Study of immobilization of bolaform ions on polymethacrylic acid

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Abstract. The study of the interactions of polyelectrolytes with organic ions, in particular bolaform ions, that is, having a mirror conformational chemical structural symmetry with respect to the centre of the molecule and exhibiting physiological activity, is particularly intriguing due to its potential for simulating biological processes and its implications for the development of novel polymer therapeutic systems. These systems possess unique features that distinguish them from low-molecular-weight medicines. Of the large assortment of polymers used for these purposes, the most convenient "substrate" is considered to be synthetic polyelectrolytes that are easily adjustable during production, possessing active functional groups for binding organic ions and the property of good solubility in water. The objects of research were an antibacterial agent, aethonium, and a drug, imidocarb, widely used in veterinary practice, which, when dissolved in water, forms complex bolaform cations and an industrially developed polymer, polymethacrylic acid. In order to develop a prolonged dosage form for veterinary medicine, the binding of these substances to a selected synthetic polymer was studied using physical and chemical methods. IR spectroscopy has proven the "soft" immobilization of the studied organic ions on polymethacrylic acid. Factors influencing the immobilization process have been established: the ratio of reagents, the nature of the solvent and temperature, and the thermodynamic parameters of the studied process.

1 Intoduction

The goal of the work was to create a prolonged dosage form with the most extended possible period of physiological activity, including veterinary drugs: aethonium - (1,2-ethylene-bis-(N-dimethyl-carbdecyloxymethyl) ammonium dichloride) and imido-carb (N1N1-bis-(3-(4,5-dihydro-1H-imidazol-2-yl)-phenyl)-urea di-propionate). When dissolved in water, the above-mentioned medicinal compounds form similar complex bolaform

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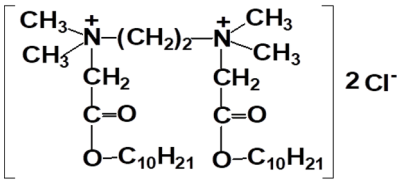
cations. Their binding requires a polymer carrier that has anionic functional groups in its structure and has the property of good solubility in water, and also keeping in mind the literature data [1, 2] about the "soft" binding of carboxyl-containing polymers of medicinal substances (DS), which is a prerequisite for preserving the chemical structure of the drug, and therefore physiological activity when immobilized on a polymer carrier [3, 4], in further studies, we will remain new as a convenient "substrate" for the created dosage form on polymethacrylic acid (PMAA). We also took into account the possibility of using various brands of polymers based on methacrylic acid produced on an industrial scale by the companies “Lubrizol Corporation”, “Wuhan Dachu Hexing Technology Co., Ltd", which are included in the Pharmacopoeias of the USA, Europe and China [5] when organizing industrial production of the developed drug forms. The antibacterial drug etonium is easily soluble in water and, from a chemical point of view, is a bis-quaternary ammonium compound [6].



It has a bacteriostatic and bactericidal effect and is effective against streptococci, staphylococci and other microorganisms. The disadvantage of the drug is that it acts in the body for a short time, which requires frequent administration [6]. In the experiments, we used the drug etonium produced by BIOLINE LLC (Russia). In recent times, the pharmaceutical compound imidocarb has gained significant popularity in the field of veterinary medicine due to its extensive application in the treatment of cattle. It exhibits a significant chemotherapeutic impact, but its concentration in the animal's body decreases relatively quickly [7]. As a result, the medication needs to be administered every 10-12 days for treatment and every 27-28 days for preventive purposes, which poses challenges, particularly for grazing livestock [8]. Imidocarb has two primary drawbacks: it has a relatively high level of toxicity, with an LD50 value of 87 mg/kg, and its period of effect is brief, lasting only 18-21 days [8]. The medicine imidocarb, manufactured by Shandong Jiulong Hisince Pharmaceutical Co., Ltd in China, was utilized in the study. In the experiments, we used linear polymethacrylic acid synthesized by radical polymerization and having the following characteristics: average viscosity molecular weight of 150,000-200,000 and an acid number of 412 [9], as well as weakly cross-linked PMAA hydrogels produced by Wuhan Dachu Hexing Technology Co, Ltd (China). 99%.

