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ВЫСОКОЧУВСТВИТЕЛЬНЫЙ СЕНСОР С ПОЛИВИНИЛХЛОРИДНОЙ ИОНООБМЕННОЙ МЕМБРАНОЙ И ЕГО ИСПОЛЬЗОВАНИЕ ДЛЯ ОПРЕДЕЛЕНИЯ ВИНПОЦЕТИНА В ЛЕКАРСТВЕННЫХ СРЕДСТВАХ

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Установлено, что правильный выбор ионообменника, пластификатора и условий измерения позволяет получить значительно лучшие аналитические характеристики винпоцетин-чувствительных электродов на основе коммерчески доступных компонентов по сравнению с аналитическими характеристиками, описанными в литературе. Определено, что влияние pH на отклик винпоцетин-чувствительных электродов происходит в гораздо более кислых средах, чем ожидается из протолитического равновесия, и обусловливается экстракцией молекулярной формы винпоцетина в фазу мембраны как из исследуемого, так и из внутреннего раствора. Хорошие значения селективности (от –7,4 до –9,8 по отношению к неорганическим ионам), нижнего предела обнаружения ($1{,}7 \cdot 10^{-7}$ моль · л$^{-1}$), линейного диапазона функционирования ($1{,}0 \cdot 10^{-6}$ моль · л$^{-1}$) и воспроизводимости потенциала (±0,06 мВ в $1{,}0 \cdot 10^{-4}$ моль · л$^{-1}$ растворе винпоцетина) достигнуты при использовании ортонитрофенилоктилового эфира в качестве пластификатора, тетракис(4-хлорфенил)бората калия в качестве ионообменника и при создании условий, исключающих необменную экстракцию винпоцетина в мембрану на стадиях как кондиционирования электрода, так и проведения измерений. Предложены методики определения винпоцетина в лекарственных формах (таблетках и растворах для инъекций) в вариантах прямой потенциометрии и потенциометрического титрования, отличающиеся простотой, экспрессностью и высокими метрологическими характеристиками.

Ключевые слова: потенциометрия; ионоселективный электрод; винпоцетин; липофильные физиологически активные амины; фармацевтический анализ.

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HIGHLY SENSITIVE ION-EXCHANGER BASED POLYVINYL CHLORIDE MEMBRANE SENSOR FOR DETERMINATION OF VINPOCETINE AND ITS USE IN DRUGS ANALYSIS

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It has been established that the correct choice of the ion-exchanger, plasticiser and the measurement conditions makes it possible to achieve analytical characteristics of vinpocetine-sensitive electrodes based on commercially available components, far superior to those described in the literature. It has been found, that the effect of pH on the vinpocetine-sensitive electrodes response takes place in much more acidic media than might be expected from protolytic equilibrium and is due to the extraction of the molecular form of vinpocetine into the membrane phase from both external and inner solutions. Very good parameters of selectivity (from –7.4 to –9.8 in respect to inorganic ions), lower detection limit ($1.7 \cdot 10^{-7}$ mol $\cdot$ L^{-1}), linear response range ($1.0 \cdot 10^{-6}$ mol $\cdot$ L^{-1}), and potential reproducibility ($\pm$0.06 mV in $1.0 \cdot 10^{-4}$ mol $\cdot$ L^{-1} solution of vinpocetine) are achieved using 2-nitrophenyl octyl ether as a plasticiser, potassium tetrakis(4-chlorophenyl)borate as an ion-exchanger and creating conditions that exclude non-exchangable extraction of vinpocetine into the membrane at the stages of both conditioning the electrode and performing measurements. Methods for the determination of vinpocetine in dosage forms (pills and solutions for injections) using both direct potentiometry and potentiometric titration techniques characterised by simplicity, rapidity and high metrological characteristics have been proposed.

Keywords: potentiometry; ion-selective electrode; vinpocetine; lipophilic physiologically active amines; pharmaceutical analysis.

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Introduction

Potentiometric method of analysis using ion-selective electrodes (ISE) due to a number of objective advantages (high selectivity, sensitivity, the ability to work in turbid and coloured media, ease of sample preparation, rapidity, low cost of instrumentation, ease of automation, the possibility of non-destructive control, monitoring, remote signal transmission, etc.) is widely used in the analysis of technological, medical, agricultural and natural objects, as well as in scientific research.

The prospects of ISE application in pharmaceutical analysis are due to the following factors. Firstly, the presence of a large number of potential objects of analysis, since many hundreds of physiologically active substances of dosage forms are substances of ionogenic nature, easily determined with the help of ISE. Secondly, the relative ease of development and fabrication of ISEs reversible to physiologically active cations and anions, since their selectivity with respect to inorganic ingredients of dosage forms, as a rule, is predetermined by the higher lipophilicity of the ion to be determined, and selectivity with respect to accompanying organic ingredients can often be controlled by rational choice of membrane components and pH of the solution under study. Thirdly, it is important that the composition of pharmaceutical objects is deterministic, and this makes it possible to estimate in advance the influence of the matrix effect and guarantee the absence of gross blunders possible in the analysis of objects of uncertain composition, for example, environmental, due to insufficient selectivity of ISE [1]. The distinctive feature of performing pharmaceutical analyses by means of ISE, as compared to the high-performance liquid chromatography method, is the absence of the need to use expensive and toxic solvents that pollute the environment (potentiometry is recognised as a «green», environment-friendly technique), as well as the possibility of monitoring the release of the active substance from dosage forms in real time. Highly lipophilic physiologically active amines usually form poorly soluble precipitates with general alkaloid precipitators; thus, it is possible to use the method of precipitating potentiometric titration [2; 3]. Direct potentiometry and potentiometric titration methods are essentially independent, which allows one to control the reliability of the analysis results.

