Structural transformation of terpolymer poly(L-lactide--glycolide-trimethylene carbonate) with shape memory effect during the degradation process*)

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Abstract: The purpose of this study was to analyze the changes of the structure of shape memory polymer (SMP) surgical staple made from poly(L-lactide-glycolide-trimethylene carbonate) during in vitro degradation. It is crucial to understand the structure and properties of SMP biomedical polymers during the degradation process as their biodegradation rate should match the therapeutic period. It was confirmed that degradation results in a decrease of T_g and that degradation at a temperature above T_g involves faster dynamics. The hydrolysis of amorphous regions lead to increased crystallinity and erosion of the polymer.

Keywords: shape memory polymers (SMP), supermolecular structure, WAXS.

Transformacja struktury terpolimeru z pamięcią kształtu — poli(L-laktydo--glikolido-trimetylowęglanu) — podczas biodegradacji

Streszczenie: Analizowano zmiany zachodzące w strukturze klamry chirurgicznej wykonanej z polimeru z pamięcią kształtu, podczas degradacji prowadzonej w warunkach in vitro. Istotne znaczenie ma określenie wpływu tych zmian na właściwości fizyczne materiału klamry, ponieważ biodegradacja nie może zakłócać procesu terapeutycznego. Stwierdzono, że degradacja polimeru prowadzi do obniżenia wartości temperatury zeszklenia (T_g). W temperaturze powyżej wartości T_g obserwowano zwiększoną dynamikę procesu degradacji. W wyniku hydrolizy obszarów amorficznych zwiększał się stopień krystaliczności, a w skali mikroskopowej następowała erozja tworzywa.

Słowa kluczowe: polimery z pamięcią kształtu, struktura nadcząsteczkowa, WAXS.

Shape memory polymers (SMPs) are stimuli responsive materials that are sensitive to various external factors, e.g. changes of temperature (thermoresponsive SMP), pH (chemosensitive SMP) or light wavelengths (photoactive SMP), etc. In the case of thermoresponsive SMPs, a permanent shape (A) can be formed by a melt processing. Then, in the so called "programming" process, within a given temperature range, the SMP needs to be deformed to the temporary shape (B), which is finally fixed by rapid cooling while the permanent shape is stored in the "memory". The permanent shape can be regained by a change of temperature above a certain switching temperature [1—3].

SMPs can be potentially used for biomedical applications such as implantable materials. Various biomedical devices using SMPs, such as a variety of expandable stents [4, 5], self-tensioning sutures [3], an occlusive device for embolization of aneurysms [6], tissue engineering scaffolds [7] and a microactuator for removing clots in ischemic stroke patients [8, 9] have been described in the literature. A number of synthetic shape memory polymers have been developed. However, because of a lack of complete biocompatibility, only a few of them can be implanted [10]. Due to the good biocompatibility of aliphatic polyesters already used in medicine, such as poly-L-lactide (PLLA), polyglycolide (PGA) and poly-ε-caprolactone (PCL), they are often considered as the basic elements of SMP macromolecular chains [10].

Three main parameters are crucial for SMPs used for biomedical implants and stents: the switching temperature, the permanent shape recovery rate and the biodegradation rate. Even if the SMP has confirmed shape memory properties and its biodegradation rate is satisfactory, it is unsuitable for use in the human body if its' shape recovery rate is low and switching temperature is

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too high [11]. In medical applications, too high switching temperatures may be harmful for the surrounding tissues. One of the possibilities of decreasing the SMP glass transition temperature, and the same switching temperature, is copolymerization. It was confirmed that it is possible to modulate the switching temperature of copolymers of L-lactide with glycolide and cyclic trimethylene carbonate (TMC), and it is possible to obtain copolymers with glass transition temperatures in the range of physiological human body temperatures [10].

Shape memory ability, combined with bioresorption properties, can be advantageous in order to minimize surgical impact as it enables insertion of small-size, temporary shape elements that then regain their permanent shapes at body temperature [10]. In the case of biodegradable/bioresorbable materials, the biodegradation rate determines the mechanical function and stability of the implanted device as the properties of the implanted or inserted material change with time. The biodegradation rate must meet the therapeutic requirement, which is the period needed to heal the lesion. Thus, it is very important to study and understand the structure and properties of those special SMP biomedical polymers within the degradation process.