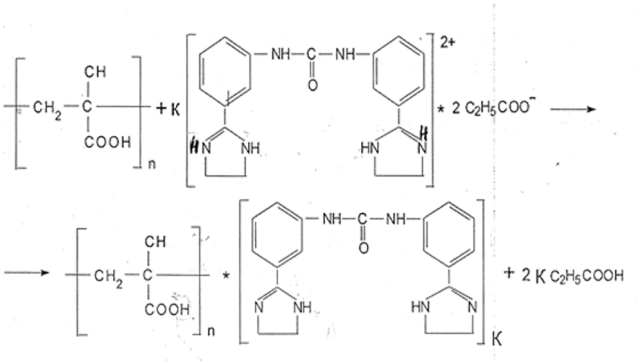
2 Methods

The synthesis of polymer complexes of PMAA with drugs was carried out by mixing aqueous solutions of the reagents. An aqueous solution of PMAA and a drug solution with a calculated concentration were preliminarily prepared with continuous stirring and slight heating to 305K. Then, the drug solution was placed in a dropping funnel and poured dropwise into the PMAA solution, stirring constantly for one to two hours. At low drug/PMAA ratios, the polycomplexes retained water solubility, but at high ratios, the etonium-PMAA and imidocarb-PMAA polycomplexes precipitated. The resulting polycomplexes were filtered and freeze-dried.

The complexes are white powders. Potentiometric titration was carried out on an I-130 ion meter with a glass electrode with a measurement accuracy of 0.02 pH units at

298K. The ionomer was preliminarily calibrated with buffer solutions. IR spectroscopic studies of the reagents and products of their interaction were carried out on a Nicolet iS50 Fourier transform IR spectrometer (Thermo Scientific, USA) in the region of 400-4000 cm^{-1}. Samples of the starting substances and poly-complexes were used in the form of pressed tablets with KBr.

Viscometer measurements of solutions were carried out during thermostatting with an accuracy of 0.1 K in a capillary viscometer of the Ubbelohde type. Calculations were carried out using the classical method. The drug concentration in solutions was determined by analyzing a graph that plotted the optical density (D) of the solution against the drug concentration. The optical density of medication solutions was measured using a Spectrophotometer UV-1800 Shimadzu (Japan) at specific wavelengths: 239 nm for imizhocarb and 225 nm for aethonium. The reaction between aqueous solutions of a drug and PMAA, using imidocarb as an example, can be depicted according to the following scheme:



The above-presented scheme was confirmed when studying the interaction of PMAA with the studied drugs using the potentiometric method at a fixed temperature. To study the impact of the amount of aethonium on the formation of the polycomplex, potentiometric titration of the polyacid solution was carried out at various concentrations of aethonium (Figure 1).

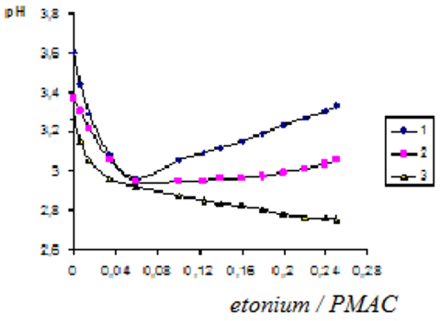


Fig. 1. Curves of pH versus component ratio etonium-PMAC. 1, 2, 3 – concentration of an aqueous solution of ethenium, respectively 0.5; 1.0; 2.0%.

