THIOTRIAZOLIN ANALYSIS BY ELECTROCHEMICAL METHODS IN PHARMACEUTICAL PRODUCTS

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Introduction. 1,2,4-triazole derivatives are known as effective cardioprotective, anti-ischemic, antiarrhythmic, hepatoprotective, cerebroprotective, anti-inflammatory, immunomodulatory, antioxidant medicines. One of these compounds is thiotriazolin – morpholine salt of 3-methyl-1,2,4-triazol-5-thioacetic acid.

In the literature sources it was described the procedures of determining the content of the main ingredient in the biologically active substance of thiotriazolin by the method of acidimetric non-aqueous potentiometric titration, and also the procedures of simultaneous quantitative determination of thiotriazolin and piracetam, thiotriazolin and carbamazepine or isoniazid in combined medicines when their joint presence by the method of high-performance liquid chromatography (HPLC). Therefore, the actual analytical problem is to develop new alternative procedures of thiotriazolin quantitative determination; they should be of required analytical and metrological parameters, high sensitivity and rapidity, and may be used to determine thiotriazolin both in substance and dosage forms.

Materials and methods. ***Amperometric titration.*** *Reagents.* 12-phosphomolybdic acid (PMA) $H_3PMo_{12}O_{40}\cdot 26H_2O$ and 12-phosphotungstic acid (PTA) $H_3PW_{12}O_{40}\cdot 29H_2O$ were of analytical grade.

Place 2.2940 g of PMA into the measuring flask with the capacity of 100.0 mL, dissolve in distilled water when heating on a water bath and dilute the solution to the volume with the same solvent (the concentration is $1.0\cdot 10^{-2}$ mol/L).

Thiotriazolin ($C_9H_{16}N_4SO_3$) was of pharmacopoeial purity and purchased from the State Enterprise «The Plant of Chemical reagents» of Scientific and Technological Corporation of «Institute for Single Crystals», Kharkiv, Ukraine.

Equipment. The device «АУ-4М» consisted of such units as the microammeter M-95, the power supply and the system of two electrodes; the indicator electrode is the butt graphite electrode with the working surface diameter of 5 mm (rotation speed is 660 rps); the reference electrode is saturated calomel half-cell.

Results and discussion. Keggin structure heteropolyacids (HPAc) are widely used analytical reagents for determination of a number of biologically active substances, which contain a basic atom of nitrogen. However, in the literature sources there is not enough data about application of such Keggin structure

heteropolyacids as 12-phosphomolybdic heteropolyacid and 12-phosphotungstic heteropolyacid for analysis of nitrogen-containing biologically active compounds. Keggin structure heteropolyacids are used owing to the ion-exchange properties, and the ability to reduce easy, to precipitate large organic cations with formation of slightly soluble compounds with associative nature of chemical bond, and these compounds are able to dissolve in organic solvents and are poorly soluble in water. Experimental data analysis has shown that the optimal electrode characteristics has the ISE with the following parameters:

– electrode-active substance has the composition of $(TTZH_2)_3(PMo_{12}O_{40})_2$;
– the quantitative content of the EAS in the ISE membrane is equal to 0.01 g;
– application of dibutyl phthalate as a solvent-plasticizer.

The response time of the electrodes is 40 – 50 s, the linearity range of the dependence of $E = f(pC)$ is from 10^{-5} to 10^{-2} mol/L with the slope S of 29 – 30 mV, which is close to Nernst value for the divalent cations. It has been investigated the possibility of application of the developed ion-selective electrode with EAS based on the associate of thiotriazolin OC and heteropolyanion of 12-phosphomolybdic acid in the analysis (Table 6) of pharmaceutical dosage forms (the tablets and solution for injections of the JSC «Kyivmedpreparat» and also the combined tablets of thiotriazoline and famotidine). The study of dependence of ISE electrochemical properties on the solution pH has shown that the slope of the calibration curves has the constant value within the pH range from 4.0 to 6.0. It is observed narrowing of the linearity range and decreasing the slope of the electrode function when shifting the solution pH in the acid or alkaline medium (Fig.). Therefore, we used the batch of thiotriazolin standard solutions with pH = 4.0 for further studies.

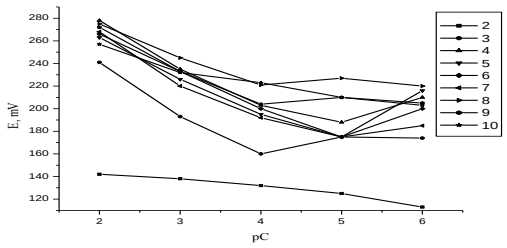

Fig. Influence of pH on the electrode function of ISE, which is reversible to thiotriazolin OC

The conducted investigations of the reaction between heteropolyanion of $PMo_{12}O_{40}^{3-}$ with organic cation of thiotriazolin nave been used for the development of the procedures of thiotriazolin quantitative determination by the methods of amperometric titration and direct potentiometry (using the developed ISE), which allow to carry out the analysis without complicated steps of sample preparation and preliminary separation of interfering components.