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Synthesis of Heteropolymetallophosphate Ionophores and Development of Ion-Selective Electrodes for Rapid Detection of Pharmaceuticals

Abdurakhmanova Zamira[1][a], Abdurakhmanov Ergashboy[2][b], Murodova Zulfiya[2][c], Salimova Shokhista[2][d], Suvonkulov Shokhjakhon[2][e]
[1]*Samarkand State Medical Institute, Samarkand, Uzbekistan*
[2]*Samarkand State University, Samarkand, Uzbekistan*
salimovashohista98@gmail.com

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Abstract: The optimal conditions for obtaining poorly soluble electrode-active substances based on molybdenum- and tungsten-containing heteropolycompounds (HPCs) and pharmaceutical drugs were selected. 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 analysis. During the research, ion-selective electrodes (ISEs) for pharmaceutical drug detection based on HPCs were developed, and their electroanalytical characteristics were studied. A total of 24 types of ion-selective membranes were synthesized using dodecamolybdophosphate (DDMP) and dodecatungstophosphate (DDTP) ionophores, polyvinyl chloride (PVC), and dioctyl phthalate. It was proven that DDMP-based membranes exhibit high sensitivity (10^{-5}–10^{-6} mol/L) to dibazole and pyridoxine, while DDTP-based membranes show the same level of sensitivity to diprazine and bromhexine.

1 INTRODUCTION

Currently, extensive research is being conducted on the development of chemical sensors for detecting toxic components in atmospheric air as well as inorganic and organic compounds in liquid phases. Chemical sensors enable the creation of rapid monitoring methods in various sectors of the national economy. Due to the rapid development of the chemical-pharmaceutical industry and the increasing number of pharmacies at all levels, there is a growing demand for fast, accurate, and simple methods for analyzing pharmaceutical substances (PS). Therefore, the development of rapid, relatively simple, and cost-effective methods suitable for screening pharmaceutical compositions is of particular importance. Plasticized membrane ion-selective electrodes (ISEs) are a successful solution to this problem. These electrodes are easy to manufacture and use, and they provide a wide concentration range for detection.

Thus, developing a new generation of electrode-active materials (EAMs) and creating selective electrodes based on them for pharmaceutical drug detection is of great practical importance and relevance.

The performance of ISEs, including high sensitivity and selectivity in detection, depends on the composition of the EAM. Therefore, selecting the optimal composition and ratio of EAM components is of significant scientific importance in the development of ion-selective electrodes.

The aim of this study is to develop rapid-detection ISEs for pharmaceutical drugs based on heteropolymetallophosphate ionophores containing

a
b
c https://orcid.org/0009-0002-6940-2184-5844
d https://orcid.org/0009-0001-5037-6394-3822-4X
e

https://orcid.org/0009-0002-1539-9890

molybdenum and tungsten and to investigate their characteristics.

2 MATERIALS AND METHODS

During the study, dodecamolybdate and dodecatungstate acids, as well as ionophores, were synthesized. For this purpose, 12 pharmaceutical drugs widely used in medical practice were selected, including pyridoxine, dibazole, drotaverine, diphenhydramine, inazine, paracetamol, diprazine, papaverine, trimecaine, bromhexine, diphenhydramine, and lidocaine.

Achieving the stated objective required selecting the optimal conditions for obtaining poorly soluble electrode-active substances based on heteropolycompounds (HPCs) containing molybdenum and tungsten and pharmaceutical drugs. 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 analysis. Additionally, research was conducted on the development of ion-selective electrodes (ISEs) based on HPCs for pharmaceutical drug detection, as well as on the determination of their electroanalytical characteristics.

3 RESULTS AND DISCUSSION

The development of highly sensitive ion-selective electrodes (ISEs) for pharmaceutical drugs remains a relatively unexplored area. Therefore, studying the principles of creating ISEs based on tungsten and molybdenum heteropolycompounds (HPCs) is of both theoretical and practical significance. In this study, a total of 12 pharmaceutical drugs were selected for investigation.

