spa)		PPVCM based on IA of MD cations with derivatives of tetraphenylborate and organic and inorganic anions	LR $5.0\times10^{-2}-n\times10^{-7}$, DL up to 1×10^{-7}, $S = 51-61$, pH 1.8–7.0	32, 37
		carbon-paste electrode for FIA with PPVCM (esters of phthalic acid and TTP) containing IA of MD cations with $[SiW_{12}O_{40}]^{4-}$ and BPh_4^-	LR $1.0\times10^{-2}-5.0\times10^{-7}$, DL $= 5.0\times10^{-7}$, $S = 59\pm2$, pH 2.5–7.0	202
Mebeverine		SC-ISE (for FIA) and ISE with PM (DBP) based on IA of MD cations with heteropolyanions	LR $1.0\times10^{-2}-4.0\times10^{-6}$, DL $= 3.1\times10^{-6}$, $S = 55-59$, pH 1.0–7.2	36

Table 3 (continued).

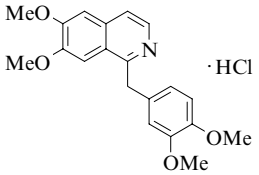
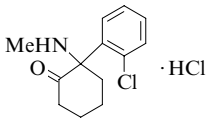
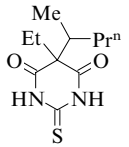
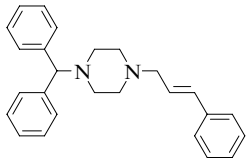
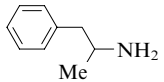
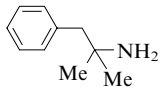
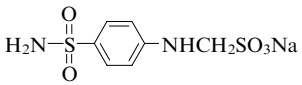
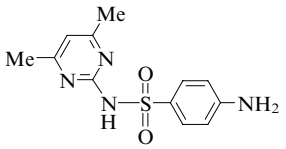
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Spasmolytics				
Papaverine		ISE with liquid membrane (chlorobenzene) based on IA of MD cations with BPh_4^-	LR $5.0\times10^{-2}-1.0\times10^{-5}$, $S = 62.6$, pH 3.5–5.5	181
		PPVCM based on IA of MD cations with organic and inorganic anions	LR $5.0\times10^{-2}-1.0\times10^{-5}$, DL $= 3.7\times10^{-6}$, $S = 42-56$, pH 2.0–6.0	34
Anaesthetics				
Ketamine hydrochloride		membrane with active ion-exchange sites synthesised by polymerisation directly in the plasticiser medium (NPOE)	LR $1.0\times10^{-2}-1.0\times10^{-5}$, DL $= 1.0\times10^{-6}$, $S = 59$, pH 4.0–8.5	35
Thiopental		graphite SC sensor with polyurethane membrane based on IA of thiopental with complexes of Co(II) and Cu(II) with batophenanthroline	LR $1.0\times10^{-1}-5.0\times10^{-5}$, DL $= 5.0\times10^{-6}$, $S = 28$, pH 6–11	269
Drugs for improving blood circulation of internal organs and tissues				
Cinnarizine		PPVCM (DOP) with IA of MD cations with BPh_4^-, flavianate, $[Cr(NH_3)_2(NCS)_4]^-$ and $[PMo_{12}O_{40}]^{3-}$	LR $n\times10^{-2}-n\times10^{-6}$, DL $= (1.1-8.1)\times10^{-6}$, $S = 27.1-38.2$, pH 2.0–3.3	198
Stimulators of central nervous system				
Amphetamine		PPVCM (EHS) based on neutral carriers	LR $1.0\times10^{-2}-2.0\times10^{-6}$, DL $= 7.0\times10^{-7}$, $S = 53-55$, pH 5.0	68
		PPVCM with an *N*,*N*-dioctadecyl-*N*′,*N*′-dipropyl-3,6-dioxaoctanediamide ionophore and addition of $Na[B(C_{14}H_9O_2F_{12})_4]$	LR $1.0\times10^{-2}-2.0\times10^{-6}$, DL $= 1.0\times10^{-6}$, $S = 59$, pH 5.0	69
Phentermine		PPVCM (EHS) based on dibenzo-18-crown-6 and other ionophores with addition of $K[B(C_6H_4Cl\text{-}4)_4]$	LR $1.0\times10^{-2}-2.0\times10^{-6}$, DL $= 7.0\times10^{-7}$, $S = 53-55$, pH 5.0 (acetic acid–magnesium acetate buffer)	68
Sulfonamides				
Streptocidum solubile		PPVCM with IA of MD anions with different QAB cations	LR $1.0\times10^{-1}-1.0\times10^{-5}$, DL up to 7.4×10^{-6}, $S = 42-57$, pH 7.0–11.0	29, 275, 276
Sulfamethazine		the same	the same	29, 275, 276

Table 3 (continued).

