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## POLYURETHANES IN BIOLOGICAL MEDIA

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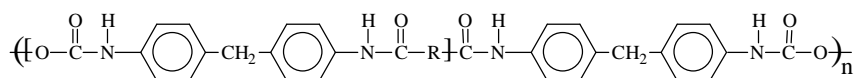
**Abstract.** This paper provides information about macrokinetics of the degradation of polyesterurethanes in model biological media. Special attention was paid to stability of segmented polyurethanes in blood and development of colloid structures at long incubation in blood serum.

**Keywords:** polyurethanes, biological media, stability, colloid, incubation, blood, structures, serum.

## 1. Macrokinetics of the Degradation of Polyesterurethanes in Model Biological Media

### 1.1. Introduction

Segmented polyesterurethanes (PEU) are urethane block copolymers that consist of soft (long chains of simple polyesters in general) and hard segments. The latter include urethane units and aromatic groups:



Because of thermodynamic incompatibility, soft and hard segments form separate phases. Semicrystalline domains predominate in the hard segments, playing the role of physical crosslinks in an elastic polyester matrix. High tensile strength, elasticity, and processability are imparted by the physical network of crosslinks [1].

The totality of the physical and chemical properties of PEU combined with their biocompatibility (especially thromboresistance) makes their application in biomedical applications possible. The examples are: artificial aorta, arterial, venous, and capillary prostheses of blood vessels, devices to assist blood circulation, dialysis membranes, and artificial heart and cardio-stimulators [2-5].

According to one source, the degradation of polyesterurethanes in biomedical applications can proceed in three ways:

(i) S-type, with degradation proceeding from the polymer surface, with mass loss and decrease in molecular weight, without any change in the mechanical properties;

(ii) Degradation in the bulk (V-type), characterized by an abrupt change of the mechanical properties as a result of random breaks of the chemical bonds in the polymer matrix without significant mass loss;

(iii) Mixed type possessing with characteristics of both V- and S-types.

Determination of the degradation mode enables quantitative description of the degradation process. This can be done with the help of some semi-empirical equations and effective rate constants for the destruction of chemically unstable bonds on the surface or in the bulk. These equations are determined from experimental kinetic curves.

Increasing PEU bioresistance requires better understanding of the biodegradation mechanism, which has been rather neglected until now because of contradictions between much of the experimental data.

Besides confirming the above-mentioned biocompatibility of PEU as a thromboresistant material, a knowledge of the polymer chemical stability in the living organism is required (or in a medium where the components of the tissue liquid, such as water, salts, acids, alkali, and enzymes are active degrading agents [6-9]).

### 1.2. Materials and Methods

The process of degradation of two segmented polyesterurethanes Avcothane-51 (Cardiothane, Control Inc., USA) and Biomer (Ethicon Co., Holland) in water and in a phosphate buffer of pH 7.4 has been investigated. Avcothane-51 is a copolymer of polydimethylsiloxane (10% by weight) with a polymer consisting of soft and

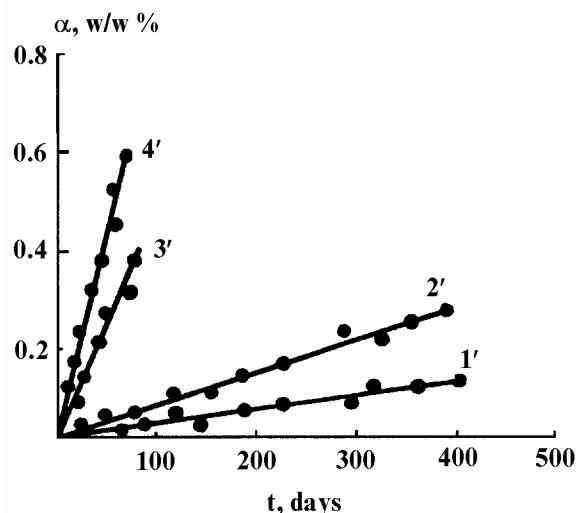
hard units of polypropylene oxide and toluene diisocyanate. Biomer is a segmented PEU consisting of soft units of polytetramethylene glycol and hard units derived from diisocyanates.

The films of Avcothane-51 were prepared from a 6 % solution of the polymer in tetrahydrofuran and dioxane (2:1) in argon, at a relative humidity of 12-14 %, in a vessel carefully cleaned from dust. The films of Biomer were prepared from a 10% solution in dimethylacetamide at 323 K. A film of FDMS was obtained by liquid polymer vulcanization at room temperature.

