# DEVELOPMENT OF ION-SELECTIVE ELECTRODES FOR RAPID DETECTION OF PHARMACEUTICALS BASED ON HETEROPOLYMETALLOPHOSPHATE IONOPHORES

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## ABSTRACT

Optimal conditions were selected for the synthesis of sparingly soluble electrode-active materials based on pharmaceutical preparations and heteropoly compounds (HPCs) containing molybdenum and tungsten. The composition and structure of the obtained electrode-active compounds were determined using IR spectroscopy, scanning electron microscopy, X-ray diffraction, and X-ray fluorescence methods. During the conducted studies, ion-selective electrodes (ISEs) based on HPCs were developed for the determination of pharmaceutical substances, and their electroanalytical characteristics were evaluated.

**Keywords:** molybdenum- and tungsten-containing heteropoly compounds, ionophores, pharmaceuticals, ion-selective electrode.

## INTRODUCTION

The rapid development of the chemical–pharmaceutical industry and the expansion of pharmacy networks at all levels have led to a steadily increasing demand for fast, accurate, and simple methods for the analysis of pharmaceutical substances (PS) [1–4]. Therefore, the development of rapid, relatively simple, and cost-effective methods suitable for screening assessment of drug composition is of particular importance [5–7]. Plasticized membrane ion-selective electrodes represent a successful solution to this problem. Such electrodes are easy to manufacture and use and provide a wide concentration range of determination [8,9]. Consequently, the creation of a new generation of electrode-active materials (EAMs) and the development of selective electrodes based on them for the determination of pharmaceuticals are of significant practical relevance and scientific importance.

The performance characteristics of ion-selective electrodes (ISEs), including high sensitivity and selectivity, depend on the composition of the EAM. Therefore, selecting the optimal composition and ratios of EAM components in the development of ion-selective electrodes is of considerable scientific importance.

The aim of this study is to develop ISEs for the rapid determination of pharmaceuticals based on heteropolymetallophosphate ionophores containing molybdenum and tungsten and to evaluate their performance characteristics.

## MATERIALS AND METHODS

In the course of the study, dodecamolybdate and dodecatungstate acids were synthesized, and ionophores were prepared using pharmaceutical substances widely applied in current medical practice. The selected pharmaceuticals included pyridoxine, dibazol, drotaverine, dimedrol, aminazine, paracetamol, diprazine, papaverine, trimecaine, bromhexine, diphenhydramine, and lidocaine, for a total of 12 pharmaceutical substances.

At the next stage, studies were carried out to develop ISEs based on heteropoly compounds for the determination of pharmaceuticals and to evaluate their electroanalytical characteristics.

Results and Discussion. During the experiments, ionophores were synthesized based on dodecamolybdophosphoric and dodecatungstophosphoric acids and pharmaceutical preparations.

Table 1 presents the results of studying the effect of pH on the ionophore synthesis process.

**Table 1.**

**Effect of pH on the ionophore synthesis process (Spiridox – 0.01 M, STFPA – 0.01 M, SMFPA – 0.01 M; pyridoxine/acid = 3:1).**

| Reaction medium (pH) | Reaction yield, % | | | |
|---|---|---|---|---|
| | DTFPA + pyridoxine | | DMFPA + pyridoxine | |
| | $\overline{X}$ ±Δx | Cp·$10^{-2}$ | $\overline{X}$ ±Δx | Cp ·$10^{-2}$ |
| 2 | 84±0,6 | 0,57 | 87±0,7 | 0,68 |
| 4 | 94±0,6 | 0,51 | 98±0,6 | 0,49 |
| 6 | 89±0,5 | 0,45 | 90±0,5 | 0,44 |
| 8 | 80±0,3 | 0,30 | 82±0,4 | 0,41 |
| 10 | 62±0,4 | 0,51 | 64±0,4 | 0,53 |

From the table, it can be seen that for both acids used, salt formation with pyridoxine proceeds through a maximum reaction yield at pH = 4. The resulting precipitate consisted of easily filterable crystalline solids.

