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THE INVESTIGATION OF PHYSICAL AND CHEMICAL PROPERTIES OF WATER SOLUTIONS OF POLYMERS AND THEIR APPLICATION IN COMBINATION WITH DRUGS

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ABSTRACT

In this article are shown soft dosage forms (ointments) obtained based on polymer reagents. Water-soluble polymers are synthesized based on acryl-containing compounds. Aqueous solutions of polymeric reagents and their physical and chemical properties (viscosity and optical density) have been investigated. It was shown that polymers can be used for the transportation of drugs. The polymer macromolecule at pH = 3.5 is in a folded state. The macromolecule is unfolded with increasing pH. This leads to an increase in viscosity, the optical density does not change. The drugs are passed toxicological control. Based on toxicological investigate and analysis of the data obtained, it was concluded that the polymers have insignificant functional accumulation. Do not show skin-resorptive and allergic effects. The compatibility of polymers with antibiotics (levomycetin, levomycetin sodium succinate) was investigated. To establish the compatibility of copolymers with the antibiotics levomycetin, levomycetin sodium succinate and neomycin sulfate, it is necessary to identify the antimicrobial activity of antibiotics, which is determined by diffusion into agar. The properties of soft dosage forms (ointments) were sinvestigated using the agar diffusion method, it was shown that antibiotics are compatible in combination with the polymer reagent and their antimicrobial activity was revealed.

Keywords: Optical Density, Viscosity, Drug, Ointment, Levomycetin, Modifier, Sodium

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INTRODUCTION

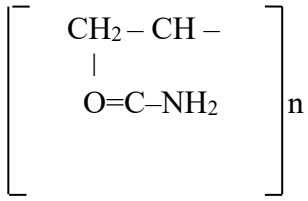
Copolymers of acrylic acid, which are well mixed with water forming viscously fluid mass, were synthesized based on the Department of chemistry and fundamentals of chemical technology in M.Auezov SKSU. Their properties and consistency are of interest for research in terms of the possibility of their use as auxiliary substances in pharmaceutical technology in the preparation of external dosage forms. The drugs were toxicologically tested. Based on the conducted toxicological studies and analysis of the data obtained, it was concluded that the polymers possess little functional cumulation. They do not show skin-resorptive and allergic action.

HPAA-PV, HPAA-MEA

The viscosity (η_{rel}) of 0.2% solution is 4.15 - 5.69. With time, viscosity increases. 24 hours after the synthesis, it was 5.64; after the 30 days expiration, η = 4.12, that means it increased to 36 times.[1] This property can be used in the preparation of films.

Polyacrylamide (PAA)

PAA is an irregularly shaped yellowish or slightly brown granules, the polymer has a polymer mass fraction of 50-57%, moisture content 10-15%, ammonium sulfate 30-40%. pH of 0.1% aqueous solution is 7-8. The kinematic viscosity of 0.1% aqueous solution is not less than $(1.7 \pm 2)\ 10^{-6}$.[2,3]



EXPERIMENTAL

The optical density was recorded on a spectrophotometer SF-26.The turbidity was determined on a FEK-56 calorimeter at α = 434 Nm. solutions of the corresponding polymer fractions were used as comparison solutions.

The effect of the PAA,PV and MEA based polymers mixtures ratio, in this case, is manifested in the fact that when the content of PE based on PAA the ratio of PV- MEA increases, the optical density of sludge also increases, and with decreasing of their content, the optical density of filtrates practically does not change.

Table-1: Polymers Optical Density of Investigation Results

Polymer	% Solution	Additive	Density
HPAA-IEA	3.5	МЭА IEA	1-0,1158 2-0,1162 3-0,1168 4-0,1179 0,1182 Dist.water-0.1215
HPAA-IEA	5	МЭА IEA	1-0,1165 2-0,1193 3-0,1198 4-0,1204 5-0,1208 Dist.water-0.1235
HPAA-PV	3.5	Hydrogenpe roxide	1-0,1114 2-0,1156 3-0,1162 4-0,1164 5-0,1166 Dist.water-0.1189
HPAA-PV	5	Hydrogenpe roxide	1-0,1121 2-0,1148 3-0,1153 4-0,1156 5-0,1162 Dist.water-0.1174
HPAA-PV	3.5	Hydrogenpe roxide	1-0,1162 2-0,1159 3-0,1172 4-0,1173 5-0,1191 Dist.water-0.1228
HPAA-PV	5	Hydrogenpe roxide	1-0,1014 2-0,1168 3-0,1191 4-0,1179 5-0,1167 Dist.water-0.1194
HPAA-IEA	3.5	IEA	1-0,1202 2-0,1212