According to the work [4], potentiometry ranks third among all analytical methods in the pharmaceutical industry after chromatography and spectrophotometry, and about 20 % of all publications devoted to pharmaceutical analysis are on potentiometric techniques. Hundreds of articles describing the use of ISE for quality control of pharmaceuticals have been published and summarised in reviews and monographs [4–9] and this method is included as an official one in the state pharmacopoeias of leading countries [10–12].

One of the promising objects for potentiometric determination using ISE is vinpocetine, widely known as «Cavinton», apovincaminic acid ethyl ester, synthetic compound derived from vincamine, a substance found naturally in the leaves of the lesser periwinkle plant (*Vinca minor*). Various dosage forms of vinpocetine are widely used in medical practice for the treatment of disorders arising from cerebrovascular and cerebral degenerative diseases and are produced by a number of pharmaceutical enterprises in the Republic of Belarus. The structural formula of vinpocetine is shown in fig. 1.

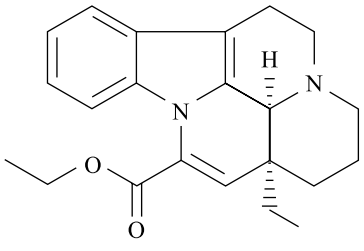

Fig. 1. The vinpocetine formula

Currently, for quantitative determination of vinpocetine in dosage forms and other objects, the high-performance liquid chromatography method with reversed phases in variants of gradient [13; 14] or isocratic [15] elution is recommended. The disadvantages of this method are labour-intensive sample preparation procedure due to the necessity of separation from insoluble matrix components, duration, use of toxic organic solvents and expensive equipment as well as the duration and labouriousness of sample preparation due to the need to separate matrix components (when analysing pills), which can damage the chromatographic column.

Vinpocetine is a very hydrophobic substance (the logarithm of the distribution constant between water and *n*-octanol is 4.23) [16], and according to the pK_a values given in the literature (from 6.94 [17] to 7.31 [18–20]), which agree with each other quite well, it exists in the cationic form in a rather wide pH range. This opens up the possibility of its potentiometric determination using ISE. To date, only one electrode for the determination of vinpocetine with a dioctylphthalate-plasticised polyvinylchloride membrane containing a salt of vinpocetine with phosphorus-tungstic acid as an ion-exchanger has been described [21]. However, the choice of membrane composition is not justified in any way, the electrode is characterised by a narrow range of functioning (from $1 \cdot 10^{-2}$ to $1 \cdot 10^{-4}$ mol $\cdot$ L^{-1}) and insufficiently high selectivity to metal ions (values range from $n \cdot 10^{-3}$ to $n \cdot 10^{-4}$). In addition, according to the information given in the work [21], the potential of the electrode was not affected by the pH over a range of 1.5–5.8 for $1 \cdot 10^{-2}$ mol $\cdot$ L^{-1} vinpocetine solution. These data are puzzling, because they are in flagrant contradiction both with the literature data on the solubility of vinpocetine [19], according to which the solubility of vinpocetine in water at pH 5 is 93 mg/L or $2.7 \cdot 10^{-4}$ mol $\cdot$ L^{-1}, and at pH 6 it is 12 mg/L or $3.4 \cdot 10^{-5}$ mol $\cdot$ L^{-1}, and with the results of our studies, according to which at pH values >5.5 precipitation from $1 \cdot 10^{-4}$ mol $\cdot$ L^{-1} solution was observed.

The aim of the present study was to show that a reasonable choice the ion-exchanger, plasticiser and the measurement conditions makes it possible to achieve very good analytical characteristics of vinpocetine-sensitive electrodes (Vin-SE) based on commercially available components, far superior to those described in the literature, and to provide very high accuracy of analysis results.

Experimental part

Reagents and materials. Potassium tetrakis(4-chlorophenyl)borate (KTpClPB), 2-nitrophenyl octyl ether (2-NPOE), tris(2-ethylhexyl)phosphate (TEHPh) and high molecular weight polyvinyl chloride (PVC) were of Selectophore grade (*Fluka*, Switzerland). Vinpocetine substance was obtained from republic unitary enterprise «Center for Expertise and Testing in Health Care» (Belarus). Sodium tetraphenylborate (NaTPhB) of grade «p. a.» was from AppliChem (Germany). Tetrahydrofuran (THF) was from Vekton (Russia). Tris(octyloxy)benzene sulfonic acid (TOBS), 97 % main substance content, was synthesised at the department of analytical chemistry (Belarusian State University) and purified by column chromatography according to [22]. All other salts, alkalis and acids used for the preparation of solutions were purchased from the company «Reachim» (Russia) and were of grade «puriss.» or «pur.». Pills «Vinpocetine forte borimed» in dosage 10 mg (*Borisov Plant of Medical Preparations*, Belarus), «Vinpocetine» in dosage 5 mg (*Pharmland*, Belarus) and solutions for injections in ampules «Cavinton» in dosage 10 mg in 2 mL (*Gedeon Richter*, Hungary) were purchased from the pharmacy chain in Minsk.

