

THE STUDY OF PHYSICAL AND CHEMICAL PROPERTIES OF WATER-SOLUBLE POLYMER REAGENTS AND THEIR COMPATIBILITY WITH ANTIBIOTICS

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ABSTRACT

The article considers the processes of synthesis of water-soluble polymers HPAA-HP (hydrolyzed polyacrylamide with the modifier hydrogen peroxide), HPAA-MEA (hydrolyzed polyacrylamide with the modifier monoethanolamine), HPAA-TEA (hydrolyzed polyacrylamide with the modifier triethanolamine). The physical and chemical properties of water solutions of water-soluble polymers are investigated. It is shown that they are high-molecular polyelectrolytes. The compatibility of polymers with antibiotics is shown. Synthesized polymers have been proposed as ointments of soft carriers for use with medications. Many known ointment bases are easily exposed to microbial contamination (hydrogenated fats, fatty and vegetable oils, gelatin gels and others). The effect of the antibacterial ointments we are researching is aimed at the destruction of pathogenic microorganisms and products of their vital activity, which are the cause of infectious and inflammatory processes in the wound. Therefore, one of the most important requirements expressed to ointment bases, is resistance to microbial contamination, because the latter can significantly reduce the concentration of antibiotics in ointments, thereby reducing the therapeutic effect of the preparations, and can be the cause of secondary infection of the wound or burn surface. The study of colloidal-chemical properties of aqueous solutions of the studied polymers allowed establishing the relationship between poly electrolyte effects and functional composition, the degree of hydrolysis. The conditions for obtaining HPAA-HP, HPAA-MEA polymers, most clearly showing polyelectrolyte properties were determined based on the research of physical and colloidal - chemical properties, their polyelectrolytic character is revealed and they belong to high-molecular surfactants they relate to high-molecular surface-active substances.

Keywords: Water-soluble Polymer, Soft Carriers, Antimicrobial Activity, Antibiotics, Hydrolyzed polyacrylamide, Ointment, Viscosity.

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INTRODUCTION

The article presents the results of studies of physical and chemical properties of water-soluble polymer reagents and their compatibility with antibiotics. The creation of new polymer reagents from their synthesis in the laboratory to their industrial production as an ointment is a relatively long and expensive process. Therefore, the most promising and justified way is to expand the range of polymer reagents by modifying the already known base samples. We studied HPAA-HP, HPAA-MEA, HPAA-TEA (hydrolyzed polyacrylamide) polymers. Synthesized polymers have been proposed as soft carriers for

drug transport. To obtain reproducible results, strict standardization of experiments is necessary. The rate of solutions diffusion in agar depends on the chemical nature of the antibiotic, the composition, pH of the agar medium, the buffer in which the working solutions of the standard and the test material are prepared, the temperature and incubation time. Therefore, when determining the concentration of antibiotics and maintenance of their antibacterial activity in test samples we should select the conditions for culturing the test culture, the optimal composition and pH of the medium, buffer solutions, ensuring the maximum diffusion of the solutions of antibiotic into the medium and the sharpness of the zones outlines. The determination is carried out according to the scheme common to all antibiotics.¹

Characteristics of the Studied HPAA-HP, HPAA-MEA Copolymers

Copolymers of acrylic acid, which are well mixed with water forming a viscous fluid mass, were synthesized based on the Department of chemistry and fundamentals of chemical technology in the M. Auezov SKSU. Their properties and consistency are of interest for the possibility of their use as auxiliary substances in pharmaceutical technology in the preparation of external medical forms.

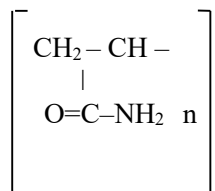
The preparations have undergone poison control. Based on toxicological studies and analysis of the data obtained, it was concluded that polymers have a slight functional cumulation. They do not show skin-blistering and allergic effects.²

1. HPAA- HP, HPAA-MEA

Hydrolyzed polyacrylamide with the modifier hydrogen peroxide was obtained based on hydrolysis with alkali of polyacrylamide in the presence of a modifier at a temperature of 368 K for a time of 2-2.5 hours. Hydrolyzed polyacriamide with the monoethanolamine modifier was prepared based on hydrolysis of polyacrylamide with an alkali in the presence of monoethanolamine modifier at a temperature of 368 K and reaction time of 2 hours.