			3-0,1225 4-0,1227 5-0,1235 Dist.water-0.1256
HPAA-IEA	5	IEA	1-0,1160 2-0,1184 3-0,1209 4-0,1213 5-0,1214 Dist.water-0.1240
HPAA-TEA	3.5	TEA (1 ml)	1-0,1376 2-0,1179 3-0,1473 4-0,1573 5-0,1181 Dist.water-0.1580
HPAA-TEA	5	TEA (1 ml)	1-0,1171 2-0,1376 3-0,1474 4-0,1375 5-0,1474 Dist.water-0.1480
HPAA-TEA	3.5	TEA (0.5ml)	1-0,0883 2-0,0883 3-0,0982 4-0,0982 5-0,180 Dist.water-0.0990
HPAA-TEA	5	TEA (0.5ml)	1-0,0982 2-0,0981 3-0,1081 4-0,1080 5-0,1278 Dist.water-0.1280

The increase in optical density of PAA and PV, MEA polyelectrolytes can be explained by conformational transformations of macromolecules. For samples of the HPAA-TEA, the optical density value in all the studied concentration intervals varies insignificantly (Table-1), which indicates the homogeneity of the solutions and their thermodynamic stability.

Study of Viscous Properties of GRP by Viscometry.

The viscosity of polyelectrolytes solutions was measured in a Ubbelohde viscometer, with a suspended level. Re-precipitated and thoroughly dried polymers were used for viscosimetric studies. The viscometer was placed in a thermostat, the temperature was maintained with an accuracy of ± 0.01 ° C.

The concentration of the solution after dilution was calculated from the formula:

$$C = \frac{gVi - 100}{V(Vi + Vj)} Pi / P_2 = \frac{ciVi}{Vi + Vj}$$

Where g is the polymer weight, g;

V is the volume of the volumetric flask, ml;

Vi is the volume of the solution filled in viscosimeter, ml;

VJ - volume of the added solvent, ml;

P_i/P_J is the ratio of the solvent densities.

The calculation of the relative (ηrel), specific (η_{spec}) and reduced (ηred) viscosities was carried out according to the following formulas:

$$\eta_{relative} = \frac{\tau_i}{\tau_0};$$

$$\eta_{specific} = \eta_{relative}{}^{-1};$$

$$\eta_{red} = \frac{\eta_{rel}}{C}$$

The intrinsic viscosity (η) was found from the graphical dependence of ηred = t (C) by extrapolating the lines to the zero polymer concentration.[3]

Studies of hydrodynamic properties of hydrolyzed mixtures of HPAA-PV in a wide range of concentrations (0.001-1), pH, temperature (Fig.-1), etc., show that polymer mixture solutions obey the general patterns characteristic of polymer solutions containing ionizing functional groups. Dependences of the specific and reduced viscosity (ηred/c) on the concentration of solutions mixture have an anomalous shape of the curves, which is typical for high molecular weight polyelectrolytes. This is due to the influence of ionizable hydrophilic functional groups on the hydrodynamic volume of macromolecular coils.

