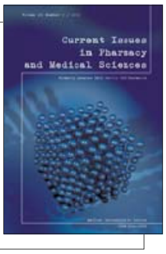
2012 © Curr. Issues Pharm. Med. Sci. Vol. 25, No. 3, Pages 331-337

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA
on-line: www.umlub.pl/pharmacy



Dependence of analytical parameters of ion-selective electrodes on the membrane solvents used in the construction of membranes

Joanna Drozd*, Anna Garbaty

* Department of Medicinal Chemistry, Faculty of Pharmacy, Medical University of Lublin, Poland

ABSTRACT

The aim of this study was analysis of the suitability of available membrane solvents and their application to obtain liquid membrane ion-selective electrodes that are sensitive to diazepam or fluoxetine. Sensitive and reasonably selective poly(vinyl chloride) membrane electrodes are based on using water insoluble ion-pair of diazepam – [tetrakis(3,5bis-(trifluoromethyl)phenyl]borate or fluoxetine – [tetrakis(4-fluorophenyl)]borate as electroactive material. As membrane solvents for construction of membranes there were used 2-nitrophenyloctyl ether, bis(2-ethylhexyl) sebacate, 1-isopropyl-4-nitrobenzene, bis (1-buthylpentyl) adipate, tris(2-ethylhexyl) phosphate. Evaluation of analytical parameters of the obtained electrodes, their selectivity and evaluation of analytical parameters for membranes subjected to a process of "accelerated aging" in a climate chamber at 60 °C and humidity of 70 % without the VIS and UV light, were developed. There was carried out an analysis of the suitability of the electrodes, which will show the best stability and reproducibility of the analytical parameters for the determination of substances in respect of which exhibit selectivity. The determination was developed using potentiometric titration method.

Keywords: ion-selective electrode, potentiometric titration, drug analysis, solvent mediators, fluoxetine hydrochloride determination, diazepam determination

INTRODUCTION

Membrane electrodes used in chemical and pharmaceutical analyses expand the perspective of the analytical electrochemical methods. Modernization of the methods used in potentiometry is the result of the introduction of new indicator electrode for better selectivity and higher ratios of applicability. They make a direct determination of the compounds possible, without prior isolation from the matrix, so that the determination is accurate and fast. This results from better knowledge of the mechanism of action of the electrodes, as well as the introduction of new, more perfect and simple structural systems. Ion-selective electrodes are widely used in chemical analyses in the determination of many organic and inorganic compounds, as well as medicines of various chemical groups. Due to the development and improvement of a number of therapeutic agents, they have been analysed using new membranes electrodes system.

In the liquid membranes of ISEs, the porous matrix of poly (vinyl chloride) is an inert carrier, which is about 30-35% of the membrane; other components: the plasticizer (solvent membrane) which is 60-65% and the ion exchanger - 1%, - the most important component of determining the potential of the electrode. The analyzed substances should be in two phases, which are sufficiently different, allowing the chemical potential occurrence of stroke. In the organic phase there must be the appropriate group of opposite ionic charges to ion denoted which would be able to form sparingly soluble compound. Membrane solvents should have a low vapor pressure, high molecular weight, low dielectric constant and high viscosity, so that the passage through the pores of the membrane could take place at an appropriate speed [8]. Amount of plasticizer in membrane can reduce the resistance of the membrane, which also affects the increase in selectivity of the electrode. However, the substance used as a plasticizer should have several properties. High lipophilicity is a parameter that affects the usability of electrodes - called "Life time" because at that time the amount of plasticizer decreases, which significantly changes the performance characteristics of the electrode. Solvent mediator should dissolve in the polymeric membrane; it should not create forms in the diaphragm or crystallize; with other ingredients of the membrane it should provide a single phase [8].

Corresponding author
* Department of Medicinal Chemistry, Faculty of Pharmacy,
Medical University of Lublin,
4 Jaczewskiego Str., 20-090 Lublin, Poland
e-mail address: joanna.drozd@umlub.pl

Over the past 10 years, numerous studies on the use of ion-selective electrodes in pharmaceutical analysis have been published. The most frequently used as solvents mediators to obtain ISEs are dioctyl phtalate [3, 5, 7, 13, 15, 19, 21], dibutyl phthalate [9, 10, 12, 16, 19, 23], bis (2-ethylhexyl) sebacate [1, 6, 19, 22] and 2-nitrophenyl octyl ether [1, 6, 11, 14-16, 18, 19].