2. Polyacrylamide (PAA)

PAA is granules of irregular shape, yellowish or slightly brown. The mass fraction of the polymer in the product is 50-56%, moisture is 10-14%, and ammonium sulphate is 30-40%. The pH of 0.1% water solution is 7-8. The kinematic viscosity of 0.1% water solution is not less than $(1.7 - 2) \cdot 10^{-6}$.³



EXPERIMENTAL

Conductivity.pH of HPAA-HP, HPAA-MEA, HPAA-TEA polymers solutions were measured on a potentiometer pH-340 with an accuracy of ± 0.05 in a thermostatically controlled cell in which the temperature was maintained with an accuracy of $25 \pm 0.01^\circ\text{C}$. Further, the electrical conductivity was determined by the formula (χ):

$$\chi = \frac{\alpha}{R \cdot x};$$

Where, α is the cell constant, it was determined by the formula:

$$\alpha = 0.000147 \text{ m}^{-1}\text{cm}^{-1} \text{ at } T = 250^\circ\text{C}$$

The electrical conductivity of GRP HPAA-HP, HPAA-MEA, HPAA-TEA solutions is studied on the device assembled according to the bridge circuit with the frequency of 1000Hz; voltage was produced by the ZG-6m sound generator. The output voltage is 6V. The electrical cell has the form of a cylindrical vessel with a capacity of 25 ml; electrodes are made of blackened platinum. The arrangement of

electrodes is vertical. The thermostat of the cell is carried out in a water thermostat. The cell constant (K) at 298 K is 0.37.⁴

Specific conductivity (χ) is calculated according to the formula:

$$\chi = K/R \times (\text{Ohm}^{-1} \times \text{cm}^{-1}),$$

Where, R- is resistance (Ohm^{-1}) of the studied solution;

K- is cell constant.

Potentiometric titration is carried out on a laboratory pH meter – millivoltmeter LPM-60 m with a sensor DL-01 at $298 \pm 0,1$ K in a nitrogen current. The meter is a glass electrode ESL IIG-0.4, and a comparison electrode is calomel electrode.⁵

Microbiological Method of Direct Diffusion into Agar

To establish the compatibility of HPAA with levomycetin sodium succinate and gentamycin sulfate antibiotics it is necessary to detect the antimicrobial activity of antibiotics, which is determined by diffusion into agar.

The method for carrying out this research is described in detail in the USSR pharmaceutical regulations XI ed., V.II. Because it does not consider some of the features of our experiment (for example, the determination of antimicrobial activity in ointments), we modified the method to be able to apply it in our work.

The method of diffusion into agar is based on comparing the degree of inhibition of the test microbe growth zone with certain concentrations of the antibiotic in the test material with inhibition of its growth zone by the known concentrations of the antibiotic standard. The suppression of the test microbe growth is due to the antibiotic diffusion from the test material into a dense nutrient medium.

To obtain reproducible results, strict standardization of experiments is necessary. The rate of solutions diffusion in agar depends on the chemical nature of the antibiotic, the composition, pH of the agar medium, the buffer in which the working solutions of the standard and the test material are prepared, and the temperature and incubation time. Therefore, when determining the concentration of antibiotics and maintenance of their antibacterial activity in test samples we should select the conditions for culturing the test culture, the optimal composition and pH of the medium, buffer solutions, ensuring the maximum diffusion of the solutions of antibiotic into the medium and the sharpness of the zones outlines. The determination is carried out according to the scheme common to all antibiotics.⁶

Spectrophotometric Quantitative Determination of Levomycetin Sodium Succinate in Antibacterial Ointments

This highly sensitive method of quantitative determination of the drug in solution is described in Pharmaceutical standard-42-737-78.

The optical density of the 0.002% preparation solution was measured on the SF at a wavelength of 275 nm compared to water in a sample-holder with a layer thickness of 1 cm. The same measurement was carried out with a 0.002% solution of a standard sample at a wavelength of 278 nm.