In this paper, we present the results of structural and calorimetric studies of poly(L-lactide-glycolide-trimethylene carbonate) terpolymer through a 18 weeks in vitro biodegradation process. Scanning electron microscopy allowed us to follow changes of polymer morphology during biodegradation, while an X-ray diffraction method enabled us to demonstrate that the crystallinity of the polymer clearly increases and the crystalline structure evolves as a function of biodegradation time. In order to understand more about the arrangement of macromolecules in the polymer, we relied upon thermal analysis.

EXPERIMENTAL PART

Materials

Poly(L-lactide-glycolide-trimethylene carbonate) terpolymer composed of LA(L-lactide) 68.6 %, GL (glycolide) 12.4 %, o-TMC (trimethylene carbonate) 19.0 % was synthesized at The Center of Polymer and Carbon Materials, Polish Academy of Sciences, in Zabrze, by ring-opening polymerization using low-toxicity zirconium(IV) acetylacetonate $Zr(acan)_4$ as an initiator, according to the procedure described elsewhere [4]. The post-reaction form of the polymer was melted at 130 °C and processed into surgical staples using a micro injection molding machine.

Degradation process

During in vitro degradation experiments, samples were immersed in buffered solution (phosphate buffer, pH = 7.4; temp. 39 °C, shaking) and incubated for up to 18 weeks. The buffer solution was changed every week. Finally, samples were dried. The remaining mass and water absorption was calculated after each aging time and after removing the samples from the buffer solution. The surfaces of the samples were dried and their wet weight was determined. Then, the samples were dried and the remaining mass and water absorption were evaluated by the comparison of dry weight and wet weight versus initial weight. The temperature of 39 °C was selected for the in vitro biodegradation process as this is the normal body temperature of a pig, which was the model selected for further in vivo biodegradation studies.

Methods of testing

— SEM analyses were performed in conventional SEM mode using a Jeol JSM 5500LV instrument operating at 10 kV after coating the samples with a thin layer of gold by sputter deposition. The surfaces of samples were observed at ×5000 magnifications.

— The crystalline structure was investigated using an URD 6 Seifert diffractometer (CuKα, $\lambda = 0.154$ nm) operated at 40 kV and 30 mA. The system was equipped with a nickel filter for beam monochromatisation and a scintillation detector. Data were collected in 0.1° steps (for 20 s) within a 2θ range of 3—60°. Polymer samples were ground into a powder before measurements. Diffraction curves were resolved into the crystalline peaks and the amorphous halo by the Hindeleh & Johnson method [12, 13] using OPTIFIT/WAXSFIT software [14]. Individual peaks corresponding to the diffraction reflections from lattice planes were approximated using the Gaussian function and a linear profile background was assumed. The fraction of the crystalline phase was calculated from the ratio of the integral intensities of crystalline peaks to the total scattering intensity. Sizes of crystallites in the direction perpendicular to crystalline planes (200), (110), (203) and (211) were calculated from Scherrer's equation [14].

— Differential scanning calorimetry (DSC) measurements were performed using a TA Instruments Thermal Analysis System 5100 equipped with a MDSC Calorimeter 2920 and RCS cooling system. The temperature was calibrated with the melting point of indium (156.6 °C) and the enthalpy was calibrated with indium (28.4 J/g). The measurements were registered in the temperature range — 40—200 °C, using TA standard aluminum pans, under a nitrogen atmosphere (flow 40 cm^3/min) with a heating and cooling rate of $\beta_+ = \beta_- = 10$ deg/min. The data were evaluated by means of the Universal V2.6D (TA Instruments) software.

— Thermogravimetric analysis was performed on a Q 500 TA Instruments system within a temperature range of 25—800 °C. Samples were heated at the rate of 10 deg/min under a nitrogen atmosphere (flow 60 cm^3/min). At the temperature of 800 °C, the atmosphere

in the furnace was changed for air for 2 min in order to oxidize the organic residues from thermal decomposition of terpolymer. TG data were analyzed using Universal V2.6D software by TA Instruments.

