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Potentiometric Sensors with Plastized Poly(Vinyl Chloride) Membranes Selective to Penicillin Antibiotics: Properties and Applications

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Abstract—Potentiometric sensors with plasticized poly(vinyl chloride) membranes based on β-lactam–tetraalkylammonium ion associates sensitive to penicillin antibiotics are proposed. The physicochemical characteristics (solubility product constants and dissociation constants) of active membrane components and the electrode, transport, and selective properties of the membranes of liquid- and solid-contact sensors have been studied. The quantitative characteristics of membrane transport (penetrability, ion flux, and transport rate) have been evaluated. The main charge carriers in the membranes and at the membrane/solution interface have been determined from the membrane transport characteristics. The potentiometric sensors are shown to be applicable to the determination of penicillin antibiotics in biological fluids (blood serum and oral fluid) from patients with urinary tract infection.

Keywords: plasticized poly(vinyl chloride) membranes, potentiometric sensors, penicillins, permeability, ion flux, drugs, biological fluids

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INTRODUCTION

At present, antibiotics occupy a key place in medicine and veterinary medicine in the treatment of different infectious inflammatory diseases and for antiinfective prophylaxis in surgery [1, 2].

Antibiotics are widely used for improving the quality and preservation of fodders and in the manufacture of products from meat, milk, vegetables, etc. [2]. The effluents of pharmaceutical enterprises and clinics are the sources of the release of antibiotics into the environment. In connection with this, the concentrations of antibiotics in drug products, the biological fluids of human and animal bodies, food products, pharmaceutical industry wastewater, and other materials should be monitored.

Electrochemical, spectroscopic, chemiluminescence, chromatographic, microbiological, and immunological methods and capillary electrophoresis are used for the determination of the most widely used β-lactam (β-lac) antibiotics—different penicillins and cephalosporins—in drug preparations, foodstuffs, and biological fluids [3]. Many of these methods require expensive equipment and reagents and highly skilled operators; they are time-consuming and not applicable to the rapid monitoring of the concentrations of antibiotics in clinical and biochemical laboratories.

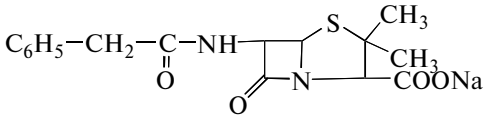
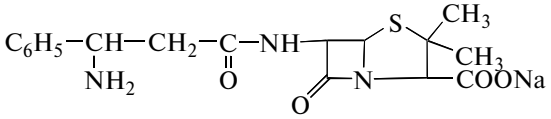
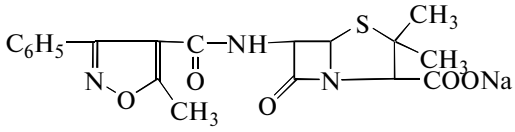
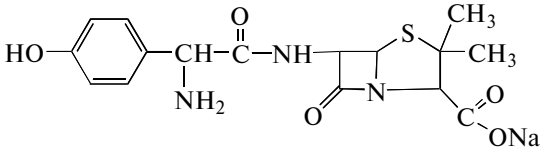
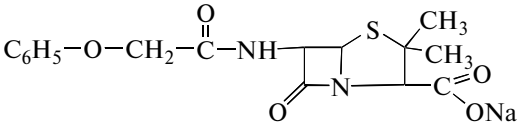
Potentiometry with the use of different sensors is a promising method for determining antibiotics in pharmaceutical products and biological fluids. This method is characterized by rapidity, selectivity, simplicity, and accessibility of equipment.

Different sensors were proposed in the literature for the determination of β-lactam antibiotics: biospecific [4, 5] and semiconductor sensors [6] and sensors with plasticized polymer membranes [7–11]. Sensors make it possible to detect benzylpenicillin, ampicillin, amoxicillin [5, 8, 9], and some cephalosporins [6, 10, 11]. The cited studies are applied studies.

In this work, we studied the electrode, transport, and selective properties of potentiometric sensors with plasticized poly(vinyl chloride) membranes sensitive to penicillin antibiotics and evaluated the physicochemical characteristics of electrode-active components based on β-lactam–tetraalkylammonium.

We demonstrated the applicability of the potentiometric sensors with plasticized poly(vinyl chloride) membranes to the rapid determination of penicillin antibiotics in drug preparations and biological fluids (blood serum and oral fluid) from patients with different pathologies.