The percentage (X) of levomycetin in the preparation is calculated by the formula:

$$X = \frac{D + C_0 + 100}{D_0 + C},$$

Where,

D-is the optical density of the test solution

D0- is the optical density of a solution of a standard sample

C-is the concentration of the test solution

C0- is the concentration of the solution of the standard sample.

The content of levomycetin in the preparation should be at least 65%. Each flask should contain at least 90% and not more than 110% of the amount indicated on the label.⁷

Note: The standard sample is levomycetin (Pharmaceutical Standard for Levomycetin).

Fractional Sterilization (Tundalization).

The objects to be sterilized are heated at 30 ° C for 1 hour every 24 hours. In the intervals between heating, the object is kept in a thermostat at a temperature favorable for the spore germination (25-37°C). Three cycles are enough for all the spores contained in the object to germinate and die with subsequent heating.

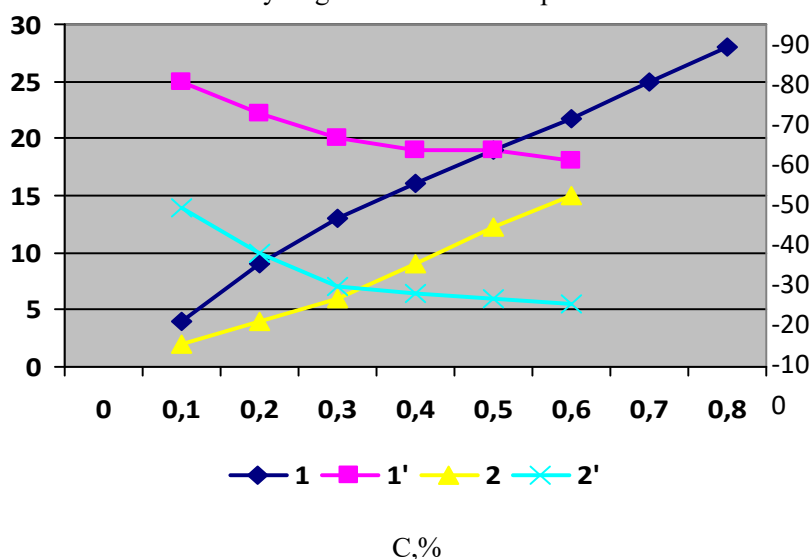
The Method of Equilibrium Dialysis According to Kravchinsky.

The dialysis device proposed by Kravchinsky consists of a beaker that places 50 ml of the model medium, a dialysis tube with an internal diameter of 32 mm and a height of 160 mm. Put 1.0 g of the test sample of the ointment in the lower end of the tube. Put the tube into a glass with a dialysis medium to a depth of 2 mm. A thermometer for temperature control and a pipette for sampling are put into the glass. The glass is placed in a water bath. Samples have a volume of 2ml.

RESULTS AND DISCUSSION

The property of HPAA-HP, HPAA-MEA, HPAA-TEA polymers to dissociate in aqueous solution allows us to study the electrical conductivity of aqueous solutions of polymers and to research the ionizability of macromolecules in solution. It is known that electrical conductivity depends on the concentration of polymers. With the increasing concentration of the studied samples of GRP, the specific conductivity increases, and then this dependence is exponential. Thus χ_{sp} depends on a ratio of polymers functional groups.⁸

In such systems, it is seen that the distribution of mobile ions between the areas occupied by poly ions and in the surrounding space is not regulated by Donnan balance. The activity coefficients of ions must be compressed at the expense of the existing electrostatic forces, which lead to a decrease in the potential and, accordingly, in their electrical conductivity. Also, the possible formation of ion pairs, associates, chelates formed due to the hydrogen bonds can take place.



Specific (1, 2) and Equivalent (1', 2') Conductivity of Solutions: 1-HPAA-HP; 2-HPAA-MEA
Fig.-1: Relationship of Specific and Equivalent Conductivity in HPA-PV, HPA-IEA Polymer Solutions

Figure-1 shows that the initial incident portion of the curve corresponds to the region of the complete ionization of functional groups and thermodynamic stability of the system. Straight section parallel to the absciss axis corresponds to the area of structured solutions in which macromolecules are associated. The fracture on the curve can be considered as the beginning of the conformational transformation of macromolecular tangles in HPAA-HP, HPAA-MEA polymer solutions with the possible formation of supramolecular structures in concentrated polymersolutions.

