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Mediterranean Journal of Chemistry **2017**, 6(2), 7-14

Potentiometric Membrane Sensors for Levamisole Determination

Natalia Zubenya [1], Zholt Kormosh [1,*], Diana Saribekova [2] and Sergei Sukharev [3]

[1] Eastern European National University, Voli av., 13, 43025 Lutsk, Ukraine

[2] Kherson National Technical University, Beryslavske av., 24, 73008 Kherson, Ukraine

[3] State High Educational Establishment «Uzhgorod National University», Pidgirna str., 46, 88000 Uzhgorod, Ukraine

Abstract: The ion pair (IP) of levamisole with BiI_4^-(SbI_4^-) for the levamisole-selective sensor with a PVC membrane containing - ions were developed. Thermal behavior of obtained IP was investigated by differential thermal analysis that would show the thermal stability and the character of the decomposition of the complex. The thermolysis of $Lev^+BiI_4^-$ IP undergoes three stages that fit a theoretical interpretation. The linearity ranges of levamisole sensors function are $7.9 \times 10^{-6} - 1 \times 10^{-1}$ ($7.9 \times 10^{-5} - 1 \times 10^{-1}$) M. The Nernstian slope of 50.6 – 53.4 mV pC^{-1} and detection limit of $5.0 \times 10^{-5} - 1.5 \times 10^{-4}$) M. The working range of pH is 2.8 – 6.0. The efficiency of the use of electrodes for levamisole content control in pharmaceutical preparations was shown by direct potentiometry and potentiometric titration methods.

Key words: Levamisole; Tetraiodobismutate; Tetraiodostibiate; Ion Pair; Potentiometry.

Introduction

Levamisole (Lev), (S)-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole (Fig. 1) is a potent broad-spectrum antihelmintic drug, which is widely used in veterinary medicine for the control of gastrointestinal parasites in cattle, sheep and pigs. It is normally administered orally, by pour-on or by subcutaneous or intramuscular injection. The recommended dose is 8 mg/kg body weight. It has been used as an immunostimulant in humans. Levamisole hydrochloride is used in the treatment of a variety of immune diseases and autoimmune diseases. Levamisole hydrochloride liniments have been developed for the administration of this drug, which can treat skin type immune therapy effectively. Lev - white to off-white crystalline powder (light yellow crystalline powder), soluble in water, methanol, slightly soluble in ethanol, very slightly soluble in chloroform, insoluble in acetone; stable under ordinary conditions [1].

A great deal of work has been done by the scientists about the current application and future possibilities for altering the drug activities and evaluation with new method development by instrumental methods.

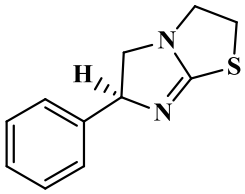

Fig. 1. The chemical structure of Levamisole.

Various techniques have been used for the determination of levamisole in biological fluids. They include gas chromatography with nitrogen–phosphorus detection (GC-NPD) [2] and flame ionization (GC-FID) [3] and liquid chromatography (LC) with ultraviolet (UV) detection [4-7]. Several methods have been developed for levamisole quantification such as polarography [8], by a turbidimetric method and flow-injection analysis [9]. Were used as potentiometric methods [10, 11].

Potentiometric determination based on ion-selective electrodes (ISEs) offers several advantages such as speed and ease of preparation and procedures, simple instrumentation, relatively fast response, wide dynamic range, reasonable selectivity and low cost [10-19]. The present work establishes a new simple, accurate, rapid and reproducible

**Corresponding author: Zholt Kormosh*
Email address: kormosh@eenu.edu.ua; zholt-1971@yandex.ua
DOI: http://dx.doi.org/10.13171/mjc61/016111516/kormosh

Received August 9th, 2016
Accepted September 14st, 2016
Published November 15th, 2016

technique for determination of levamisole, by construction and electrochemical evaluation of novel potentiometric sensors. The sensors incorporate the ion-pair (IP) complex of levamisole cation with SbI_4^-, BiI_4^- as counter anions in plasticized polyvinyl chloride (PVC) matrix. Due to the functional properties of IP to donate both a cation and an anion as potential-determining ions, they are universal ionophores [18]. It is likely that solubility is the main restriction for their use as ionophores. The solubility of IPs should be sufficiently low in aqueous phase; otherwise they will be washed out from the membranes, and at the same time, high in the membrane phase; otherwise, it will be difficult to obtain a homogeneous membrane. Previously, we analyzed the applicability of ISEs based on ion-pair as electrode-active substances in analysis of pharmaceuticals [12-19].