Table 1. Names and formulas of the test antibiotics

Antibiotic	Abbreviated name	Formula
Benzylpenicillin	Pen	
Ampicillin	Am	
Oxacillin	Ox	
Amoxicillin	Amox	
Phenoxymethylpenicillin	Phen	

EXPERIMENTAL

The sodium salts of benzylpenicillin, ampicillin, oxacillin, amoxicillin, and phenoxymethylpenicillin were the test materials (Table 1). The 0.1 M stock solutions of the antibiotics were prepared using accurately weighed portions; the 1×10^{-2}–1×10^{-5} M solutions were prepared by the subsequent dilution of the stock solutions. The freshly prepared solutions were used because the antibiotics are hydrolysable [12].

The ion associates of penicillins with the cations of tetraalkylammonium salts (TAA^+) were used as the electrode-active components of sensor membranes (Table 2). The ion associates were synthesized as follows: a 1×10^{-3} M solution of TAA^+ in chloroform and an aqueous 1×10^{-2} M solution of an antibiotic were placed in a separatory funnel; the contents were vigorously shaken for 2 h and centrifuged for better phase separation. The chloroform layer was separated from the aqueous phase into a preliminarily weighed weighing bottle, and chloroform was evaporated in a water bath at 50–60°C (at higher temperatures, the electrode-active components were decomposed).

The synthesis of electrode-active compounds with the use of tetradecylammonium–antibiotic as an example occurs according to the following reaction scheme:

$$(C_{10}H_{21})_4NBr + \beta\text{-lacNa}$$
$$\longrightarrow (C_{10}H_{21})_4N^+\beta\text{-lac}^- + NaBr.$$

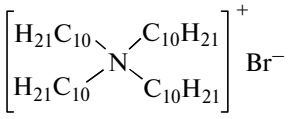
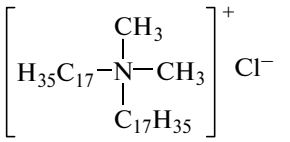
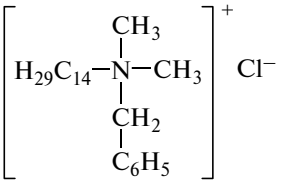
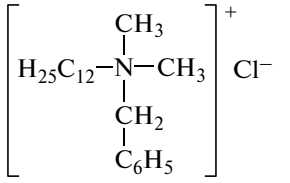
The formation of ion associates occurs at the carboxyl group of β-lactams.

For the preparation of the plasticized poly(vinyl chloride) membranes, the weighed portions of electrode-active components were dissolved in dibutyl phthalate (DBP) with continuous stirring; then, cyclohexanone and poly(vinyl chloride) (PVC) were added, and the mixture was thoroughly stirred until complete homogenization. The mixture was poured into a Petri dish and allowed to stand in air until the complete removal of cyclohexanone. Elastic and transparent membranes with a thickness of about 0.5 mm were obtained, from which disks were cut out. The concentration of electrode-active components in the membranes was varied from 0.3 to 2.1% at the ratio poly(vinyl chloride) : dibutyl phthalate = 1 : 3. Blank membranes (without electrode-active components) were prepared by an analogous procedure.

The membranes of the sensors had the following composition: a plasticizer solvent (dibutyl phthalate), an inert matrix (poly(vinyl chloride)), and an electrode-active compound.

Poly(vinyl chloride) tubes served as the housings of liquid contact sensors; the membrane disks were glued to the thoroughly ground ends of the tubes (the diameter of membranes corresponded to the diameter of tubes). The glue was prepared by the dissolution of

Table 2. Names and formulas of used for the synthesis of electrode-active components

Tetraalkylammonium salts	Abbreviated name	Formula
Tetradecylammonium bromide	TDA^+	
Dimethyldistearylammonium chloride	$DMDSA^+$	
Benzyldimethyltetradecylammonium chloride	$BDMTDA^+$	
Benzyldimethyldodecylammonium chloride	$BDMDDA^+$	

0.5 g of PVC in 1 g of DBP and 5 mL of cyclohexanone. The internal solution contained a 1×10^{-3} M solution of an antibiotic and 1×10^{-3} M of sodium chloride in a ratio of 1 : 1. For the preparation of solid contact sensors, a plasticized poly(vinyl chloride) membrane was glued to a thoroughly ground graphite rod (Fig. 1). The sensors were kept in a 1×10^{-3} M solution of the corresponding antibiotic before operations.