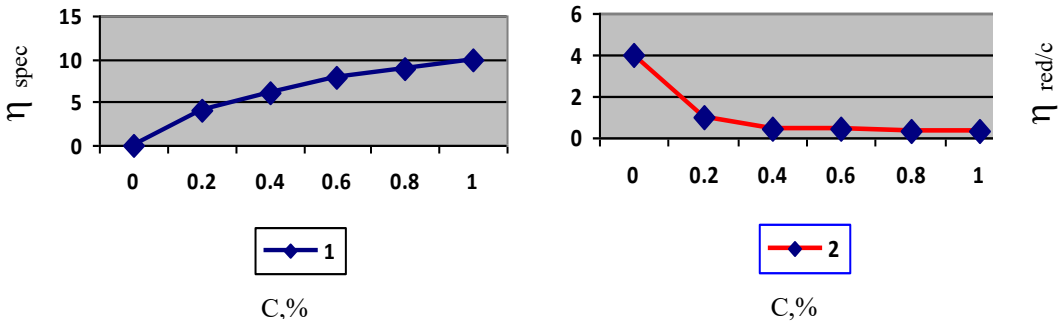


Fig. -1: Dependence of the Specific Viscosity (1) and the Reduced Viscosity (2) on the Concentration of Solutions of the HPAA-PV Dispersions Mixture

The deviation of the reduced viscosity from the linear dependence in the region of dilute solutions of HPAA-PV is because the dissociation of ionogenic groups and the electrostatic repulsion of the likely charged functional groups in the polymer chain are intensified with dilution, which leads to straightening of the macromolecular coil and, consequently, to an increase in the hydrodynamic volume and viscous resistance of the system.

The changes in viscosity at a constant ionic strength produced by electrolyte additives, which suppresses the ionization of functional groups and, accordingly, changes the conformational state of macromolecular coils, provide a linear dependence of the reduced viscosity on concentration.

The hydrodynamic properties of solutions of polyelectrolytes, especially poly ampholytes, are significantly affected by the pH of the medium and the degree of ionization (Fig.-2). The shape of the ηred/c in fluencial curves for polyelectrolytes HPAA-PV solutions and pH produced by acid or alkali additives shows the dependence of the hydrodynamic volume of macromolecules on the ionization of functional groups. The maximum of ηred/c -pH curves corresponds to pH = 7.6 - 7.9 and coincides with the data for HPAA-PV, etc. In this pH range, the macromolecule assumes the most unfolded confirmation due to the ionization of the functional groups and the optimal value of the ionic strength. All preparations in this pH range exhibit the properties of polyanions.[4-6]

In all GRP HPAA-PV, the viscosity decreases with increasing ionic strength in the alkaline range pH> 10 (behind the maximum point), which is associated with an excess of low-molecular-weight electrolyte ions and an increase in the ionic strength of the solution. With an increase in the acidity of the medium, the dissociation of the acidic groups is suppressed, the intramolecular interaction is enhanced by the formation of hydrogen bonds between the amide and carboxylate groups, the macromolecular coils become denser, the interaction with solvents decreases, which leads to a drop in viscosity at pH = 3.

A similar pattern is observed in the samples of GRP HPAA-PV obtained in an aqueous solution of sodium hydroxide and various alcohols (normal isobutyl and normal isopropyl alcohol) in the acidic medium at pH 3.5; then a deposit precipitates in the form of flakes, and at pH = 2.5-3.0 the dissolution of the deposit begins.

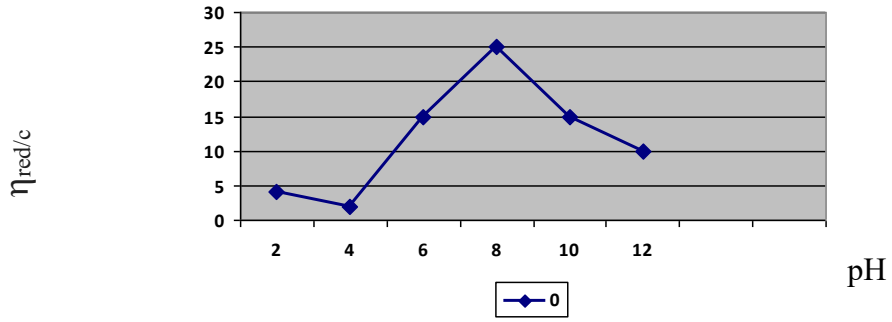


Fig. -2: Reduced Viscosity - pH of the HPAA-PV Dispersion Mixture Solutions Curve

At pH = 2.01-3.0, viscosity increases, and at a pH less than 2.01, the viscosity decreases.A further increase in the amount of hydrochloric acid results in the folding of the polymer macromolecules and the formation of a precipitate in the form of flakes, which then dissolves. At low pH values (isoelectric point) macromolecules are usually found in densely folded coils or the form of dense fibrils due to internal and intermolecular hydrogen bonds, which can be easily destroyed by ionization and the macromolecule is straightened, which leads to an increase in the size of the globules and, accordingly, the viscosity of the GRP solutions increases.