The main reasons for selecting these pharmaceutical drugs include their widespread use in modern medicine and the lack of simple, easily executable, cost-effective, and rapid quantitative control methods.

During the experiments, ionophores (ion associates) were synthesized based on dodecamolybdophosphate (DDMP) and dodecatungstophosphate (DDTP) acids, along with the 12 aforementioned pharmaceutical drugs. The synthesis of all ionophores was carried out at room temperature (25°C). In solution, HPCs act as strong tribasic acids, dissociating by releasing three protons as follows:

$$H_3[PMo_{12}O_{40}] \rightarrow 3H^+ + [PMo_{12}O_{40}]^{3-}.$$

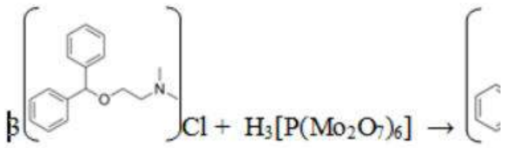
Taking into account the tribasic nature of the studied HPCs in the reactions, the molar ratio of the pharmaceutical drug to the HPC was set at 3:1. The effect of the solution pH (ranging from 2 to 10) on the reaction yield was investigated using pyridoxine and dodecaphosphomolybdate as examples (Table 1).

Table 1: Effect of pH on the ionophore synthesis process. ($C_{pyridoc}$ – 0.01M, C_{PTA} – 0.01M, C_{PMA} – 0.01M, pyridoxine/acid = 3:1.).

(pH)				
	T			
	$\bar{x} \pm\Delta x$	$C_r \cdot 10^{-2}$	$\bar{x} \pm\Delta x$	$C_r \cdot 10^{-2}$

From the table, it is evident that both acids used form salts with pyridoxine, achieving the highest reaction yield at pH = 4. The resulting precipitate consisted of easily filterable crystals. Thus, the optimal medium for ionophore synthesis based on pharmaceutical drugs and HPCs corresponds to a pH of 4.

The following scheme illustrates the formation of hybrid organic-inorganic salts using the interaction of diphenhydramine hydrochloride with DDMP acid as an example.



(1)

Under the selected optimal conditions, a total of 24 ionophores were synthesized based on HPCs and the 12 pharmaceutical drugs mentioned earlier.

The yield of the synthesized products varied between 90-99%, depending on the composition of the product.

The composition, molecular weight, and reaction yield values of some synthesized HPCs are presented in Table 2.

Table 2: Composition, molecular mass, and reaction yield values of some synthesized HPCs.

		$[P(Mo_3O_{10})_4]$	$(C_8H_{12}HO_3)_3[P(Mo_3O_{10})_4]$		
		$[P(Mo_3O_{10})_4]$	$HO)_3[P(Mo_3O_{10})_4]$		
		$[P(Mo_3O_{10})_4]$	$(C_{14}H_{14}H_2)_3$ $[P(Mo_3O_{10})_4]$		
		$[P(Mo_3O_{10})_4]$	$HO_4)_3[P(Mo_3O_{10})_4]$		
		$[P(W_3O_{10})_4]$	$10HO_2)_3$ $[P(W_3O_{10})_4]$		
		$[P(W_3O_{10})_4]$	$H_2C)_3[P(W_3O_{10})_4]$		
		$[P(W_3O_{10})_4]$	$HO_4)_3[P(W_3O_{10})_4]$		
		$[P(W_3O_{10})_4]$	B r		

The theoretical calculations of the elemental composition of the ionophore were carried out using the composition and molecular mass values presented in Table 2. The elemental analysis results of the obtained HPCs demonstrated full consistency between their experimentally determined composition and the theoretically calculated values. The composition and structure of the HPCs synthesized based on DDTP, DDMP acids, and pharmaceutical drugs were studied using IR spectroscopy, X-ray fluorescence, and scanning electron microscopy. The amount of crystallization water in the compounds was determined by the thermogravimetric method.