RESULTS AND DISCUSSION

According to SEM analysis, the structure and morphology of samples does not change greatly during the first 8 weeks of the degradation process (Fig. 1). A regular porosity is observed starting from samples collected after 12 weeks of in vitro degradation (Fig. 2), indicating hydrolytic degradation of the polymer leading finally to considerable defragmentation. The observations from SEM were substantiated with data from mass loss and water absorption analysis (Fig. 3). Those data confirm the beginning of hydrolysis as seen by mass loss after 2 weeks of in vitro biodegradation, with the most pronounced mass loss after 12 weeks of the process — almost 12 % of mass loss occurred between weeks 14 and 18. The water absorption of samples after degradation corresponds well with the mass loss as it is attributed to a larger surface area available for water molecules and easier penetration of water into the material.

The hydrolysis was conducted at 39 °C, which is at a temperature slightly below the glass transition T_g of the material at the starting point of the experiment (T_g~43.7 °C). However, along with time and the degradation progress, the T_g registered lower temperatures (after 10 weeks T_g~36.3 °C) so that further degradation was realized in the temperature range above the glass transition. Such conditions leads to the higher mobility of chains and easier migration of the released degraded fragments and it can explain the relatively intensive mass loss and water absorption after the 12th week of the experiment (Fig. 3).

The thermograms shown in Fig. 4, registered in heating mode, correspond well to the explanation given above. As shown in previous research [10], poly(L-lactide-glycolide-trimethylene carbonate) terpolymer has a multiblock structure that determines its shape memory properties. However, in the "starting conditions", i.e. in the form of a surgical staple before the degradation process, the crystallinity is relatively low. The DSC curve obtained in heating mode [range from -40 to 200 °C, Fig. 4 (1)] shows that a glass transition at 43.7 °C is accompanied by a characteristic peak of enthalpy of relaxation (48.9 °C) with relatively high intensity. At higher temperatures, one exothermic (recrystallization) and one endothermic (melting) effect with almost the same enthalpic values of ca. 4.4 J/g, were identified. This is unlike other calorimetric results for SMP samples subjected to in vitro degradation processes. The shapes of DSC curves in those cases depicts quite different behavior [line (2)—(4)