Manufacturing of electrodes. The membrane cocktails were prepared by dissolving appropriate amounts of PVC, plasticiser and ion-exchanger in the freshly distilled THF. After the cocktails were stirred for 2 h, they were poured into the glass ring fixed on the glass plate. THF was evaporated overnight yielding parent membranes of about 400 μm thickness. Disks of 11 mm diameter were cut from the parent membranes and glued to the PVC tubes with a THF – PVC composition. Concentrations of the components in the membrane were as follows: 32.8 wt. % of PVC, 66.6 wt. % of 2-NPOE, and 0.6 wt. % or approximately 0.01 mol $\cdot$ L^{-1}

of KTpClPB. The inner solution containing $1 \cdot 10^{-3}$ mol · L^{-1} vinpocetine hydrochloride was introduced, and the electrodes were conditioned overnight in $1 \cdot 10^{-3}$ mol · L^{-1} vinpocetine hydrochloride solution in $1 \cdot 10^{-2}$ mol · L^{-1} orthophosphoric acid. After conditioning the electrodes were washed with a $1 \cdot 10^{-6}$ mol · L^{-1} solution of vinpocetine in $1 \cdot 10^{-2}$ mol · L^{-1} phosphoric acid for 5 h with constant stirring of the solution. To minimise the transmembrane transfer of vinpocetine from the internal solution into the test solution (which can lead to an increase in the lower detection limit and potential drift in the low concentration region [21; 22], in some cases $1 \cdot 10^{-3}$ mol · L^{-1} tetraethylammonium chloride in $1 \cdot 10^{-3}$ mol · L^{-1} orthophosphoric acid was introduced into the internal solution instead of vinpocetine. This ensured the maintenance, due to the ion-exchange process, of a low but stable concentration of the cationic form of vinpocetine in the internal solution, which was necessary to stabilise the potential at the inner membrane interface.

Potentiometric measurements technique. All measurements were carried out at (20 ± 2) °C using pH-meter-ionometer «Ecotest-120» (*Econix*, Russia) connected to personal computer with automatic recording of electromotive force values. The saturated Ag, AgCl reference electrode EVL-1M3 and glass electrode for pH measurements ESL-43-07 were from the company «Gomel Plant of Measuring Instruments» (Belarus). The silver wire coated with electrodeposited AgCl was used as the inner reference electrode. A constant rate of stirring (500 rpm) was maintained with an RST magnetic stirrer (*IKA*, Germany). The automatic titration unit BAT-15.2MP (*Gomel Plant of Measuring Instruments*) was used to perform potentiometric titration in automatic mode.

To determine the pH range of functioning, a $1 \cdot 10^{-4}$ mol · L^{-1} solution of vinpocetine in a buffer mixture at pH value of about 2 (0.02 mol · L^{-1} acetic acid, 0.02 mol · L^{-1} boric acid and 0.02 mol · L^{-1} phosphoric acid) was prepared. To adjust the pH of the sample solution, portions of 20 μL of 2.5 mol · L^{-1} sodium hydroxide solution were used. Four minutes after each addition, the pH was recorded with a glass electrode calibrated using standard buffer solutions and the potential of the vinpocetine-sensitive electrode was measured. The maximum volume of added alkali was no more than 2 % of the initial volume of the solution, so the change in potential due to dilution of the solution was neglected.

The electrode functions were obtained by the method of sequential two-fold dilution of the initial $1 \cdot 10^{-3}$ mol · L^{-1} solution of vinpocetine with $1 \cdot 10^{-2}$ mol · L^{-1} phosphoric acid or with universal buffer mixture with pH 4. From the obtained E – log C dependences the slopes of the electrode functions, the linear response ranges and the lower detection limit values were found. The linear response ranges value was determined as the range of vinpocetine concentrations within which a deviation of measured electromotive force values from the linear dependence of E – log C did not exceed 3 mV. The lower detection limit value was determined as a vinpocetine concentration corresponding to a deviation of the experimentally determined potential value from the extrapolated linear portion of the electrode response by $RT/F \ln 2$ (in V) [23].

Unbiased selectivity coefficients were obtained using a modified separate solution method proposed by Bakker [24]. In all cases, the potentials were determined at two different concentrations of each ion, differing by an order of magnitude, and the slopes of the electrode response in solutions of each ion were checked. In the overwhelming majority of cases the slopes were close to the Nernstian one. The values of the selectivity coefficients were calculated according the formula

$$\log K_{\text{Vin},J}^{\text{Pot}} = \frac{(E_J - E_{\text{Vin}})F}{2.303RT} + \log \frac{a_{\text{Vin}}}{a_J^{\frac{1}{Z_J}}},$$

where E_J and E_{Vin} are the potentials in solutions of the foreign ion J and vinpocetine; F is the Faraday constant; R is the universal gas constant; T is the temperature, K; a_{Vin} and a_J are the activities of the corresponding ions; Z_J is the charge of the foreign ion J. The activity values were calculated using the extended Debye – Hückel equation for solutions with ionic strength up to 0.1, and using the Davis equation for solutions with higher ionic strength.