The aim of this study was analysis of the suitability of available membrane solvents and their application to obtain liquid membrane ion-selective electrodes sensitive to diazepam or fluoxetine. Sensitive and reasonably selective poly(vinyl chloride) membrane electrodes based on the use of water insoluble ion-pair of diazepam – [tetrakis (3,5bis-(trifluoromethyl)phenyl]borate or fluoxetine-[tetrakis(4-fluorophenyl)]borate as electroactive material. As membrane solvents to construction of membranes there were used 2-nitrophenyloctyl ether, bis(2-ethylhexyl) sebacate, 1-isopropyl-4-nitrobenzene, bis(1-buthylpentyl) adipate, tris(2-ethylhexyl) phosphate. Evaluation of analytical parameters of the obtained electrodes, the selectivity, and the evaluation of analytical parameters for membranes subjected to a process of "accelerated aging" in a climate chamber at 60°C and humidity of 70 % without the VIS and UV light, was performed. There was carried out an analysis of the usefulness of the electrodes, which will show the best stability and reproducibility of the analytical parameters for the determined substances in respect of which exhibit selectivity.

MATERIALS AND METHODS

Reagents and materials. Diazepam (D) and fluoxetine hydrochloride (Fl) substances were obtained from Sigma – Aldrich. Potassium [tetrakis(3,5bis-(trifluoromethyl)) phenyl]borate ([T(3,5bis-CF_3)Ph]B), potassium [tetrakis (4-fluorophenyl)]borate dihydrate ([T[(F)Ph]B), sodium tetraphenylborate (NaTPB) and 2-nitrophenyloctyl ether (NPhOE), bis(2-ethylhexyl) sebacate (b(EH)S), 1-isopropyl-4-nitrobenzene (IPNB), bis(1-buthylpentyl) adipate (b(BP)A), tris(2-ethylhexyl) phosphate t(EH)P were obtained from *Fluka* (Switzerland). Poly(vinyl chloride) (PVC) of high molecular mass was from *Aldrich* (USA), tetrahydrofuran (THF) was produced by *Romil Chemicals LTD* (England). The most of the reagents were produced by *POCh* (Gliwice, Poland), and all of them were of analytical – reagents grade.

For the preparation the standard solutions (concentration 10^{-1} mol L^{-1}) the analysed substances were used: diazepam dissolved in hydrochloric acid 0,005 mol L^{-1} under continuous stirring until complete dissolution of the substance and fluoxetine hydrochloride dissolved in water. Standard solutions with concentrations 10^{-2} – 10^{-7} mol L^{-1} for both substances were prepared in 10^{-3} mol L^{-1} KCl. The standard solution of TPB of 10^{-2} mol L^{-1} was prepared by dissolving the compound in water, diluting to 250 ml, and standardizing as previously described [20].

The solutions were prepared using bidistilled deionized water throughout.

Apparatus and electrodes. Multifunctional apparatus (pH/mV, pX/mV; temp.; O_2; hPa; Cond.) Elmetron CX (Poland) was used for measuring the electrode potentials and pH. All the potentiometric measurements were made using saturated calomel electrode (SCE) and Ag/AgCl membrane electrode; pH adjustment was made with a combination glass electrode. All the measurements were carried out at room temperature 21±2°C. A magnetic stirrer was used; however, the readings of the potential value were taken after the stirrer had been switched off.

The SCE was used as the reference electrode connected with the sample solution by a potassium nitrate bridge.

Preparation of ion – pair complexes. To 10 ml of well shaken 10^{-2} mol L^{-1} D solution, 10 ml of 10^{-2} mol L^{-1} [T(3,5bis-CF_3)Ph]B in 400 g L^{-1} ethyl alcohol solution was added. To obtain fluoxetine ion – pair complex: to 10 ml of well shaken 10^{-2} mol L^{-1} fluoxetine hydrochloride water solution, 10 ml of 10^{-2} mol L^{-1} [T(F)Ph]B in 400 g L^{-1} ethyl alcohol solution was added. The precipitates obtained after cooling and evaporation of the ethyl alcohol were filtered using a (G4) sintered glass crucible, washed with water to remove any non–complexed material, dried at room temperature and ground to a fine powder. The results of the elemental analysis agree well with the molar ratio 1:1 of the reacting substances. The theoretical percentage amount of nitrogen in the complexes was 2.439 and 1.900; while the found one was 2.384 and 1.868 for D–[T(3,5bis-CF_3)Ph]B and Fl–[T(F)Ph]B, respectively.

Preparation of the membranes. Twenty milligrams of the ion–pair complex was added to a solution of 170 mg PVC in 6 ml THF and 360 mg of NPhOE or b(EH)S or IPNB or b(BP)A or t(EH)P as plasticising solvent mediator. The homogeneous mixtures were poured into a glass ring (diameter 3.1 cm) and covered with a sheet of filter paper and a glass plate was placed over it. The membrane was forming as the THF was evaporating slowly at room temperature. The thickness of all obtained membranes was about 0.2 mm. The membranes obtained were denoted by the solvents mediator: NPhOE – I, b(EH)S) – II, IPNB – III, b(BP)A – IV, t(EH)P – V.