In all HPAA-HP GRP samples, the pH-q correlation has S-shaped form with inflection points in the acidic (3.5-4.0) and alkaline (8.5-10) areas (Fig.-2). In an acidic medium (pH=3.6-4.2), COOH groups slightly dissociate and are in a tangled state; when alkali is added, the neutralization of hydrogen ions mainly occurs at higher pH. The neutralization reaction is accompanied by the appearance of charges on the macromolecule, which affects the titration curve and the chain shape.

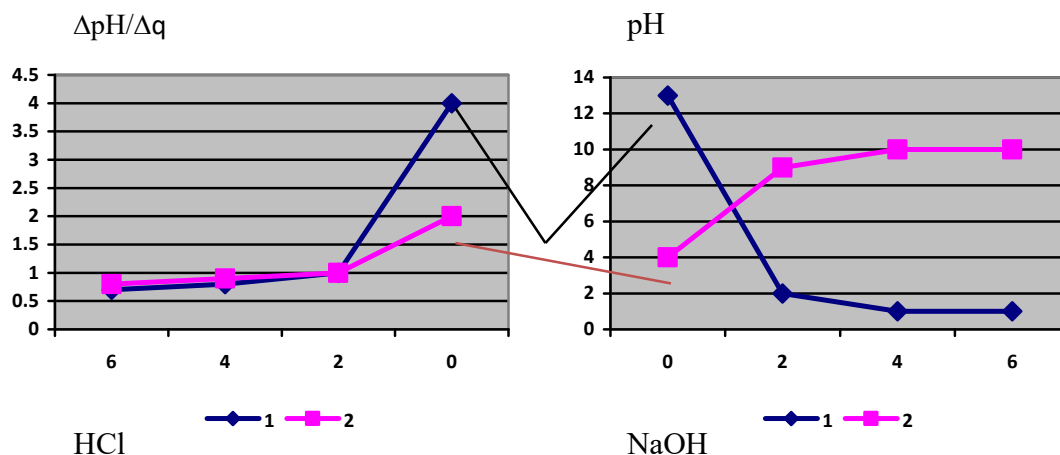


Fig.-2: Integral (1) and Differential (2) Potentiometric Titration Curves of 0.1% Solution of the HPAA-PV, HPAA-IEA Dispersions Mixture

Curves with inflection points in the acidic and alkaline regions indicate the presence of both acidic and basic functional groups. Fully titrated acidic and basic groups correspond to extreme points on the differential curves of potentiometric titration.

For HPAA-HP, HPAA-MEA amphoteric polymers, the titration curve looks more complicated than for polyacids and polybases.

Carboxyl groups of HPAA-HP, HPAA-MEA are titrated in the pH range=4-9. At pH below four, hydrochloric acid joins the amide and imide groups to form the salt of hydrochloric acid polyamide, meanwhile pH changes to three. Earlier it was established that for a polypeptide chain electrolytic interaction of closely spaced groups differs for spiral and tangle-shaped conformations; in the transition spiral-tangle region, the degree of ionization of the macromolecule increases sharply when the pH of the solution changes.⁹

The electrical conductivity of solutions HPAA-HP, HPAA-MEA (Fig.-3) is studied. An increase in the concentration of HPAA-HP, HPAA – MEA solutions leads to an increase in specific conductivity up to a certain concentration. Then this correlation becomes exponential. This can be explained by either the fact that not all ionogenic groups of the polymer are ionized, or that some factors impede electricity transfer.

Development of the Ointment Base Optimal Composition

When developing the ointment base optimal composition, 1.0 g of HPAA polymer was dissolved in different volumes of distilled water: 1 ml, 2 ml, 3 ml, 4 ml, 5 ml and 6 ml.

It was found out that to obtain an ointment base with the necessary consistency, the optimal ratio of HPAA polymer and distilled water was 1: 5.