Determination of vinpocetine in dosage forms. Vinpocetine in dosage forms was determined by direct potentiometry and precipitating potentiometric titration with NaTPhB. In case of direct potentiometry we used the method of standard solution based on alternate measurement of the potential in the analysed solution and a standard solution close to the analysed concentration. Vin-SE plasticised with 2-NPOE was chosen as an indicator electrode. Calculation of the experimentally determined concentration of vinpocetine in the analysed solution was carried out according to the formula

$$C_x = C_{\text{st}} \cdot 10^{\frac{(E_x - E_{\text{st}})}{\theta}},$$

where θ is the slope of the electrode function, mV per decade. Then, taking into account dilution, the mass of vinpocetine in tablet or concentration in solution for injection was found.

In the determination of vinpocetine by potentiometric titration method, NaTPhB solution prepared according to the following procedure was used as a titrant. Sodium tetraphenylborate weighing 35 g, weighed to the first decimal point, transferred into a beaker with a capacity of 1000 cm^3, added 500 cm^3 of distilled water, 5 cm^3 of aluminium chloride solution (mass concentration 0.5 %), brought the volume of water to 1000 cm^3, stirred and stood for 12 h. Then filtered through a paper filter. The prepared solution was diluted with distilled water 10 times, obtaining the concentration of NaTPhB ≈ 0.01 mol · L^{-1}. Solutions of lower concentration were prepared directly on the day of measurements.

Preliminary titration was carried out in manual mode with constant stirring of the solution with a magnetic stirrer. In order to avoid excessive consumption of titrant for the formation of precipitation with potassium ions, an equitransferent mixture of NaCl and Na_2SO_4 was used as the electrolyte of the external reference electrode. The ionometer reading was taken after a constant potential value was established, approximately 1 min after addition of the next portion of titrant. In the vicinity of the equivalence point, the titrant was added dropwise. Construction of titration curves and finding the equivalence point by the second derivative of the function $E = f(V_{NaTPhB})$ was carried out using the computer program *OriginPro* of version 9.5 (*OriginLab*, USA). Typical titration curves are presented in fig. 2. There is a well-defined potential jump on the curves, which allows to establish the equivalence point with high accuracy.

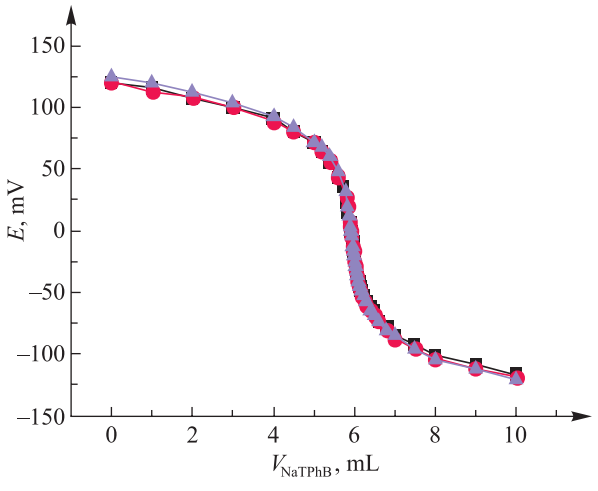

Fig. 2. Titration curves of vinpocetine standard solution with NaTPhB. The results of three consecutive measurements are presented

Further titration was carried out in automatic mode up to the set potential using the automatic titration unit BAT-15.2MP at the following values of the set parameters: titration end potential is 10 mV higher than the experimentally determined potential of the equivalence point (correction taking into account the slow establishment of the equilibrium potential value near the equivalence point); width of the titrant pulse zone is 0.9; delay time is 10 s. Equal aliquots of the test and standard solutions were titrated alternately. Titration was carried out with constant stirring of the solution with a magnetic stirrer. The time from the beginning to the end of titration did not exceed 5 min.

The concentration of vinpocetine in the tested solution was calculated according to the formula

$$C_x = \frac{C_{st} \cdot V_x}{V_{st}}, \quad (1)$$

where C_x is concentration of vinpocetine standard solution; V_x is volume of titrant at the equivalence point when titrating the vinpocetine solution under study, mL; V_{st} is volume of titrant at the equivalence point during titration of standard vinpocetine solution, mL.

Results and discussion

The data in table 1 show that the selectivity of Vin-SE significantly depends on the nature of both plasticiser and ion-exchanger. When 2-NPOE is replaced by TEHPh, as well as when KTpClPB is replaced by TOBS potassium gold (KTOBS), the interfering influence of inorganic cations sharply increases. This is explained by the strong electron-donor properties of TEHPh, which can energetically solvate small-sized cations, as well as cations of amines with a lower degree of substitution of the nitrogen atom (rimantadine, diethylamine) and is consistent with the previously discovered patterns of the influence of the nature of the plasticiser on the

selectivity of electrodes to amine cations [25; 26]. As for the selectivity to quinine, which, like vinpocetine, is a tertiary amine, the observed effect of the plasticiser is associated with the presence of a hydroxyl group in the quinine molecule, which can be solvated by electron-donor solvents by the mechanism of hydrogen bond formation. The influence of the nature of the ion-exchanger on the selectivity is logically explained by their different ability to ionic association with the basic and foreign ions. The anion $TpClPB^-$, as well as other tetraphenylborate derivatives, is characterised by a minimal ability to associate with most cations due to strong charge delocalisation. The value of the association constant depends relatively little on the nature of the cation [27]. At the same time, in the anion of $TOBS^-$ the negative charge is concentrated on the oxygen atoms of the sulfogroup. This causes a much greater ability to form ionic associates with cations compared to $TpClPB^-$, which increases with decreasing cation size, and in the series of amine cations – with decreasing degree of substitution of the nitrogen atom [27].