Experimental Section

Chemicals and reagents

All chemicals of analytical-reagent grade. Distilled water was used to prepare all solutions and in all experiments.

The modeling of the membrane composition of the ion-selective sensors utilized high molecular weight polyvinyl-chloride (PVC), dibutyl phthalate (DBP), dibutyl sebacate (DBS), diethyl phthalate (DEP), dioctyl phthalate (DOP), dinonyl phthalate (DNP), tricresyl phosphate (TCP), tetrahydrofurane (THF). They were obtained from Sigma-Aldrich.

Standard solutions and buffers were prepared freshly with deionized water. Buffer solutions were prepared by mixing corresponding amounts of 0.04 M H_3BO_3, 0.04 M CH_3COOH, 0.04 M H_3PO_4 and 0.2 M NaOH.

Procedure

The performance of the sensor was investigated by measuring the emf values of various Lev hydrochloride solutions.

An IA-123 model ionometer with Ag/AgCl reference electrode was used for the measurements of potential difference at (25.0 ± 0.1) ℃.

Stock solution (0.01 M) of levamisole was prepared as follows: accurately measured portion of the injection solution equivalent to 118 mg/L of the Lev, 5 ml of buffer solution with pH 4.0 and diluted to 50 mL with 0.1 M solution of LiCl. Further, it was diluted to produce working standards solutions with the concentration range $1\times10^{-1} – 1\times10^{-7}$ M.

An ion-pair of levamisole SbI_4^- (BiI_4^-) was prepared by mixing equal quantities of 1×10^{-2} M Lev and anions SbI_4^-, BiI_4^-. The solution was settled for 2 h and the IP sediment was filtered (quantitative rapid filter paper). This residue was treated with 50 ml of cold distilled water. The precipitate was dried as an electrode active substance for preparing the levamisole-sensitive sensor.

The description of the electrode construction and membrane phase preparation was presented in earlier papers [12-19]. The sensing membrane was prepared by mixing 70 mg of PVC powder and 15 mg of $Lev^+SbI_4^-$ or $Lev^+BiI_4^-$ with 0.12 mL of plasticizers. The mixture was stirred until the PVC was well moistened, and then the mixture was dispersed in 0.5 mL THF. The resulting mixture was transferred into a glass dish of 25 mm diameter. The solvent was evaporated slowly at a room temperature until a solid membrane with about 0.3 mm thickness was formed. A desired piece of the membrane was cut and then was attached to an end of polyethylene tube using viscous solution of PVC as an adhesive. The resulting sensor was then filled with an internal solution of 1×10^{-2} M Lev^+ and conditioned for 15 min. Then, a copper wire was immersed into the tube.

The prepared electrode was conditioned by soaking in 1×10^{-2} M Lev^+ solution for 2 h.
Aliquots (5ml) of $1\times10^{-1} – 1\times10^{-7}$ M aqueous Lev^+ in 0.04 M acetate buffer of pH 4.0 were transferred into 50 ml beakers. The Lev^+ PVC membrane sensor (indicator electrode) together with the single junction Ag/AgCl reference electrode were immersed in the Lev^+ solution. The solution was stirred and the potential reading was recorded after stabilization to ±0.3 mV. The electromotive force was plotted as a function of pC(Lev^+). The calibration plot was used for measuring samples under the same conditions.

Sample preparation

Tablets

Five tablets were accurately weighted and finely powdered. A portion of powder equivalent to one tablet of Lev^+ was accurately weighted, transferred to 50 ml volumetric flask, dissolved and shacked for 15 minutes with 5 ml of 0.04 M acetate buffer of pH 4.0 and 5 ml of 0.1 M solution LiCl. The solution was then completed to the mark.

Biological fluids (drugs in urine samples)

Aliquots of 5 ml urine were transferred to 100 ml measuring flasks, made up to the mark with the respective buffers (solution 1). Solution having concentration of 118 mg/ml levamisole was used. 1.0, 2.0 ml aliquots of the drug solution were transferred into 50 ml measuring flasks and made up to the mark with the solution 1 and were analyzed by potentiometric determination with the respective drug electrodes.