The pre-ground and screened HPAA polymer powder was weighed on a BP-1 scale in an amount of 1.0 g, transferred into a mortar and triturated with 5 ml of distilled water, added in parts. As a result of a ten-minute stirring, a thick, sticky, gel-like, transparent mass without odor, the yellowish-cream color was obtained. The base is easily applied to the skin when drying it forms a thin protective film on it, easily removable with a cotton swab dipped in water. The base does not spoil underwear and clothes, does not have an irritating effect and does not tighten the skin when it dries.

Thus, the technology of this synthetic hydrophilic base preparation is extremely simple, does not require special methods of preparation and compliance with a lot of conditions. It is convenient and quick to use.

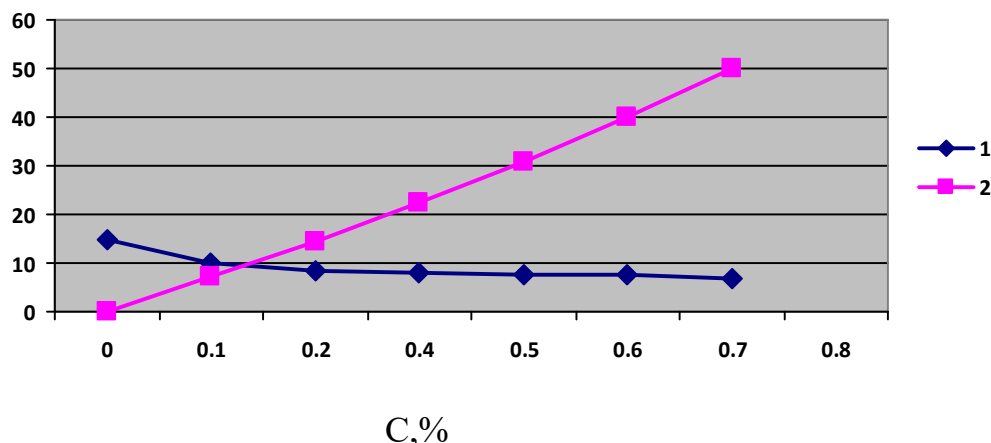


Fig.-3: Correlation of Specific (1) and Equivalent Conductivity (2) of HPA-PV, HPA-IEA Dispersion Mixture Solutions.

Determination of the HPAA New Synthetic Hydrophilic Base of Resistance to Microbial Contamination

Many known ointment bases are easily exposed to microbial contamination (hydrogenated fats, fatty and vegetable oils, gelatin gels and others). The effect of the antibacterial ointments we are researching is aimed at the destruction of pathogenic microorganisms and products of their vital activity, which are the cause of infectious and inflammatory processes in the wound.

Therefore, one of the most important requirements expressed to ointment bases, is resistance to microbial contamination, because the latter can significantly reduce the concentration of antibiotics in ointments, thereby reducing the therapeutic effect of the preparations, and can be the cause of secondary infection of the wound or burn surface.

In connection with the above, it seems necessary to research this direction, using a microbiological agar method.

For this purpose, 1 g of HPAA base was added to two tubes containing 4 ml of molten and cooled to 50 °C nutrient medium. The content of the tube was quickly and thoroughly mixed and transferred to a Petri dish containing 20 ml of a solidified aerated media.

Spread the top layer of agar evenly with a quick rocking of the Petri dish. After solidifying of the medium, the plates were incubated in a thermostat for 5 days at 35 °C.

During this period growth of the bacteria was not detected. Consequently, there are less than 10 bacteria in 1 g of the polymer base. The permissible limit of microorganisms' content in medicinal forms of local use is the presence of not more than 100 microorganisms per gram of the drug.

CONCLUSION

1. The study of colloidal-chemical properties of aqueous solutions of the studied polymers allowed establishing the relationship between polyelectrolyte effects and functional composition, the degree of hydrolysis. The conditions for obtaining HPAA-HP, HPAA-MEA polymers, most clearly showing polyelectrolyte properties were determined
2. The research of physical and colloid-chemical properties of polymers revealed 1422heir polyelectrolyte nature; they relate to high-molecular surface-active substances.
3. Compatibility of HPAA with antibiotics of *levomycetin* sodium succinate and gentamycin sulfate has been established as well as antimicrobial activity of antibiotics.

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