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HEMOSTATIC MATERIALS BASED ON ACETYLCELLULOSE AND LAGODEN

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Hemostatic polymer preparations based on Lagoden and water-soluble acetylcellulose have been obtained in the form of films and fibers. They have been subjected to hemostatic evaluation in comparison with standard products on rats and rabbits. The water-soluble fibers and films containing 5% of Lagoden that were obtained possessed good local hemostatic properties and were convenient in use. Their acute toxicity did not exceed 1500 mg/kg.

The drug Lagoden, based on a diterpenoid isolated from plants of the genus *Lagochilus*, is widely used as an effective hemostatic. However, in the organism its action lasts for only 1.5-2 h. Moreover, the use of Lagoden as a local hemostatic agent presents certain difficulties, since it is in the form of a powder.

We have developed a polymeric version of Lagoden in the form of resorbable tampons, fibers, and films by incorporating the low-molecular-mass hemostatic in the structure of a polymer.

At the present time, polymeric materials of synthetic and natural origin are being used as matrices for drugs. Most suitable for these purposes are polymers of natural origin that are well assimilated by the organism. Therefore, to develop a hemostatic preparation based on a polymeric version of Lagoden in the form of a film and fibers we chose the inert nontoxic polymer water-soluble acetylcellulose (WSAC).

Fibers were obtained by forming from spinning solutions of the water-soluble acetycellulose containing various amounts of Lagoden. Films were cast in a special apparatus with a horizontal polished surface. Table 1 gives the properties of formed fibers and films containing different amounts of Lagoden.

The formation of fibers containing up to 10% of Lagoden took place satisfactorily, but a further increase in its amount led to frequent breaks, and the physicomechanical properties of the fibers also deteriorated to some extent [1]. Apparently, at a concentration of Lagoden exceeding 10% there is a disintegration of the fibers and a change in their supermolecular structure, and, as a result of the increase in the level of the second component in the polymer matrix, the interaction between the macromolecules weakens.

The optimum conditions for the formation of water-soluble fibers containing Lagoden are: Lagoden content, 5-10%; concentration of the spinning solution, 10%; spinneret draft — 50%; plasticization draft, 0% [2]. The fibers formed under these conditions had satisfactory physicomechanical indices (strength σ 8-10 cN/tex; elongation l 18-20%).

Pharmacological and hemostatic trials of the fibers and films obtained were carried out in the pharmacological laboratory of the Institute of Bioorganic Chemistry, Academy of Sciences of the Republic of Uzbekistan. Acute toxicity was determined on white mice, which were injected intravenously with water-soluble fibers and films containing 5% of Lagoden. In these trials the LD_{50} value was not less than 1500 mg/kg.

The results of hemostatic evaluation of the fibers and films obtained, in comparison with standard products (hemostatic gauze and hemostatic sponge), are given in Tables 2 and 3.

The polymeric hemostatic materials with Lagoden possessed better hemostatic properties than the known products. The water-soluble fibers without Lagoden shortened the bleeding time in rats by 30%, and those with 5% of Lagoden by 58%, in comparison with the control. The water-soluble acetylcellulose films, which themselves affect parenchymatous bleeding, when containing 5% of Lagoden shortened the bleeding time by 54% in comparison with the control.

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TABLE 1. Some Properties of the Films and Fibers Obtained

Lagoden content, %	Strength, cN/tex		Elongation, %		Solubility, h	
	films	fibers	films	fibers	films	fibers
1	10–11	10–11	16–17	20–22	7–8	5–6
3	9–10	9–10	14–15	16–18	6–7	5–6
5	7–8	9–10	13–14	14–16	6–7	5–6
10	5–6	6–7	12–13	12–14	5–6	4–5

TABLE 2. Influence of Hemostatic Products on the Time of Parenchymatous Bleeding in Rats

Substances investigated	Blood clotting time		Significance, P<
	(M+m), s	% of control	
Control (medical gauze)	260+10	100	
Hemostatic gauze	156+15	60	0.01
Hemostatic sponge	169+14	61	0.001
WSAC fibers	181+20	70	0.01
WSAC fibers with Lagoden			
1%	170+13	65	0.001
3%	139+10	53	0.01
5%	110+10	42	0.001
10%	98+10	37	0.001
WSAC films	276+21	106	0.05
WSAC films with 5% of Lagoden	120	46	0.001

TABLE 3. Influence of Hemostatic Preparations on the Time of Parenchymatous Bleeding in Rabbits (means of six experiments)

Substances investigated	Blood clotting time		Significance, P<
	(M+m), s	% of control	
Control (medical gauze)	240+10	100	
WSAC fibers without Lagoden	168+16	70	0.001
WSAC fibers with 5% of Lagoden	84–10	35	0.001
WSAC films	254+10	105	0.05
WSAC films with 5% of Lagoden	101+10	42	0.001
Hemostatic gauze	137+14	57	0.01
Hemostatic sponge	125+15	52	0.001

The results obtained on rabbits also showed an advantage of the proposed preparations.

The hemostatic properties of the fibers and films with 5% of Lagoden were checked on a blood-clotting process experimentally disturbed by the intravenous administration of heparin to rabbits in a dose of 300 AU/kg. The time of parenchymatous bleeding in the control, when ordinary medical gauze dressings were applied to wound surfaces of livers of heparinized rabbits, was 19.8 ± 1.6 min; on the application of WSAC fibers with 5% of Lagoden it was 10 ± 0.8 min; and with WSAC films containing 5% of Lagoden it was 12 ± 1.2 min.

Thus, it may be concluded that water-soluble fibers and films based on WSAC containing 5% of Lagoden possess good local hemostatic properties and can be used in practical medicine as absorptive hemostatic agents in local bleeding.

EXPERIMENTAL

The water-soluble acetylcellulose was obtained by the deep hydrolysis of a concentrated solution of cellulose diacetate produced industrially and containing 54.3% of bound acetic acid ($\gamma = 236$) with a degree of polymerization of 280 in acetic acid [3].

We determined the bound acetic acid content of the acetylcellulose obtained, and its water solubility. The acetic acid content of the final water-soluble acetylcellulose was 18-19%, the degree of substitution γ = 50-60 [1], the degree of polymerization 200-210, and the molecular mass 36,000-37,000 [4].

Preparation of Films from WSAC and Lagoden. Lagoden (1, 3, 5, and 10% with respect to the WSAC) was added to a 10% solution of the WSAC prepared with vigorous stirring, and the mixture was homogenized. The solution was filtered under pressure through two layers of cotton tissue and was subjected to deaeration at room temperature for 24 h. Films were cast from the filtered and deaerated solutions containing various amounts of Lagoden.

The thickness of the films was regulated by a special device. Drying was carried out at 20-25°C for 24-30 h or in a vacuum-drying apparatus at 60°C for 5-6 h.

Fibers based on WSAC and Lagoden were obtained by spinning from aqueous solutions containing various amounts of Lagoden. The preparation of the spinning solution, filtration, and deaeration were carried out in the same way as for the films. The fibers were spun on a small laboratory apparatus, the precipitant being isopropyl alcohol [5].

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