The emf of the solution was measured above and the corresponding concentration was determined using the calibration plot

Results and discussion

The thermal studies

The thermal studies (TG, DTG and DTA) were carried out on an apparatus for complex dynamic thermal analysis under the following conditions: temperature range 20 – 700 °C, heating rate 5 K/min, sample weight 27.3 mg, static nitrogen medium, channel sensitivities: DTA – 150 mV, TG – 50 mV.

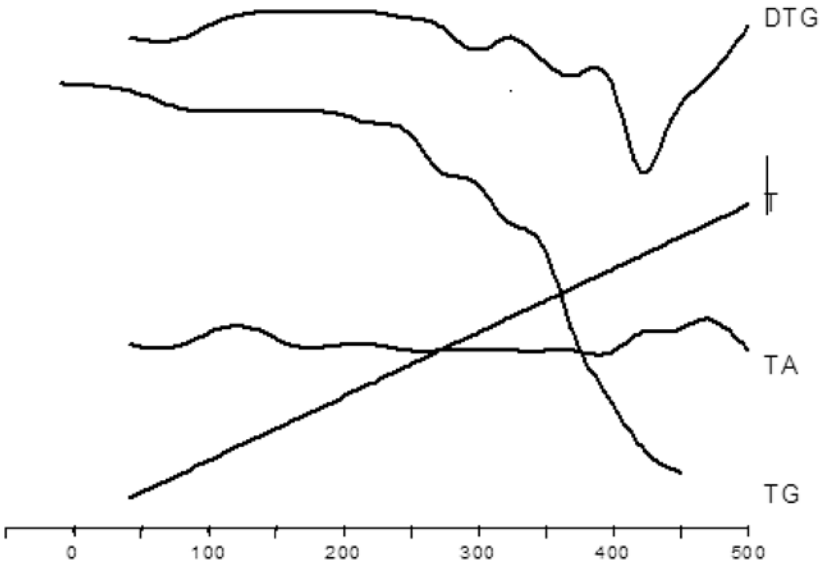

Figure 2. Simultaneous TG, DTA and DTG curves of the $Lev^{+}BiI_4^{-}$.

Thermal behavior of obtained IP was investigated by differential thermal analysis that would show the thermal stability and the character of the decomposition of the complex. The thermolysis of $Lev^{+}BiI_4^{-}$ IP undergoes three stages that fit a theoretical interpretation. The thermogram is shown in (Fig. 2).

Thermal decomposition starts above 45 °C and is accompanied by the loss of mass and the discharge of the decomposition products. This is followed by carbonization and combustion of the IP which is shown at the thermogram by an exothermal effect at 120 °C and a loss of mass. On the next stage (295 – 375 °C) we can see a loss of mass, but no significant thermal effects. At 375 – 485 °C thermal decomposition is accompanied by the loss of mass and this is followed by carbonization and combustion of the IP which is shown at the thermogram by exothermal effects at 425, 475 °C.

IR Spectroscopy

In this work, the vibration spectra analysis was carried out by using infrared spectroscopy in the range 400 – 4000 cm^{-1}. The obtained infrared spectra of the ion-pair of $Lev^{+}BiI_4^{-}$ are shown in Fig. 3, and the infrared band assignments are given in Table 1. These assignments are based on the comparison of the spectra of the formed ion pair and with the spectra of the free reactants (Table 1).

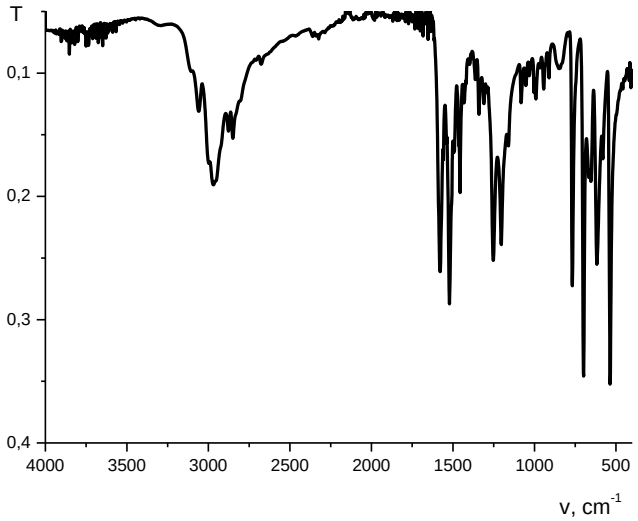

Figure 3. IR spectra of ion pair $Lev^{+}BiI_4^{-}$.

