European Journal of Research Development and Sustainability (EJRDS)
Available Online at: https://www.scholarzest.com
Vol. 2 No. 1, January 2021,
ISSN: 2660-5570

RESEARCH OF THE COMPLEX FORMATION PROCESSES OF BIOLOGICALLY ACTIVE SUBSTANCES AND SYNTHETIC POLYMERS

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Article history:

Received 26th December 2020
Accepted: 11th January 2021
Published: 23nd January 2021

Abstract:

The article considers about an oxadixyl complication with water-soluble polymers - polyacrylic and polymethacrylic acid. The main methods for studying the interaction of polymers used oxadixyl viscometry, potentiometry, conductivity, and ultracentrifugation, ultraviolet and infrared spectroscopy. The influence of different factors on the process of complication detecting that binding oxadixyl polymers leads to structing macromolecular chains of the formation of hydrogen bonds.

Keywords: Oxadixyl, polyacrylic acid, extinction coefficient, polycomplex, sedimentation, polyelectrolyte, ionic strength, shielding of acid groups.

The use of polymers and copolymers containing -NH2 and -COOH groups as carriers of biologically active substances (BAS) is due to their good solubility in water and some polar organic media, resistance to chemical and biological influences, as well as high activity and selectivity when interacting with both charged and uncharged particles and surfaces, moreover, most polyanions are biologically active and some of them have antibacterial, antiviral and other types of action [1-5].

The biologically active drug oxadixyl (2-methoxy-N-, 3, oxa-zolidin-3-yl) -acetate-2 ', 6'-xylidine, approved by MOS), code number SAN 371 F. structure of oxadixyl (OC), polyacrylic acid (PAA) and polymethacrylic acid (PMAA) were chosen as support polymers. Viscometry, potentiometry, conductometry, calorimetry, ultracentrifugation, dialysis, UV- spectroscopy, and IR- spectroscopy were used as the main methods for studying the interaction of polymers with oxadixyl [6–12].

Certain information on the change in the structure of organic matter in the process of binding can be obtained by studying the structure of polycomplexes by IR- and UV- spectroscopy. The interaction of organic molecules with the polymer chain changes the distribution of electron density in molecules, which is reflected in the IR spectra of their complexes. Analyzing the results obtained, the following conclusions can be drawn about the structure of the obtained compounds. An increase in the intensity of the absorption band at 1660-1710 cm-1, the appearance of a broad intense absorption band at 3300-3500 cm-1 and a shoulder at 2350 cm-1, all confirm the possibility of the formation of a hydrogen bond between the carboxyl group of oxadixyl and the hydroxyl of the carboxyl group of PAA and PMAA. In addition, new absorption bands at 760, 910, 1010, 1270 cm-1 appear, which are characteristic of oxadixyl. The possible influence of the carrier polymer on the structure of the bonded substance can be judged from the data of UV spectroscopy. The position of the oxadixyl solution and its polymer complex (at the same oxadixyl concentration) at 256 nm is retained, but the absorption intensity in the complex decreases. It is noted in the literature that carboxyl-containing polymers, in contrast to other ionic polymers, are characterized by a "soft" interaction with the bound organic substance, which does not lead to noticeable deformations of the chemical structure [13-16].

An increase for matter affects the value of the apparent coefficient of molar extinction (ε), which makes it possible to use UV spectroscopy to influence certain quantitative laws. The apparent extinction coefficient slightly decreases with an increase in the concentration of biologically active substances. According to Schwartz, a decrease in the extinction coefficient of polymer complexes is explained by an increase in the proportion of bound BAS and redistribution of electron density in their chromophore groups upon binding by a polymer. The tendency to a decrease in the apparent extinction coefficient with an increase in the concentration of the polymer complex indicates an increase in the proportion of bound biologically active substances in the limit; by extrapolating this dependence to an infinitely high concentration of biologically active substances, it is possible to determine the extinction coefficient of bound BAS molecules in the saturated complex (ε'). If the extinction coefficient of unbound molecules is denoted as (ε), then by the formula: γ = (ε-ε') / (εox-ε') where: γ is the fraction of unbound BAS molecules at different polymer / BAS ratios, but at a constant total concentration in the solution, the fraction of unbound BAS molecules can be determined.