Construction of electrode. To prepare an electrode (according to Craggs et al. [4]), a membrane disc of 8 mm diameter was cut from obtained film and glued onto the front end body of PVC electrode containing an inner Ag/AgCl junction. A 10^{-3} mol L^{-1} solution of the analysed substance in 10^{-3} mol L^{-1} KCl solution was used as the inner electrolyte. The membrane electrodes were conditioned overnight in a solution of the same composition as the internal filling solution, and stored in the same solution before use. Electromotive force (e.m.f) measurements were performed using the cell assembly: Ag/AgCl-10^{-3} mol L^{-1} analysed substance in 10^{-3} mol L^{-1} KCl solution-PVC membrane-test solution-SCE.

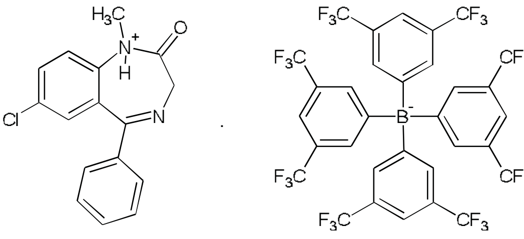
Electrode characteristics. The performance of the obtained electrodes D I, D II, D III, D IV, D V was investigated by measuring e.m.f. values of 10^{-2} - 10^{-7} mol L^{-1} of diazepam solution and in 10^{-3} mol L^{-1} KCl solution. The performance of the obtained electrodes Fl I, Fl II, Fl III, Fl IV, Fl V was investigated by measuring e.m.f. values of 10^{-2} - 10^{-7} mol L^{-1} of fluoxetine hydrochloride solution in 10^{-3} mol L^{-1} KCl solution. The potential was recorded when stable readings were obtained. A calibration graph was made by plotting the observed potential as a function of logarithm of diazepam or fluoxetine hydrochloride concentration.

Stability study received electrodes. In the climatic chamber "aging conditions" of membranes were identified, i.e.: temperature of 60 °C and 70% humidity without the VIS and UV light. After stabilization of the parameters, the membranes were inserted and sealed in the chamber. At selected intervals, the appearances of membranes were observed. The experiment was completed after 7 days. Of membranes, which were visually inspected to be useful for further testing, electrodes were prepared as above. Then, the performance of the all obtained electrodes was investigated by measuring e.m.f. values of 10^{-2} – 10^{-7} mol L^{-1} in diazepam or fluoxetine hydrochloride in 10^{-3} mol L^{-1} KCl solutions, respectively.

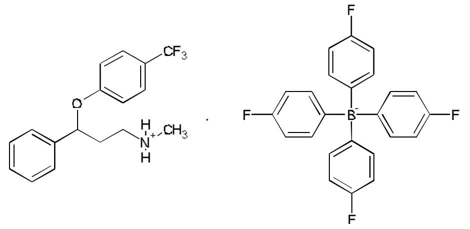
Potentiometric titration of diazepam and fluoxetine hydrochloride in pure form. Samples of solution containing 2.84 ppm of diazepam substance or 3.09 ppm of fluoxetine hydrochloride substance in 10^{-3} mol L^{-1} KCl were titrated with 10^{-2} mol L^{-1} of NaTPB standard solution. End point was determined using electrodes with membrane containing diazepam – [T(3,5bis-CF_3)Ph]B and NPhOE or b(EH)S or b(BP)A (electrodes D I, D II, D IV) or fluoxetine – [T[(F)Ph]B and NPhOE or b(EH)S or IPNB (electrodes Fl I, Fl II, Fl III), respectively.

RESULTS AND DISCUSSION

Ion-pair complexes of the diazepam with [tetrakis(3,5bis-trifluoromethyl)phenyl]borate and fluoxetine with [tetrakis(4-fluorophenyl)]borate were obtained and tested as ion-exchangers in PVC membrane electrodes. In laboratory conditions diazepam does not create ionic association connections with [T(F)Ph]B, fluoxetine with [T(3,5bis-CF_3)Ph]B. The compositions of the received crystalline ion-pair complexes 1:1 were verified by data obtained from elementary analysis. The suggested structural formulas are shown in Fig. 1. These ion-pair complexes are readily soluble in an organic solvent such as tetrahydrofuran or chloroform. The obtained compounds were incorporated into a PVC membrane with the following solvent mediators: NPhOE (electrodes I), b(EH)S (electrodes II), IPNB (electrodes III), b(BP)A (electrodes IV), t(EH)P (electrodes V).