The following electrochemical circuits were used for conducting potentiometric measurements with (1) liquid contact and (2) solid contact sensors:

$$\text{Ag,AgCl} \mid 10^{-3}\text{ M } \beta\text{-lactam,} \mid \text{membrane} \mid \text{test solution} : \text{KCl sat.} \mid \text{AgCl, Ag } 10^{-1}\text{ M NaCl,} \quad (1)$$

$$\text{C} \mid \text{membrane} \mid \text{test solution} : \text{KCl sat.} \mid \text{AgCl,Ag.} \quad (2)$$

Figure 2 shows a schematic diagram of the process installation for the measurement of emf.

The emf of a circuit was measured with the aid of an I-160 ion meter to within ±1 mV; the reference electrode was an EVL-1MZ silver–silver chloride electrode. The external solution was stirred on a magnetic stirrer to accelerate the attainment of a steady potential value. All of the electrochemical measurements were conducted at a temperature of (20 ± 0.5)°C.

The stoichiometric ratios between components in the ion associates and their solubility product constants (K_{sp}) were evaluated from the curves of the precipitation potentiometric titration of 5×10^{-3} M solutions of tetraalkylammonium halides with the solutions of antibiotics with the use of the test sensors.

A four-electrode configuration of a pair of platinum (conducting) electrodes and a pair of silver–silver chloride (sensing) electrodes connected to a V7-16A high-resistance voltmeter was used for studying energized transport processes. An F-19B microammeter was used for the monitoring of current strength in the circuit. The measurements were performed in the galvanostatic regime ($I = 5$ μA) for 8 h with changing the direction of polarization current at regular intervals of 2 h. In this case, the voltage drop across the plasticized poly(vinyl chloride) membranes on passing a direct current through the cell and the electrical resistance of the membranes in contact with the solutions of antibiotics of different concentrations were evaluated.

For the determination of the antibiotics in the blood serum of patients, a blood sample (4.0–5.0 mL) with no stabilizer taken from ulnar veins was kept for 30 min at room temperature and centrifuged for 15 min at 2000 rpm. The supernatant liquid (blood serum) was then analyzed for antibiotics.

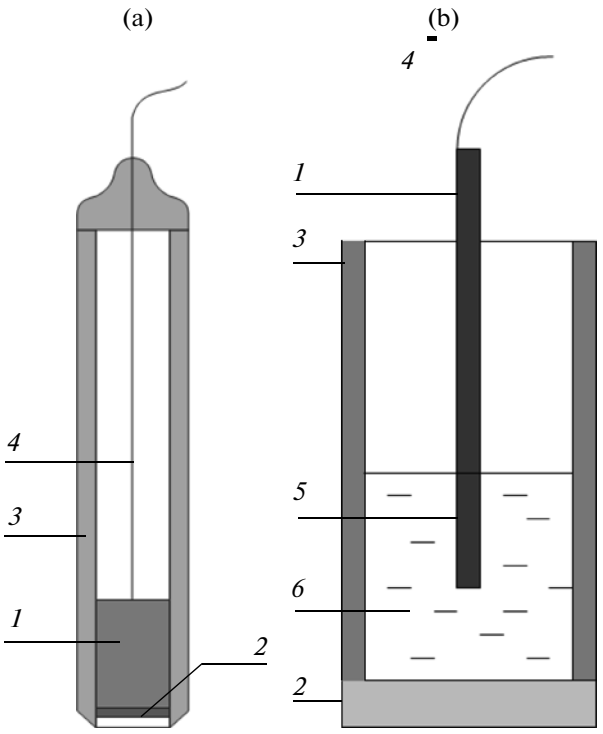


Fig. 1. Design of (a) solid contact and (b) liquid contact electrodes: (*1*) electronic conductor, (a) graphite; (*2*) selective membrane; (*3*) poly(vinyl chloride) tube; (*4*) metallic conductor wire, (a) copper wire; (*5*) internal reference electrode; and (*6*) internal reference solution.

In this work, we also used mixed saliva (oral fluid) as a test material. It is known from literature data that the concentration of a drug in saliva correlates with its concentration in blood [16, 17]. The test sample of mixed saliva (4.0–5.0 mL) from patients was centrifuged for 10 min at 3500 rpm; 0.5 mL of a precipitating agent (rectified alcohol C_2H_5OH) was added, and the mixture was centrifuged for 5 min. The sampling of blood and mixed saliva was carried out 30 min after the intramuscular injection of 0.500 g of benzylpenicillin or ampicillin.

Blood serum (1 mL) or the supernatant liquid of mixed saliva (2–3 mL) was placed in an electrochemical cell; the indicator and silver–silver chloride electrodes were immersed, and the values of emf (E_1) were measured. Then, a standard antibiotic solution was added and the value of E_2 was measured. The potentiometric sensors were preliminarily exposed for 20 min in blood serum or mixed saliva from apparently healthy persons.