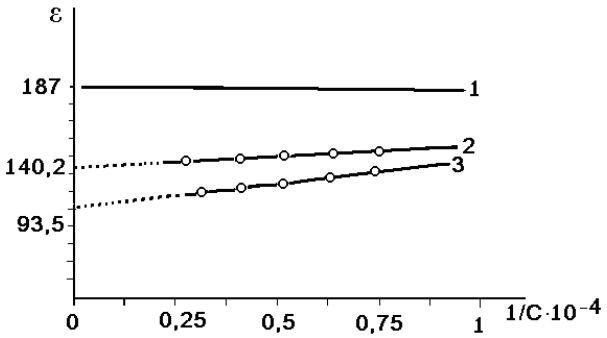

Fig. 1. Dependence of the molar extinction of oxadixyl (1). A solution of the polymeric complex PAA + oxadixyl (2) and PMAA + oxadixyl (3)

In accordance with the Schwarz theory, extrapolation of the initial portion of the γ versus P curve to the P axis makes it possible to determine the number of polymer units that bind one BAS molecule (n) in a saturated complex (Fig. 2, dashed line). The second line, which has a slope of half that, intersects the curve at the point γ'. According to the theory, the value of the influence of the γ'-fraction of unbound biologically active substances in the saturated complex makes it possible to calculate the binding constant K = γ / biologically active substances, as well as the parameter of the cooperativity of the process g according to the following formula:

$$g = n \cdot P(1 - \sqrt{\gamma}) / \gamma$$

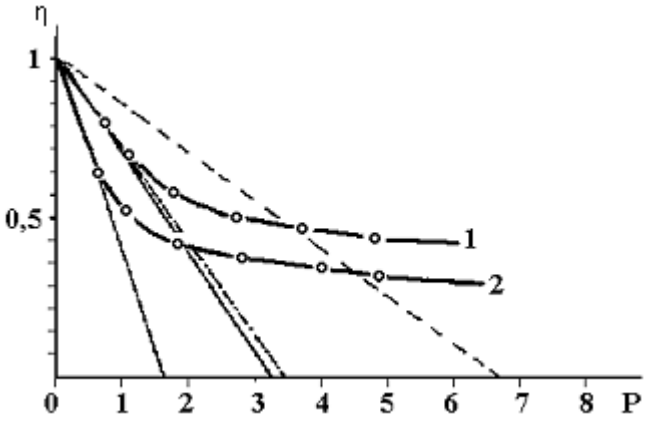

Fig. 2. Dependence of the fraction of unbound oxadixyl molecules in its polycomplexes with PMAA (1) and PAA (2). P = [polymer / oxadixyl] The calculated kinetic parameters of the process of binding of PMAA and PAA with oxadixyl are given in Table 1.

Table 1.

Kinetic Parameters of PAA and PMAA Binding with Oxadixyl

Complex	γ'	K·10^{-5}	n	g
PAA-oxadixyl	3,5	2,266	1,7	3,1-53,4
PMAA-oxadixyl	6,6	4,4	3,3	12,0-34,2

The formation of polycomplexes can also be confirmed by the method of rate sedimentation, by determining the sedimentation coefficient (S) of the initial polymer and its complexes with oxadixyl. Studies of the dependence of the sedimentation constant on the composition of polycomplexes confirm the presented model of the interaction of PAA, PMAA with oxadixyl. The results of the high-speed sedimentation of mixtures of components in the range of compositions OK / Pol = 0-2.5 indicate the formation of water-soluble complexes. The sedimentograms of mixtures of PAA, PMAA with oxadixyl show a single peak corresponding to the particles of the complex. The sedimentation coefficient of the PAA peak without addition of oxadixyl differs from the S complexes, which indicates a significant effect of organic molecules on the state of PAA in solution. Figure 3 shows the dependences of S on the composition of PAA + oxadixyl mixtures.