Films of various thicknesses (300–500  $\mu\text{m}$ ) were obtained by multiple dipping of a glass plate into the solution. The degradation of the samples was performed in a special glass vessel at 310, 331, 353 and 373 K in distilled water, followed by drying to constant weight under vacuum at 353 K. The kinetics of degradation was studied photometrically using a Pye Unicam SPS-100 and gravimetrically by mass loss. The tensile strength of polymer films has been determined using an Instron. The kinetics of the water sorption of polymers has been studied by MacBane weights with the help of a quartz spring, with a sensitivity of 0.5 mg/mm.

### 1.3. Results and Discussion

Avcothane-51 is a block copolymer of a complex polyesterurethane and a polydimethylsiloxane (FDMS), dispersed in a basic polymer matrix as domains. In general, the hydrolytic decomposition of these polymers can proceed independently. The study of the hydrolytic degradation of FDMS and FEU polymers separately in water and in aqueous solutions of phosphates was of great interest. Kinetic curves of the mass loss are presented in Fig. 1.



**Fig. 1.** Kinetic curves of PDMS samples mass losses in water (a) and phosphate buffer pH 7.4 (b) at temperatures: 310 (1, 1'), 331 (2, 2'), 353 (3, 3') and 373 K (4, 4'), air, 310 K (5).

As Fig. 1 shows, mass loss of the FDMS samples proceeds according to a zero order process. The tensile strength of the samples is not changing much during the degradation process. The data obtained can be explained if the degradation is assumed to proceed at the sample surface. To support this assumption, let us consider extremely low water solubility in PDMS because it cannot be determined experimentally (it is estimated to be 0.05 %, approximately). The following equation describes the decomposition that proceeds at the sample surface [7]:

$$m = m_0 - K_{eff}^S t S \quad (1)$$

where  $m$  and  $m_0$  are the current and the initial weights of the sample, *i.e.* at time  $t$  and 0, respectively;  $K_{eff}^S$  is the effective rate constant for polymer degradation from the surface;  $S$  is the surface area.

Bulk polymer degradation (V-type) under the influence of dissolved water can be neglected. As was mentioned above, this was testified by the absence of polymer tensile strength losses. Similar results were obtained for the phosphate buffer.

Table 1 displays the effective rate constants and activation energies calculated from the Arrhenius dependence.

Table 1

**The rate constants for PDSM degradation ( $S_0 = 6 \text{ cm}^2$ ,  $m_0 = 0.5 \text{ g}$ ) in water and phosphate buffer**

$T, \text{K}$	$K, \text{g}\cdot\text{cm}^{-2}\cdot\text{day}^{-1}$	
	Water, pH 6.5	Phosphate buffer, pH 7.4
310	$2.0\cdot 10^{-5}$	$1.8\cdot 10^{-5}$
331	$7.5\cdot 10^{-5}$	$7.3\cdot 10^{-5}$
353	$4.0\cdot 10^{-4}$	$3.8\cdot 10^{-4}$
373	$1.0\cdot 10^{-3}$	$0.9\cdot 10^{-3}$

Taking into account the experimental data obtained, the equation for mass loss may be presented as follows:

$$m = m_0 - 10^5 e^{-14000/RT} t S \quad (2)$$

where  $m$  is expressed in grams;  $S$  – in  $\text{cm}^2$ ;  $t$  – in days.

Comparing the rate constants we can note that the agent which is active in causing the degradation of PDMS is water, because there is no acceleration of the degradation process in the presence of phosphate ions.

We have investigated the degradation of the Biomer films while studying hydrolytic resistance of PEU.

Neither a mass change nor any accumulation of degradation products absorbed in the UV-range of the spectrum were observed over 100 days at 373 K in water or in phosphate buffer. We may suppose that the decomposition is probably of the V-type (the volume type). However, we have observed no changes in the tensile strength and specific viscosity of the samples subjected to degradation in water for a long time.

Thus, it may be concluded that the PDMS component of Avcothane-51 is only moderately hydrolytically stable, whereas the polyesterurethane component is practically hydrolytically stable under the experimental conditions.

The data from the experiments on ESCA and ATR in the IR-range [10-12] indicated that for a 0.8  $\mu\text{m}$  layer of Avcothane, the concentration of the siloxane polymer and that of the polyester was much greater in the air facing surface than in the substrate surface. Auger studies indicated that the air facing surface of Avcothane contains a proportionately greater amount of siloxane polymer and a much lower amount of the urethane hard segment in the first 1–15 nm deep layer than in a comparably thick layer of the substrate surface [10]. However, the chemical composition is comparable at a greater depth (of a few tenths of nm) both on the air side and on the substrate side [11].