Table 1

Effect of the nature of plasticiser and ion-exchanger on the selectivity of Vin-SE

Foreign ion	$\log K^{Pot}_{Vin,J}$		
	KTpClPB, 2-NPOE	KTpClPB, TEHPh	KTOBS, 2-NPOE
Li^+	Less –9.8	–4.15 ± 0.05	Less –5.9
Ca^{2+}	Less –9.7	–6.67 ± 0.05	–5.05 ± 0.1
Na^+	–9.0 ± 0.1	–4.99 ± 0.05	–4.23 ± 0.2
H^+	–9.0 ± 0.1	–2.98 ± 0.03	–
K^+	–7.44 ± 0.04	–5.59 ± 0.05	–4.37 ± 0.2
$Et_2NH_2^+$	–4.85 ± 0.05	–3.45 ± 0.05	–3.74 ± 0.2
Rimantadine	*–2.95 ± 0.05*	*–0.55 ± 0.05*	*–1.82 ± 0.05*
Quinine	*–2.10 ± 0.1*	*–0.77 ± 0.05*	*–1.17 ± 0.11*

The selectivity parameter is directly related to another important characteristic of the electrode, namely the lower limit of detection, which in some cases can be limited by the presence of a foreign ion [28]. The above is illustrated in fig. 3, which shows the electrode functions of electrodes with membranes plasticised with 2-NPOE and TEHPh in solutions of vinpocetine in 10^{-2} mol · L^{-1} phosphoric acid. The sharp narrowing of the linear range of function for the electrode with TEHPh plasticised membrane is explained by the strong interfering influence of hydrogen ion (see table 1). At the same time, as it was shown in [29–31], the use of low pH values is a necessary condition for reliable functioning of ISEs reversible to cations of highly lipophilic physiologically active amines.

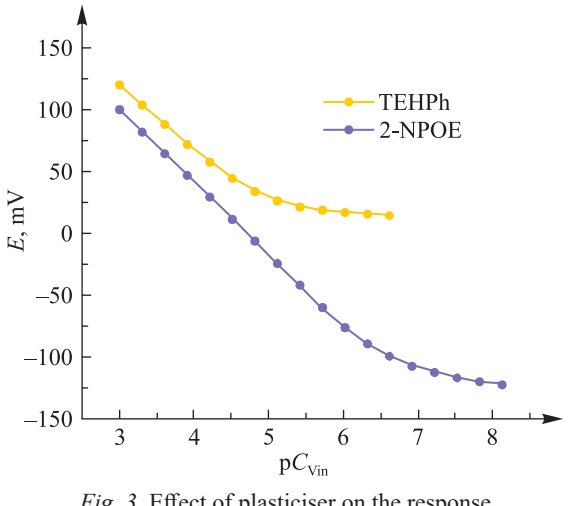

Fig. 3. Effect of plasticiser on the response of Vin-SE in 10^{-2} mol · L^{-1} phosphoric acid solutions

Further studies were carried out with an electrode with a membrane plasticised with 2-NPOE and containing KTpClPB as an ion-exchanger. Figure 4 shows the dependence of the electrode potential on pH. It can be seen that the potential drop starts much earlier than it follows from the protolytic equilibrium in solution.

Based on the vinpocetine values of pK_a given in the literature, a twofold decrease in the concentration of the protonated form should occur at pH value of about 7, which corresponds to a decrease in the potential by 18 mV. In reality, such a change occurs much earlier, at pH value of about 5. A similar effect was observed earlier for the verapamil-sensitive electrode [29] and was explained by intensive extraction of the molecular form of amine into the membrane by the mechanism of dissociative extraction. This leads to a sharp decrease in the total concentration of amine in the near-electrode layer of the solution in contact with the membrane and, accordingly, to a decrease in the concentration of the protonated form, compared to the concentration in the solution volume.