Table 1. Observed bands of levamisole, BiI_4^- and IP $Lev^+BiI_4^-$.

Wave number cm^{-1}	Assignment	Wave number cm^{-1}	Assignment	Wave number cm^{-1}	Assignment
BiI_4^-		$Lev^+BiI_4^-$		Levamisole	
		3070	ν(CH)	3430	ν(N-H)
		2961	ν(CH)	3099	ν(C-H)
				3056	ν(C-H)
				2950	ν(C-H)
				1583	Ar.ring
		1577	ν(C-N)	1525	Ar.ring
		1518	ν(C=C) ν(Ar)	1496	ν(C-N)
		1450	ν(CH)	1445	$\nu_{def.}$(C-H)
		1250	$\nu(CH)_{tiof}$	1345	ν(C-N)
		1082	$\nu(CH)_{tiof}$	1050	$\nu(C\text{-}H)_{tiof}$
		770	$\nu(CH)_{tiof}$	737	$\nu(C\text{-}H)_{tiof}$
		612	(Bi – I)	703	$\nu(C\text{-}H)_{tiof}$
470	(Bi – I)	530			

Electrochemical behavior of sensor

The present work exhibits new membrane sensors, $Lev^+SbI_4^-$ and $Lev^+BiI_4^-$, in which PVC was used as a polymeric matrix. The prepared sensor exhibits good selectivity with respect to related substances, additives in dosage forms and metal-ions. The conventional design is prepared, characterized and compared according to IUPAC recommendations.

Electrochemical characterization

Generally, the sensitivity, selectivity, working range, and stability of an ion-selective electrode depend not only on nature of the IP, but are also strongly influenced by the nature and amount of the plasticizer and additives.

To assess the effect of the plasticizer nature, uniform membranes were prepared with DBP, DOP, DBS, DNP, DEP and TCP. It was established that the best plasticizer for membranes based on IAs $Lev^+BiI_4^-$ and $Lev^+SbI_4^-$ is TCP with electrode function slope 52.8 and 54.6 mV/pC and detection limit 7.9×10^{-5} M and 2.5×10^{-6} M respectively (Table 2). On the fig. 4 there is graphical dependence of the potential of ion-selective electrode on IAs $Lev^+BiI_4^-$ from amount of plasticizer TCP.

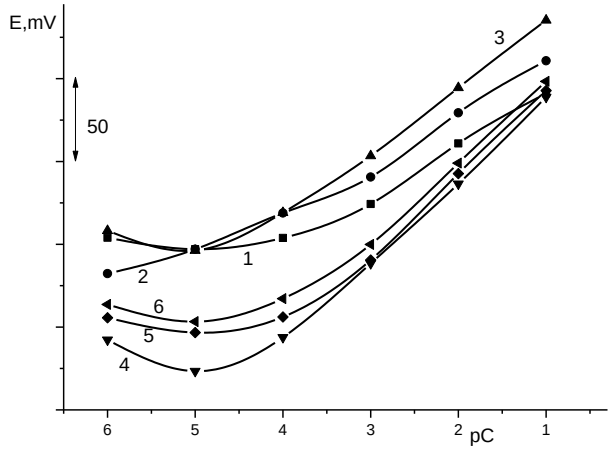

Figure 4. Graphical dependence of the ion-selective electrode potential on the Levamisole BiI_4^- (5% EAS) concentration E=f(pC). TCP content: 1–50%; 2–55%; 3–60%; 4–65%; 5–70%; 6 – 75%.

Response time

The time was measured that is necessary for the potential of the membrane electrode to reach the value within ± 1 mV of the final equilibrium value after immersing the electrode in the solution of levamisole with 10-fold difference in concentration. The sensors showed rapid response within 15 seconds for drug concentration ≥ 1×10^{-3} M and 25 seconds for 1×10^{-5} M.

Table 2. Response characteristics of PVC levamisole membrane electrode system.

