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Biodegradable polyurethanes

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The review summarizes recent progress in the development of enzymatically degradable polymers. Such polymers are based on amino acids, oligopeptides, oligosaccharides and synthetic oligomers. An enzymatically degradable bond can be located either in a side chain or in the main backbone of the polymer. These materials posses special physical–mechanical properties and can be used as endoprostheses with optimal degradation periods or as carriers of biologically active compounds in medicine and biology. The experimental results, showing the usage perspectiveness for biodegradable polyurethanes as carriers of biologically active substances (including medical drugs) for the depot-forms formation, are presented.

1. Introduction

The problem of preparing new polymers having properties of both synthetic and natural compounds is a topic of interest to many researchers. "Hybrid" polymers of this type can be conveniently produced by incorporation of natural units into the main chain of a synthetic polymer [1].

The development of these new compounds is of considerable theoretical and practical importance in view of the following factors:

(1) Biodegradable materials can be used for endoprosthetics of organs and tissues in which their enzymatic spectrum of activities can be retained.
(2) Medicinal components can be introduced into the composition of a synthetic polymer, enabling biologically active substances to be immobilized and their therapeutic effect prolonged.
(3) Certain functional groups can be modified as well as their spatial configuration being rearranged about a biologically active molecular unit, e.g. the active centre of an enzyme, allowing one to obtain valuable information on the action mechanism of the enzyme [2].

In this review the data on the preparative methods, properties and biodegradation mechanisms for polymers containing natural units in the main chain will be presented. Usage of biodegradable polymers as medicinal drugs carriers became a basis for preparation of different forms providing prolonged action [3, 4]. Below the general possibility of preparation on the basis of interaction between antileukemic drug Cytosar and monofunctional isocyanates of a depot-form, possessing high therapeutic effectiveness and low toxicity.

2. Materials and methods

Biodegradable polyurethanourea acylsemicarbazides, containing amino acid and peptide branches in the main chain, have previously been synthesized and investigated [5]. Polyester urethanoureas (PEUU) were synthesized as previously described [6].

The monomers for PEUU synthesis are symmetric esters of phenylalanine and glycols (SEPG), which can be obtained in one stage. The presence of natural-occurring amino acid phenylalanine in the PEUU branches turns these polymers into peculiar substrates, that can be subject to proteolytic enzymes action.

PEUU have been synthesized on the basis of diphenylmethane diisocyanate (DPMI), hexamethylene diisocyanate (HMDI) or toluelene diisocyanate (TDI) and polyoxytetramethylene glycol (POTMG) having M = 1000 or polyethylene glycol adipinate having M = 1500.

PEUU synthesis has been conducted in purified DMFA solution by stirring equimolar quantities of urethane for polymer and SEPG at room temperature. The polymers obtained were separated from the DMFA solution by crystallization with water.

The 20% DMFA solutions of these PEUU were used for the formation of films, having thickness of 250–300 μm, on a fluoroplastic base. 1 g portions were placed in weighing bottles containing 25 ml of 0.05% solutions of chymotrypsin, pepsin and papain; pH of the buffers corresponded to the optimal for each enzyme respectively: 0.1 M sodium-phosphate buffer (pH = 7.8) for chymotrypsin; 0.1 M citrate-phosphate buffer (pH = 4.0) for pepsin; 0.1 M sodium-phosphate buffer (pH = 7.0) for papain. The samples were thermostated at 37 °C. Enzyme solutions were refreshed twice a day for a fortnight. The intrinsic viscosity and mechanical property changes for PEUU under incubation with proteolytic enzymes are shown in Table I. The authors studied the process of preparing segmented polyurethanes containing different disaccharides, monosaccharides and sugar alcohols as chain extenders. The reaction was conducted in

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TABLE I PEUU properties changes under incubation in proteolytic enzymes solutions for 14 days at 37 °C

