DEVELOPMENT OF POLYMERIC DOSAGE FORMS OF THE ANTIBACTERIAL COMPOUND ETHONIUM

Urinova Zebo Khudoyorovna
Doctoral student at Samarkand State University
Babaev Tuygun Mirzaakhmedovich
Professor of the National University of Uzbekistan, Doctor of Chemical Sciences
Karimov Makhmud Muratovich
Associate Professor of the National University of Uzbekistan, Doctor of Chemical Sciences
Mavlonova Sevinch Hasan kizi
Chirchik branch Tashkent Medical Academy

Annotation: The complex formation of the medicinal compound aethonium with the natural polymer apple pectin was studied using the methods of IR spectroscopy, potentiometric titration and viscometry. The ways of modifying a carboxyl-containing polymer, highly soluble in water, with an organic physiologically active compound, aethonium, used in veterinary practice as an anti-inflammatory agent to obtain its prolonged dosage forms have been studied.

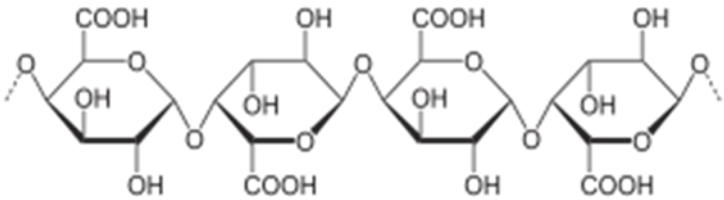
Key words: pektine, etonij, polyelectrolytes, polymer complex, antisflam-matory mean, hidrodinamical property, IK-spectroskopy, potentiometric titration, viscosimetry.

Introduction. The second half of the twentieth century was marked by a number of breakthroughs in the chemistry of macromolecular compounds in various fields of natural science. Evidence of one of them is the emerging direction - the chemistry of medical and biological polymers [1,2], one of the tasks of which is to solve the problems of chemical modification of natural and synthetic polymers and the synthesis of new polymers for use in medicine, biology and veterinary medicine [3 -5]. In this regard, the study of the interactions of polyelectrolytes with various ions of physiologically active substances, which is due to the possibility of creating new effective drugs for practical use, is of great scientific interest [6,7]. Promising in this regard is the modification of medicinal substances by complexing them with polyelectrolytes in order to improve solubility in water and biological fluids, protect them from premature destruction by enzymes, reduce the dose, and give them a prolonged and targeted effect on the body [8].

When polyelectrolytes form complexes with biologically active compounds, the conformational state of polymers in solution and the hydrodynamic properties of their macromolecules change significantly. Therefore, the study of the structure, structure, conditions of formation and processes of conformational transformations of polymers and their changes under the influence of various factors is an urgent task in polymer chemistry.

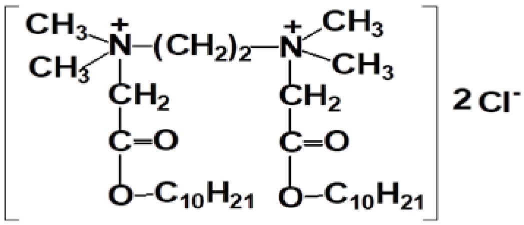
The use of pectin and its derivatives as carriers of pharmacologically active compounds is based on its ability for exchange-sorption interactions of both ions and molecules as a whole [9], as well as the ability to gel as a result of aggregation of pectin and water macromolecules [10].

Objects and methods of research. The objects of research were apple pectin and the drug etonium. According to modern concepts, pectins are colloidal complexes of acidic polysaccharides, consisting of arabinan, galactan and so-called pectic acid with the following chemical structure [11]:



The molecular weight of pectins ranges from 3000 to 300,000 [12]. Apple pectin from the Russian company "WATT-NUTRITION" (brand for food products) was used in the studies.

Etonium 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 [13]. In the experiments, we used ethonium produced by the Russian company BIOLINE LLC (reagent grade), which has the following chemical structure:



Polycomplexes of pectin with aethonium were obtained by mixing aqueous solutions of the reagents. For example, 1 g of pectin was dissolved in portions in 20 ml of distilled water. Then, 2 ml of a solution containing 0.02 g of aethonium was added from a dropping funnel with stirring, and this mixture was stirred for 4 hours at room temperature [14]

IK spectroscopy. IK spectra were recorded on a Nicolet iS50 Fourier transform IK spectrometer (Thermo Scientific, USA). Samples of the starting substances and poly-complexes were used in the form of pressed tablets with KBr.