Fig. 2 displays the kinetic curves for polymer mass loss in water at different temperatures. These curves consist of two characteristic parts: the first part shows an abrupt mass loss (0.5–1.0 % of the film mass); then the linear part occurs, related to the much slower part of the degradation process.

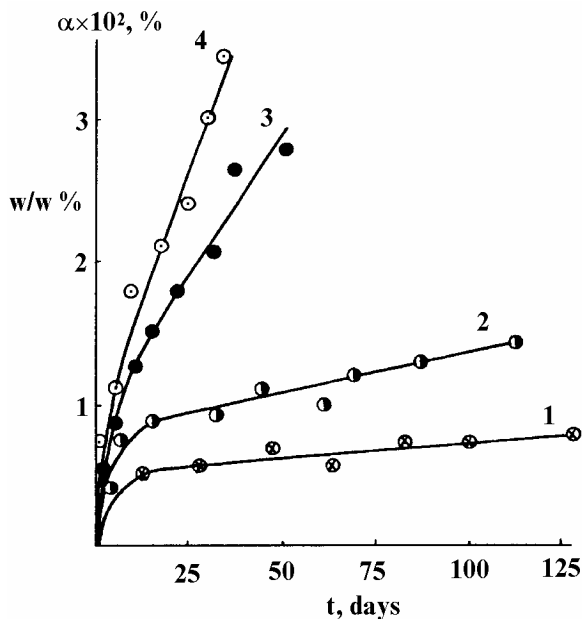


Fig. 2. Kinetic curves of Avcothane-51 mass loss in water at various temperatures: 310 (1), 331 (2), 353 (3) and 373 K (4)

To identify the category of Avcothane-51 degradation, the data on water sorption are required. We have investigated the kinetics of water sorption in Avcothane-51 and Biomer under various conditions. The diffusion coefficient was calculated according to the following equation [6]:

$$M_t = M_\infty \left( 1 - \frac{8}{p^2} \times e^{-p^2 D t / l^2} \right) \quad (3)$$

where  $M_t$  and  $M_\infty$  are amounts of water sorbed by a film of thickness  $l$  at a time  $t$ , and in the sorption equilibrium state, respectively;  $D$  is the diffusion coefficient.

Table 2 displays the sorption limit and the coefficients of water diffusion into Avcothane-51 compared with Biomer. The parameters are similar for both polymers. Considering the virtual insolubility of water in PDMS it can be supposed that water sorbed by Avcothane-51 will be localized in the polyesterurethane component.

Table 2

**Equilibrium values of the sorption, heat of sorption, coefficients of water diffusion, and activation energy of water diffusion in Biomer and Avcothane-51**

$T, \text{K}$	$C \cdot 10^2, \text{g/g}$	$H, \text{J/mol}$	$D \cdot 10^6, \text{cm}^2/\text{g}$	$E, \text{J/mol}$
<b>Biomer</b>				
310	1.0	$33.4 \pm 4.2$	0.7	$37.7 \pm 4.2$
323	1.6	$33.4 \pm 4.2$	1.3	$37.7 \pm 4.2$
333	2.5	$33.4 \pm 4.2$	2.2	$37.7 \pm 4.2$
<b>Avcothane-51</b>				
310	1.2	$33.5 \pm 4.2$	0.4	$41.9 \pm 4.2$
323	1.8	$33.5 \pm 4.2$	0.9	$41.9 \pm 4.2$
333	2.9	$33.5 \pm 4.2$	1.5	$41.9 \pm 4.2$

The following explanation of the macrokinetics of Avcothane-51 degradation is suggested:

The first part of the kinetic curve relates to the degradation of PDMS in the Avcothane-51 surface layer. The degradation rate decreases with time because of the decrease in PDMS concentration in the surface layer, and the decrease in surface water concentration. The initial rate is close to the corresponding rate of degradation of PDMS films of the same area.

The second part of the kinetic curve relates to the degradation of PDMS in domains that are uniformly distributed in deeper layers of Avcothane-51. The degradation of PDMS proceeds on the surface of domains (formed by hard segments) under the influence of water dissolved in the polymer. As the total surface area of the domains is unknown, the rates of the degradation process at different temperatures (Table 1) are shown here. It is of great interest that the activation energy for degradation calculated for the PDMS films from these rates is close to that for Avcothane-51 and Biomer (Table 2).