The antibiotics were determined in drug formulations with the use of a calibration graph. The values of emf were measured in the standard solutions of benzylpenicillin (1×10^{-5}–1×10^{-1} M). The graph was plotted in the E–$\log(C_{\beta\text{-lac}})$ coordinates.

The statistical treatment of the experimental results and the processing of linear dependences by the least squares method conducted with the aid of Microsoft Excel.

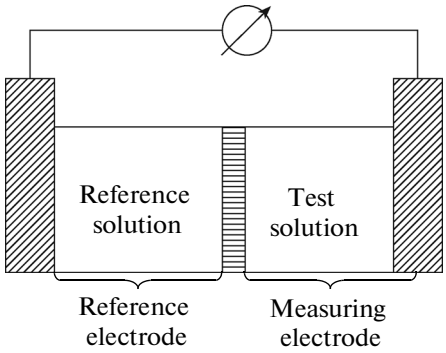


Fig. 2. Schematic diagram of the process installation for the measurement of emf.

RESULTS AND DISCUSSION

Electroanalytical (Surface) Properties of Potentiometric Sensors in Solutions of Antibiotics

The membranes based on the β-lactam–tetraalkylammonium ion associates exhibited sensitivity to benzylpenicillin, ampicillin, oxacillin, phenoxymethylpenicillin, and amoxicillin in the concentration range $n \times 10^{-6}$ ($n \times 10^{-3}$)–$n \times 10^{-2}$ ($n \times 10^{-1}$) M. The slope of the electrode responses was close to a theoretical value for singly charged ions (Table 3).

The electrode-active components of the membranes form the basis of sensor membranes; they ensure the sensitivity of a sensor to antibiotics and partially dissociate in a membrane phase into the anions of penicillins (β-lac$^-$) and the cations of tetraalkylammonium (TAA^+):

$$\beta\text{-lac}^-TTA^+ \longleftrightarrow \beta\text{-lac}^- + TTA^+.$$

Upon the immersion of a sensor into the solution of an antibiotic, an ion exchange reaction occurs at the membrane–solution interface: the antibiotic cations from the membrane are exchanged for the antibiotic cations from the solution.

$$\beta\text{-lac}^-_m \longleftrightarrow \beta\text{-lac}^-_p,$$

$$E = E^0 - \frac{2.3RT}{F}\log C_{\beta\text{-lac}}.$$

The test solutions of drug preparations and diagnostically significant biological fluids have a complex composition and contain both organic and inorganic compounds. It was necessary to estimate the selectivity of the sensors; that is, the possibility of determining the antibiotics in the presence of interfering ions.

The Inorganic anions Cl^-, I^-, Br^-, HCO_3^-, $H_2PO_4^-$, and $H_2PO_4^{2-}$ can also enter into an ion exchange reaction; in this case, the concentration

Table 3. Fundamental electrochemical characteristics of the potentiometric sensors sensitive to the penicillin antibiotics ($n = 3$, $P = 0.95$)

Antibiotic	Electrode-active components	Linearity range for E as a function of $\log(C_{\beta\text{-lac}})$, M	Slope S, mV/pC	Limit of detection of antibiotic, M	Solubility product constants of the electrode-active components $K_{sp} \pm \Delta K_{sp}$
Pen	Pen-TDA	1.0×10^{-5}–1.0×10^{-1}	58 ± 2	1.9×10^{-5}	$(6.9 \pm 0.1) \times 10^{-8}$
Am	Am-TDA	6.3×10^{-6}–1.9×10^{-1}	59 ± 1	1.3×10^{-6}	$(8.5 \pm 0.2) \times 10^{-8}$
Ox	Ox-TDA	3.2×10^{-6}–1.0×10^{-2}	49 ± 3	1.1×10^{-6}	$(4.6 \pm 0.1) \times 10^{-10}$
Amox	Pen-TDA	2.1×10^{-6}–1.0×10^{-2}	51 ± 2	1.0×10^{-6}	$(6.9 \pm 0.1) \times 10^{-8}$
Fen	Pen-TDA	1.9×10^{-5}–1.0×10^{-2}	57 ± 3	1.0×10^{-5}	$(6.9 \pm 0.1) \times 10^{-8}$
Ox	Ox-DMDSA	1.0×10^{-3}–1.0×10^{-1}	51 ± 2	7.1×10^{-4}	$(6.55 \pm 2) \times 10^{-5}$
	Ox-BDMTDA	1.0×10^{-4}–1.0×10^{-1}	51 ± 2	6.9×10^{-5}	$(5.93 \pm 3) \times 10^{-7}$
	Ox-BDMTDA	1.0×10^{-3}–1.0×10^{-1}	47 ± 2	6.3×10^{-3}	$(1.5 \pm 0.9) \times 10^{-5}$

dependence of emf is described by the Nicolsky equation [19] $E = E^0 - \frac{2.3RT}{F}\log(a_i + K_{i/j}^{pot} a_j)$, where $K_{i/j}^{pot}$ is the potentiometric selectivity coefficient, which shows in the presence of what quantities of interfering ions the primary ion can be determined.

