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DETERMINATION OF RIMANTADINE IN DOSAGE FORM «GRIPPOMIX» USING THE ION-SELECTIVE ELECTRODE[1]

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The possibility of direct potentiometric rimantadine determination in dosage form «Grippomix» using the ion-selective electrode (ISE) with the membrane based on *tetrakis*(4-chlorophenyl)borate (TCPB) as the ion-exchanger was investigated. It was shown that from all components of the dosage form only cetirizine can significantly influence on the electrode functioning. It was found that the replacement of *o*-phenyloctylether as the plasticizer by the *tris*(2-ethylhexyl)phosphate (TEHP) in the electrode membrane can reduce the influence of cetirizine almost in 30 times. The ISE membrane with 0.5 % of TCPB, 66.5 % of TEHP and 33.0 % of polyvinylchloride as the polymer matrix demonstrates the linear response to rimantadine in the concentration range $1 \cdot 10^{-5}$–$1 \cdot 10^{-1}$ mol/l with the slope of electrode function close to the nernstian one (58.6 mV/decade at 20 °C), lower detection limit $6 \cdot 10^{-6}$ mol/l and retains operability for 6 months. Standard deviation of electrode potential in the $1 \cdot 10^{-3}$ mol/l rimantadine solution is 0.33 mV. The pH variation from 2 to 9 do not affect at the ISEs response to rimantadine. On the other hand, the response to cetirizine cation depends on pH and at pH ≥ 3 it drastically reduces because of cetirizine transformation to electrode inactive zwitterion form. The influence of cetirizine on the rimantadine-selective electrode response is fully suppressed if analysis is carried out in phosphate buffer medium (pH 6.86). Standard solution method (one-point calibration) and limiting solutions method (two-point calibration) are proposed for direct potentiometric rimantadine determination. Both techniques are characterized by high reproducibility ($S_r \leq 0.6$ %), precision estimated by the criterion «introduced/labeled – found» was no worse than 0.8 %.

Key words: ion-selective electrode; direct potentiometry; rimantadine; pharmaceutical analysis.

ОПРЕДЕЛЕНИЕ РЕМАНТАДИНА В ЛЕКАРСТВЕННОМ ПРЕПАРАТЕ «ГРИППОМИКС» С ПОМОЩЬЮ ИОНОСЕЛЕКТИВНОГО ЭЛЕКТРОДА

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Изучены возможности прямого потенциометрического определения ремантадина в лекарственном препарате «Гриппомикс» с помощью ионоселективного электрода с ионообменной мембраной на основе *тетракис*(4-хлорфенил)бората. Показано, что из всех ингредиентов лекарственной смеси только цетиризин влияет на отклик

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ионоселективного электрода. Установлено, что замена *орто*-нитрофенилоктилового эфира в качестве пластификатора *трис*(2-этилгексил)фосфатом позволяет снизить мешающее влияние цетиризина почти в 30 раз. Ионоселективный электрод с мембраной, содержащей 0,5 % *тетракис*(4-хлорфенил)бората, 66,5 % *трис*(2-этилгексил)фосфата и 33 % поливинилхлорида в качестве полимерной матрицы, проявляет линейный отклик на ремантадин в интервале концентраций $1 \cdot 10^{-5}$–$1 \cdot 10^{-1}$ моль/л с наклоном электродной функции, близким к нернстовскому (58,6 мВ/дек. при 20 °С), имеет нижний предел обнаружения $6 \cdot 10^{-6}$ моль/л и сохраняет работоспособность 6 мес. Стандартное среднеквадратическое отклонение потенциала при концентрации ремантадина $1 \cdot 10^{-3}$ моль/л составляет 0,33 мВ. Изменение pH в пределах от 2 до 9 не влияет на отклик ионоселективного электрода по отношению к ремантадину. Напротив, отклик на катион цетиризина зависит от pH и при pH ≥ 3 резко уменьшается с ростом pH, что обусловлено переходом цетиризина в электродно-неактивную цвиттер-ионную форму. При проведении измерений в среде фосфатного буфера (pH 6,86) влияние цетиризина на отклик ремантадин-СЭ полностью подавляется. Предложены методики прямого потенциометрического определения ремантадина в препарате «Гриппомикс» в вариантах ограничивающих растворов (калибровка по двум точкам) и стандартного раствора (калибровка по одной точке). Методики характеризуются высокой воспроизводимостью ($S_r \leq 0{,}6$ %), правильность, оцененная по критерию «введено – найдено», не хуже 0,8 %.

Ключевые слова: ионоселективный электрод; прямая потенциометрия; ремантадин; фармацевтический анализ.