Parameter	$Lev^+SbI_4^-$	$Lev^+BiI_4^-$
Slope mV/decade	54.6	52.8
Lower linear of range (M)	7.9×10^{-6}	8.9×10^{-5}
Lower limit of detection (M)	2.5×10^{-6}	7.9×10^{-5}
Response time for 10^{-3} M (s)	15	15
Life span (week)	4	4
Working pH range	2.8 – 6.3	2.8 – 5.8

The lifetime of the sensors were examined by repeated calibration every 2 days. There was no noticeable deterioration in the sensor performance in terms of detection limit, calibration curve slope and response time over a period of 30 days.

Table 4. Effect of time on response characteristics of PVC levamisole membrane electrode system.

Lev-BiI_4^-	Day	Slope mV/decade	Linear range (mol/l)	Lower limit of detection (mol/l)
	2	**3**	**4**	**5**
	10	53,5	$1\cdot10^{-1} – 7{,}2\cdot10^{-5}$	$6{,}9\cdot10^{-5}$
	20	50,3	$1\cdot10^{-1} – 7{,}9\cdot10^{-4}$	$7{,}2\cdot10^{-5}$
	60	48,7	$1\cdot10^{-1} – 3{,}6\cdot10^{-5}$	$2{,}2\cdot10^{-5}$
	90	44,9	$1\cdot10^{-1} – 3{,}2\cdot10^{-5}$	$1{,}6\cdot10^{-5}$

Effect of the medium acidity

The pH effect of the tested solution on the electrochemical behavior of the sensor was studied under a constant concentration of levamisole hydrochloride and varying the content of the hydrogen ions in the pH range of 2.0–7.5 which was adjusted with an HCl or NaOH solution. The results are illustrated in Fig. 5. The potentials keep constant in the pH range of 2.8–6.0. The observed potential drift at lower pH values may be attributed to the membrane response to H^+ and at higher pH values (pH > 9) could be due to the formation of levamisole in ionic form (p*K*a = 9.5).

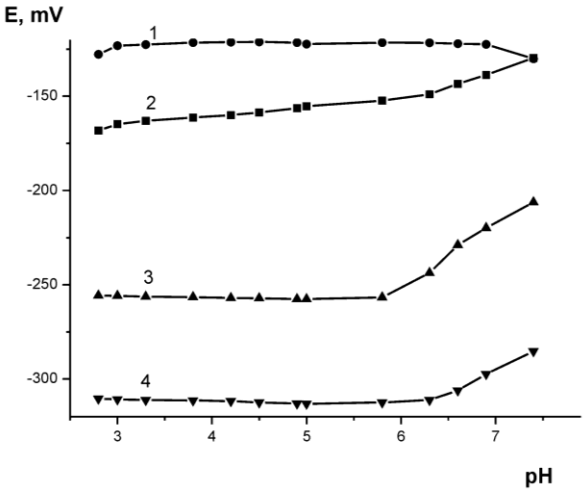

Figure 5. Effect of pH of test solution on the potential response of the proposed sensors: $Lev^+SbI_4^-$: 1 - 1.0×10^{-2} M, 2 - 1.0×10^{-3} M; $Lev^+BiI_4^-$: 3 - 1.0×10^{-2} M, 1.0×10^{-3} M levamisole hydrochloride solutions.

Sensor selectivity

The potentiometric selectivity coefficients ($K^{pot}_{Lev^+,I^+}$) of the levamisole electrodes were determined for a number of ion species by the separate solutions and matched potential method. The influences of some inorganic cations were investigated by separate solution method in which the Nicolsky-Eisenman equation was used. The potentiometric coefficients in cases of electrically neutral species were determined using the matched potential method. The potentiometric selectivity coefficients are defined in this method as the activity ratio of primary ions and interfering ions that give the same potential charge under identical conditions.

Table 3. Potentiometric selectivity coefficients ($K^{pot}_{Lev^+,I^+}$) for some common cation with levamisole -PVC membrane sensors.

Interferant, I^+	-lg ($K^{pot}_{Lev^+,I^+}$)	
	$Lev^+SbI_4^-$	$Lev^+BiI_4^-$
NH_4^+	>4	>4
Cu^{2+}	2.6	3.8
K^+	>4	>4
Na^+	>4	>4
Co^{2+}	>4	>4
Ba^{2+}	>4	>4
Ca^{2+}	>4	>4
Mg^{2+}	>4	3.9
2,3,5-Triphenyltetrazolium chloride	0.9	2.3
N-cetylpyridinium chloride	>4	>4
Tetramethylammonium bromide	>4	>4
Cetyltrimethylammonium bromide	>4	>4
Tetrabutylammonium iodide	>4	>4
Benzyltrimethylammonium chloride	>4	>4
Benzalkonium chloride	2.3	3.3