The potentiometric selectivity coefficients ($K_{i/j}^{pot}$) were determined in accordance with IUPAC recommendations using separate solution and mixed solution methods [13–15]. According to the separate solution method, the emf of the solutions of the determined ion (E_1) and then of an interfering ion (E_2) are measured; in this case, the concentrations of the determined and interfering ions are chosen equal to each other. An equation for calculating the potentiometric selectivity coefficient takes the form

$$\log K_{i/j}^{pot} = \frac{E_2 - E_1}{2.3RT/zF}.$$

In the case of $E_1 = E_2 K_{i/j}^{pot} = \frac{a_i}{a_j}$.

According to the mixed solution method, the emf of a cell is measured in solutions at a constant concentration of an interfering ion (a_j) and a variable concentration of the determined ion (a_i). The dependence of the emf on the logarithm of the activity of the determined ion is plotted. The point of intersection of the asymptotically linear sections corresponds to the equality of the potentials of primary and interfering ions in the mixed solution. The $K_{i/j}$ is calculated from the following equation: $K_{i/j}^{pot} = \frac{a_i}{a_j}$.

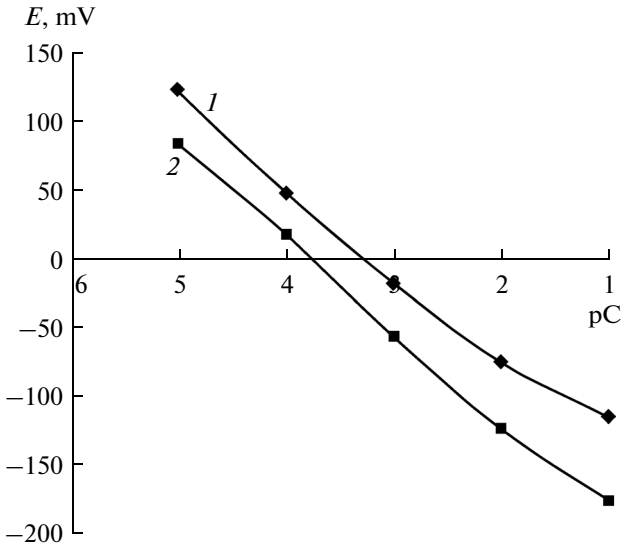


Fig. 3. Dependence of electrode potential on the negative logarithm of concentration for (*1*) the primary ion of ampicillin and (*2*) the interfering ion I^-.

Figures 3 and 4 exemplify dependences for the determination of selectivity coefficients by different methods.

The potentiometric selectivity coefficients of the membranes indicate that the sensors are highly selective for a number of the inorganic ions Cl^-, I^-, Br^-, HCO_3^-, $H_2PO_4^-$, and HPO_4^{2-} ($K_{i/j}^{pot} < 10^{-3}$) and nonselective for the antibiotics of their group ($K_{i/j}^{pot} \longrightarrow 1$). The sensors can be used for the determination of the individual antibiotics or their total concentrations in drug preparations and biological fluids.

The sensors based on the β-lactam–tetraalkylammonium ion associates possess stable electrochemical and operating characteristics: a potential drift of 1–2 mV/day and a service life of 6–8 months. The stable electrochemical characteristics of the sensors were retained in a range of pH 5.0–6.0 for Pen and Ox or 8.7–9.2 for Am.

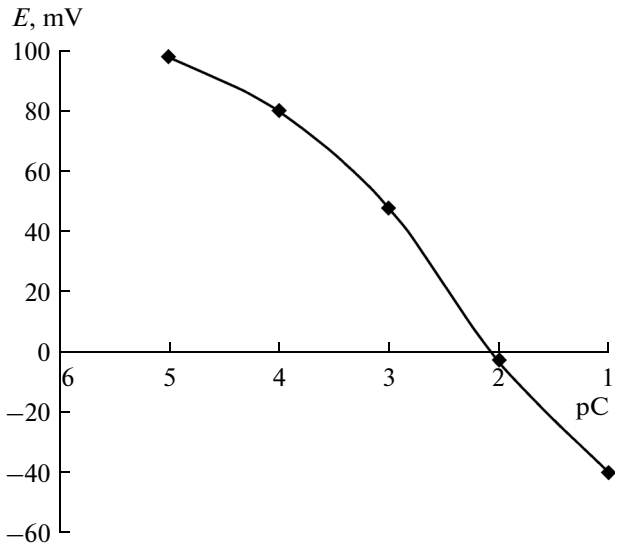


Fig. 4. Dependence of electrode potential on the negative logarithm of ampicillin concentration in the presence of 10^{-3} M $NaHCO_3^-$.