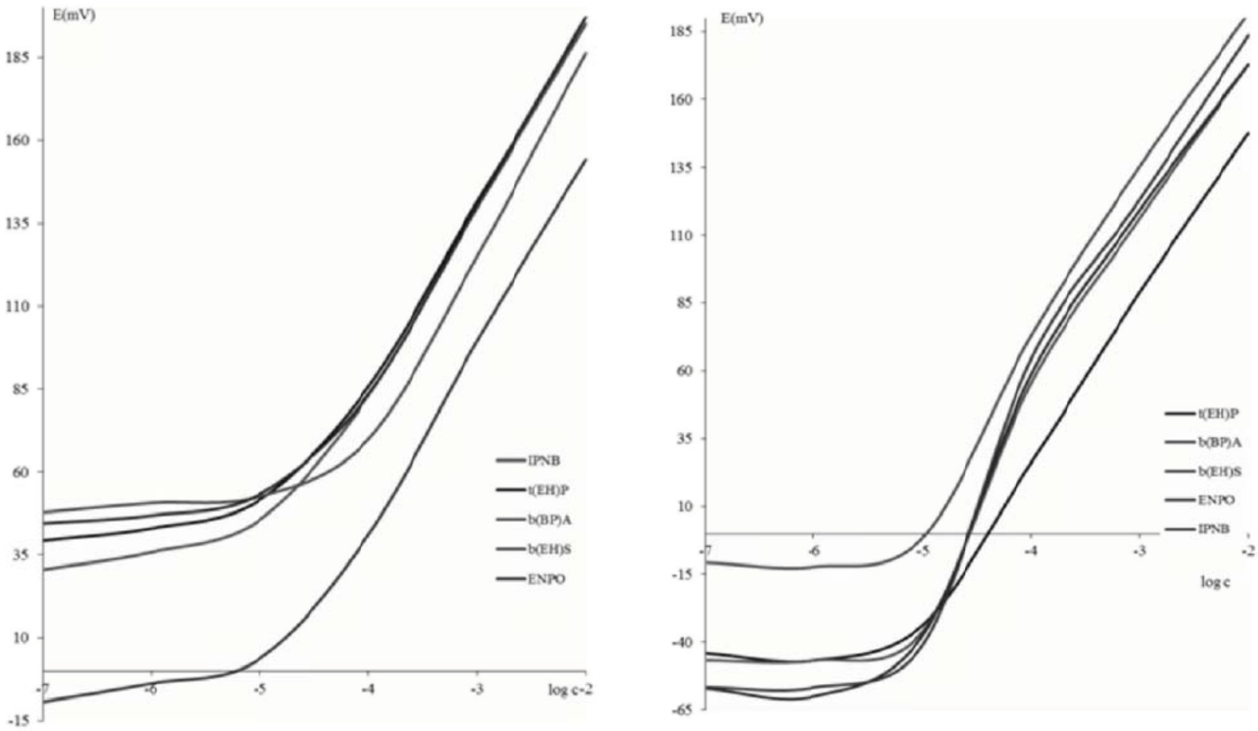
Diazepam - [tetrakis (3,5 bis-trifluoromethyl)phenyl]borate



Fluoxetine – [tetrakis(4-fluorophenyl)]borate

Fig. 1. Suggested structural formulas of ion-pair complexes

The working characteristics for the investigated electrodes D I – D V and Fl I – Fl V were assessed on the basis of the calibration curves obtained by measuring of the e.m.f. values of the set of diazepam or fluoxetine hydrochloride solutions respectively, in intervals of 10^{-2} – 10^{-7} mol L^{-1} concentrations in an ionic strength adjusted to 10^{-3} mol L^{-1} KCl. The E(mV) vs. log (c) graph obtained for D I – D V, Fl I – Fl V electrodes in KCl solution are presented in Fig. 2. The results obtained indicate that the tested electrodes have Nernstian cationic response to diazepam or fluoxetine activity, respectively in different concentration ranges. Slopes of electrodes D I – D V and Fl I – Fl V depend on the properties of the solvent mediator. Drift potential differences were also observed for sensitive electrode to diazepam or fluoxetine. The response of electrodes sensitive to relative fluoxetine potential was fast with maximum variability ±1.0205 mV and for the diazepam sensitive electrodes the slow setting of the potential with variability from 0.205 to 6.440 mV was noted. The response times of the electrodes were tested for 10^{-7} – 10^{-2} mol L^{-1} diazepam or fluoxetine solutions, respectively. The sequence of measurements was low to high concentrations. Those electrodes exhibited a fast dynamic response of about 5s for as the higher concentrations, below 10^{-4} mol L^{-1} the response time was expectedly sluggish, about 15-20s, which is typical for ion-selective electrodes containing bulky PVC membranes of similar thickness (about 0.2 mm). Table 1 shows the values obtained for general operating characteristics of diazepam and fluoxetine electrodes. There are differences between the linearity ranges and response slopes for different electrodes. The differences are insignificant. This implies that the different solvent mediators used do not significantly influence the response characteristics of electrodes.