Sample	Beginning data			Chymotrypsin (pH = 7.8)			Pepsin (pH = 4.0)			Papain (pH = 7.0)		
	η (dl/g)	σ (MPa)	E (MPa)	η (dl/g)	σ (MPa)	E (MPa)	η (dl/g)	σ (MPa)	E (MPa)	η (dl/g)	σ (MPa)	E (MPa)
1	0.30	4.7	4.7	0.20	3.9	3.9	0.25	4.5	–	0.25	3.8	–
2	0.46	6.6	4.7	0.35	4.5	4.5	0.38	5.1	4.1	0.36	4.9	4.4
3	0.27	4.6	4.6	0.24	Sample fragmented		0.24	4.0	3.7	0.24	4.1	3.9
4	0.42	11.8	5.9	0.33	5.9	5.2	0.34	6.6	4.4	0.30	7.5	5.5
5	0.48	6.0	2.4	0.44	5.0	2.1	0.44	5.3	1.9	0.38	4.9	1.7
6	0.25	5.2	4.6	0.25	4.5	3.6	0.25	4.3	4.3	0.25	4.8	4.2
7	0.26	3.3	2.4	0.25	2.4	2.3	Sample fragmented			0.25	Sample fragmented	
8	0.40	5.9	4.7	0.30	Sample fragmented		0.27	3.9	3.0	0.30	4.6	4.6

η-intrinsic viscosity; σ – tearing strength, E – modulus of elasticity.
Measurement error for η – not greater than ± 0.01 dl/g; for mechanical characteristics – ± 8.5%.
Samples 1–4 and 6–8 synthesized on the basis of L-phenylalanine, sample 5 on the basis of DL-phenylalanine.

the aprotic solvents: dimethyl acetamide (DMAA), hexamethyl phosphotriamide (HMPA), N-methyl-2-pyrrolidone (MP) and dimethylformamide (DMFA). The highest ultimate yield was observed with DMAA. It follows that amide solvents exert great influence on the yield of both polymers and their intrinsic viscosity. The yield depends on the reactivity of hydroxyls in the sugar. Thus, the yield of block copolymers (BCPU)-3 containing maltose with two equally reactive hydroxyls was higher than that of BCPU-5 containing glucose which has one primary and semi-acetal hydroxyls of different reactivity. This was described earlier in greater detail [7].

Synthesis of isocyanate-containing carriers – polyurethane prepolymers with different molecular weights (1600, 2500, 4500 Da) – and immobilization of cytosine arabinoside (Ara-C) were performed as previously described [8]. However, it is worth noting that the carriers bound Ara-C via covalent bond formation as well as through sorption in the volume of polymer.

Experiments *in vivo* were done on mice DBA_2 inoculated with leukemia L1210.

3. Results and discussion

As the investigations have shown, the intrinsic viscosity of PEUU decreases nearly equally under the action of chymotrypsin, pepsin and papain (Table I). For the incubated samples average intrinsic viscosity decrease is: for chymotrypsin, 15%; for pepsin, 14%; for papain, 16%. Loss of tearing strength was 26, 21, 20%, and modulus of elasticity 40, 21, 12%, respectively.

Therefore, the conclusion can be made that of the three proteolytic enzymes used, chymotrypsin solution had the greatest influence upon PEUU. This can be explained by its closer substrate specificity to PEUU, as cleavage is most likely to occur at the C-terminus of phenylalanine.

Considering the data in Table I, it can be noted that the greatest intrinsic viscosity loss is observed for samples 2 and 8. The mechanical characteristics decrease is most noticeable for samples 2 and 4. Sample 2 has been synthesized on the basis of POTMG = 1000 and HMDI, with SEPG diethylene glycol as the glycol component and is the most destructible upon action of the enzymes used.

TABLE II Intrinsic viscosity of polyurethanes containing sugars in the main chain after 21-day incubation in model media

Model medium	Intrinsic viscosity (m^3/kg)	
	BCPU-3	BCPU-5
Control	0.075	0.062
0.15 M citrate-phosphate buffer (pH = 5.5)	0.073	0.059
1% α-amylase solution in 0.15 M citrate-phosphate buffer (pH = 5.5)	0.055	0.059
0.2 M sodium-phosphate buffer (pH = 7.2)	0.075	0.061
1% β-galactosidase solution in 0.2 M sodium-phosphate buffer (pH = 7.2)	0.075	0.045

Degradation data for samples 4 and 5 (sample 4 is based on L-phenylalanine, while N5 on DL-phenylalanine) shows, that destruction of sample 4 by all three enzymes is remarkably more intense than that for sample 5, as the concentration of enzymatically cleavable C-terminal bonds of L-phenylalanine in the first sample is twice that in the latter.