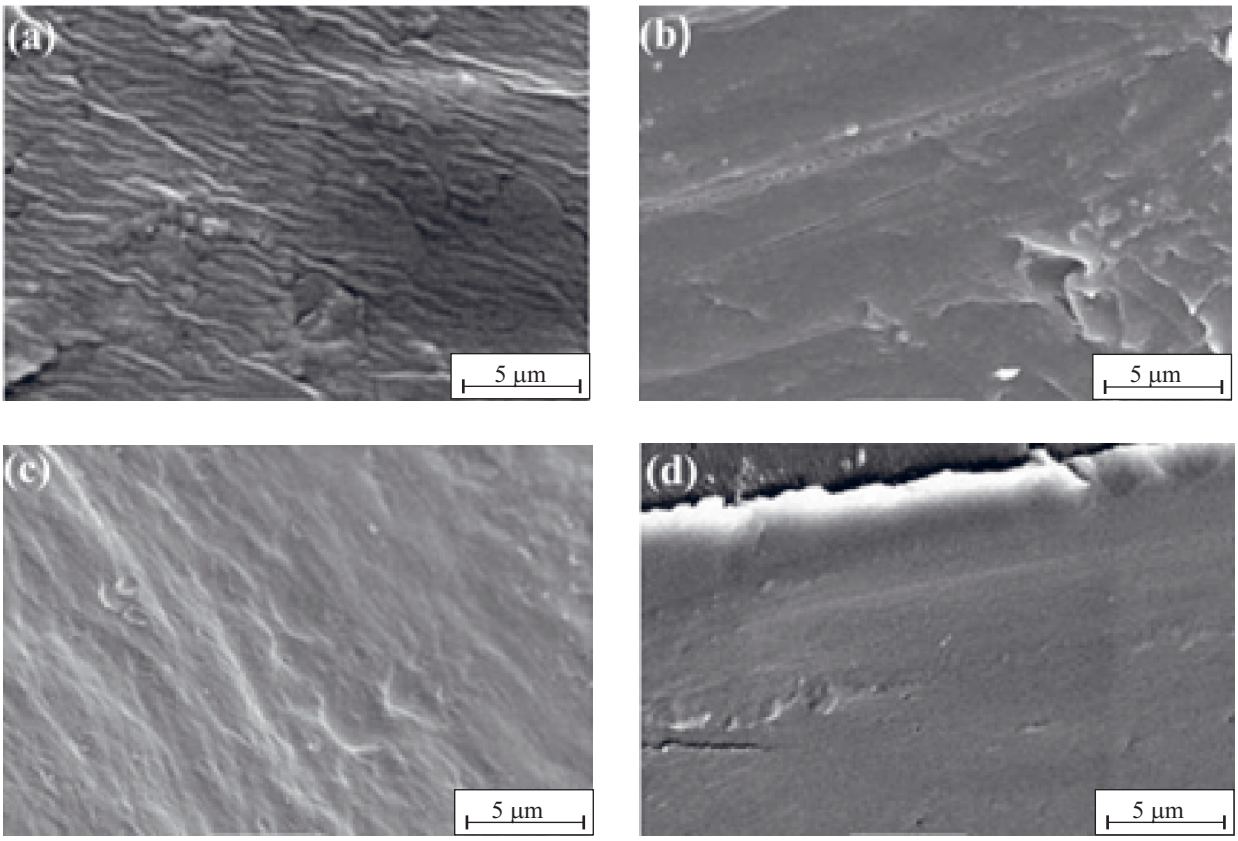

Fig. 1. SEM microphotographs of degraded staple samples, degradation respectively: (a) — 2 weeks, (b) — 4 weeks, (c) — 8 weeks and (d) — 10 weeks