The potentiometric selectivity coefficient of the levamisole based sensors depends on the selectivity of the ion-exchange process at the membrane-sample interference, the mobility of the respective ions in the membrane. The free energy transfer of the Lev ion between the aqueous and the organic phase could also control the selectivity of the proposed sensor. Obtained results are summarized in Table 3. No interference from ions such as NH_4^+, K^+, Na^+, Co^{2+}, Ba^{2+}, Ca^{2+}, Mg^{2+} etc. was recorded. The proposed sensors exhibited a high selectivity towards levamisole with respect to the test ion.

Analytical application

Levamisole in various drugs formulation was determined by direct potentiometric measurements, potentiometric titration using these sensors. The potentials measured by those sensors were recorded and compared with the calibration graph. The proposed membrane sensor based on ion-pair of levamisole SbI_4^- ($Lev^+BiI_4^-$) was found to work well under laboratory conditions. It was applied for the determination of levamisole in pharmaceutical forms (Table 4). Comparing the dispersion of the direct potentiometric and potentiometric titration methods of the levamisole determination using *F*-test, one can see that the techniques are uniformly correct. The comparison of the set of averages Student's test shows that the uniform correctness of obtained data is observed for both proposed sensors. Calculated value of *F*-test (*F**) and Student's test (*t**) are significantly lower that the respective table data ($F^* < F_{tabl.} = 5.05$, $t^* < t_{tabl.} = 2.78$).

Table 4. Result of the determination of levamisole ($F_{tabl.} = 5.05$; $t_{tabl} = 2.78$).

Sample	**Label amount, mg**	**Found by proposed sensor**			**Found by potentiometric titration**			***F****	***t****
		mg	S^2	RSD (%)	mg	S^2	RSD (%)		
Decaris*	150	150.2 ±1.08	0.75	0.58	151.1±1.24	0.99	0.66	1.32	1.18
Decaris*	50	50.3 ±0.49	0.16	0.79	50.3 ± 0.49	0.16	0.79	1.00	0
Levamisole-Zdorovye,	150	151.1 ±1.24	0.99	0.66	151.4 ±1.39	1.14	0.71	1.15	0.34
Urine	59	58.0 ± 1.1	0.74	1.46	57.9 ± 1.1	0.8	1.51	1.08	0.14