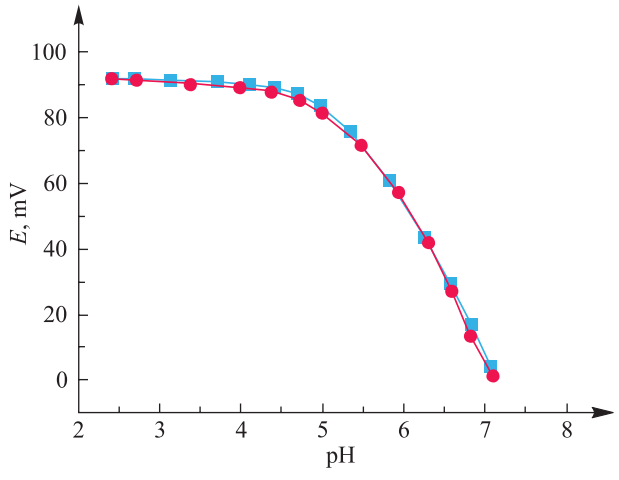

Fig. 4. Dependence of Vin-SE potential on pH

Figure 4 shows that the electrode potential does not change much up to pH 4. However, in practice, the requirements for the pH range should be even more stringent, especially when working with low concentrations. The above is illustrated by the data shown in fig. 5. It can be seen that the concentration range of Vin-SE response in 10^{-2} mol · L^{-1} phosphoric acid (pH value of about 2.3) is significantly extended, and the lower limit of detection is reduced by more than an order of magnitude than in solutions with pH 4. Thus, not the entire width of the operating pH range, determined from the potential versus pH, provides optimal electrode performance. This apparent contradiction is due to the fact that the dependence of the potential on pH is studied at a fixed concentration of vinpocetine in solution, therefore, a decrease in the concentration of vinpocetine in the near-electrode layer of the solution by several percent compared to the bulk concentration has little effect on the value of the potential. However, when a concentrated solution is replaced for a dilute one, the increase in the amine concentration in the solution due to re-extraction from the membrane can be significant. So, the correct choice of the pH value is of paramount importance when working with highly lipophilic physiologically active amines like vinpocetine. In the following all measurements were carried out against 10^{-2} mol · L^{-1} phosphoric acid.

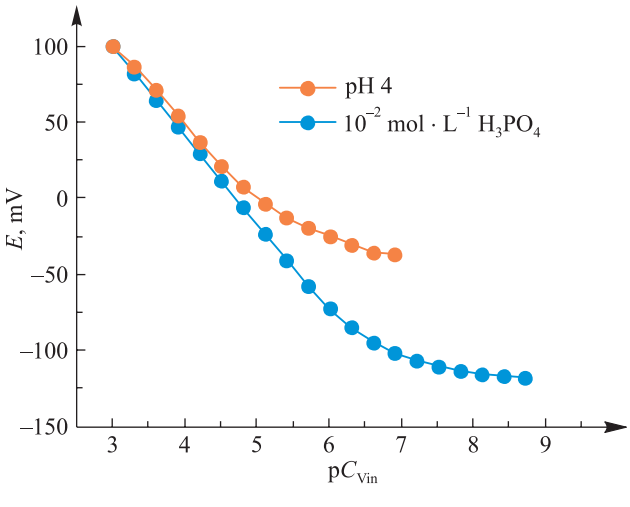

Fig. 5. Effect of pH on the Vin-SE response

Determination of vinpocetine in pills «Vinpocetine forte borimed» (*Borisov Plant of Medical Preparations*) by direct potentiometry. One package contains 3 blisters, 10 pills each; the nominal weight of vinpocetine in one pill is 10 mg. In addition to vinpocetine, the pills contain excipients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, talc, povidone (low molecular weight medical polyvinylpyrrolidone 12 600 ± 2700), potato starch. First, the total masses of the pills in each of the three blisters were determined, which were 1.956 0; 1.964 0 and 1.984 4 g. Next, the average content of vinpocetine per pill in a blister with an intermediate mass of 1.964 0 g was determined and individual pills with minimum, maximum and intermediate weight, selected from the two remaining blisters were analysed.

To determine the content of vinpocetine in one individual pill, it was placed in a chemical beaker, 40 mL of $1 \cdot 10^{-2}$ mol $\cdot$ L^{-1} phosphoric acid was added and stirred on a magnetic stirrer for about 30 min. Then the content of the beaker was quantitatively transferred into a 100 mL volumetric flask, rinsed repeatedly with a solution of $1 \cdot 10^{-2}$ mol $\cdot$ L^{-1} phosphoric acid, adjusted to the mark with the same solution, mixed and allowed to stand for 5–10 min. The sediment of insoluble ingredients of the pill present at the bottom did not interfere with the determination. When determining the content of vinpocetine in a blister (10 pills), the volume of phosphoric acid used for dissolution was increased 10 times. At the same time, a standard solution containing 50.00 mg of vinpocetine substance in 500 mL of $1 \cdot 10^{-2}$ mol $\cdot$ L^{-1} phosphoric acid, as well as a solution for washing the electrode between measurements ($1 \cdot 10^{-6}$ mol $\cdot$ L^{-1} vinpocetine in $1 \cdot 10^{-2}$ mol $\cdot$ L^{-1} phosphoric acid) were prepared.

To perform measurements, about 20 mL of the test, standard and washing solutions were placed in chemical beakers with a capacity of 50 mL and the magnetic stirrer arms were immersed there. Next, the indicator electrode and the reference electrode were immersed in a standard solution and kept under stirring until the potential was close to constant (so that the drift did not exceed 0.1 mV/min). Then the electrodes were blotted with filter paper, immersed in a washing solution and washed with stirring to a potential value 90–100 mV lower than the potential in the standard solution. Next, alternate measurements of potential values were carried out in the test and standard solutions at the same stirring rate (500 rpm), recording the potential value exactly 2 min after turning on the stirrer and each time washing the electrode between measurements. It is important to note that there is no need to wash the electrode to the lowest possible potential, which may require a long time and several changes of the washing solution, but it is important to wash the electrode to the same potential each time. In this case, each subsequent measurement begins from the same «starting position» of the electrode. Standardisation of washing and measuring procedures (constant stirring conditions and equal potential recording times) allows very high reproducibility of results to be achieved. The mass of vinpocetine in a pill (m_x) was calculated using the formula (1).