Rimantadine hydrochloride (1-(1-adamantyl)ethylamine hydrochloride) is widely used in medicine to prevention and treatment of flu [1]. The generally accepted pharmacopeia method for determination of rimantadine in pure substance and in tablets is titration with perchloric acid in acetic anhydride medium [2]. The obvious disadvantage of this technique is high toxicity of the solvent. Besides of that, the provided technique is unacceptable for quantitative analysis of different dosage forms containing ingredients, which also can react with titrant. So chromatographic [3; 4], electrophoretic [5; 6] and spectroscopic [7–9] techniques for rimantadine determinations in pharmaceutical formulations have been proposed. The main drawbacks of these methods are cumbersome and expensive equipment, long sample preparation and the usage of toxic solvents.

Practical demands for monitoring the main component in pharmaceutical dosage forms and for intermediate technological control of their manufacturing stimulate development of new simple and rapid analytical methods, and potentiometry with ion-selective electrodes (ISEs) is one of the most perspective among them. Potentiometric method of analysis is characterized by its rapidity, simplicity and low cost of equipment, possibility of analyzing in turbid and colored solutions without any prior separation. At the same time, this method is characterized by high precision, reproducibility and reliability and due to these apparent advantages it has acquired increasing prominence for pharmaceutical quality control over the last two decades [10]. According to [11] the potentiometry takes third place among all methods of analysis in pharmaceutical industry after chromatography and spectrophotometry and about 20 % of all publications in pharmaceutical analysis is devoted to potentiometric techniques. Several thousands of research articles on ISE application in pharmaceutical research and quality control have been published for more than forty years, they are partly generalized in reviews and monographs [10–15].

However in spite of growing popularity of potentiometric method only one example of ISE usage for determination of rimantadine in tablets was demonstrated up to date [16]. The goal of the present paper is to develop the method for rimantadine determination in far more complicated preparation «Grippomix» containing about a dozen of organic and inorganic ingredients with rather small (0.75 %) content of the target component.

Experimental part

Reagents and solutions. For the electrode membrane preparation tetrahydrofurane (THF) (Vecton), polyvinylchloride (PVC), cation-exchanger – potassium *tetrakis*(4-chlorophenyl)borate (TCPB), plasticizers – *o*-nitrophenyloctylether (NPOE) and *tris*(2-ethylhexyl)phosphate (TEHP), all from Selectofore, A. G. Fluka were used.

Rimantadine hydrochloride, cetirizine dihydrochloride, paracetamol, aspartame, citric and ascorbic acids, calcium carbonate-sorbitol and flavor enhancers used for the solution preparation were of pharmacopeia purity (the content of the main component no less than 99 %). All inorganic substances used were of puriss grade (*Reakhim*, Russia).

Powder for oral use «Grippomix» with rimantadine under investigation was obtained from local drug stores.

Electrode preparation and potentiometric measurements. Electrode membrane was prepared according to the common technique [17]. PVC (211 mg) and a plasticizer (425 mg) were weighed precisely and thoroughly mixed together using the magnetic stirrer. The obtained mixture was dissolved in 3 ml of THF. The calculated weight of ion-exchanger was very small. Thus, the solution of TCPB was firstly prepared by weighting 10.3 mg of ion-exchanger and dissolving in 3 ml of THF. Further 1 ml of TCPB solution was added to the mixture of PVC

and plasticizer in THF. The obtained cocktail was poured into the glass ring with inner diameter 42 mm fixed on the glass plate and the solvent was allowed to evaporate overnight. Membrane disks (approx. 0.5 mm thick) were cut out from the master membrane and glued on the top of poly(metylmetacrylate) tubes with PVC – THF composition. The electrode membranes contained 0.01 mol/l TCPB, 33 mass. % PVC, the rest – NPOE or TEHP. Newly prepared electrodes were soaked in $1 \cdot 10^{-3}$ mol/l rimantadine hydrochloride solution within 24 hours. The internal reference solution of the rimantadine-selective electrode contained $1 \cdot 10^{-3}$ mol/l rimantadine hydrochloride and 0.01 mol/l NaCl.

The silver-silver chloride electrode EVL-1M3.1 with 3.5 mol/l KCl as a filling solution was used as the reference electrode. The pH measurements were carried out with the ESL-43-07 glass electrode. The electromotive force of electrochemical sell was measured using the ionometer Ecotest-120 at 20 ± 2 °C temperature.