Characteristics of Medical Preparations Used in the Work

Antibacterial Preparation

Neomycin Sulfate

Neomycin is a complex of antibiotics (neomycin A, B, C) formed during the life of the radiant fungus Streptomycessfradiae: in the form of sulfates they are part of the preparation neomycin sulfate.[7]

The main component of the neomycin complex (more than 90%) is neomycin B, which has a small antimicrobial activity. The antibiotic is active against pathogenic staphylococci, corynebacteria, listeria, anthrax and most gram-negative bacteria (Escherichia coli, Shigella, Salmonella, etc.).

Neomycin sulfate is a white and yellowish-white fine crystalline powder almost odorless, easily soluble in water, insoluble in alcohol and insoluble in other organic solvents. It is hygroscopic. The aqueous solution at pH 2.0-9.0 is stable (at pH 8,0 stable for a year).

The characteristic physical constant is the specific rotation from + 50 to + 58^0 (5% aqueous solution of the preparation).[8-10]

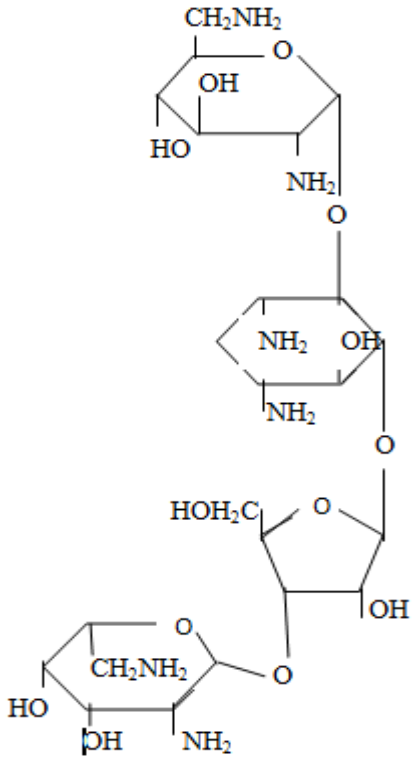
To test the authenticity of neomycin sulfate color reaction with alcoholic solution of orcein and concentrated hydrochloric acid in the presence of iron (III) chloride is used. The drug forms a green substance by heating the reaction mixture. [10]

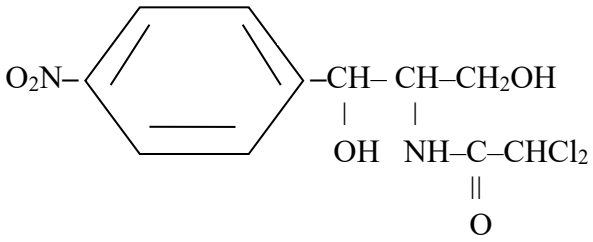
Biological activity is determined by diffusion in agar with test microbes.[11] Cereurvar bacillus mycoides is used as the microbal test.

Levomycetin – Laevomycetinum

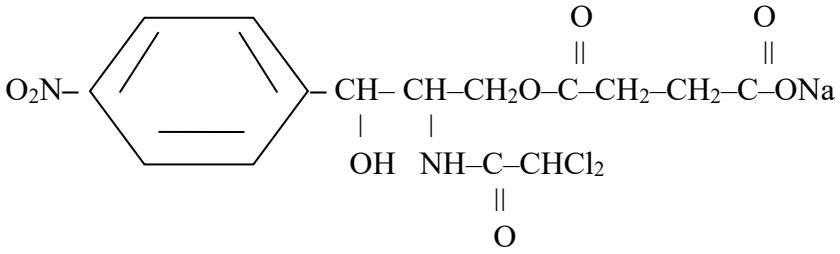
A synthetic substance identical to the natural antibiotic chloramphenicol, which is a product of the vital activity of the micro-organism Streptomyces venezuelae. In industry, antibiotic production is carried out mainly by chemical synthesis.[10]

The chemical structure of the drug is a D-(-)-three-1-para-Nitrophenyl-2-dichloracetylamin-propanediol-1,3. It is white or white with a weak yellowish-greenish tinge crystalline powder with a bitter taste. It is slightly soluble in water, easily soluble in alcohol[11].Laevomycetini succinatis solubileis a soluble form of Levomycetin.