The solubility of the synthesized compounds at 200°C was investigated, showing that most of the obtained compound's dissolve well in polar solvents such as water, acetone, and ethanol, while they are almost insoluble in non-polar solvents. During the research, the IR spectroscopic analysis of the ionophore compounds synthesized from pharmaceutical drugs and heteropoly acids was conducted. These studies were carried out using a Shimadzu UV-260°C spectrometer.

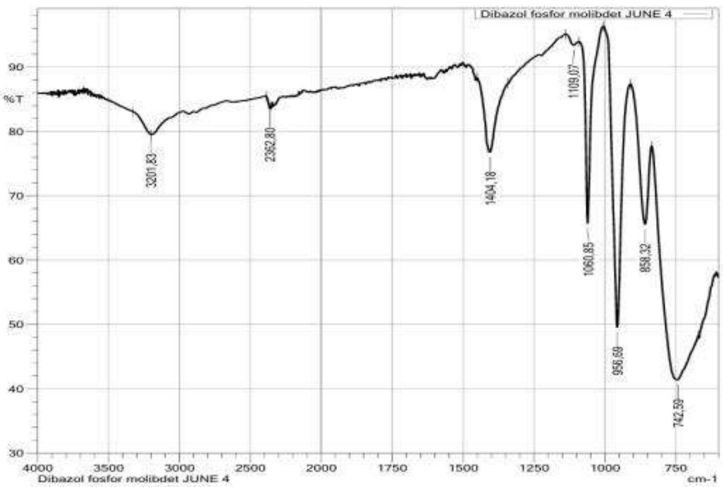


Figure 1: Analysis of the IR Spectrum of Dibazolphosphomolybdate.

The IR spectrum analysis of dibazolphosphomolybdate reveals characteristic absorption regions corresponding to its structural components. The peak at λ = 742.59 cm⁻¹ is attributed to the phenyl radical, while the λ = 858.32 cm⁻¹ region corresponds to the molybdenum-oxygen ligand. The λ = 956.69 cm⁻¹ peak represents the molybdenum atom bonded to an oxygen atom via a double bond. The λ = 1060.85 cm⁻¹ absorption region is associated with the phosphorus atom bonded to an oxygen atom through a single bond. Additionally, secondary ammonium groups exhibit characteristic absorption within the λ = 2250–2700 cm⁻¹ range.

The IR spectroscopic studies of the synthesized ionophore compounds confirm their structural consistency with the proposed chemical formulas.

According to RSA data, the synthesized compounds share similar structural arrangements, comprising an isolated complex heteropolyanion $[PMo_{12}O_{40}]^{3-}$ or $[PW_{12}O_{40}]^{3-}$, along with an outer sphere cation formed by three pharmaceutical drug fragments.

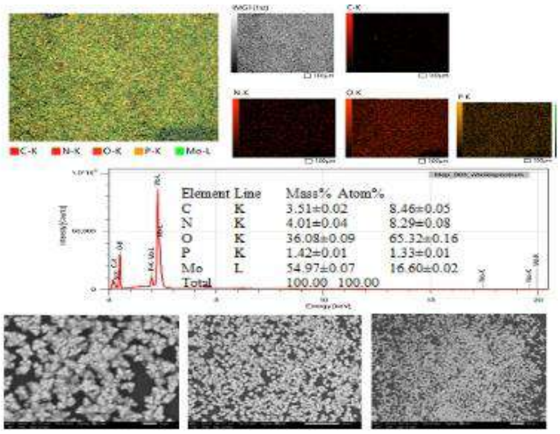


Figure 2: SEM Image of Dibazol Phosphomolybdate Sample.