The pH-dependence of potential was studied in $1 \cdot 10^{-2}$ mol/l rimantadine and $1 \cdot 10^{-3}$ mol/l cetirizine solutions. Previously the pH value of the solution was brought to pH ≈ 2 with 1 mol/l HCl. Then the analyzed solution was alkalized at steps of about 0.5 pH units by adding minimum volumes of NaOH of various concentrations.

Electrode function was obtained using the consecutive double dilution method of the initial ($1 \cdot 10^{-1}$ mol/l) rimantadine hydrochloride solution on the 0.05 mol/l phosphate buffer background. The same phosphate buffer solution with pH 6.86 ± 0.02 was used as a diluent.

The quantitative analyses were made using standard solution method (SSM) and limiting solutions method (LSM). The LSM is based on the determination of the potential value in calibration solutions (E_1 and E_2) as well as in the solution under investigation (E_x) in order of increasing concentration ($C_1 < C_x < C_2$). After that the content of analyzed ion is count using the next formula:

$$c_x = 10^{\frac{E_x(\lg c_2 - \lg c_1) + E_2 \cdot \lg c_1 - E_1 \lg c_2}{E_2 - E_1}}.$$

In the SSM method, the potential value is measured in the standard (E_1) and investigated (E_x) solutions in order of increasing concentration. However, this method requires preliminary determination of the electrode function slope (S) in the working range of concentrations. The ascertained slope is accepted constant in following calculations. The content of analyzed ion is calculated using the next formula:

$$c_x = c_1 \cdot 10^{\frac{E_x - E_1}{S}}.$$

Before any potential measurement the rimantadine-selective electrodes were at first washed in the solution with contents of rimantadine $1 \cdot 10^{-6}$ mol/l until the identical fixed value of potential. The aim of this procedure was to provide better reproducibility of the analysis results. The constancy of solutions pH was kept by the 0.05 mol/l phosphate buffer background (pH 6.86 ± 0.02).

The calibration solutions for quantitative analysis contained only rimantadine hydrochloride in concentrations $5.02 \cdot 10^{-4}$ and $1.00 \cdot 10^{-3}$ mol/l and were prepared on the same phosphate buffer background.

To establish the influence of cetirizine and other components of the dosage form the results of rimantadine determination in three types of model solutions were investigated and compared. In the first case, model solutions contained only rimantadine in concentration $7.08 \cdot 10^{-4}$ mol/l, in the second case the mixture of rimantadine and cetirizine in concentrations $7.07 \cdot 10^{-4}$ and $1.20 \cdot 10^{-5}$ mol/l respectively and in the third case all the components of the model «Grippomix» mixture.

The model «Grippomix» mixture was prepared by exact weighting of 75.4 mg of rimantadine hydrochloride (correspond to $6.99 \cdot 10^{-4}$ mol/l concentration in analyzing solution), 325 mg of paracetamol, 20 mg of aspartame, 125 mg of ascorbic acid, 200 mg of anhydrous citric acid, 50 mg of each flavor enhancer (three types), 89.3 mg of calcium carbonate-sorbitol, 9.113 g of sugar and transferring into the 500 ml volumetric flask. The specified weight (2.5 mg) of cetirizine was very small. So its solution was firstly prepared by weighting 25 mg of cetirizine dihydrochloride and dissolving in 50 ml of working phosphate buffer in volumetric flask. Further, the 5 ml aliquot of cetirizine solution was added to the mixture of other ingredients.

To prepare the real sample solution powder from one pack of «Grippomix» (labeled amount of rimantadine hydrochloride is 75 mg per pack; produced by *Lekfarm*, Belarus) was quantitatively transferred into the 500 ml volumetric flask.

As far as «Grippomix» powder contains rather large quantities of citric and ascorbic acids, the capacity of used phosphate buffer is insufficient to keep pH constant. So before preparing the solutions, one pack of «Grippomix» was titrated with 1 mol/l NaOH in the presence of pH-selective electrode. Next the determined volume of NaOH needed for the neutralization was added into the volumetric flask in preparation of both model and real «Grippomix» solutions. After that, flasks were filled up with 0.05 mol/l phosphate buffer solution up to the label.

Results and discussion

The electrode selectivity. The key factor determining the possibility of using the ISE in pharmaceutical formulations analysis is their sufficient selectivity to the principal ion over other components. Physiologically active organic ions, in particular cations of physiologically active amines are generally much more hydrophobic than inorganic components of dosage forms, so sufficient level of ISE selectivity to these ions against inorganic ones is usually predetermined by their own lipophilicity. As for the selectivity against the interfering organic components of the dosage, it can be often effectively regulated by the appropriate choice of the membrane composition [18].