3 Results and discussion

As can be seen from the data in Figure 1, during potentiometric titration of a solution of PMAA with a drug substance, the pH value decreases since a significant part of the hydrogen ions in the carboxyl groups of PMAA at pH 3-4 is replaced by a chlorine counterion in the aethonium molecule. The interaction between PMAA and ethonium is believed to be caused by the production of hydrogen bonds between the carboxyl groups of PMAA and the quaternary nitrogen of the medication. This contact results in a reduction in the pH of the medium. A rise in the PMAA-ethonium ratio above 1:0.2 does not lead to a change in the pH of the system since, to a certain extent, some of the carboxyl groups remain unbound in the polycomplex, and they do not have a noticeable effect on the pH of the medium in this area.

A reduction in pH is seen when titrating an aqueous PMAA solution with an aqueous ethonium solution; this pH value reaches a limit when the resulting polyelectrolyte complex, which has a composition about equimolar, is saturated. As demonstrated by the potentiometric titration curve (Figure 1), a further increase in the amount of aethonium after reaching saturation only slightly changes the pH. Figure 2 shows the titration curve of an aqueous PMAA solution with an imidocarb solution without taking into account the effect of diluting the system. Based on these curves, according to the method described in the literature [10], the parameters of electrostatic binding were calculated: $\theta 1=\Delta[H+]/[P]=2.79\%$ and $\theta 2=\Delta[H+]/[LV]=47\%$, which indicate that only a tiny part of the carboxyl groups are involved in the binding of base molecules. At the same time, almost half of the amine introduced into the system is associated with the polymer matrix (in systems where the polymer complex is still soluble in water).

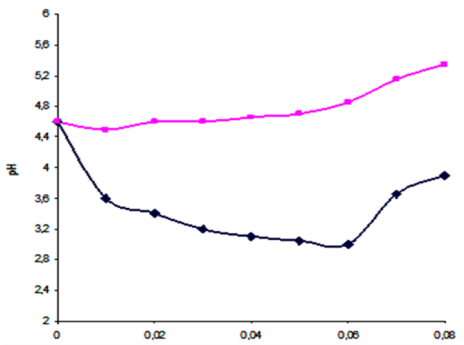


Fig. 2. Potentiometric titration curves of PMAA (1) with imidocarb dipropionate and (2) without the effect of dilution.

The product of the interaction of the studied components is a water-insoluble polyelectrolyte polycomplex, which is due to the hydrophobization of molecules since the ionogenic groups responsible for the solubility of polymers in aqueous solutions are blocked. Using IR spectroscopy, when studying the formed poly-complexes, The band shift corresponding to the stretching vibrations of the carboxyl group into the high-frequency region (Figure 3) allows direct observation of the creation of hydrogen bonds.

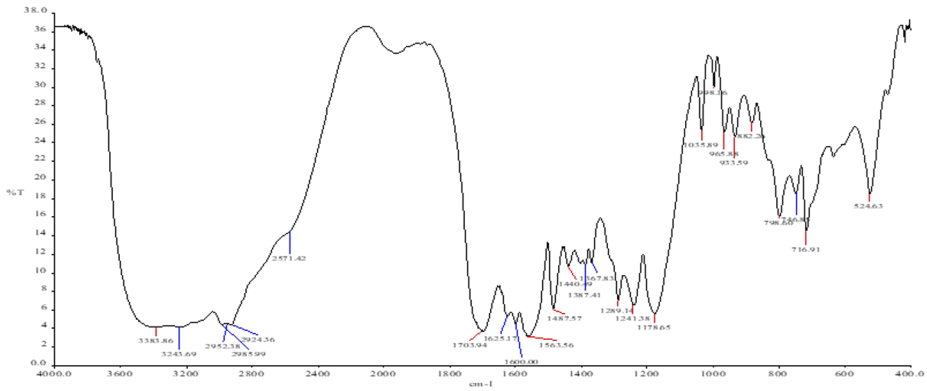


Fig. 3. IR spectrum of the polymer complex of imidocarb with PMAA.