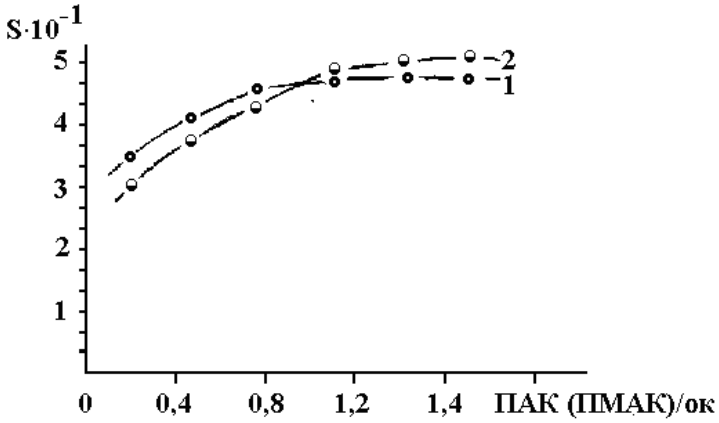

Fig. 3. Dependences of the sedimentation coefficient of mixtures of PAA (1), PMAA (2) on the relative concentration of oxadixyl. As can be seen from this figure, at OA / PAA = 0.1, the sedimentation coefficient of the complexes increases sharply, which indicates the binding of oxadixyl to PAA, leading to an increase in the sedimentation coefficient. A further increase in oxadixyl does not affect the sedimentation coefficient of the macromolecule. Hydrophobic interactions between PAA and oxadixyl strongly change the dependence of S on the initial ratio of components.

The addition of a small amount of oxadixyl increases the sedimentation coefficient of macromolecules, being a consequence of hydrogen bonding; as it increases, the influence of hydrophobic interactions on the binding process also increases, due to which, as already noted, a polycomplex is formed that is soluble at all ratios. The depth of complexation and the stability of the resulting products are influenced by various factors: the length of the reacting chains, their flexibility, conformation, the microstructure of the polymer chain, as well as the properties of the medium (concentration of components and the degree of their ionization, temperature and composition of the solvent, pH of the medium).

It is known that the conformations of the PAA and PMAA chains in aqueous solutions in the non-ionized state differ sharply. This is due to the presence of a structured state of α-methyl groups among themselves. It can be expected that the compact conformation of PMAA macromolecules should affect its interaction with various substances. Thus, the works show the high stability of polymer-polymer complexes, one of the components of which is PMAA. An interesting question about the nature of the interaction in these systems. The low degree of ionization of the carboxyl groups of polyacids and the very weak basicity of the tertiary nitrogen in OA, apparently, excludes the electrostatic attraction between them. The reduced viscosity of polymeric HMX compounds decreases upon dilution, which is characteristic of nonionic high-molecular substances, while PAA and PMAA behave like ordinary polyelectrolytes. Obviously, for weak polyacids, it can be assumed that they interact with OA through hydrogen bonds due to carboxyl and hydroxyl groups. In this case, the screening of acidic groups will lead to a decrease in the concentration of hydrogen ions and, consequently, to an increase in pH (Fig. 3, curve 3).

The different nature of the ηsp / C - composition curves for polymeric compounds of HA with PAA and PMAA can probably be explained by the peculiarities of the conformational state of the polymers used. The presence of various functional groups in a molecule or biologically active substance promotes the formation of several types of bonds, the proportion of which varies depending on the composition and reaction conditions. Thus, the study investigated the interaction of kanamycin with a copolymer of vinyl alcohol and vinyl amido succinic acid and found that the binding of a drug substance is characterized by the presence of cooperativity, i.e. the dependence of the amount of bound kanamycin on the degree of "filling" of the polymer macromolecules of the carrier with the drug molecules.

At low concentrations of biologically active substances, an interaction occurs between the hydroxyl of the carboxyl group and two carboxyl groups of oxadixyl. As a result, the polymer macromolecule becomes more compact, as a result of which a decrease in the reduced viscosity is observed, but a further increase in the oxadixyl concentration leads to a slight increase in viscosity, apparently due to an increase in the size of the polymer macromolecule. It is known that with an increase in temperature or with the use of organic solvents, which are competitors for hydrogen bonds, weakening and destruction of the latter occurs. The study of the temperature stability of OK-PAK showed that an increase in temperature leads to the appearance of an anomalous dependence of the reduced viscosity on concentration, i.e. the OK-PAA complex is destroyed and an unbound polyelectrolyte appears in the solution. The polymeric compound of HA and PAA is characterized by high resistance to thermal effects - an increase in temperature to 70 ° C does not affect the stability of the complexes (Table 2).