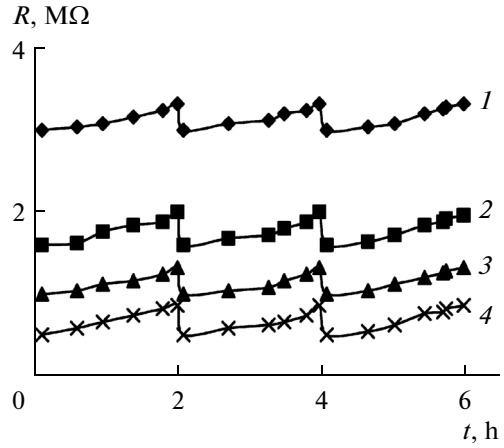


Fig. 5. Dependences of the resistance of the membranes based on the oxacillin–tetradecylammonium ion associate on the time of contact with a 1×10^{-3} M solution of oxacillin at a constant current (I = 5 μA) with a polarization change (↓). Concentrations of the electrode-active component in the membrane, %: (*1*) background, (*2*) 0.3, (*3*) 1.0, and (*4*) 2.1.

The applicability of the test sensors to the potentiometric titration of antibiotics with tetraalkylammonium salts was demonstrated. The solubility product constants of the active constituents of the membranes were evaluated based on the potentiometric titration curves.

The value of K_{sp} was calculated from the formula

$$K_{sp} = 10^{\frac{E-E_0}{S}} \frac{C_{ant}(V_2 - V_{TEP})}{V_1 + V_2},$$

where E is the potential found from a titration curve after the titration end point (TEP), mV; E_0 is the initial potential, mV; S is the slope of the electrode response, mV/pC; C_{ant} is the concentration of an antibiotic solution, M; V_1 is the volume of a tetraalkylammonium solution taken for the titration, mL; V_2 is the antibiotic volume after TEP, mL; and V_{TEP} is the antibiotic volume at TEP, mL.

We found that the test ion associates are sparingly soluble (Table 3) and suitable as electrode-active components; K_{sp} varies over a range of $n \times 10^{-5}$–$n \times 10^{-10}$; and the ion exchangers based on β-lactam–tetradecylammonium, which were subsequently used as the active constituents of potentiometric sensor membranes, exhibit the lowest solubility. These sensors are also characterized by a low limit of detection of the antibiotics.

Transport (Bulk) Properties of the Membranes

The study of the bulk (transport) properties of the blank membranes and membranes containing electrode-active components at constant current showed that the membranes are characterized by steady conductivity currents over a prolonged time interval even after changing the direction of current. The steady-state resistance values were established 2 h after the onset of passing the current through the cell in one direction or another; this fact is indicative of the reversible ion exchange of the antibiotics between the membrane and the external solution. After changing the direction of current, the resistance changed within 2 h to reach a steady-state value, which indicates the equilibration of exchange processes at the membrane–solution interface. The resistance of the membranes decreased with the concentration of electrode-active components; this was due to an increase of the concentration of ion-exchange centers in the phase of the membranes.

Figure 5 shows the examples of the time dependences of the resistance of the membranes based on Ox–TDA at a constant applied current.

The resistance of the blank membranes and the membranes based on ion associates depends on antibiotic concentration in the external solutions and is 0.5–3 MΩ. A decrease in the steady-state resistance with the concentration of antibiotics in the external solution was observed; this was also due to an increase in the amount of absorbed ions from the solution and, hence, an increase in the concentration of mobile charge carriers in the membrane phase. The anions of antibiotics are the main charge carriers in the membranes. In the blank membranes, the absolute values of resistance were considerably higher than those in the membranes containing electrode-active components because of the low rate of the penetration of mobile carriers (Ox^-) into the membrane phase.