The band at around 1150 cm^{-1}, which represents the stretching vibrations of tertiary nitrogen, is observed in both the ethenium molecule and the polycomplex. Figure 3 displays the infrared spectra of the polymer complex formed by imidocarb and PMAA. A shift in the absorption band frequencies in the range of 2500-3500 $cm^{-1}$was seen when comparing the IR spectra of the polymer complex with the spectra of imidocarb and PMAA. The spectra of the polymer complex exhibit a broad absorption band ranging from 3200 to 3400 cm^{-1}. This band is indicative of the presence of intermolecular hydrogen bonds formed between the constituents of the polymer complex. In the IR spectrum of the polymer complex, the band of the ketone group of the substance at 1714 cm^{-1}overlaps with the band of the acid carbonyl of PMAA. As a result, there is a simultaneous decrease in the maximum and a shift of the absorption bands to a lower frequency region of 1703 cm^{-1}, which indicates a relatively mild interaction between the drug and the polymer [2, 3].

As a result, the density and size of polyacid coils can change significantly, as evidenced by viscometric studies (Figure 4). At low polymer/drug substance ratios, the resulting complexes are soluble in water, but at large quantities of the drug substance, precipitation occurs. The polymer complex of ethonium is capable of forming aqueous solutions with a concentration of more than 2% (in terms of drug). To confirm this, the number of free (unsubstituted) carboxyl groups in the PMAA-ethonium complex was determined (Table 1). As can be seen from the table, the acid number drops sharply to the ratio etonium/PMAA = 1:0.2, and then with an increase in the amount of added drug, the acid number begins to increase from 57 to 96 at the ratio etonium/PMAA = 1:1. Data from studying the curves of the dependence of pH on the ratio of the components of ethanium/PMAA (Figure 1) and determining the acid number (Table 1) indicate

Table 1. Composition of the aethonium/PMAA poly complex existence of equilibrium in the system under study: Etonium + PMAA poly complex.

etonium/PMAC	Acid number	Composition of the poly complex, %	
		PMAK	Etonium
0.05	320.0	77.67	22.33
0.1	92.0	22.33	77.67
0.2	54.4	13.20	86.80
0.4	62.4	15.15	84.85
0.5	62.4	15.15	84.85
0.6	70.4	17.09	82.91
0.8	78.4	19.03	80.97
1.0	94.4	22.91	77.09

The data obtained from determining the acid number of the polycomplex revealed that the composition of the latter was calculated. Data for calculating the composition of the polycomplex based on the acid number are given in Table 1.

As is known from the literature [11], during the interaction of such complex organic ions with polyelectrolytes, various types of binding are realized. To identify the contribution of individual types of interaction, the process of interaction of the polymer with imidocarb in the systems: water-methanol, water-dimethyl sulfoxide (DMSO) and an aqueous solution of KCl was studied using viscometry and gravimetry. It was experimentally established that an elevation in the ionic concentration of the solution most strongly affects the process in a given drug/polymer pair (Figure 4).

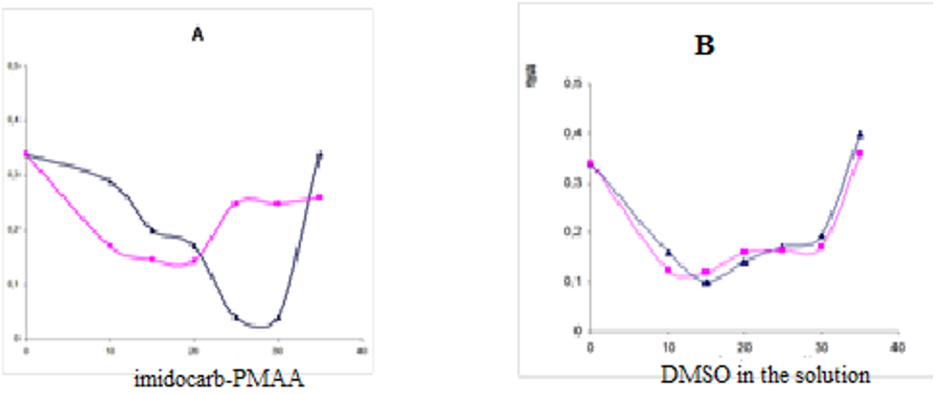


Fig. 4. Dependence of the specific viscosity of the PMAA solution (1) and the imidocarb-PMAA polymer complex (2) on the content of methanol (A) and DMSO (B) in the solution; on the ionic strength of the solution (B). PMAA concentration is 0.058 basic mol/l, imidocarb/PMAA ratio is 0.007 mol/basic mol (A, B) and 0.0067 mol/basic mol (C). T=308 K (A, B), T=298 K (V).