Chemically, it is D-(-)-three-1-para-Nitrophenyl-2-dichloroacetylamino-1,3-propanediol–3 sodium succinate:



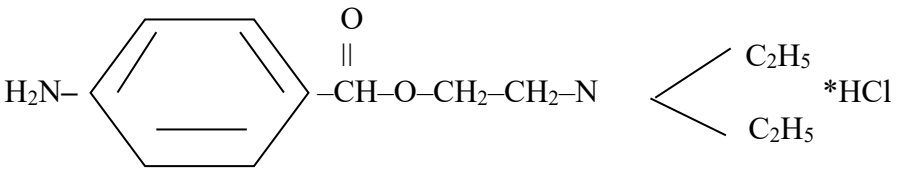
It is a dry porous mass of white or white with a yellowish tint with a weak specific smell and bitter taste. It is very easily soluble in water, slightly soluble in alcohol. It is hygroscopic. pH of 30% water solution is 6.4-7.5 . The drugs have a wide spectrum of antimicrobial activity; they are active against many Gram-positive and Gram-negative bacteria, rickettsia, spirochaete, and chlamydia.

To test the authenticity of both drugs, hydrolytic cleavage reactions are used in alkaline and acidic media, followed by identification of the products formed.

For qualitative and quantitative determination of levomycetin and ascomycetin succinate, spectrophotometry in the UV region is used at a wavelength of 278 nm and 275 nm, respectively.

The quantitative determination of levomycetin is performed by a nitrite-metric method after preliminary reduction in acid medium by zinc dust according to the USSR pharmaceutical regulations [10].

Local Anesthetic Preparation
Novocainum
β-diethylaminoethyl ester of paraminobenzoic acid hydrochloride:



They are colorless crystals or white crystalline powder without odor, with a bitter taste. It is easily soluble in water (1: 1), easily soluble in alcohol (1: 8). Melting point: 154-156^{0}C.
The authenticity is established by the reactions of azo dye formation with β-naphthol, also with some precipitation (total alkaloid) reagents (picric, phosphoric tungsten, phosphomolybdenum acids).
Quantitative determination is carried out by titrometric method according to USSR pharmaceutical regulations. The preparation represents hydrochloride and can be quantified by the method of neutralization according to the bound hydrochloric acid.

RESULTS AND DISCUSSION

Determination of Antibiotics Antimicrobial Activity by Microbiological Method of Diffusion in Agar

To establish the compatibility of the copolymers with the antibiotics levomycetin, levomycetin sodium succinate and neomycin sulphate it is necessary to reveal their antimicrobial activity, which is determined by the method of diffusion in agar. The methodology of this research is described in detail in USSR pharmaceutical regulations.
Because the method does not take into account some features of our experiment (for example, the determination of antimicrobial activity in films), we have modified the method to be able to use it in our work.
The diffusion in agar method is based on comparing the degree of the test-microbe growth zone inhibition by certain concentrations of the antibiotic in the test material with the inhibition of its growth zone by the known concentrations of the standard antibiotic. Suppression of the growth of the test-microbe is carried out by diffusion of the antibiotic from the studied material into a dense nutrient medium.[10]
To obtain reproducible results, strict standardization of experiments is necessary. The rate of solution 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, which consists of several stages.

CONCLUSION

1. The conformation of the macromolecule is changed from one form to another (when the pH changes). The macromolecule is collapsed at pH = 3.5, which corresponds to the isoelectric state.
2. Increasing the viscosity of the solution occurs at pH = 4.5, as the molecule unfolds. At pH = 8.0, the viscosity is reached its maximum value.
3. The joint action with antibiotics was investigated.
4. The antimicrobial activity of antibiotics (chloramphenicol, etc.) and their compatibility with the HPAA-HP, HPAA-MEA polymers have been shown.

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