Segmented polyurethanes based on symmetric esters of phenylalanine and glycols are new macromolecular compounds which can be employed for organ and tissue plastics as a result of their enzymatic spectrum.

Generation of block copolyurethanes (BCPU) containing sugar branches in the main chain is of great practical importance.

The possible effect of enzyme-free buffer solutions on the physical-mechanical properties or intrinsic viscosity of block copolyurethanes with sugar units in the main chain have been examined [9]. The intrinsic viscosity of BCPU containing maltose and lactose decreases considerably after 21 days incubation in 1% buffer solutions of α-amylase and β-galactosidase, respectively, Table II. In this case both α-amylase and β-galactosidase exhibit a distinctive affinity for the substrate. The enzymatic degradation of BCPU is accompanied by a significant decrease of molecular weight. At the same time, in BCPU containing arabinose, xylose, glucose and dulcitol, without O-glycoside bond, changes in intrinsic viscosity due to model media effect, with the above enzymes and without them, were not observed.

TABLE III Change of the numbers of leukocytes (1×10^9) in blood of the leukemic mice with and without (control) Ara-C depot-form versus time

Days	1	2	3	4	5	6	7	8	11	30	60	90
Control	7.3	7.5	7.6	7.9	9.9	12.1	63.2		Death of all animals			
Ara-C	10.1	10.4	10.2	10.3	8.2	10.3	8.7	8.9	10.1	14.1	14.0	5.0

When these BCPU were implanted in experimental animals for a period of 6 months, a considerable loss of their tearing strength and elongation occurred, which gives evidence of intensive degradation of polymer films [10].

The intrinsic viscosity of the above polymers decreases at different rates and depends on the nature of the sugar, oligoesterdiol and diisocyanate. More hydrophobic diisocyanate (DPMI) retards degradation compared to less hydrophobic types (HMDI).

The presence of an O-glycoside bond in the polyurethane chain leads to higher degradation. Thus BCPU containing oligosaccharides are biodegradable to a greater extent than polymers containing monosaccharides and sugar alcohols, although the initial mechanical properties and intrinsic viscosity of the latter are lower than for the former.

Analysis of the intensity variations of the X-ray diffraction as a function of the implantation periods of BCPU samples, reveal the relation between the biodegradability of these polymers and their supermolecular structure [7]. The degradation of BCPU implants occurs apparently due to the cleavage of bonds at the interface of flexible and rigid segments, i.e. in the boundary layer. Since the microphase separation of initial polymers is not complete, degradation occurring in the boundary level allows a higher degree of microsegregation of the implanted BCPU, resulting in a higher intensity being observed in the X-ray patterns. Longer periods of implantation of polymers with a relatively highly developed component segregation and the degradation going on at the interface of flexible and rigid segments cause a gradual decrease of rigid domain sizes. The degradation leads to an even higher microphase separation of the polymer system and to a further increase in the intensity of the activity. A smaller phase separation should retard BCPU degradation due to the blocking of degradable sugars with glycol segments [11].

The investigations of kinetics and mechanisms of polyurethane formation in the presence of different organometallic catalysts resulted in the creation of a new biodegradable single-component polyurethane adhesive for gluing soft tissues under condition of wet operational wound. The presence of active isocyanate groups gave an opportunity for immobilization of biologically active compounds in the volume of the polymer matrix.

Experiments *in vivo* showed that Ara-C in the depot-form, having reduced general toxicity, prolonged the lifetime of the animals as compared to a control group (Table III).

For polymers synthesized on the basis of prepolymers having M = 1600 and 2500 Da (concentration of Ara-C 70–200 mg per 1 g of polymer, dose 80, 200, 300, 500 and 1000 mg/kg) no positive results were obtained.

Under immobilization of Ara-C on the polymer matrix (M = 4500 Da, concentration Ara-C = 70 mg/g, dose = 160 mg/kg) curing of approximately, 50% of animals has been registered. The blood tests for these animals have shown three peaks in the increase of the number of leukocytes – it nearly doubles on the 11th, 30th and 60th days.

At all other times deviations were within normal range. The number of leukocytes by the end of the test corresponded to that of the starting conditions.

The experimental results showed the promising possibility of developing on the base of biocompatible, biodegradable polyurethanes, the depot-forms of antileukemic and, more generally, anticancer medicines, continuously retaining their cytostatic activity.

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