Diazepam – [tetrakis (3,5 bis-trifluoromethyl) phenyl]borate Fluoxetine – [tetrakis(4-fluorophenyl) borate

Fig. 2. Potentiometric response of obtained ISEs in solution KCl 10^{-3} mol L^{-1}

Table 1. Effect of plasticizer on response of diazepam and fluoxetine sensitive electrodes (average of six measurements)

Electrode	Membrane composition	Linear range LR		Detection limit LD		Slope S (mV)	Potential drift (mV)	The parameters of linear regression in LR y = ax + b		
		mol L^{-1}	mg ml^{-1}	mol L^{-1}	mg ml^{-1}			r	a	b
D I	D – T(3,5bis-CF3)PhB NPhOE	10^{-2} – $10^{-4.95}$	2.85 x 10^6 – 3.195	$10^{-5.23}$	1.666	51.80	±0.98 – ±5.05	0.9890	0.0141	- 4.6123
D II	D – T(3,5bis-CF3)PhB b(EH)S	10^{-2} – $10^{-5.00}$	2.85 x 10^6 – 2.847	$10^{-5.15}$	2.016	51.93	±0.015 – ±6.44	0.9920	0.0144	- 4.6072
D III	D – T(3,5bis-CF3)PhB IPNB	10^{-2} – $10^{-5.00}$	2.85 x 10^6 – 2.847	$10^{-5.17}$	1.943	52.03	±0.915 – ±6.18	0.9879	0.0134	- 4.5986
D IV	D – T(3,5bis-CF3)PhB b(BP)A	10^{-2} – $10^{-4.98}$	2.85 x 10^6 – 2.963	$10^{-5.15}$	2.025	51.24	±0.325 – ±5.47	0.9978	0.0156	- 5.0386
D V	D – T(3,5bis-CF3)PhB t(EH)P	10^{-2} – $10^{-4.85}$	2.85 x 10^6 – 4.184	$10^{-5.18}$	1.959	49.22	±0.235 – ±2.18	0.9994	0.0164	- 4.4414
Fl I	Fl – T[(F)PhB] NPhOE	10^{-2} – $10^{-4.43}$	3.09 x 10^6 – 11.689	$10^{-4.47}$	5.326	54.40	±0.415	0.9912	0.02011	- 5.8862
Fl II	Fl – T[(F)PhB] b(EH)S	10^{-2} – $10^{-4.67}$	3.09 x 10^6 – 6.674	$10^{-4.92}$	3.753	53.41	±0.615	0.9960	0.0196	- 5.7761
Fl III	Fl – T[(F)PhB] IPNB	10^{-2} – $10^{-4.67}$	3.09 x 10^6 – 6.952	$10^{-4.88}$	4.089	53.56	±6.500	0.9957	0.0194	- 4.9507
Fl IV	Fl – T[(F)PhB] b(BP)A	10^{-2} – $10^{-4.00}$	3.09 x 10^6 – 30.934	$10^{-4.3}$	15.572	56.00	±1.205	0.9751	0.0208	- 5.7632
Fl V	Fl – T[(F)PhB] t(EH)P	10^{-2} – $10^{-4.50}$	3.09 x 10^6 – 9.956	$10^{-4.87}$	4.211	52.23	±0.565	0.9947	0.0203	- 5.9107

The effect of pH on the potential readings of the diazepam D I – D V and fluoxetine electrodes Fl I – Fl V was checked by recording the e.m.f. of 10^{-3} mol L^{-1} diazepam or fluoxetine hydrochloride in 10^{-3} mol L^{-1} KCl solution with various pH values. They were obtained by the addition of small volumes of HCl and/or NaOH solution of 10^{-1} or 1 mol L^{-1} each to the basic solution of substances, respectively. For electrodes sensitive to fluoxetine the potential did not fluctuate by more than about ± 1 mV in the pH range 5.0-5.8 for all obtained electrodes. The graph for diazepam sensitive electrodes remained linear but had different slopes in the pH range 3-7, indicating that no significant effect on the electrode potentials was observed for all electrodes. Bellow pH 3, they become nonlinear as the electrodes began to respond to hydrogen ions. Above pH 7, formation of very slightly soluble diazepam substance base caused the electrode potentials to decrease [2]. The influence of potential drugs on the response characteristics of the developed electrodes was investigated. Potentiometric selectivity coefficients were performed by standard separate solution method [17] and calculated from the equation:

$$\log K_{ij}^{pot} = (E_j - E_i)/S$$

where: E represents the e.m.f. measured for the primary ion (i), and the interfering ion (j), respectively, and S is the slope of the corresponding diazepam and fluoxetine electrode.

The values given were evaluated from the e.m.f. readings obtained from 10^{-3} mol L^{-1} KCl solution. Interfering substances different for diazepam and fluoxetine, were selected on the basis of pharmacological, chemical structure, their relative impact on the selectivity of the electrodes.