Thus, this stage of the degradation process involves removing the PDMS component from Avcothane-51, which must influence the mechanical properties of the polymer. Actually, the tensile strength and the calculated

resistance of the Avcothane-51 decrease during the degradation process. Similar data were obtained for the degradation of Avcothane-51 in phosphate buffer. As in the case of PDMS films, where water is the active agent, the phosphate ions display no catalytic influence.

## 2. The Stability of Segmented Polyurethanes in Blood. The Development of Colloid Structures at Long Incubation in Blood Serum

### 2.1. Aims and Background

Changes in polymer structures at external influences, and connection of these changes with polymer properties are an important sphere of polymer science. In the present paper series of polymers which are of interest for heart-vascular surgery are investigated. These are segmented polyurethanes (SPU) of Vitur-RM trademark. The best complex of biocompatibility, thromboresistance, and high and stable strength of the material is important for the articles applied in the conditions of long contact with blood (artificial heart, additional blood circulation pumps, balloon-catheters, etc.). Some SPU satisfy this complex of demands. SPU on the basis of polyphurite with MM 1000–2000, MDI (4,4'-diphenylmethanediisocyanate) and diamines – for example, the material of Ethycon Co. (USA) – biomer – are considered as the most useful of them. SPU of Vitur-RM trademark from the native materials of that type belong to that group.

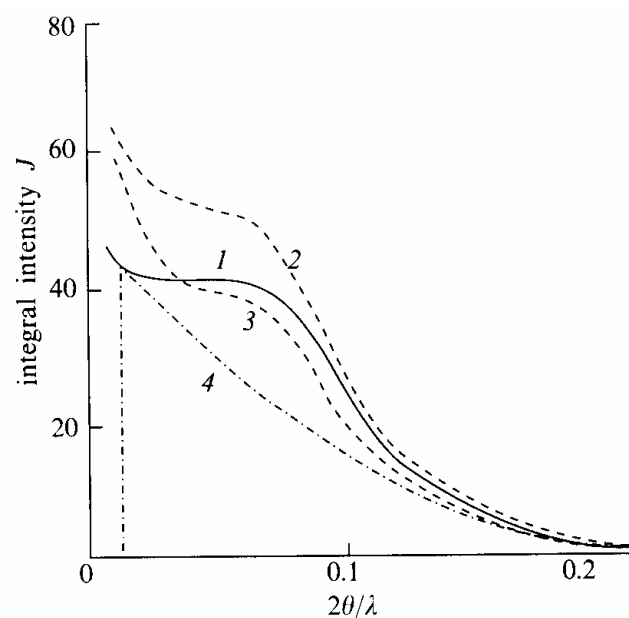
### 2.2. Experimental

In the present work structural (according to the data of small-angle and wide-angle X-ray diffraction scattering) and strength properties of Vitur-RM series were investigated. These SPU were synthesized on the basis of MDI, ethylenediamine, and polyphurite with MM of 1000, 1500, 1800, 2000 (further referred to as RM-1000, RM-1500, etc.), before and after the incubation of their films of 150–200  $\mu\text{m}$  thickness in blood serum at 313 K during 6, 12 and more months. Sample preparation, the analysis of structural, and mechanical characteristics are the same as in [13–16]. Small-angle X-ray diffraction patterns (SAXS) were obtained by the device with linear coordinate detector. Measurements were performed with a slit band collimation of X-ray, beginning from the scattering angle of  $2\theta = 0.1^\circ$ , with the step of  $0.02^\circ$ . X-ray tube BSV27-Cu with nickel filter and amplitude discriminator ( $\text{CuK}_\alpha$  irradiation,  $\lambda = 1.54 \text{ \AA}$ ) was used. Background scattering was excluded from experimental curves. After that they were normalized by sample thickness, smoothed, and used in further analysis.

### 2.3. Results and Discussion

Dense side packing of chain molecules and some longitudinal stacking is characteristic for macromolecular structure of Vitur-RM of the present series and other SPU. This follows from the existence of intensive strike reflex of about  $4.5 \text{ \AA}$  period and less intensive reflex of about  $12 \text{ \AA}$  [17] at wide-angle X-ray scatterings (WAXS), respectively. At WAXS of RM-1000 sample, mostly rigid and strong in the series, the reflexes existed, which show the presence of some percentage of rigid block crystallites of about a hundred of  $\text{\AA}$  [18].