The IR spectrum of the obtained dibazol phosphomolybdate is shown in Figure 1.

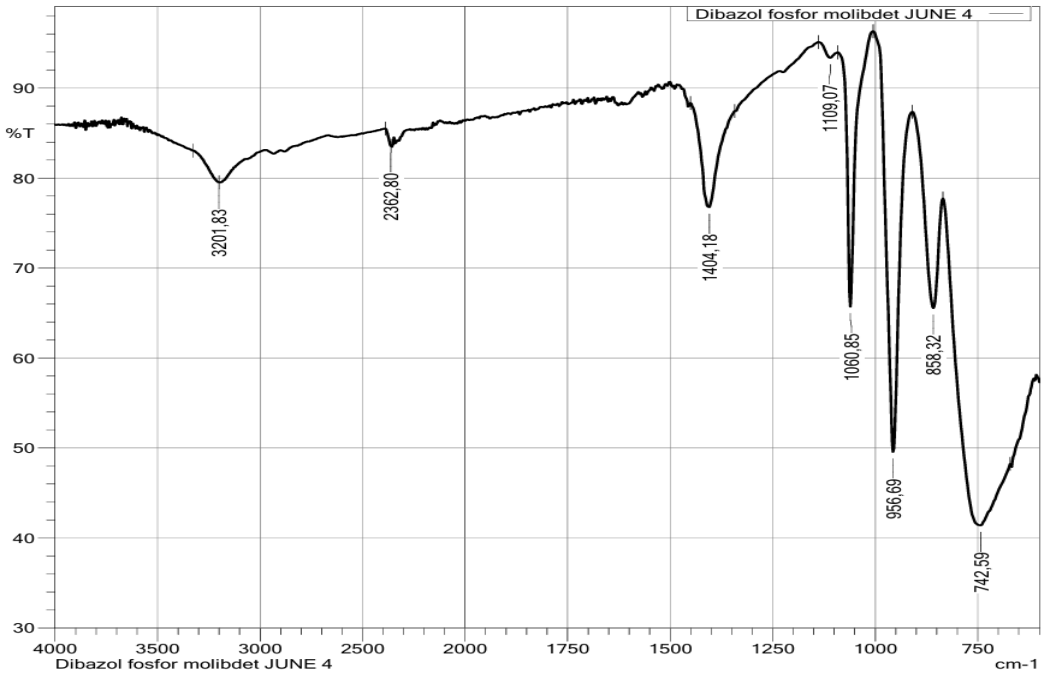


**Figure 1. Analysis of the IR spectrum of dibazol phosphomolybdate.**

Its composition shows characteristic regions in the IR spectrum: at $\lambda$ = 742.59 $cm^{-1}$, a band corresponding to the phenyl radical; at $\lambda$ = 858.32 $cm^{-1}$, a band from the molybdenum–oxygen ligand; at $\lambda$ = 956.69 $cm^{-1}$, a region corresponding to molybdenum bonded to oxygen via a terminal bond; at $\lambda$ = 1060.85 $cm^{-1}$, a band from phosphorus bonded to oxygen via a single bond; and at $\lambda$ = 2250–2700 $cm^{-1}$, regions characteristic of the secondary ammonium group are observed.

According to PCA data, the structures of the synthesized compounds are similar, consisting of an isolated complex heteropolyanion $[PMo_{12}O_{40}]^{3-}$, $[PW_{12}O_{40}]^{3-}$, and an outer-sphere cation formed by three pharmaceutical fragments.