For the diazepam sensitive electrodes, antidepressants antipsychotics and anxiolytics were selected; for the fluoxetine sensitive electrodes, anxiolytics, antipsychotics and inert fillers were chosen. The selectivity coefficients values are summarized in Table 2. Thioridazine hydrochloride, chlorpromazine hydrochloride, chlorprothixene hydrochloride are likely to cause interference with respect to PVC diazepam sensitive electrodes. Diazepam, chlorpromazine hydrochloride, promazine hydrochloride may cause harmful interference to determine the potential of the electrodes sensitive to fluoxetine. Fortunately, these substances are seldom formulated in combination with diazepam or fluoxetine, respectively.

Table 2. Potentiometric selectivity coefficients of diazepam and fluoxetine PVC membrane electrodes

Diazepam PVC membrane electrodes						
Lp.	Interferent (j)	log K_{ij}^{pot}				
		D I	D II	D III	D IV	D V
1	Imipramine hydrochloride	-0.35342	-0.05634	0.00783	-0.72438	-0.40902
2	Thioridazine hydrochloride	0.19245	0.13788	0.21284	0.07126	-0.10771
3	Chlorpromazine hydrochloride	0.21796	0.13981	0.16499	0.05553	-0.10027
4	Chlorprothixene hydrochloride	0.25243	0.19792	0.17260	0.09784	0.00146
5	Opipramol hydrochloride	-1.04135	-0.7299	0.00000	-1.43858	-1.20119
6	Fluoxetine hydrochloride	-0.49471	-1.0363	-0.08117	-0.41472	-0.27381
Fluoxetine PVC membrane electrodes						
	log K_{ij}^{pot}					
		F I	F II	F III	F IV	F V
1	Diazepam	0.20863	0.14682	0.13335	0.72250	0.07895
2	Chlorpromazine hydrochloride	0.66025	0.85045	0.54275	0.87722	0.77369
3	Promazine hydrochloride	0.89028	2.0040	0.77004	2.05808	0.34692
4	Sodium acetate	-0.17976	-0.22659	-0.25966	-0.13886	-0.24916
5	Sodium benzoate	-0.17635	-0.23117	-0.25658	-0.13462	-0.26434
6	Lactose	-0.15839	-0.20686	-0.25068	-0.07234	-0.22772
7	Glucose	-0.15480	-0.19263	-0.23772	-0.06572	-0.20544

In order to verify the stability and strength of electrodes, the received membranes were placed for 7 days in a climatic chamber, where the "aging conditions" were set, i.e. temperature of 60°C and a relative humidity of 70%. After this time, their properties were analyzed.

The membrane containing the ion pair D-[T(3,5bis-CF_3)Ph]B and IPNB as a solvent was dry and stiff. Membrane with b(BP)A changed color (to orange), became greasy and wet, which means that it was squeezed out of the plasticizer. Due to these changes, these membranes were not used for further studies. Other membranes containing NPhOE, b(EH)S t(EH)P slightly hardened, and the color became more intense, but they maintained stretch and flexibility, and therefore were used for further experiments.

The membrane containing ion pair complex Fl-[T(F)Ph]B and IPNB as a plasticizer in the same way as for diazepam, was dry and stiff. This excluded it from further research. Membranes containing NPhOE, b(EH)S, b(BP)A slightly hardened, and the color became more intense, but survived flexibility and stretch. In the membrane with t(EH)P no changes were observed, it was flexible, ductile and transparent. For this reason, these membranes were used for further studies. Electrodes were obtained as before and the procedure of the performance of characteristic was described above. The analytical parameters of the studied electrodes after "aging conditions" are presented in Table 3. Parameters of the diazepam-sensitive electrodes are insignificantly different but the potential drift for all diazepam electrodes increased from ±19.35 mV (membrane contain t(EH)P as solvent mediator) up to ±21.83 mV (NPhOE). The measurable correlation coefficient (r) was more varied: NPhOE 0.9774, b(EH)S 0.9855, t(EH)P 0.9912. The fluoxetine-sensitive electrodes showed comparable linear range and detection limit. Correlation coefficient of linearity (r) for NPhOE was 0.9973, b(EH)S 0.9986 and t(EH)P 0.9961. Differences with each slope and drift potential, for NPhOE 45.71 mV ± 9.15 mV, b(EH)S 46.99 mV ± 8.65 mV and t(EH)P 46.87 mV ± 10,85 mV were observed. At least, in comparison to the baseline parameters, the changes in the electrode containing b(EH)S indicated that the electrode proved to be the best. The range increased by 3.203 mg mL^{-1}, the detection limit by 1.296 mg mL^{-1}, the slope decreased by 6.42 mV and increased drift of 8.035 mV. Research of "accelerated aging" showed that the fluoxetine-sensitive electrode with b(EH)s as solvent mediator meets the requirements of the analytical usefulness for long periods of time.