Table 2. Intrinsic viscosity η of oxadixyl complex with PAA and PMAA with a change in temperature and ionic strength of the solution

PAA - oxadixyl				PMAA - oxadixyl			
T°C	[η]	μ	[η]	T°C	[η]	μ	[η]
20	0,48	0,0	0,48	20	0,46	0,0	0,46
25	0,43	0,01	0,39	25	0,52	0,01	0,52
35	0,34	0,05	0,26	35	0,38	0,05	0,38
45	0,38	0,1	0,44	45	0,31	0,1	0,31
55	0,51	0,2	0,43	55	0,42	0,2	0,42
75	0,44	0,3	0,10	75	0,44	0,3	0,44

Since the only difference between PMAA and PAA lies in the presence of side methyl groups in PMAA, it can be assumed that hydrophobic interactions play a significant role in the contact of OA with PMAA. In organic solvents, as is known, not only H-bonds are destroyed, but also hydrophobic interactions weaken. The stability of polymeric HMX compounds to the action of dimethyl sulfoxide was studied. On. fig. 4. shows the dependence of the relative viscosity (the viscosity of solutions of mixtures of HA - PAA (PMAA), divided by the viscosity of the polyacid) on the composition of the mixed H2O + acetone-DMSO. In the case of polymeric compounds OK-PAA, a monotonic increase in the size of macromolecules is observed when the mixture is enriched with dimethyl sulfoxide (curve 2). On the curve ηrel (OK-PMAA) -composition of the solvent, a minimum is seen, i.e. in the OK-PMAA system, the addition of an organic solvent first causes a noticeable decrease in the size of macromolecules and only then their growth (curve 3). A similar dependence is typical for free PMAA macromolecules (curve 1). The drop in viscosity is possibly due to the rearrangement of the formed structures and a change in the interaction between them and the solvent. The nature of the ηrel-composition curves of the mixed solvent for the systems under study indicates a certain role of hydrophobic interactions in the formation of polymeric compounds of HMX with PMAA (Fig. 5).

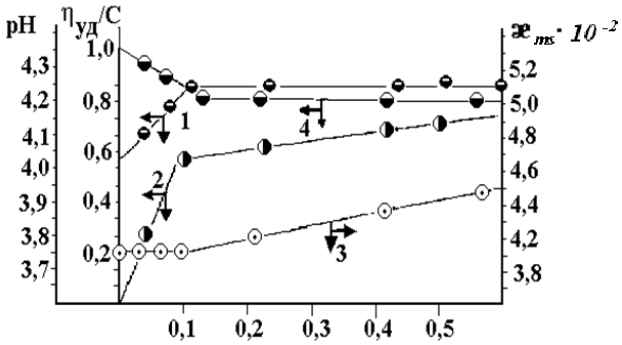

Fig. 4. Change in the reduced viscosity (1.4), pH (2) and specific electrical conductivity (3) of PAA - oxadixyl (1,2,3) PMAA + oxadixyl (4) complexes depending on the ratio of the components

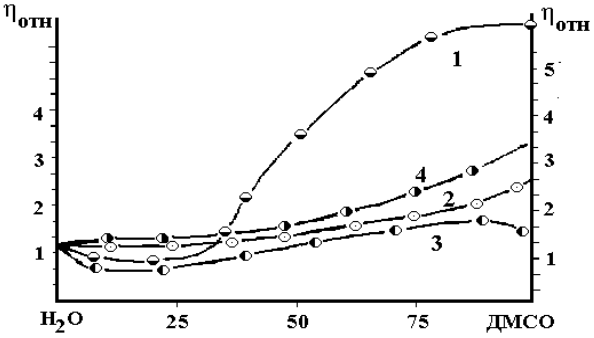

Fig. 5. Influence of the composition of the solvent H2O - DMSO on the relative viscosity of PMAA (1), PAA - oxadixyl (2) and PMAC - oxadixil

Thus, the binding of OA with PAA and PMAA leads to the structuring of macromolecular chains due to the formation of hydrogen bonds between the functional groups of both components and hydrophobic interactions.

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