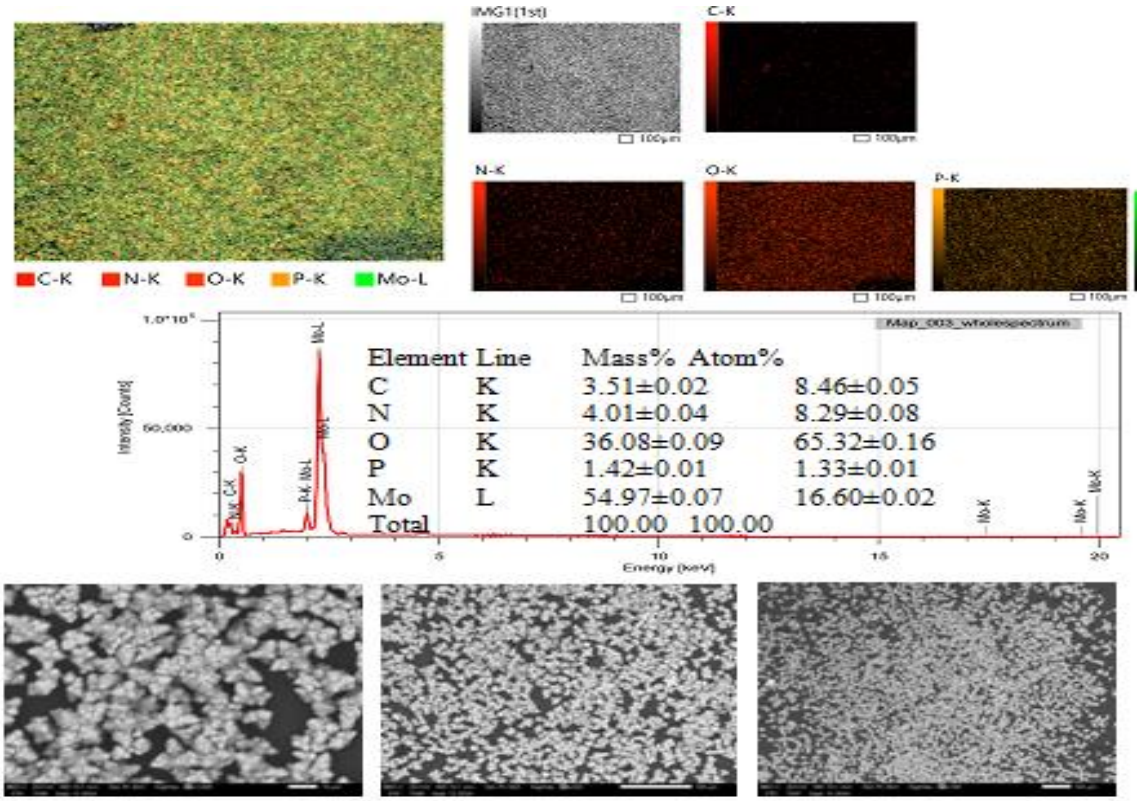


**Figure 2. SEM image of the dibazol phosphomolybdate sample.**

The SEM image of the dibazol phosphomolybdate sample shows a homogeneous layered structure in the form of fine powder, with rhombic crystals forming aggregates resembling snowflake fragments, approximately 3.5–4.5 μm in size (Figure 2). Elemental mapping of the sample revealed the following:

- Carbon atoms are homogeneously distributed, with very low concentration;
- Nitrogen atoms are distributed homogeneously on the surface;
- Phosphorus, molybdenum, and oxygen atoms are co-distributed with nearly uniform concentration.

The rhombic shape of the crystal grains indicates that the compound possesses a phosphomolybdate structure.

In the next stage of the work, rapid-detection ISEs for pharmaceuticals were developed based on synthesized HPC-containing membranes, and their analytical characteristics were evaluated. The ISE membrane was prepared by mixing PVC, dioctyl phthalate as a plasticizer,

and the electrode-active compound (EAC) in tetrahydrofuran and then dissolving. The mass fraction of EAC in the membrane was 2–5%, and the PVC-to-plasticizer weight ratio was 1:2.