Diazepam and fluoxetine hydrochloride were analyzed and their concentrations were determined using proposed electrodes with the best analytical parameters. Determination was carried out by the standard addition of an aqueous solution 10^{-2} mol L^{-1} of TPB to a solution of D or Fl. Electrodes were prepared "ex tempore". For diazepam, the membranes containing: NPhOE, b(EH)S and b(BP)A were chosen, and for fluoxetine, the membranes containing: NPhOE, b(EH)S and IPNB as plasticizers were chosen. Titration was performed for each electrode. Potential-time response was measured soon after stabilising, the jump was checked, and the results were repeatable. One clear stroke corresponded to the ratio 1:1 of the potential reaction of analyzed substance - tetraphenylborate. The application of least squares method for the first two determinations gave a 95% confidence level for the slopes and intercepts. Correlation coefficient values for diazepam electrodes of 0.9970-0.9880 were obtained. The relative mean errors obtained ranged from 1.74-3.15% with recovery from 94.26 to 99.28% and standard deviation SD 0.68–1.84. For fluoxetine selective electrodes correlation coefficient values 0.9984–0.9892 were obtained. The relative mean errors obtained ranged from 0.74-2.15 % with recovery from 0.9726 to 99.28 % and standard deviation SD 0.068-0.184 and variation coefficient 0.40-1.12.

Table 3. Effect of plasticizer on response of diazepam and fluoxetine sensitive electrodes after "stress conditions" (average of six measurements)

Lp	Membrane composition	Linear range LR		Detection limit LD		Slope S (mV)	Potential drift (mV)	The parameters of linear regression in LR y = ax + b		
		mol L^{-1}	mg ml^{-1}	mol L^{-1}	mg ml^{-1}			r	a	b
D I	D – T(3,5bis-CF3)PhB NPhOE	$10^{-2} – 10^{-5.00}$	2.85×10^{6} – 2.847	$10^{-5.28}$	1.494	57.73	± 21.83	0.9774	0.0167	- 5.3075
D II	D – T(3,5bis-CF3)PhB b(EH)S	$10^{-2} – 10^{-5.00}$	2.85×10^{6} – 2.847	$10^{-5.18}$	1.881	67.17	± 21.09	0.9855	0.0145	- 5.3809
D III	D – T(3,5bis-CF3)PhB IPNB	under "stress" experienced squeezing solvent and crystallization electroactive material of membrane								
D IV	D – T(3,5bis-CF3)PhB b(BP)A	under "stress" experienced squeezing solvent and crystallization electroactive material of membrane								
D V	D – T(3,5bis-CF3)PhB t(EH)P	$10^{-2} – 10^{-5.00}$	2.85×10^{6} – 2.847	$10^{-5.15}$	2.016	57.90	± 19.35	0.9912	0.0168	- 5.6301
Fl I	Fl – T(F)PhB NPhOE	$10^{-2} – 10^{-4.95}$	3.09×10^{6} – 3.471	$10^{-5.10}$	2.457	45.71	± 9.15	0.9973	0.0215	- 5.3756
Fl II	Fl – T(F)PhB b(EH)S	$10^{-2} – 10^{-4.95}$	3.09×10^{6} – 3.471	$10^{-5.10}$	2.457	46.99	± 8.65	0.9986	0.0211	- 5.5543
Fl III	Fl – T(F)PhB IPNB	under "stress" experienced squeezing solvent and crystallization electroactive material of membrane								
Fl IV	Fl – T(F)PhB b(BP)A	$10^{-2} – 10^{-4.10}$	3.09×10^{6} – 24.572	$10^{-4.45}$	10.976	34.68	±19.1	0.9746	0.0269	- 6.3837

The results were obtained for the two repetitions after each renewal of electrode (it was done three times). After analyzing subsequent titration curves of the electrodes and the results, it can be concluded that all the electrodes can determine the reproducibility of determinations only when they are used two times. Further, their use means that between titrant portions consecutive potential jumps are smaller, and in addition, the precipitated D-TPB or Fl-TPB accumulate on the membrane, thus the titration curve flattens, reducing the sensitivity of the electrodes, thereby reducing the sensitivity of the determination.

CONCLUSION

The type of membrane solvent (plasticizer) affects the performance characteristics of ion-selective electrodes with liquid membranes heterogeneous cations function received with the diazepam and fluoxetine. The best performance was presented by diazepam electrode membrane, which contained 1-isopropyl-4-nitrobenzene. The potential response was quick, it was sensitive, selective, and the only drawback is the short "life." The best results are obtained with fluoxetine electrode containing bis(2-ethylhexyl) sebacate. It was a sensitive, selective, and its performance characteristics were also satisfactory when subjected to accelerated aging diaphragm action. The proposed membrane electrode system based on diazepam or fluoxetine with fluorine derivatives phenylborate as cations exchangers and different solvent mediators, offers a simple, rapid, high-degree-of-precision and accurate "ex tempore" technique for the determination of diazepam and fluoxetine in pure substance.

