SYNTHESIS OF PHYSIOLOGICALLY ACTIVE COPOLYMERS OF N-VINYLPYRROLIDONE AND THEIR PROPERTIES

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At the present time one of the most important applications of polymers in medicine lies in the use of their solutions as plasma substitutes. Polyvinylpyrrolidone has been widely used in plasma-substituted solutions [1]. For this reason synthesis of N-vinylpyrrolidone (I) copolymers with different physiologically active monomers is of considerable interest for medicine since this makes it possible to extensively modify the properties of synthetic plasma substitutes.

Copolymers of I are known which are suitable for use as anticoagulants, antisclerotic plasma substitutes, etc. [2].

In the present investigation we have synthesized a copolymer of I with the acrylic ester of the alkaloid lupinine (II) and attempted to modify the properties of the synthetic plasma substitute and to study the relationship between the composition, structure, and molecular weight of the polymers and their physiological properties.

A copolymer of I and II was synthesized in a solution of ethanol in the presence of initiator. The conditions for copolymerization and the properties of the copolymers obtained are shown in Table 1.

The copolymers obtained, which contain up to 30-35% II, are soluble in water, ethanol, and the physiological solution. In aqueous solutions the copolymers exhibit the properties of polyelectrolytes, i.e., there is an increase in the viscosity of the solution with dilution. For this reason the intrinsic viscosity of the copolymer solution was determined in a 0.01 N solution of potassium hydroxide. For calculation of the molecular weights of the copolymers containing up to 20% molar of II the relationship \[ \eta = 1.4 \times 10^{-4}M^{0.75} \] was used. This relationship was established for polyvinylpyrrolidone [3]. The copolymer was divided into 12 fractions by fractional precipitation. The molecular weight of the fractions varied from 7000 to 50,000.

The results of elemental analysis and IR-spectroscopic investigations confirmed the formation of a copolymer of the following structure:

<table>
<thead>
<tr>
<th>TABLE 1. Composition and Molecular Weight of Copolymers</th>
<th>TABLE 2. Toxicity of Copolymers</th>
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<tr>
<td>Composition of original mixture (%)</td>
<td>Composition of copolymer (molecular: %)</td>
</tr>
<tr>
<td>II</td>
<td>I</td>
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<tr>
<td>5</td>
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Fig. 1. Variation in duration of bleeding in rats 30 min after injection of the preparations (intraperitoneal, dose 10 mg/kg). The unshaded columns show the duration of bleeding before injection of the preparations; the shaded columns show the duration of bleeding after injection of the preparations. 1) The alkaloid lupinine; 2) monomer II; 3, 4, 5) copolymers of I containing 4.3, 10, and 14.3 M% II respectively; 6) homopolymer II.

The absorption bands characteristic of the vinyl group of both monomers are absent in the IR spectra of the copolymer. However, there are absorption bands characteristic of the lactam group of polyvinylpyrrolidone (1670 and 1720 cm\(^{-1}\) and others) and the quinolizidine groups of lupinine in the region 2700–2800 cm\(^{-1}\).

The physiological activity of the copolymers was characterized by acute toxicity and by the influence of the copolymer on arterial pressure and breathing in animals.

Tests on the toxicity of the copolymer were carried out by intraperitoneal injection of an aqueous solution of the copolymer in white mice of weight 16-20 g. The variation of toxicity with composition of the copolymer is shown in Table 2.

The data presented in Table 2 indicate the lower toxicity (LD\(_{50}\) calculated by the Lichfield–Wilkinson method) of the copolymers as compared with the homopolymers of II (control). Consequently, combination of II with polyvinylpyrrolidone, which has no toxic action, leads to a decrease in toxicity. A uniform decrease in toxicity of the copolymers with increase in the concentration of I in the copolymer is also observed.

The influence of the copolymers on the cardiovascular system and breathing was investigated in dogs and cats under urethane narcosis. The investigations showed that the alkaloid lupinine, which was the original material used in forming the copolymer, only decreases arterial pressure and excites the breathing of narcotized animals very slightly in a dose of 15 mg/kg. However, the copolymers of I with the alkaloid lupinine in the polymeric chain are more effective. Thus, for example, a copolymer containing 10% II in a dose of 1 and 5 mg/kg decreases the arterial pressure to a greater extent (by 60–80%) for a time of 30–40 min. It was noted that, in contrast to the known polymers of I, the synthesized copolymer has a hemostatic influence. To estimate the hemostatic influence of the copolymers, we studied the duration of bleeding in rats by the method described in the literature [4].

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Figure 1 shows the results of experiments on the characteristic hemostatic properties. With an intraperitoneal injection of aqueous solution of the preparations in a dose of 10 mg/kg the duration of bleeding in rats is considerably decreased. From the results it may be seen that the original alkaloid lupinine and the monomer II are of low activity. However, the homopolymer II is very active. After injection of the polymer into the animals the duration of bleeding decreases by 80%. This activity is also shown by copolymers of I and II. It is characteristic that the physiological activity of the copolymer depends strongly on the concentration of II and the molecular weight. The data presented in Fig. 1 indicate the possibility of changing the physiological activity of the copolymer by increase or decrease in the concentration of active component. This is one of the advantages of physiologically active polymeric compounds.

A further advantage of such compounds lies in the fact that the length of the chain of the high-molar- weight preparation may be altered as required. By this means it is possible to change not only the activity but also the time for which the preparation is present in the organism and, consequently, the duration of its effect. Figure 2 shows the variation in activity of the copolymers synthesized depending on molecular weight. It is obvious that with increase in the molecular weight of the copolymer the physiological activity initially increases and then falls.

**EXPERIMENTAL**

The synthesis of the copolymers was carried out with different monomer ratios in a solution of alcohol in glass ampoules in the absence of atmospheric oxygen. The concentration of monomers was 20%. Azoisobutyric acid dinitrile in a concentration of 0.5% with respect to the weight of monomers was used as