Table 2 shows typical measurement results, which are characterised by very good repeatability. Similar results were obtained for other samples as well. The results of statistical processing of the obtained data are shown in table 3.

Table 2

Results of determining the content of vinpocetine in an individual pill with an intermediate weight (m = 198.75 mg)

Serial number of measurement	E_{st}, mV	E_x, mV	$E_x - E_{st}$, mV	m_x, mg
1	173.0	173.3	0.3	10.12
2	173.1	173.4	0.3	10.12
3	173.0	173.2	0.2	10.08
4	172.9	173.2	0.3	10.12
5	173.0	173.2	0.2	10.08
6	172.9	173.2	0.3	10.12
7	173.0	173.2	0.2	10.08
8	173.0	173.4	0.4	10.16
9	173.1	173.4	0.3	10.12
10	173.0	173.4	0.4	10.16

Note. $E_{washing}$ is 86 mV, vinpocetine content in the standard solution was 100 mg/L, standard deviation (SD) is 0.030 mg, standard relative (S_r) is 0.3 %, mean mass is (10.12 ± 0.02) mg.

Table 3

Results of vinpocetine determination in pills

Serial number (i) of the sample	Type of the sample	Mass of the analysed pill, mg	Mean mass of vinpocetine in the analysed pill, mg	Standard deviation in repeated measurements ($SD_{i,n}$), mg	Standard deviation of means (SD_i), mg	$F_{exp} = \frac{(SD_{max})^2}{(SD_i)^2}$	t_{exp} ($P = 0.95$; $f_1 = f_2 = 9$)	Mean normalised mass of vinpocetine, mg	$t_{exp.,\,norm}$ ($P = 0.95$; $f_1 = f_2 = 9$)
1	Pill with mean mass	198.75	10.12 ± 0.02	0.030	0.010	1.96	$t_{1,2} = 14.6$ $t_{1,3} = 12.3$ $t_{1,4} = 7.84$	10.02 ± 0.02	$t_{1,2,norm} = 3.84$ $t_{1,3,norm} = 6.15$ $t_{1,4,norm} = 0.00$
2	The heaviest pill	203.60	10.31 ± 0.02	0.028	0.009	2.25	$t_{2,3} = 24.4$ $t_{2,4} = 20.8$	9.97 ± 0.02	$t_{2,3,norm} = 9.39$ $t_{2,4,norm} = 3.35$
3	The lightest pill	192.90	9.92 ± 0.03	0.042	0.013	–	$t_{3,4} = 4.47$	10.12 ± 0.03	$t_{3,4,norm} = 5.59$
4	Blister with mean mass	196.40*	10.00 ± 0.03	0.038	0.012	1.22	–	10.02 ± 0.03	–

Notes: 1. Sign * is mean mass of the pill in the blister with total mass 1.9640 g. 2. Normalised masses of vinpocetine in the analysed samples were calculated as experimentally determined ones multiplied by the ratio of mean mass of one pill in the set of three blisters (taken equal to 196.81 mg) to the mass of the analysed sample. 3. F_{table} ($\beta = 0.05$; $f_1 = f_2 = 9$) = 3.18; t_{table} ($P = 0.95$; $f_1 = f_2 = 9$) = 2.10.

One can see that the results of the determination of vinpocetine in all four samples are characterised by very high repeatability (the SD of the average value does not exceed 0.013 mg, which corresponds to $S_r = 0.13$ %). According to the Fisher test, the results of the analysis of all samples are equally accurate at a significance level of 0.05. However, the discrepancy in the mass of vinpocetine in individual pills reaches 0.4 mg, which significantly exceeds the values of the confidence intervals, and the observed differences, according to the Student's test, are statistically significant. Since the highest content of vinpocetine was found in the pill with the maximum weight, and the lowest – in the pill with the minimum weight, it was of interest to compare the normalised contents of vinpocetine in individual pills, corrected for the deviation of the weight of the individual pill from the average value:

$$m_{x,\,\mathrm{norm}} = m_x \frac{m_{\mathrm{averaged}}}{m_{\mathrm{sample}}},$$

where m_{averaged} is the averaged weight of one pill in the package, equal to 196.81 mg; m_{sample} is the weight of the pill of the test sample.

It turned out that although the normalised values agree much better with each other (the maximum difference is 0.15 mg), the differences, according to the Student's test, are still statistically significant. This allows us to conclude that the observed differences in the content of vinpocetine in individual pills may be due not only to dosing inaccuracy during their formation, but also to the non-uniformity of the molding mass. At the same time, neither the discrepancy in the masses of the pills, nor the variation in the content of vinpocetine in them goes beyond the requirements of the Pharmacopoeia [12], according to which for pills weighing from 80 to 250 mg, the deviation of the mass from the declared value should be no more than 7.5 %, and the relative SD of the active substance in the dosage form should not exceed 6 %.