* - Richter Gedeon Ltd, Hungary; ** - Kharkiv Ukraine

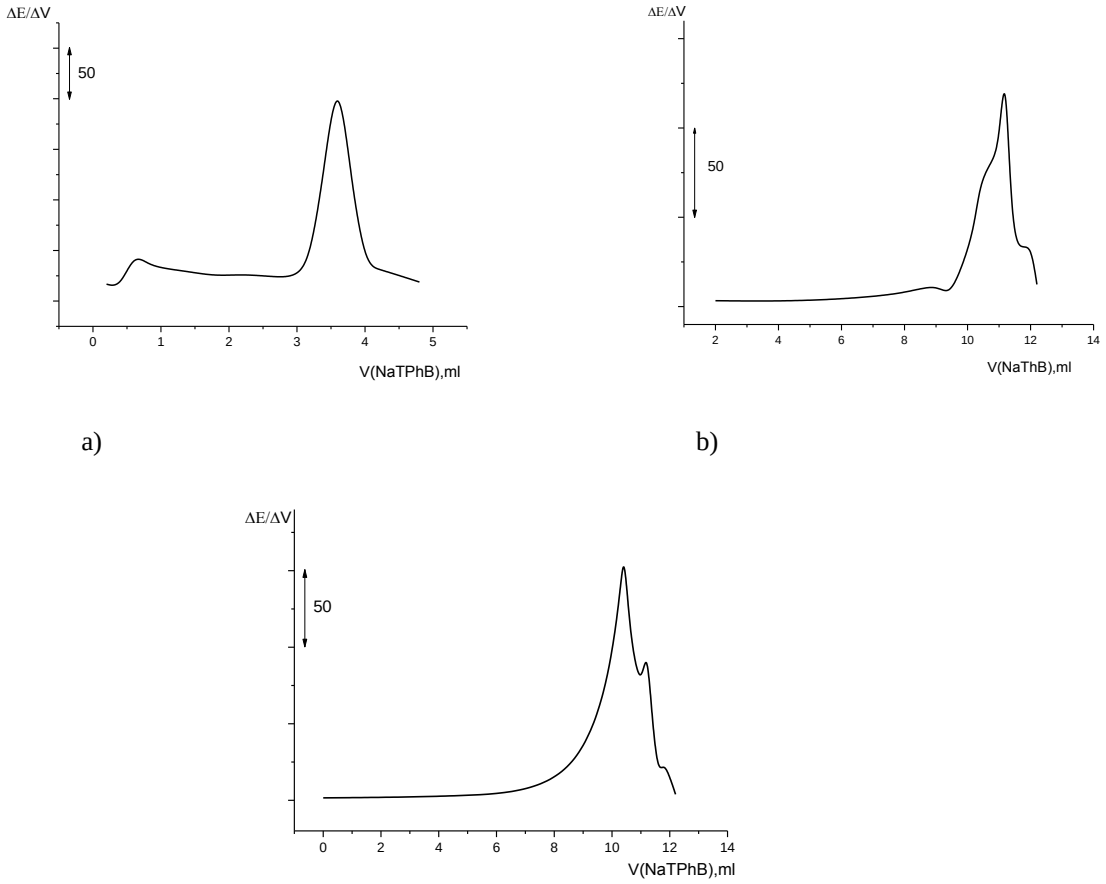

Figure 6. Potentiometric titration curve in the pharmaceutical forms (a - Decaris, Richter Gedeon Ltd,50 mg/tablet; b – Decaris, Richter Gedeon Ltd,150 mg/tablet; c - Levamisole-Zdorovye, Kharkiv Ukraina, 150 mg/tablet.

The sensor was also successfully applied as an indicator electrode in the potentiometric titration of levamisole with tetraphenylborate (NaTPhB) (Fig. 6). The 0.01 M solution of sodium NaTPhB was used as titrant. As the solubility product of the formed precipitate is sufficiently low, the concentration of levamisole in the solution near the equivalency point decreases sharply, which is manifested in a potential jump at the titrant curve.

The recovery results are shown in Table 5. Three replicate determinations at different concentration levels were carried out using the three electrodes to test the precision of the method. The standard deviations were found to be 1.0 – 1.5, indicating reasonable repeatability and reproducibility of the selected method. The precision of the method was calculated in terms of (intra-day and inter-day). The %RSD values of intra-day and inter-day studies for the repeated determination were less than 2% indicating good precision.

Table 5. Validation of the proposed method for the determination of Lev in pure form.

Conc. (mol/l)	**$Lev^+BiI_4^-$**			**$Lev^+SbI_4^-$**		
	Recovery %	RSD % *	Error %**	Recovery %	RSD % *	Error % **
Intraday precision						
$1\cdot10^{-6}$	99.02	0.65	0.29	99.00	0.72	0.32
$1\cdot10^{-5}$	99.12	0.48	0.21	99.05	0.55	0.25
$1\cdot10^{-4}$	99.56	0.38	0.17	99.56	0.45	0.20
Interday precision						
$1\cdot10^{-6}$	98.04	0.69	0.31	99.03	0.65	0.29
$1\cdot10^{-5}$	99.12	0.54	0.24	99.18	0.58	0.26
$1\cdot10^{-4}$	99.86	0.42	0.19	99.22	0.49	0.22

*%RSD=(S.D/Mean)100
**%Error= %RSD/√n

Conclusion

New levamisole electrode with polyvinylchloride membrane was developed that contain ion-pairs of levamisole with inorganic counter-ions SbI_4^- or BiI_4^- as electrode-active substances. Thermal behavior of obtained IP was investigated by differential thermal analysis that would show the thermal stability and the character of the decomposition of the complex. The thermolysis of $Lev^+BiI_4^-$ IP undergoes three stages that fit a theoretical interpretation. The proposed electrodes exhibit long lifetime, good stability, sensitivity, precision, accuracy and selectivity. They are low-cost, easy to prepare and to use.

On the basis of experimental results we have shown the successful applicability of the new membrane electrodes based on the ion-pairs of Lev^+ with SbI_4^- (BiI_4^-) for the determination of levamisole in pharmaceutical forms and urine. The comparison of the set of averages Student's test shows that the uniform correctness of obtained data is observed for both proposed sensors.

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