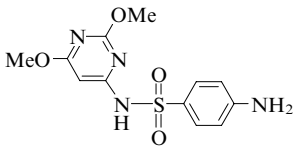
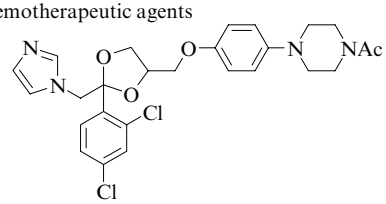
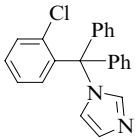
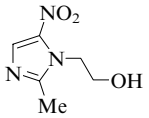
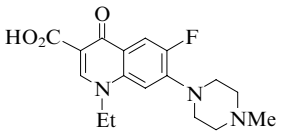
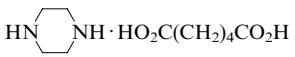
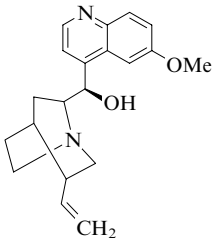
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Sulfonamides				
Sulfadimethoxine		PPVCM with IA of MD cations with different QAB cations	LR $1.0\times10^{-1}-1.0\times10^{-5}$, DL up to 7.4×10^{-6}, $S = 42-57$, pH 7.0–11.0	29, 275, 276
Miscellaneous chemotherapeutic agents				
Ketoconazole		PPVCM (NPOE) based on IA of MD cations with BPh_4^- or $[PMo_{12}O_{40}]^{3-}$	LR $6.3\times10^{-3}-7.1\times10^{-6}$, DL $= 5.0\times10^{-6}$, $S = 72\pm2$, pH 3.0–5.0	180
Clotrimazole		the same	LR $1.0\times10^{-3}-1.4\times10^{-5}$, DL $= 1.0\times10^{-5}$, $S = 59\pm2$, pH 1.5–2.5	189
Metronidazole		PVC membrane with Mn(III) complex with 5,10,15,20-tetrakis[2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)phenyl]porphyrin and with addition of graphite powder and epoxy resin	LR $2.9\times10^{-3}-5.8\times10^{-8}$, DL $= 5.8\times10^{-8}$, $S = 25-28$, pH 4.3	312
Perfloxacin		PPVCM with IA of MD cations with BPh_4^-	LR $1.0\times10^{-2}-5.0\times10^{-5}$, $S = 23$	200
Piperazine adipinate		PPVCM (DOP) based on IA of MD cations with heteropolyanions	LR $1.0\times10^{-1}-1.0\times10^{-4}$, DL $= 3.2\times10^{-5}$, $S = 35$, pH 3–8	240
Quinine		PPVCM based on lipophilic derivatives of tetraphenylborate	LR $1.0\times10^{-2}-6.3\times10^{-6}$, DL $= 2.5\times10^{-6}$, $S = 52-59$, pH 4.4–8.0	312

Table 3 (continued).