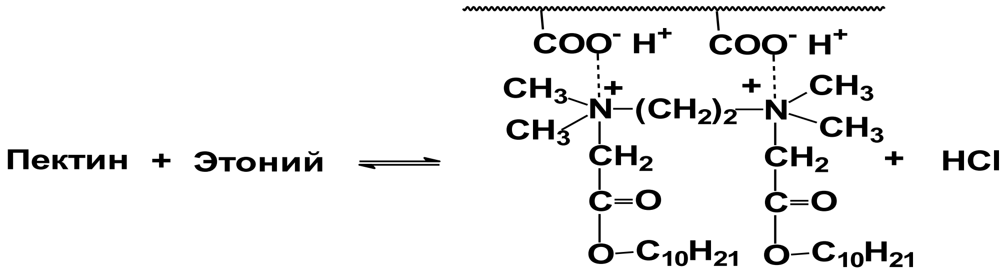
Potentiometric titration. Titration of an aqueous solution of pectin with an aqueous solution of sodium hydroxide or an aqueous solution of ethnium was carried out on an I-130 ion meter with a glass electrode, measurement accuracy 0.02 units. pH at 20℃. The ionomer was preliminarily calibrated with buffer solutions. 0.01 N was added dropwise to an aqueous solution of 0.1% pectin. NaOH solution.

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 [15].

The results obtained and their discussion. One of the methods for producing medicinal polymers is complex formation between the carrier polymer and the medicinal compound, which is a promising direction for practical use [7,8].

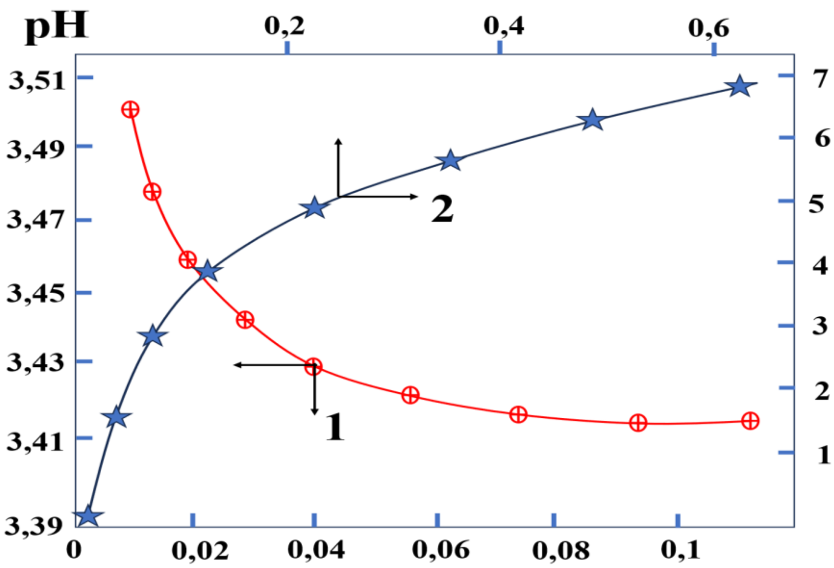
In this regard, it is interesting to study the interaction of a natural polymer - pectin, which has a unique more complex structure than synthetic polyelectrolytes with organic amines, containing both hydrophilic and hydrophobic groups. Pectin is a substance that is obtained exclusively from raw materials of plant origin [11,12]. From a chemical point of view, pectin is a high-molecular structural polysaccharide (fiber), which is part of the cell wall and intercellular structures of almost all non-aquatic plants. The ability of pectin to exhibit specific sorption properties, dissolve in water and a tendency to gel, and its practical harmlessness to the body determines its use as a carrier polymer for medicinal substances [14,15].

When mixing aqueous solutions of pectin and aethonium, turbidity and a decrease in the pH value of the solution are observed, which is explained by the interaction of pectin and aethonium with the formation of a polyelectrolyte complex according to the following scheme [19,21]:



The product of the interaction of the studied components is a water-insoluble polyelectrolyte complex, which is due to the hydrophobization of molecules, since the ionogenic groups responsible for the solubility of polymers in aqueous solutions are blocked [9,10].

When titrating an aqueous solution of pectin with an aqueous solution of ethnium, a monotonous decrease in the pH value of the medium is observed. As the data show (Figure 1), the addition of increasing amounts of aethonium to a pectin solution is accompanied in the initial section of the curve by a decrease in the pH of the medium, which is a consequence of the ion exchange reaction, and in the range of Cet/Spc values from 0.04 the pH of the solution practically does not change.