Colloid level structure of Vitur-RM also typical for SPU: small-angle X-ray scatterings (SAXS) show one not very intensive wide reflex at the background, which decreases with the scattering angle increase (Fig. 3). SAXS reflex is caused by volumes with regular alternating of rigid and flexible blocks of SPU – regular fraction of the structure. Macroperiods of Vitur-RM were determined according to the position of SAXS reflexes. They increased from  $110 \text{ \AA}$  for RM-1000 up to  $130 \text{ \AA}$  for RM-2000. The lengths of rigid blocks, found according to the methodics of [19], changed from  $\sim 55$  up to  $70 \text{ \AA}$ . SAXS background is caused by an irregular fraction of SPU structure, which includes both layer-like structures, where alternating regularity of rigid and flexible segments is disturbed by more than 20 % (for more detail see [13]), and domains of larger and smaller size than in regular fraction, as well as density fluctuations up to micropores.



**Fig. 3.** Small-angle X-ray diffraction patterns (SAXS) for RM-1800: for initial samples (1); for samples incubated in blood serum during 12 months (2); for the ones incubated during 18 months (3) and (4) shows the principle of determination of integral intensities  $J$  for regular and irregular parts participating in the structure diffraction

It is known from common principles of X-ray scattering that the greater the structure heterogeneity of the present material (at the level of colloid sizes) the higher SAXS intensity ( $J$ ). SPU structure heterogeneity, connected with the presence of electron density fluctuations, increases with the development of both microphase division and pore system or other density variations.

The comparison of heterogeneity characteristics of the present Viturs before and after incubation is illustrated by the histogram in Fig. 4. Integral intensities of SAXS ( $J$ ) are gathered in it. They are normalized to the general conditions of obtaining (exposition, thickness, beam intensity) for regular fraction of structure (B) and irregular one (A) (the method that we took for separation of SAXS intensity of regular and irregular fractions of structure is illustrated by Fig. 3). From the left to the right the data groups for RM-1000, RM-1500, RM-1800, RM-2000 samples are presented; in the left side column data for initial Vitur-RM are shown; to the right data for incubation during 6, 12, 18 and 30 months are given.

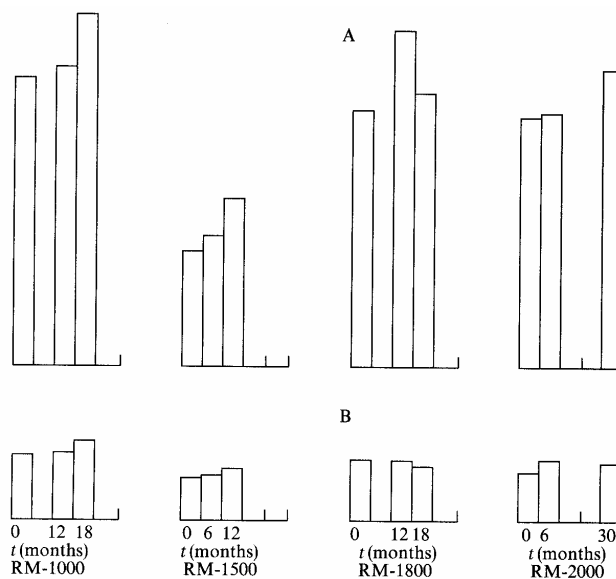
It follows from Fig. 4 that:

1. Initial heterogeneity of the structure, advantageously dependable on microphase separation degree, is not similar for Vitur-RM investigated.
2. Changes in regular part of the structure at incubation in blood serum are practically within the limits of the value obtaining procedure mistake.
3. For irregular fractions of the structure intensities differ sufficiently for various Vitur-RM, and for various times of their incubation in blood serum.

Fig. 5 shows the data on stable characteristics of Vitur-RM of the present series before and after incubation in blood serum. Having compared it with Fig. 4 it can be seen that the most stable Vitur RM-1000 gives the most intensive SAXS, and the sample which has the lowest initial strength allowed by the Russian Standard (RM-1500) shows SAXS of the lowest intensity.

The development of heterogeneity in the polymer structure under the influence of water and water solutions of acids were observed before: in polyamides [20], in polyvinyl alcohol [21], at incubation of low-stable Vitur RM-1500 in blood serum [14]. In the present paper we confirm the effect of structure heterogeneity development in Vitur-RM during incubation:  $J$  increase appears, *i.e.* the increase of heterogeneity.