An observed correlation exists between an elevation in ionic strength and a corresponding reduction in viscosity, which can be attributed to the inhibition of PMAA macromolecule ionization. At high ionic strengths of the solution, the specific viscosity values of the polymer and the polymer complex become close, which is a consequence of the conformational compression of macromolecules and the destruction of the complex [12, 13].

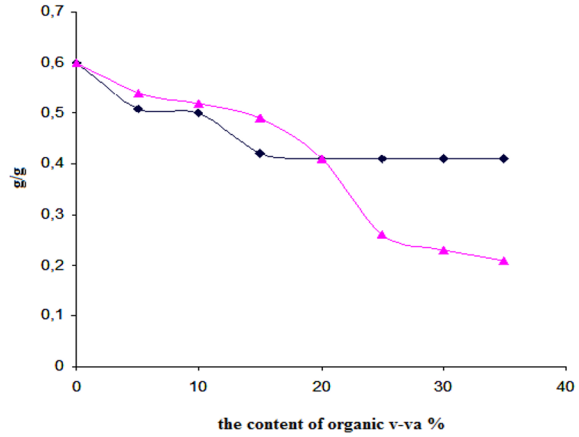


Fig. 5. Dependence of imidocarb binding on PMAA in aqueous-organic solvents: water-methanol (1) and water-DMSO (2) under stationary sorption conditions. The imidocarb/PMAA ratio is 0.24 mol/basic mol. T=308K.

The influence of DMSO on the process under study is quite complex since it is known that DMSO is capable of interacting with phenols, alcohols, as well as carboxylic acids with the formation of strong hydrogen bonds and its high solvating ability with respect to cations (Figure 5). At the same time, as can be seen from viscometric studies, at a specific concentration, DMSO can induce a conformational transformation of macromolecules as a result of changes in the local microenvironment, as indicated by very similar values of the specific viscosity of the polymer solution and the polymer complex in water-DMSO mixtures. In contrast, in water-DMSO mixtures, methanol differs significantly (Figure 4).

The strong influence of the conformational state of macromolecules on their immobilization ability is also indicated by the complex nature of the binding curve of the organic PMAA dication at different temperatures (Figure 6).

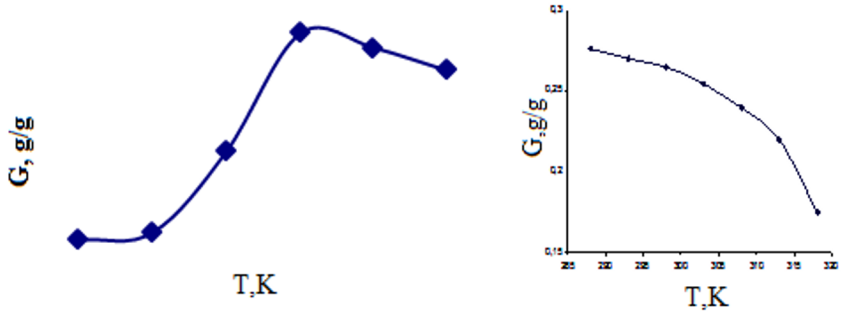


Fig. 6. Dependence of immobilization of imidocarb on PMAA (1) and specific viscosity of the polymer complex (2) on temperature. Imidocarb/PMAA ratio 0.155 mol/bas-mol.