The SEM image of the dibazol phosphomolybdate sample reveals a fine powder with a homogeneous layered structure. The observed rhombic crystals, measuring approximately 3.5–4.5 µm, form aggregates resembling snowflake-like structures.

Analysis of the element distribution map of the sample indicates the following:

- Carbon atoms are homogeneously distributed, with a very low concentration.
- Nitrogen atoms are uniformly dispersed across the surface.
- Phosphorus, molybdenum, and oxygen atoms are co-distributed, maintaining nearly identical concentration levels.

The rhombic crystal morphology confirms that the sample exhibits a phosphomolybdate structure.

In Chapter 4, ion-selective electrodes (ISEs) based on synthesized heteropolymetallophosphate membranes were developed for the rapid detection of pharmaceutical drugs, and their analytical performance characteristics were determined.

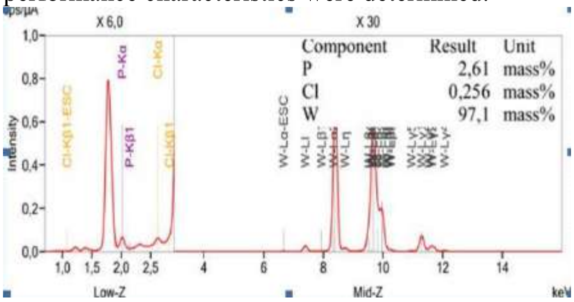


Figure 3: X-ray Fluorescence Spectrum of Pyridoxine Phosphotungstate.

The determination of phosphorus and tungsten content in the pyridoxine-phosphotungstate ionophore, which is part of the ISE composition, was carried out using the Rigaku NEX DE X-ray fluorescence spectrometer.

The ISE membrane films were prepared by dissolving PVC, the plasticizer dioctyl phthalate, and the electrode-active compound (EAC) in tetrahydrofuran under continuous stirring. The mass fraction of EAC in the membrane composition was 2–5%, while the weight ratio of PVC to plasticizer was 1:2. During the experiments, ion-selective membranes were prepared based on heteropolymetallophosphate ionophores with the component ratios mentioned above for detecting various pharmaceutical drugs. The mass of these membranes varied between 0.2–0.5 g, depending on their size (thickness and diameter). The prepared membranes were installed in electrode bodies and stored in distilled water.

The developed membrane electrodes consist of a cylindrical Teflon body, with the plasticized membrane sealed at its tip using a special adhesive. The electrode body was filled with ~1.5–2.0 mL of internal reference solution, containing 1×10^{-5} – 1×10^{-4} M of the potential-determining ion and 1–2 drops of 3M KCl. Before measurements, the plasticized membrane ISEs were conditioned for 12–24 hours in salt solutions of varying potential-determining ion concentrations.

During the research, the detection range and sensitivity of the developed electrodes were examined for analyte concentrations within the 10^{-1}–10^{-7} mol/L range.

The study results demonstrated that ISEs based on DDMP ionophores and pharmaceutical drugs exhibited the highest signal values and a broad linear detection range for dibazole and pyridoxine detection. Therefore, electrodes based on DDMP can be used for

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the quantification of dibazole and pyridoxine over a wide concentration range.

Additionally, it was observed from the data that ISEs developed using DDTP-based ionophores and pharmaceutical drugs provided a wide concentration range and a strong signal response for diprazine and bromhexine detection.

Based on these findings, the applicability of ISEs based on DDMP for dibazole and pyridoxine detection, as well as ISEs based on DDTP for diprazine and bromhexine detection, was confirmed. These electrodes were selected for further experiments.

In subsequent experiments, the principles of dibazole, pyridoxine, diprazine, and bromhexine detection using ISEs based on DDMP and DDTP ionophores were investigated.

One of the most critical parameters affecting ISE signal values is the ionophore content in the membrane. Therefore, to determine the optimal ionophore concentration ensuring high sensitivity and selectivity, the signal response of different ISEs was studied in relation to ionophore content in the 0.5–3.0% range. The results of studying the relationship between the ISE signal and ionophore concentration in the membrane for pyridoxine and bromhexine detection are presented in Table 3.