Table 4. Rates of transfer, permeability, and the ion flows of the antibiotics through the plasticized membranes under applied potential conditions (*C* electrode-active component = 0.3%; $n = 3$; $P = 0.95$)

Electrode-active component (antibiotic solution)	Carrier concentration in the source, M	Rate of transfer, mol $m^{-2} h^{-1}$	Ion flux J, mol $m^{-2} s^{-1}$	Permeability P, m/s
Pen-TDA (Amox)	1×10^{-3}	$(3.21 \pm 0.12) \times 10^{-6}$	$(5.14 \pm 0.41) \times 10^{-5}$	$(4.46 \pm 0.17) \times 10^{-7}$
	1×10^{-4}	$(2.89 \pm 0.28) \times 10^{-6}$	$(4.21 \pm 0.36) \times 10^{-5}$	$(1.91 \pm 0.16) \times 10^{-6}$
	1×10^{-5}	$(5.17 \pm 0.31) \times 10^{-6}$	$(2.94 \pm 0.28) \times 10^{-5}$	$(2.93 \pm 0.23) \times 10^{-6}$
Pen-TDA (Fen)	1×10^{-3}	$(2.32 \pm 0.21) \times 10^{-6}$	$(4.38 \pm 0.18) \times 10^{-5}$	$(2.18 \pm 0.32) \times 10^{-7}$
	1×10^{-4}	$(2.86 \pm 0.32) \times 10^{-6}$	$(3.16 \pm 0.22) \times 10^{-5}$	$(3.21 \pm 0.18) \times 10^{-7}$
	1×10^{-5}	$(1.76 \pm 0.21) \times 10^{-6}$	$(1.89 \pm 0.19) \times 10^{-5}$	$(4.23 \pm 0.19) \times 10^{-6}$

The apparent dissociation constants (K_d) of the β-lactam–tetradecylammonium electrode-active components in the membrane phase were calculated from the steady-state resistance values using the Kraus–Bray method [18]. In this case, it was assumed that the equilibrium between the ions and associates at low concentrations obeys the Ostwald dilution law

$$K_d = \frac{\alpha^2 c}{1-\alpha},$$

where c is the total molar concentration of a compound, and α is the degree of dissociation.

Expressing α through the relative equivalent conductance λ/λ_0 (λ is the equivalent conductance, and λ_0 is the maximum electrical conductivity), we obtain the following expression for the dissociation constant:

$$K_d = \frac{c\lambda^2}{\lambda_0^2\left(1-\frac{\lambda}{\lambda_0}\right)}.$$

The dissociation constants of the test compounds were evaluated using the Fuoss–Krauss iterative technique by converting the last expression:

$$1/\lambda = 1/\lambda_0 + \lambda c/K_d\lambda_0^2.$$

The dependence of $1/\lambda$ on λc is expressed as a straight line with the slope $1/K_d\lambda_0^2$ and the intercept $1/\lambda_0$ on the axis of ordinates. The dissociation constants were calculated from the found values of $1/\lambda_0$ and the slopes.

We found that the K_d of the electrode-active components in the membrane phase have similar values of $(7.62 \pm 0.09) \times 10^{-2}$, $(3.65 \pm 0.11) \times 10^{-2}$, and $(5.12 \pm 0.15) \times 10^{-2}$ mol/L for Pen–TDA, Am–TDA, and Ox–TDA, respectively, with the confidence coefficient $P = 0.95$ and the number of measurements $n = 3$. The test compounds occur in the membrane phase in a dissociated state; the nature of an antibiotic in the composition of the active constituents of the membranes does almost not change the properties of the membranes on their basis.

We evaluated the rates of transfer, permeability, and ion fluxes for antibiotics in the plasticized membranes based on the β-lactam–TDA electrode-active components on varying the concentration of near-membrane solutions (Table 4).

The rates of antibiotic ion transfer were calculated using the following formula:

$$v = \frac{\Delta c}{\Delta t},$$

where Δc is the difference of concentrations in the receiver and the source, M, and Δt is the time interval, s.

The following simplified flow equation was used for the quantitative description of transport processes in a cell [19–21]:

$$J = P(c_1 - c_2),$$

where J is the ion flux, P is the ion flow rate in the near-membrane solution (permeability coefficient), and c_1 and c_2 are the concentrations of solutions in the source and the receiver, respectively; in this case, $c_1 > c_2$. For the permeability of the membranes, the following equation was used [18]:

$$\ln\left\{1 - \left(1 + \frac{V_2}{V_1}\right)\frac{c_2^t}{c_1^0}\right\} = -PS\left[\frac{1}{V_1} + \frac{1}{V_2}\right]t,$$

where c_2^t is the average molar concentration of solution in the receiver section at the point in time t; c_1^0 is the initial molar concentration of solution in the source section; V_1 and V_2 are the volumes of the source and receiver sections of the cell, m^3; $V_1 = V_2$; S is the surface area of the membrane, m^2; and t is the time interval, s.