Some data on the nature of heterogeneities, appeared during incubation, give the effect of SAXS intensity decrease during long incubation in blood serum that was not observed before and was found for RM-1800. The matter is that the decrease of SAXS under the effect of nitric acid water solutions on polyamides was observed also in [19]. The authors reported that SAXS intensity increased after long influence of water. Taking into account



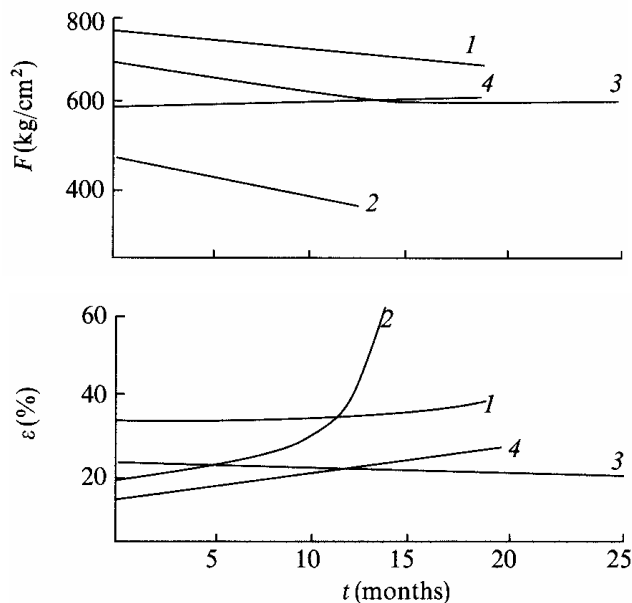
**Fig. 4.** Histograms of SAXS integral intensity  $J$  changes at SPU incubation in blood serum, in relative units: for the irregular fraction of the structure (A) and for the regular one (B)

parallel diffusion measurements this was explained as diffractive result – not because of real changes in structure of colloid level, but as the consequence of the decrease of electron density difference of the “polymer - pores” system at filling pores by nitric acid solution, which were closed for water before. The fact of SAXS decrease in RM-1800 witnesses that there were pores in Vitur, and some of them were filled during incubation. At long incubation of Viturs in blood serum in the range of decreased density (micropores) non-water components could appear during that time and stay there. Evidently, in the case of RM-1800 sample there were some peculiarities of the structure either of the sample or during the incubation procedure, which led to the formation of pores or spheres of decreased density.

To estimate the distribution of structure heterogeneities by sizes one can use curves of  $J_d j^3$  dependence on  $j$  (where  $J_d$  is the SAXS intensity,  $j^3$  the X-ray scattering angle). It was found that for all Vitur-RM samples before and after incubation in blood serum the range of heterogeneity inertia radii is quite wide, not less than 10 to 50 Å, most often the obtained radius is in the range of 20–25 Å. These values do not change noticeably after Vitur incubation in blood serum, but the content of heterogeneities in SPU volume does change (Fig. 4).

Thus, it is sufficient for medical practice that long incubation of Vitur-RM in blood serum does not practically change tensile strength and residual lengthening of the samples with rather high initial strength. Probably, special attention should be paid to the application of materials with the most high stable characteristics for the definite SPU trademark using Vitur-RM in corresponding articles (this

points out the case with RM-1500). It follows from X-ray scattering that at long incubation the common character of Vitur-RM structure did not change: rigid domain sizes, their alternating period in regular SPU fraction, average domain inertia radii and their distribution by sizes.



**Fig. 5.** Dependence on incubation duration in blood serum at 313 K: (a) – of tensile strength  $F$ ; (b) – of residual lengthening  $\varepsilon$  for films of RM-1000 (1), RM-1500 (2), RM-1800 (3), RM-2000 (4)

The present X-ray scattering investigation of Vitur-RM supplements our preliminary information about changes in some polymers at the diffusion of water and water solutions. Evidently, heterogeneity development in polymers in conditions of macromolecule mobility increase is the display of their own properties, typical for chain macromolecules [22].

To conclude, we can say that Biomer possesses high hydrolytic resistance in water and in aqueous solutions of phosphates. Avcothane-51 possesses lower hydrolytic resistance, because the PDMS component of the material is vulnerable to hydrolysis.

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## ПОЛІУРЕТАНИ В БІОЛОГІЧНОМУ СЕРЕДОВИЩІ

**Анотація.** Наведено макрокінетику розкладу поліестеруретанів в модельному біологічному середовищі. Особливу увагу приділено стабільності сегментованих поліуретанів у крові та розвитку колоїдних структур при довгому інкубаційному періоді у сироватці крові.

**Ключові слова:** поліуретани, біологічне середовище, стабільність, колоїд, інкубація, кров, структура, сироватка.