Table 3: Dependence of ISE signal on ionophore content in the membrane. Analyte: Bromhexine $C_{14}H_{20}N_2Br_2HCl$ (n=5, p=0.95).

For all the studied pharmaceuticals, the dependence of the ISE signal on the ionophore content follows a relationship that passes through a maximum. For bromhexine detection, the ionophore content in the sensitive material that ensures the maximum signal value is 2.0% for dodecatungstophosphate. This value is also 2.0% for diprazine and dibazol, while for pyridoxine, it is 2.5%.

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

To determine the electrode function of the developed ISEs, $1\cdot10^{-1}$ - $1\cdot10^{-5}$ M solutions of dibazol, pyridoxine, diprazine, and bromhexine hydrochloride were used. For the study, six electrodes were manufactured from each membrane.

Figure 4 presents the electrode functions of electrodes based on DDMP and DDTP for pyridoxine hydrochloride determination. The slope coefficients of the electrode function for ion-selective electrodes developed using DDMP and DDTP for pharmaceutical analysis are given in Table 4.

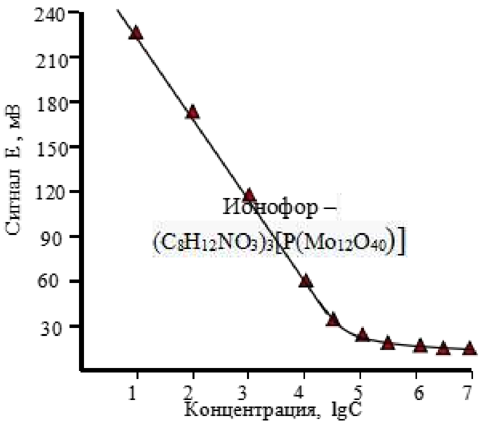

Figure 4: The working range of electrode function for ISEs based on heteropolymetallophosphate ionophores.

From the figure, we observe that the working range of the electrode function (Nernstian region) for the ISE based on heteropolymetallophosphate ionophores in the determination of pyridoxine hydrochloride corresponds to the concentration range of $1\cdot10^{-1} - 1\cdot10^{-5}$ M.

Table 4: Results of determining the slope coefficient of the electrode function for ISEs developed based on DDMP and DDTP.

		ΔE	ΔC	K	K
$H_2)_3[P(Mo_{12}O_{40})]$					
$HO_3)_3[P(Mo_{12}O_{40})]$					
$H_2C)_3[P(W_{12}O_{40})]$					

$H_2)_3[P(W_{12}O_{40})]$						

The results presented in the table show that the determined slope coefficient of the electrode function for the developed electrodes corresponds to the theoretical value with an accuracy of 90–96%. This confirms the full applicability of the developed electrodes for the determination of pharmaceutical compounds.

4 CONCLUSIONS

The synthesis of ionophores based on heteropoly acids containing molybdenum and tungsten for pharmaceutical analysis was studied. The following optimal conditions for the development of selective membranes were determined: temperature of 70–85°C, heating duration of 10 minutes, pH = 4, and component ratio of 3:1 (molar ratio).

The sensitive ionophores developed for pharmaceuticals were studied using modern analytical methods, including SEM, IR spectroscopy, X-ray fluorescence, and thermogravimetric analysis, which confirmed the composition and structure of the obtained compounds.

A total of 24 different ion-selective membranes were synthesized based on DDMP (DDTP), PVC, and dioctyl phthalate. It was demonstrated that the DDMP-based membrane exhibits high sensitivity in the concentration range of 10^{-5} – 10^{-6} mol/L for dibazole and pyridoxine, while the DDTP-based membrane shows similar sensitivity for diprazine and bromhexine.

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