The masses of the prepared membranes varied according to their dimensions (thickness and diameter), ranging from 0.2 to 0.5 g. The prepared electrode body was filled with 1–2 drops of 3 M KCl as an internal reference solution and $1 \cdot 10^{-5}$ – $1 \cdot 10^{-4}$ M solution of the target ion. During the study, the detection range and sensitivity of the developed electrodes were investigated within the concentration range of $10^{-1}$–$10^{-7}$ mol/L of the analyte.

Results indicated that ISEs based on DDMF ionophores and pharmaceutical substances showed the highest signal values and a wide linear detection range for dibazol and pyridoxine. Thus, DDMF-based electrodes can be used for determining dibazol and pyridoxine over a wide concentration range. Similarly, electrodes based on DDVF ionophores and pharmaceuticals demonstrated a wide detection range and high signal values for diprazine and bromhexine.

Based on these results, it was confirmed that DDMF-based ISEs are suitable for detecting dibazol and pyridoxine, while DDVF-based ISEs can be applied for diprazine and bromhexine. These electrodes were selected for further experiments.

Subsequent experiments studied the behavior of DDMF- and DDVF-based ISEs in determining dibazol, pyridoxine, diprazine, and bromhexine.

One of the most important parameters affecting ISE signal value is the amount of ionophore in the membrane. The dependence of the signal on ionophore content during the determination of pyridoxine and bromhexine is presented in Table 2.

**Table 2.**

**Dependence of ISE signal on the ionophore content in the membrane. Determined component – Bromhexine $C_{14}H_{20}N_2Br_2 \cdot HCl$ (n = 5, p = 0.95).**

| **Ionophore type** | Ionophore content, % | Sensor signal, mV at analyte concentration, mol/L | | | |
|---|---|---|---|---|---|
| | | $10^{-2}$ | $10^{-3}$ | $10^{-4}$ | $10^{-5}$ |
| | | Sensor signal, mV | | | |
| Bromhexine dodecatungstophosphate | 0,5 | 115,0±1,0 | 114,8±1,3 | 66,5±0,5 | 46,8±0,3 |
| | 1,0 | 144,7±1,3 | 166,5±1,5 | 84,2±0,9 | 58,8±0,6 |
| | 1,5 | 209,2±1,8 | 182,7±1,9 | 121,5±1,4 | 83,9±0,7 |
| | 2,0 | 230,0±1,9 | 183,3±1,7 | 133,5±1,2 | 91,3±0,8 |
| | 2,5 | 218,5±1,9 | 167,5±1,3 | 125,9±1,1 | 87,7±0,9 |
| | 3,0 | 216,5±1,8 | 159,0±1,4 | 117±1,9 | 46,8±0,4 |

For all studied pharmaceuticals, the dependence of the ISE signal on the ionophore content exhibited a maximum. For bromhexine determination, the ionophore content of dodecatungstophosphate that provided the highest signal in the sensitive material was 2.0%. This optimal content was also 2.0% for diprazine and dibazol, and 2.5% for pyridoxine.

The effect of temperature on the ISE signal was studied within the range of 10–50 °C, with 5 °C increments, using $10^{-2}$ and $10^{-3}$ mol/L solutions of dibazol, bromhexine, diprazine, and pyridoxine. The results demonstrated that the developed electrodes could reliably determine diprazine and pyridoxine in the temperature range of 10–50 °C.

To evaluate the electrode function of the developed ISEs, solutions of dibazol, pyridoxine, diprazine, and bromhexine hydrochloride in the concentration range of $1 \cdot 10^{-1}$ – $1 \cdot 10^{-5}$ M were used. Figure 3 shows the electrode functions for pyridoxine hydrochloride determination using electrodes based on DDMF and DDVF.