The influence of temperature on the interaction of a macromolecule with organic ions is very ambiguous. On the one hand, with increasing temperature, the destruction of the hydration shells of macromolecules and the displacement of low molecular weight ligands - propionic acid is facilitated; on the other hand, the stability of polymer complexes decreases due to an increase in their dissociation. The experimental results suggest that up

to a temperature of 308 K, the first factor prevails, and above this temperature, the compaction of macromolecular coils leads to interaction difficulties.

Based on the results obtained, isotherms of the binding of imidocarb* to cross-linked PMAA were constructed in Klotz coordinates. From the constructed graphs, the Ksw and the n-ratio of the number of units on the polymer chain per molecule of the immobilized drug were calculated (Table 2).

Table 2. Thermodynamic parameters of imidocarb sorption hydrogels based on cross-linked PMAA.

T, K	n	$K_{cv} \cdot 10^4$	ΔG J/mol	ΔH - J/mol	ΔS- J/mol·
293	0.19	1.23	-21928.385	36361	198.427
301	0.1	1.46	-22097.475	36361	193.715
311	0.06	2.87	-21081.558	36361	184.220

Table 2 demonstrates that higher temperatures result in higher values of Kcv and n during the study. With higher system temperature, the amount of drug molecules attached to macromolecules increases. This results in an increase in the Kw value of a low-molecular substance with a single active center on the polymer. This suggests that the absorption of this drug by cross-linked PMAA is of a chemical nature. Also, under the same conditions, a similar type of curve was obtained for the etonium-PMAA system by stationary sorption (Figure 7). At a ratio of ethonium/PMAA = 0.5:1.0, the yield of the polycomplex reaches its maximum value (80%), which was also confirmed by potentiometric studies (Figure 8).

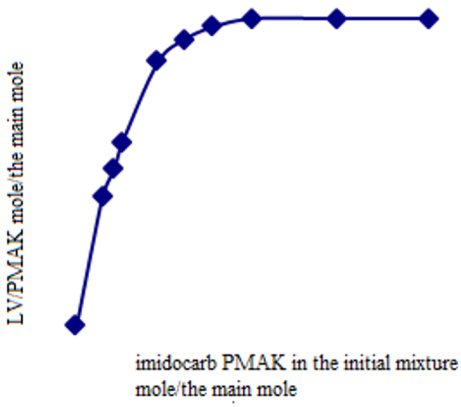


Fig. 7. Dependence of the content of imidocarb* in the polymer complex on its initial content in solution. PMAK concentration - 0.07 basic-mol/l; T=298K.

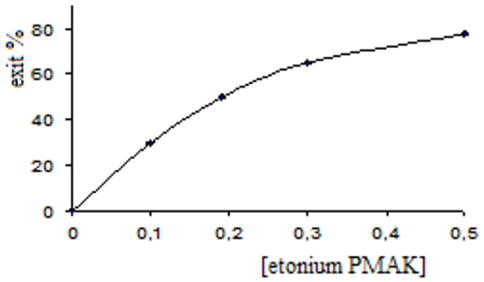


Fig. 8. Dependence of the yield of the etonium/PMAA poly complex on the ratio of the reacting components.

4 Conclusions

The physicochemical studies conducted on the binding process of this organic ion with PMAA indicate that electrostatic interactions between the ionized groups of the polymer and the substance play a primary role in their immobilization. This is followed by hydrogen bonds between the drug and the polymer and weaker hydrophobic interactions that complement them.

At the same time, the process of drug immobilization on PMAC is dynamic. When concentrated solutions of the components under study interact, we first observe the cross-linking of different macromolecules with dications, which leads to the thickening of the solution. This pair of reagents is interesting because, even visually, one can observe transparent packs of crystalline PMAA macromolecules. One hundred eighty minutes after the start of the interaction, without external mechanical or any other influence, a change occurs in the system; that is, a relatively stable colloidal solution is formed - a white suspension. This indicates a redistribution of the binding of dications within macromolecules, which leads to the formation of spherical structures [14-16]. Based on the research conducted on the basis of the studied organic molecules and PMAC, a new prolonged dosage form was developed for use in veterinary medicine. The results obtained confirm that the use of linear functional polymers, in this case polymethacrylic acid, to create modified drugs with the correct selection of drug-polymer interaction conditions can lead to positive results [15-19].