The permeability coefficient P of an ion-exchange membrane can be calculated from the slope of a graph plotted in the coordinates of $-\ln\left\{1 - \left(1 + \frac{V_2}{V_1}\right)\frac{c_2^t}{c_1^0}\right\}$ as a function of time.

Table 5. Results of the determination of penicillin antibiotics in drug dosage forms after different storage periods ($n = 3$, $P = 0.95$)

Drug dosage form	Antibiotic	Year of manufacture	Active drug substance content, %	S_r^*
Tablet	Am	1999	65 ± 2	0
Tablet	Fen	1998	33 ± 2	0
Tablet	Amox	2001	64 ± 3	0
Powder	Ox	2003	89 ± 5	0
Capsule	Ox	2003	94 ± 3	0

* S_r is the relative standard deviation, which characterizes the random error of determination.

It is likely that the decrease of permeability with the concentration of antibiotics in the source was related to the more rapid saturability of the membrane and, as a result, the appearance a significant potential difference at the surface and in the membrane phase. In turn, this led to a decrease in ion transfer through the interphase, and the transfer was limited not only by diffusion through the membrane but also by diffusion through an aqueous boundary layer formed on its surface as a result of contact with the aqueous solutions of antibiotics.

In general, the flow rate was characterized by an increase with increasing the concentration of near-membrane solution, which indicates that diffusion through the aqueous boundary solution formed at the surface of the membrane upon its contact with water is a rate-limiting step (Table 4).

Application of Sensors with the Plasticized Poly(vinyl chloride) Membranes to the Determination of Penicillins in Biological Fluids and Pharmaceuticals

We developed procedures for the rapid determination of the penicillin antibiotics in pharmaceuticals and biological fluids (blood serum and mixed saliva). Mixed saliva (oral fluid) was chosen because its sampling is painless, simple, and convenient; in this case, there is no risk of infection and injuries to skin and vessel walls; the concentration of substance is adequate to a pharmacotherapeutic effect in the oral cavity; the penetration of substances through histo-hematic barriers can be taken into account; etc.

The concentrations of antibiotics were calculated from the formula

$$C_x = \frac{V_a C_a}{V_x + V_a}\left(10^{\frac{|E_1 - E_2|}{S}} - \frac{V_x}{V_a + V_x}\right)^{-1},$$

where C_x is the concentration of an antibiotic, mol/L; V_x is the test sample volume, mL; C_a is the concentration of an additive, M; V_d is the volume of the additive, mL; E_1 and E_2 are the electrode potentials in the test solution and a solution with the additive, respectively, mV; and S is the slope of the electrode response.

After 0.500-g intramuscular injections to patient with urinary infections, the maximum β-lactam concentrations of 28–39 μg/mL (blood serum) and 5.3–9.6 μg/mL (oral fluid) were detected.

The drug content of different pharmaceutical preparations was determined from a calibration graph plotted with the use of standard antibiotic solutions in the E–$\log(C_{\beta\text{-lac}})$ coordinates. It was found that excipients have no effect on the results of the determination of drug substances in pharmaceutical preparations. For evaluating a systematic error, the determination of drug substances was also carried out by a pharmacopoeial iodometric method [22].

Table 5 summarizes the results of the determination of penicillins in drug dosage forms after different storage periods.

The drug content (g) was calculated from the formula

$$m = C_x MV,$$

where C_x is the antibiotic concentration found according to a calibration graph, mol/L; V is the dilution volume, L; and M is the molar mass of the antibiotic, g/mol.

CONCLUSIONS

In this work, we studied the electrode, transport, and selective properties of potentiometric sensors with plasticized PVC membranes based on the ion associates of tetraalkylammonium with β-lactam antibiotics; we determined their main electrochemical and transport properties. Based on the solubility product constants, we determined optimum electrode-active components. We evaluated the following quantitative characteristics of membrane transport: the rate of transfer, the permeability, and the ion flows of antibiotics at a constant current. We demonstrated the reversibility of ion-exchange processes between a membrane and an external solution.

We found that the resistance of the membranes depends on the concentration of the electrode-active components, which occur in a dissociated state in the membrane phase. The apparent dissociation constants of electrode-active components were calculated from

the steady-state values of the resistance of the membranes.

We demonstrated the applicability of potentiometric sensors to the rapid determination of antibiotics in drug preparations and biological fluids (mixed saliva and blood serum).

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