Determination of vinpocetine in pills «Vinpocetine» (*Pharmland*) by direct potentiometry. A solution of 5 pills in 500 mL of 10^{-2} mol · L^{-1} phosphoric acid was prepared and the potential values in the standard and analysed solutions were measured alternately according to the algorithm described above. The vinpocetine content was determined in the same solution by potentiometric titration. Aliquots of the analysed and standard solutions were 50 mL, vinpocetine concentration in the standard solution was $1 \cdot 10^{-4}$ mol · L^{-1} (35.05 mg/L), titrant with concentration of about $1 \cdot 10^{-3}$ mol · L^{-1} was used. The results obtained are summarised in table 4.

Table 4

Results of vinpocetine determination in pills by direct potentiometry and potentiometric titration methods

Direct potentiometry			Potentiometric titration		
E_{st}, mV	E_x, mV	m_x, mg	V_{st}	V_x	m_x, mg
47.7	56.8	5.03	5.48	7.88	5.04
47.6	56.5	4.99	5.46	7.88	5.06
47.6	56.5	4.99	5.38	7.82	5.09
47.4	56.4	5.01	5.46	7.88	5.06
47.5	56.4	4.99	5.42	7.88	5.11
49.3	58.5	5.05	5.46	7.88	5.06
49.9	59.0	5.03	5.48	7.88	5.04
50.4	59.5	5.03	5.48	7.82	5.00
50.9	60.0	5.03	5.50	7.88	5.02
51.2	60.1	4.99	–	–	–

N o t e. For direct potentiometry method $<m_x>$ is 5.014 ± 0.016, SD is 0.023, S_r is 0.46 %, F_{exp} is 2.18, for potentiometric titration method $<m_x>$ is 5.053 ± 0.026, SD is 0.034, S_r is 0.67 %, F_{table} is 3.39.

It is clear from the above data that the results obtained by both methods have a very good reproducibility and are equivalent according to the Fisher's criterion. At the same time, the determination results obtained by both methods are in excellent agreement with each other. Since the methods of direct potentiometry and potentiometric titration are essentially independent, the observed coincidence of the analytical results indicates their reliability.

Determination of vinpocetine in solution for injection (*Gedeon Richter*). The contents of 5 ampoules were combined, 10 mL of the solution was withdrawn by pipette and brought to 1 L with 10^{-2} mol · L^{-1} phosphoric

acid solution. The concentration of vinpocetine in the resulting solution was determined by potentiometric titration. The concentration of vinpocetine in the standard solution was 35.05 mg/L.

The total vinpocetine content in the ampoule and its concentration were determined by direct potentiometry method. For this purpose, the density of the solutions of this set was determined by pycnometric method (1.0329 g/mL), and the mass of the solution was found by the difference of the ampoule with and without solution, which was quantitatively transferred into a 100 mL measuring flask. The concentration of vinpocetine in the standard solution was 100.0 mg/L. The results of the determination are summarised in table 5.

Table 5

Comparative data of vinpocetine determination in solution for injection by direct potentiometry and potentiometric titration methods

Direct potentiometry (V_{amp} = 2.165 mL)			Potentiometric titration		
E_{st}, mV	E_x, mV	C_x, mg/mL	V_{st}	V_x	C_x, mg/mL
206.2	208.2	5.0103	5.40	7.78	5.05
206.2	208.1	4.9900	5.40	7.78	5.05
206.0	208.2	5.0511	5.38	7.70	5.02
205.9	208.2	5.0716	5.38	7.70	5.02
206.1	208.4	5.0716	5.40	7.74	5.02
206.2	208.4	5.0511	5.40	7.74	5.02
206.2	208.6	5.0923	5.40	7.70	5.00
206.3	208.5	5.0511	5.40	7.70	5.00
206.3	208.6	5.0716	5.40	7.72	5.01
206.2	208.2	5.0308	5.40	7.70	5.00

Note. For direct potentiometry method $<C_x>$ is 5.0492 ± 0.0223, SD is 0.031, S_r is 0.61 %, F_{exp} is 2.66, for potentiometric titration $<C_x>$ is 5.02 ± 0.0223, SD is 0.019, S_r is 0.38 %, F_{table} is 3.18.

It can be seen that, as in the case of tablet analysis, the methods of direct potentiometry and potentiometric titration are characterised by very high accuracy and agree well with each other.

It should be noted that the difference between the results of single measurements and the average values calculated from 10 repetitions in the vast majority of cases does not exceed 0.5 %, which makes it possible to get by with a minimum number of repeated measurements when performing real analyses. Taking into account the low cost, simplicity, rapidity and high accuracy of the described method, it may be of interest for use in laboratories of pharmaceutical enterprises, primarily at the stages of inter-operational control of technological processes, for example, to control the uniformity of the composition of the molding mass.

Conclusions

It is shown that rational choice of plasticiser (low solvating ability) and ion-exchanger (low propensity to ion association), which can be carried out on the basis of general principles of functioning of ion-selective electrodes allows to obtain an electrode with very good analytical characteristics. The choice of conditions for performing measurements that exclude the extraction of the molecular form of lipophilic amine into the membrane phase is also very important. Standardisation of the procedures for performing measurements and washing the electrodes ensures very high reproducibility of direct potentiometric determination, which is not inferior to the reproducibility of the most advanced methods of instrumental analysis. The good agreement of the results obtained by direct potentiometry and potentiometric titration methods indicates their reliability. We believe that similar approaches may be useful in the development of electrodes for the determination of other highly hydrophobic physiologically active amines.

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