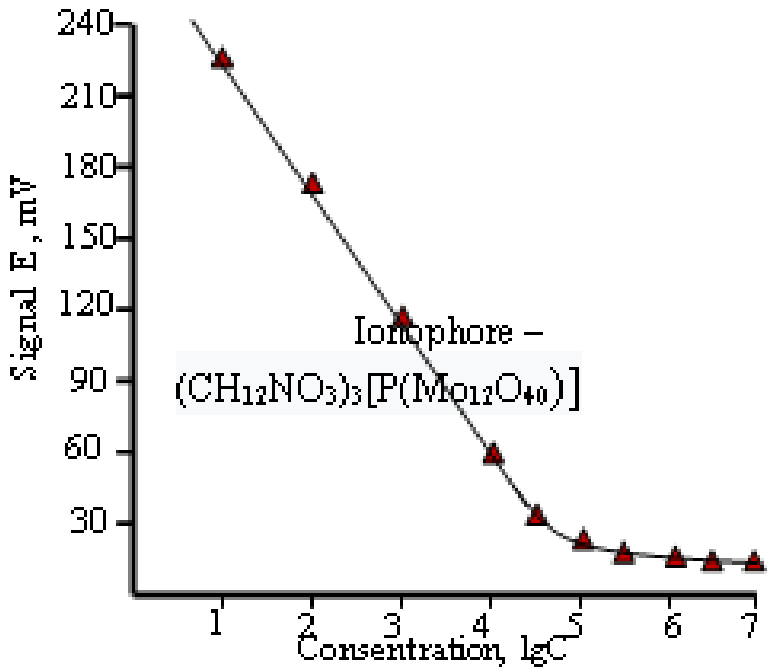


**Figure 3. Operating range of the electrode function of ISEs based on heteropolymetallophosphate ionophores.**

From the figure, it can be seen that the operating range (Nernstian region) of the electrode function of ISEs based on HPC ionophores for pyridoxine hydrochloride corresponds to the concentration range of $1 \cdot 10^{-1} – 1 \cdot 10^{-5}$ M.

The results for the determination of the slope (sensitivity) of the electrode function of ISEs based on DDMF and DDVF are presented in Table 3.

**Table 3.**

**Determination of the slope (sensitivity) of the electrode function of ISEs based on DDMF and DDVF.**

| **Ionophore composition** | Analyte | Δ E | Δ C | K | K,% |
|---|---|---|---|---|---|
| $(C_{14}H_{14}H_2)_3[ПР(Mo_{12}O_{40})]$ | Dibazol | 23 1 | 4, 11 | 56,2 0 | 95,3 |
| $(C_8H_{12}NO_3)_3[P(Mo_{12}O_{40})]$ | Pyridoxine | 17 1 | 3, 30 | 51,8 0 | 87,8 |
| $(C_{17}H_{21}N_2S)_3[P(W_{12}O_{40})]$ | Diprazine | 24 1 | 4, 53 | 53,1 0 | 90,1 |
| $(C_{14}H_{21}Br_2H_2)_3[P(W_{12}O_{40})]$ | Bromhexine | 23 3 | 4, 12 | 56,7 0 | 96,1 |

The results presented in the table indicate that the experimentally determined slope of the electrode function for the developed electrodes corresponds to 90–96% of the theoretical value. This confirms the full applicability of the developed electrodes for the determination of pharmaceutical substances.

## CONCLUSIONS

The synthesis regularities of ionophores based on heteropoly acids containing molybdenum and tungsten and pharmaceutical substances were studied, and the optimal

conditions for the development of selective ISEs were established: temperature 70–85 °C, heating time 10 min, reaction mixture pH 4, and component molar ratio of 3:1.

The developed ionophores sensitive to pharmaceutical substances were characterized using modern SEM, IR spectroscopy, X-ray fluorescence, and thermogravimetric analysis, which allowed the composition and structure of the obtained compounds to be determined.

A total of 24 ion-selective membranes were synthesized based on DDMF (DDVF) ionophores, PVC, and dioctyl phthalate. It was demonstrated that DDMF-based membranes exhibit high sensitivity toward dibazol and pyridoxine, while DDVF-based membranes are highly sensitive to diprazine and bromhexine, with detection limits in the range of $10^{-5}$–$10^{-6}$ mol/L.

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