References

1. A. Akhgari, F. Sadeghi, H. Afrasiabi Garekani, Combinatio of time-dependent and pH-dependent polymethacrylates as a single coating formulation for colonic delivery of indimethacin pellets. Int. J. Pharm. **320** (2006)
2. D. Gallardo, P. Kleinebudde, B. Skalsky, Pharm. Dev. Technol. **13**, 5 (2008)
3. K. Dissanayake, M. Rifky, M Jesfar, J. Makhmayorov, S. Rahimkulov, B. Abdullayev, IOP Conf. Ser.: Earth Environ. Sci. **1275**, 1 (2023)
4. S. A. Kedik, V. V. Suslov, E. A. Shnyak, A. P. Malkova, Y. M. Domnina, Polymer material for medical purposes for embolization. RF patent. **2669801**, 13 (2018)
5. A. A. Demin, I. A. Chernova, L. K. Shataeva, Ion exchange sorption of biologically active substances (Ed. St. Petersburg University, St. Petersburg, 2008)

6. S. S. Kamaeva, L. A. Potselueva, F. M. Sabirova, Spermicidal activity of aethonium. RF patent. RU 2229878 (2004)
7. Bakhodir, M Rifky, J. Makhmayorov, I. Usmanov, T. Deng, M. Samadiy, International Journal of Engineering Trends and Technology **71**, 9 (2023)
8. G. M. Andreev, I. D. Barantsev, E. O. Vorobyov, N. M. Kalishin, Directory of veterinary paramedic (Agropromizdat, Leningrad, 1988)
9. M. M. Karimov, N. S. Nurmukhamedova, F. A. Umarov, T. M. Babaev, Application of mathematical static analysis to evaluate certain chemical reactions. Dokl. Academy of Sciences of the Republic of Uzbekistan **2** (2020)
10. N. I. Bystrova, V. A. Kemenova, A. B. Zezin, B. A. Kabanov, Interaction of aminosine with polymethacrylic and polyacrylic acids in acidic media. Chem. Pharm. Zhur. **4** (1984)
11. E. W. Charles, A. D. Charles, W. S. James, PVC Handbook. Akron, Ohio, 316-317 (2007)
12. L. Ran, X. Ci, L. Liu, et al., International Journal of Biological Macromolecules **260**, 129615 (2024)
13. M. M. Karimov, M. K. Rustamov, M. G. Mukhamediev, L. O. Khozyaeva, *Interaction of synthetic polyelectrolyts with some organic bications*, in Proceedings of the PR 7th Inter. Symp. Molecular mobility and order in polymers systems. St. Petersburg. p.171 (2011)
14. D. Gallardo, P. Kleinebudde, B. Skalsky, Pharm. Dev. Technol. **13**, 5 (2008)
15. L. I. Valuev, T. A. Valueva, I. L. Valuev, N. A. Plate, Polymer systems for the controlled release of biologically active compounds. Advances in Biological Chemistry, **43** (2003)
16. D. Ziyodullo, M. Absattorov, S. Rifky, et al., SE3S Web of Conferences **411**, 10 (2023)
17. B. Abdullayev, N. Askarova, R. Toshkodirova, M. Rifky, N. Ayakulov, B. Kurbanov, M. Samadiy, Asian Journal of Chemistry **36**, 2 (2024)
18. J. E. Sykes, M. G. Papich, Antiprotozoal Drugs. Imidocarb Dipropionate. Canine and Feline Infectious Diseases (2014)
19. O. V Kraskov, E. A. Sernova, R. R. Vlasov, S. A. Ryabov, Preparation of methacrylic acid polymers for selective delivery of antitumor drugs. News of Volgograd State Technical University **5** (2022)