This paper was developed using the equipment purchased within the Project called "The equipment of innovative laboratories doing research on new medicines used in the therapy of civilization and neoplastic diseases" within the Operational Program Development of Eastern Poland 2007 – 2013, Priority Axis I Modern Economy, Operations I.3 Innovation Promotion.

REFERENCES

1. Al Attas A.S.: Construction and analytical application of ion selective bromazepam sensor. *Int. J. Electrochem. Sci.*, 4, 20, 2009.
2. Alaa Eldin A.S. et al.: Potentiometric determination of some 1,4-benzodiazepines in pharmaceutical preparations and biological samples. *J. Electroanal. Chem.*, 536, 1, 2002.
3. Ammar R.A., Otaif H., Al-Warthan A.: Quantitative determination of duloxetine hydrochloride in pharmaceuticals and urine using prepared ion selective membrane electrode. *International J. Electrochem. Sci.,* 7, 2531, 2012.
4. Craggs A., Moody G.J., Thomas J.D.R.: PVC matrix membrane ion-selective electrodes. *J. Chem. Ed.,* 51, 541, 1974.
5. Dobaria N.B., Shah S.G., Rajput S.J.: Development of novel plastic membrane ion-selective electrode for metformin hydrochloride. *Indian J. Pharm. Sci.,* 68, 562, 2006.
6. Drozd J., Hopkała H.: Cyproheptadine ion-selective electrodes and their applications in some pharmaceutical formulations. *Desalination*, 163, 119, 2004.
7. El-Naby E.H.: Polymeric membrane sensors for the selective determination of dextromethorphan in pharmaceutical preparations. *Anal. Sci.*, 24, 1409, 2008.
8. Eugster R. et al.: Plasticisers for liquid polymeric membranes of ion-selective chemical sensors. *Anal. Chim. Acta*, 289, 1, 1994.
9. Gupta V.K., Agarwal S., Singhal B.: Potentiometric assay of antipsychotic drug (Ziprasidone Hydrochloride) in pharmaceuticals, serum and urine. *Int. J. Electrochem. Sci.,* 6, 3036, 2011.
10. Gupta V.K., Singh A.K., Gupta B.: Potentiometric sensor for the high throughput determination of tetramisole hydrochloride. *Comb. Chem. High T. Scr.,* 10, 583, 2007.
11. Hassouna M.E.M., Elsuccary S.A.A.: PVC membrane electrode for the potentiometric determination of Ipratropium bromide using batch and flow injection techniques. *Talanta*, 75, 1175, 2008.
12. Ibrahim H., Issa Y.M., Abu-Shawish H.M.: Potentiometric flow injection analysis of dicyclomine hydrochloride in serum, urine and milk. *Anal. Chim. Acta,* 532, 79, 2005.
13. Jalali F., Arkan E., Bahrami G.: Preparation of a gabapentin potentiometric sensor and its application to pharmaceutical analysis. *Sensor. and Actuat. B-Chem.*, 127, 304, 2007.
14. Khalil S., Kelzieh A.: New polyvinyl chloride membrane electrode without inner reference solution for the determination of methadone. *J. Pharmaceut. Biomed. Anal.*, 31, 601, 2003.
15. Malongo T.K. et al.: Amodiaquine polymeric membrane electrode. *J. Pharmaceut. Biomed. Anal.,* 41, 70, 2006.

16. Nassory N.S., Maki S.A., Al-Phalahy B.A.: Preparation and potentiometric study of promethazine hydrochloride selective electrodes and their use in determining some drugs. *Turk. J. Chem.,* 32, 539, 2008.
17. Pungor E., Toth K., Hrabeczy-Pall A.: Selectivity coefficients of ion-selective electrodes. *Pure & Appl. Chem.*, 1913, 51, 1979.
18. Sales M.G.F., Tomás J.F.C., Lavandeira S.R.: Flow injection potentiometric determination of chlorpromazine. *J. Pharmaceut. Biomed. Anal.*, 41, 1280, 2006.
19. Shawish H.M.A. et al.: Effect of plasticizers and ion-exchangers on the detection limit of tramadol-PVC membrane electrodes. *Eurasian J. Anal. Chem.*, 6, 70, 2011.
20. Siska E., Pungor E.: Potentiometric determination of tetraphenylborate ions with silver nitrate. Determination of silver, potassium and tallium. *(I) Z. Anal. Chem.* ,257, 12, 1971.
21. Wassil A.A., El-Ftaah Bastawy Farag A., Moukdad F.A.: Polymer membrane electrodes for sensitive potentiometric determination of â-blockers. *Drug Dev. Ind. Pharm.,* 33, 57, 2007.
22. Wołyniec E. et al.: Batch and flow-injection determination of catecholamines using ion selective electrodes. *Instr. Sci. Technol.*, 35, 241, 2007.
23. Zayed S.I.M., Issa Y.M.: Sibutramine selective electrodes for batch and flow injection determinations in pharmaceutical preparations. *Anal. Sci.*, 26, 45, 2010.