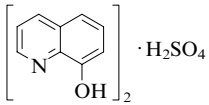
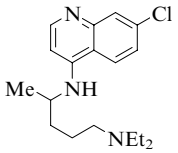
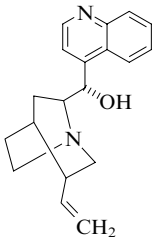
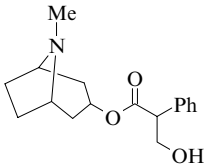
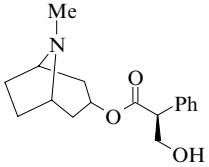
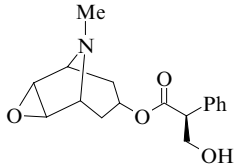
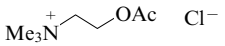
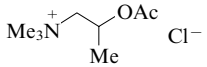
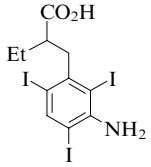
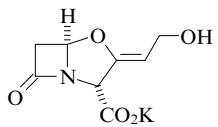
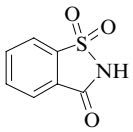
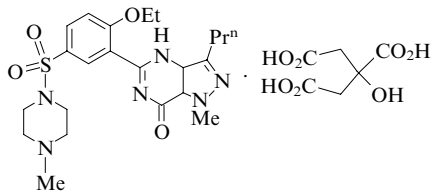
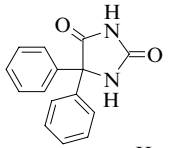
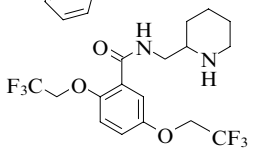
Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Miscellaneous chemotherapeutic agents				
Oxine		SC-ISE (graphite substrate) with PPVCM (DOP) and IA of MD cations with BPh_4^-	LR $1.0\times10^{-1}-1.0\times10^{-6}$, DL $= 4.0\times10^{-7}$, $S = 59.0\pm0.5$, pH 1.8–4.7	190
Chloroquine (Lariam)		PPVCM with IA of MD cations with $[B(C_6H_4Cl\text{-}4)_4]^-$ (ISE for FIA)	DL up to 5.0×10^{-7}, $S = 28-32$	226
Cinchonine		IA cinchonine–picrolonate in an electropolymerised *o*-phenylenediamine film on the gold electrode surface	LR $1.3\times10^{-5}-2.5\times10^{-7}$, DL $= 1.0\times10^{-7}$, pH 7.0	288
Anticholinergic drugs				
Atropine		ion-selective piezoelectric microquartz sensor based on PVC membrane with IA atropine–BPh_4^- and atropine–dipicrylamine anion	LR $1.0\times10^{-3}-1.0\times10^{-8}$, DL $= 5.0\times10^{-9}$, pH 3.0–8.0	168
Hyoscyamine		ISE and FIA sensors with PPVCM based on IA of MD cations with BPh_4^- and $[PW_{12}O_{40}]^{3-}$	LR $1.3\times10^{-2}-1.0\times10^{-5}$, DL $= 3.9\times10^{-6}$, $S = 56.5-57.8$, pH 3.0–10.0	255
Scopolamine		PPVCM with IA of MD cations with 5-nitrobarbiturate PPVCM with IA of MD cation with $[PMo_{12}O_{40}]^{3-}$	LR $1.0\times10^{-2}-1.0\times10^{-4}$ LR $1.0\times10^{-2}-1.0\times10^{-6}$, DL $= 8.0\times10^{-7}$, $S = 54.5\pm0.5$, pH 3.0–7.0	295 243
Acetylcholine chloride		PPVCM (NPOE) with lipophilic derivatives of β-CD and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	DL up to 2.0×10^{-7}, $S = 60-62$, pH 7.0	80–82

Table 3 (continued).

Medicinal drug	Formula	Membrane composition and electrode type [a]	Major electrode characteristics [b]	Ref.
Choline mimetic				
Methacholine		PPVCM (NPOE) with lipophilic derivatives of β-CD and addition of $Na[B\{C_6H_3(CF_3)_2\text{-}3,5\}_4]$	DL up to 2.0×10^{-7}, $S = 60-62$, pH 7.0	80–82
Miscellaneous drugs				
Iopanoic acid		IA of the acid anion with $[(n\text{-}C_8H_{17})N]^+$ in *p*-isopropylnitrobenzene	LR $5.0\times10^{-3}-5.0\times10^{-5}$, pH 12	274
Potassium clavulanate		PPVCM (NPOE) based on IA clavulanate–bis(triphenylphosphoranylidene)ammonium with addition of *p*-(*tert*-octyl)phenol	LR $1.0\times10^{-1}-2.4\times10^{-3}$, DL = 8.0×10^{-4}, $S = 59.4\pm0.9$, pH 4.8–7.1	282
Saccharin		tubular ISE for FIA, PVC membrane with IA of MD anions with organic dye cations	LR $2.0\times10^{-2}-1.0\times10^{-4}$, DL = 8.0×10^{-5}, $S = 53.1\pm0.4$, pH 2.5	313
		PPVCM (NPOE or DOP) with IA of Aliquat 336S cations with MD anions	LR $1.0\times10^{-1}-5.0\times10^{-5}$, DL = 3.0×10^{-5}, $S = 59-60$, pH 4.5–11.0	279
Sildenafil citrate (Viagra)		PM containing IA of MD cations with BPh_4^- and $[PMo_{12}O_{40}]^{3-}$	LR $n\times10^{-2}-n\times10^{-5}$, $S = 54-56$, pH 3.0–6.0	175
Phenytoin		surface acoustic wave selective PVC sensor	LR $8.0\times10^{-4}-6.7\times10^{-8}$, DL = 1.0×10^{-8}, pH 10.0	314
Flecainide		PPVCM based on IA of MD cations with dipicrylamine anions and dodecyl sulfate	LR $n\times10^{-2}-n\times10^{-5}$, DL = $(1-830)\times10^{-9}$, $S = 51-54$	285, 286

[a] PM and PPVCM stand for the plasticised membrane and the plasticised PVC membrane (plasticiser is shown in parentheses, see Table 2; DBPhos is dibutyl phosphate), FIA is flow-injection analysis, SC-ISE is solid-contact ISE, ISFT is ion-selective field transistor.