Proceeding from the formulas of the ingredients of «Grippomix» one can conclude that the only substance that can essentially influence on the response of rimantadine-selective electrode is cetirizine as far as it is a rather lipophilic tertiary amine (fig. 1). As it was shown before [18] the selectivity of electrodes based on liquid ion-exchangers for amine cations with different degree of substitution can be optimized by the variation of the plasticizers basicity. The increase of the last one will lead to the increase of the selectivity to the alkylammonium cations with the lower degree of substitution. For example in case of tetrabutylammonium-selective electrode the replacement of NPOE in the electrode membrane for TEHP will cause the increase of selectivity coefficients values to tertiary amine cations on 2.0–2.3 orders when the increase of selectivity coefficients values to primary amine cations will reach 4.5–5.0 orders. It was shown that the described regularities of the plasticizer influence on the potentiometric selectivity in general are also applicable for electrodes selective to physiologically active amine cations with the different degree of substitution [19].

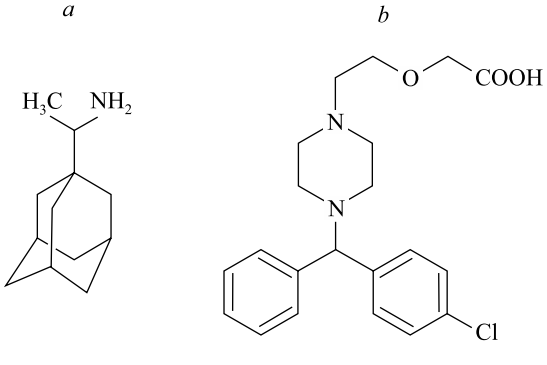

Fig. 1. Structures of rimantadine (*a*) and cetirizine (*b*)

From this point of view usage of highly basic TEHP as the membrane plasticizer seems to be promising for the enhancement of the electrode selectivity to primary rimantadine cation. However, on the other hand the presence of carboxylic group in cetirizine molecule can lead to the growth of its affinity to TEHP phase due to the formation of the hydrogen bond with the phosphoryl oxygen atom. So the electrodes with two membrane compositions containing either NPOE or TEHP as plasticizers were investigated and the selectivity coefficients for rimantadine against cetirizine were determined. It turned out that in spite of the presence of the carboxylic group in cetirizine molecule the interference of cetirizine on the rimantadine-selective electrode response was about 30 times smaller for the electrode with the membrane plasticized with TEHP (the corresponding selectivity coefficient for the electrodes with TEHP and NPOE-plasticized membranes were 2.8 and 81.0). It means that the efficiency of the protonated primary ammonia group solvation prevails over the solvation of the molecular carboxylic group. However the interference of cetirizine remains too high, so one more way for the selectivity control, namely the optimization of pH conditions has been exploited.

The pH-dependence. From the schedule presented on fig. 2 it is seen that in the pH range 2–9 electrode is weakly sensitive to the change of pH in rimantadine solution, while the maximum potential value in cetirizine solution is observed in acid medium (pH < 3) where cetirizine exists in the form of cation. The considerable decrease of potential under further alkalization is due to the formation of zwitterion form of cetirizine. According to obtained data, it was decided to choose the phosphate buffer with pH 6.86 as the background to prepare working solutions. It was found that the selectivity coefficient of rimantadine-selective electrode against sodium is $2.8 \cdot 10^{-5}$, so up to 300-fold excess of sodium can be used in the background solution, if necessary.

Electrode function, lower detection limit and potential reproducibility. From the schedule presented on the fig. 3 it is seen that the electrode potential dependence versus the rimantadine concentration logarithm is linear in the concentration range ($1 \cdot 10^{-5}$–$1 \cdot 10^{-1}$ mol/l) with the slope of the electrode function close to the nernstian one (58.6 mV/decade). The detection limit found graphically is $6 \cdot 10^{-6}$ mol/l. Taking into account that the content of rimantadine in «Grippomix» is 75 mg per dose and its concentration in the real sample solution is about $7 \cdot 10^{-4}$ mol/l the working range of the electrode confidently covers the analytically relevant concentration. The standard deviation of potential determined for $1 \cdot 10^{-3}$ mol/l rimantadine solution is 0.33 mV so good reproducibility of the analysis results can be expected.