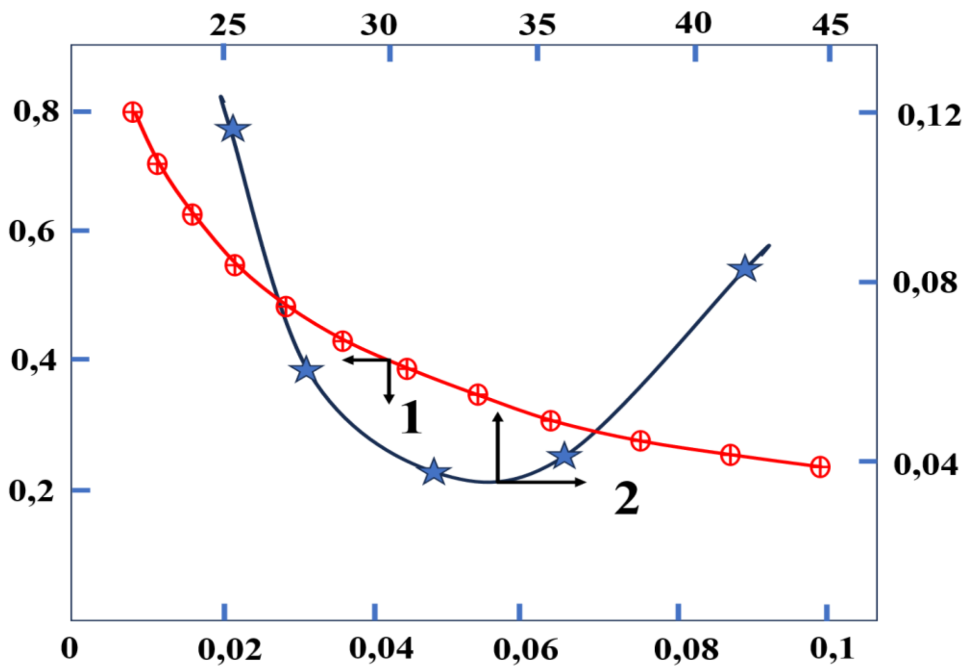


[ethonium]:[pectin]

Pic. 1. 1 - Potentiometric titration of an aqueous solution of pectin (C = 0.2%) with a solution of ethonium (0.06%); 2 - Dependence of the degree of electrostatic binding on the relative molar content of aethonium.

Apparently, the resulting electrostatic interactions are stabilized by hydrophobic bonds. The degree of electrostatic binding (el) was calculated from the number of hydrogen ions released (pH). The nature of the curve (Figure 1) indicates the

Viscometric titration showed (Figure 2.1.) that the addition of aethonium to a pectin solution at low concentrations leads to a sharp.

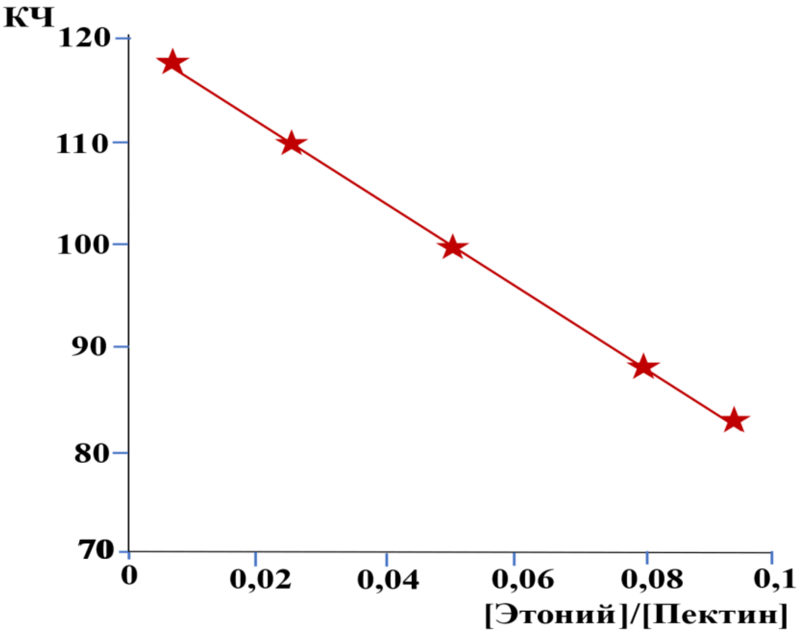


[ethonium]:[pectin]

Pic.-2 1 - Dependence of the reduced viscosity of a pectin solution on the [ethonium/pectin] ratio; 2 - Dependence of beat/s of an aqueous solution of a polymer complex (pectin + ethonium) on temperature reduction in reduced viscosity values, but with large quantities of the drug substance precipitation occurs. The decrease in reduced viscosity is explained by the folding of pectin macromolecules into compact coils due to their hydrophobization as a result of electrostatic binding of organic cations [14,20].

With an increase in temperature from 278 to 308 K, the value of the specific viscosity of the solution of the product of the interaction of the components sharply decreases from 0.13 to 0.03 and at higher temperatures begins to increase, which is explained by the strengthening of hydrophobic interactions that arise between the hydrophobic regions of the macromolecule and the drug substance, which to a certain extent, they unfold the macrochain of the polycomplex (Figure 2.2) [9,12].

To confirm that the pectin-ethonium interaction is carried out due to the formation of H-bonds between the -COOH group of pectin and the quaternary nitrogen of the drug, the number of free (unsubstituted) carboxyl groups in the pectin-ethonium polycomplex was determined.



Pic.-3. Change in the acid number of the aethonium:pectin polycomplex depending on the ratio of the components

As can be seen from Figure 3, the value of the acid number drops sharply with an increase in the amount of drug in the polymer-ethonium mixture, which is consistent with literature data [12,15].

Conclusion

Thus, the possibility of using water-soluble pectin to modify the properties of the antibacterial drug etoniya is shown. It has been established that the association of pectin and aethonium is realized as a result of electrostatic and hydrophobic interactions. The influence of these types of binding on each other is determined by the ratio of the reacting components and the pH of the environment.

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