[b] LR is the linearity range of the electrode function (mol litre^{-1}); DL is the detection limit (mol litre^{-1}), S is the slope of the electrode function [mV (pC)$^{-1}$].

accuracy of MD determination in the flow mode was $98.6 \pm 2.5\%$. The electrode was also used in the determination of tetraphenylborate anions at pH from 2.5 to 11.5; the electrode function slope was 56.4 mV $(pC)^{-1}$, the detection limit was 3.8×10^{-6} mol litre^{-1}.

In the mercurimetric titration of barbiturates, a $Hg(ClO_4)_2$ solution was used as the titrant and an I^--ISE served as the indicator electrode.[300] The titration curve demonstrated two jumps, the first corresponding to the stoichiometric reaction of mercury(II) with the titrated MD and the second, to the titrant reaction with the borate buffer solution.

Redox titration was used in the flow-injection determination of ascorbic acid, where the latter was consumed in the reduction of IO_3^- ions to I^- (Ref. 301). An I^--ISE monitored the concentration of iodide ions. A specially developed computer-governed system of automatic control over the ascorbic acid content provided the automation of this procedure and the reduction of experimental errors. This method can be used in the acid concentration range from 7.5 to 15.0 mmol litre^{-1} ($S_r \sim 0.01$).

The method of artificial neural networks was used in the processing of results of potentiometric titration of mixtures of derivatives of hydroxycinnamic acid (*p*-coumaric and sinapic acids) and hydroxybenzoic acid (vanillic and isovanillic acids) with a solution of tetrabutylammonium hydroxide in propan-2-ol.[302] A four-layer recurrent neural network with back propagation of errors was used in the modelling of the nonlinear dependence between the analytical signal and the hydroxy acid concentration. To test the chosen model and train the neural network, the results of potentiometric titration of a series of standard solutions with different concentrations of the determined component were processed. The obtained results served as the basis for the formation of a random data sample, which was used in the training of the neural network. The changes in the signal elements were normalised in a range of 0.1 – 0.9 according to the equation

$$X_N = 0.1 + \frac{0.8(X - X_{\min})}{(X_{\max} - X_{\min})},$$

where X_N is the normalised signal (at the input and output of the network), X is the initial signal, $X_{\min}$ and $X_{\max}$ are the minimum and maximum signal values.

The optimisation of the network architecture involved choosing the number of layers (the input layer, one or two inner layers and the output layer) and the number of neurons in each layer. Two neurons were used in the input layer (the analytical signal and the titrant volume) as the variables independent from one another. Neurons in the inner layer were optimised for each concrete solution and their mixture, and the number of neurons was determined by the choice of the neural network (this is very important, because the correctness of the results of determination depends on the choice). The chosen network employed the algorithm of back propagation of errors, which allowed minimisation of the least-squares deviation of the current output of a multilayer perceptron from the desired output.

The developed procedure makes it possible to analyse four-component mixtures of *p*-coumaric, sinapic, vanillic and isovanillic acids with the total concentration of $n \times 10^{-3}$ mol litre^{-1} by the acid – base potentiometric titration with 0.02 M solution of tetrabutylammonium hydroxide in propan-2-ol with the relative error of less than 5%.[302]

Ion associates of MD with the corresponding counter-ions were used as the EAC in membrane ISE with liquid filling and solid-contact ISE. Table 3 shows the data on the composition of selective membranes and the basic electroanalytical characteristics of ISE for the MD determination.

* * *

In the past 10 years, different versions of ISE (membrane ISE with liquid filling, solid-contact and flow ISE), which can operate under conditions of flow-injection analysis, were developed for the determination of MD in patented medicinal drugs and biological fluids. The composition of selective membranes may include both the IA of MD cations and anions with lipophilic counter-ions and the neutral carriers. The latter allows one to enhance the ISE selectivity in the presence of lipophilic ions. The linearity range of the electrode function of ISE is usually in a range of $10^{-1} - 10^{-5}$ mol litre^{-1}.

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