Determination of rimantadine in the model solutions and dosage form «Grippomix». To explore the applicability of the fabricated rimantadine-selective electrode for the analysis of dosage form under investigation first of all model solutions were analyzed. The inaccuracy of determined rimantadine content in pure rimantadine solution did not exceed 0.74 % (with relative standard deviation 0.36 %) for both LSM and SSM

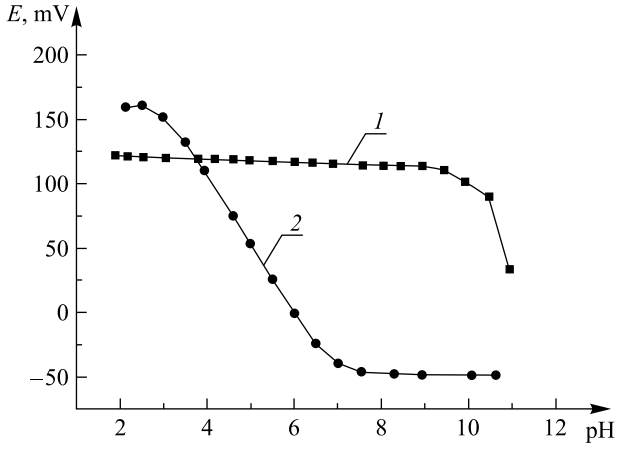

Fig. 2. The dependence of rimantadine-selective electrode potential on pH in *1* – $1 \cdot 10^{-2}$ mol/l rimantadine solution; *2* – $1 \cdot 10^{-3}$ mol/l cetirizine solution

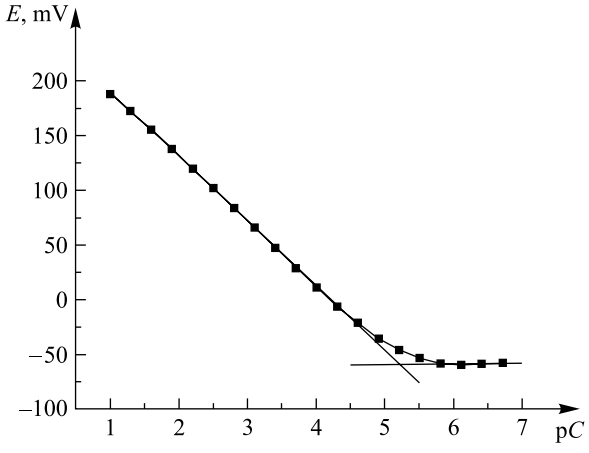

Fig. 3. Rimantadine-selective electrode function

direct potentiometric techniques. For the solution containing rimantadine with cetirizine, the inaccuracy did not exceed 0.85 % (with relative standard deviation 0.44 %). These results prove that under chosen conditions the interference of cetirizine on rimantadine determination is eliminated. To explore the influence of other dosage form components on the analysis results the remantadine content in the prepared model mixture containing all the components of «Grippomix» was determined.

It follows from the obtained data (table) that the proposed electrode allows carrying out quantitative determination of rimantadine in the model mixture «Grippomix» with high accuracy and reproducibility of the results. The inaccuracy and the relative standard deviation are comparable with those obtained for pure rimantadine solution. So the components of the dosage form do not influence on the electrode functioning.

The results of rimantadine determination using the developed electrode (n = 5, P = 0.95)

Analysis technique	Model «Grippomix» solution		Real sample «Grippomix»	
	SSM	LSM	SSM	LSM
Introduced / labeled amount, mg	75.4		75.0	
Found amount, mg	75.4	76.1	79.4	79.9
S_r, %	0.33	0.35	0.55	0.42
Inaccuracy/difference, %	0.00	0.80	5.78	6.52

The results of determination of rimantadine in real «Grippomix» powder are also characterized by quite good reproducibility for both LSM and SSM techniques, however the difference between found and labeled content of rimantadine is about 6 % (see table). According to Fisher and Student criteria the results obtained by both techniques are uniformly precise and the difference between the obtained results (79.4 and 79.9 mg) is statistically insignificant. So the results can be considered as reliable and the observed difference between the labeled and found content of rimantadine can be attributed to nonuniformity of rimantadine distribution in the initial powder matrix used for packing of the dosage form «Grippomix». At the same time the analysis results satisfy the pharmacopeia requirements, according to those, the deviation from the labeled amount of the main component content in the powder dosage form can be ±10 % for the average sample or not more ±25 % for the individual powder pack. So the proposed method is applicable for both determination of rimantadine in the average sample and for control of the uniformity of individual dosages as well.

Conclusion

Thus, the proposed potentiometric techniques are characterized by high reproducibility and accuracy that fulfill the requirements of pharmacopeia analysis. Taking into account the simplicity of sample preparation procedures and rapidity of analysis, as well as exclusion of the application of toxic solvents and expensive equipment, these techniques may be recommended for routine quantitative determination of rimantadine in industrial laboratories on the intermediate and final stages of the dosage form production.

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