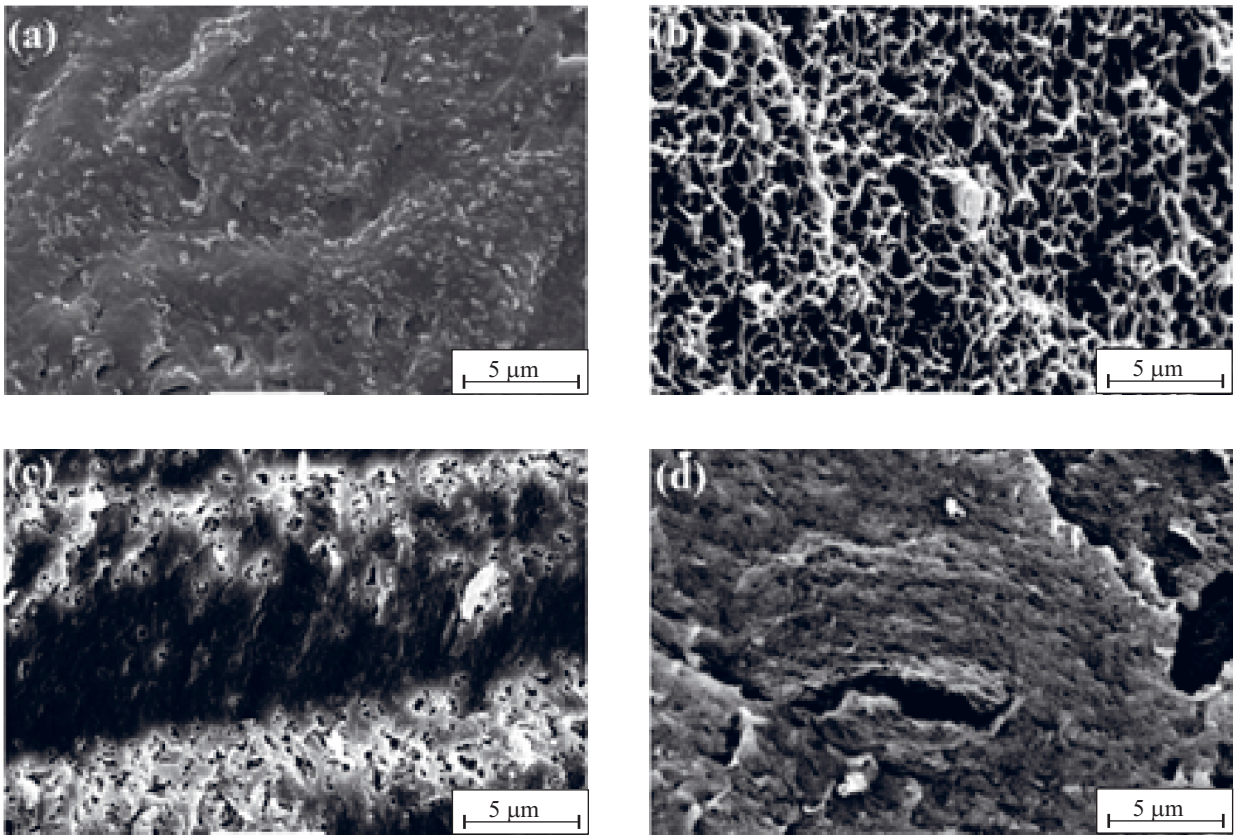

Fig. 2. SEM microphotographs of degraded staple samples, degradation respectively: (a) — 12 weeks, (b) — 14 weeks, (c) — 16 weeks and (d) — 18 weeks

in Fig. 4]. The values of characteristic temperature and enthalpy changes corresponding to the transitions reflected in the curves are given in Table 1.

The curves for degraded samples at temperatures above 70 °C show a very clear melting peak, which indicates that a structure ordering process occurs simultaneously with degradation. Crystallites created in this process melt when heated above 70 °C, as seen in DSC measurements. This property of the material intensifies with the time of the degradation process and almost disappears after 18 weeks of degradation. This effect may be associated with arrangement appearing among the oligomeric degradation products, released at the end from the material as the effect of the polymer erosion.

Further heating of the samples, as seen in the DSC curves presented in Fig. 4, leads to an increased exothermic recrystallization effect as a function of the degradation time up to 10 weeks [lines (1)—(3)]. The ability to recrystallize no longer appears to be the case for samples degraded for 18 weeks. The initial melting temperature of

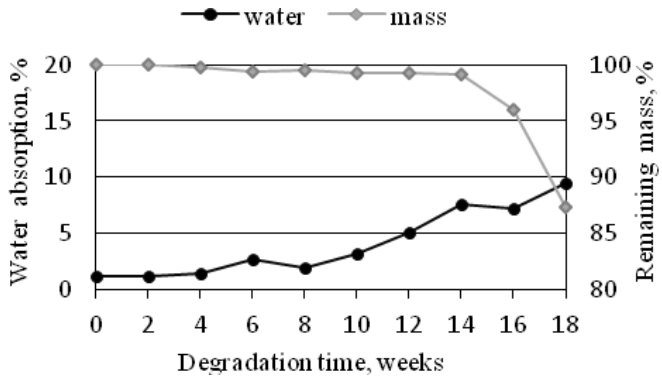

Fig. 3. Changes of sample mass during degradation and changes of water sorption

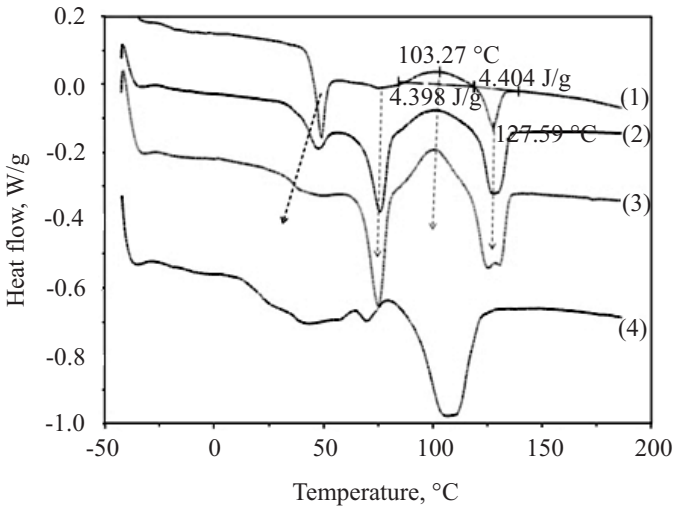

Fig. 4. DSC curves of samples: (1) — before degradation, (2) — after 8 weeks, (3) — after 10 weeks, (4) after 18 weeks of degradation

T a b l e 1. Thermal properties (T_g, T_{m1}, T_{m2}, ΔH_{m1}, ΔH_{m2} ΔH_r) evaluated on the basis of DSC curves (Fig. 4) for samples of terpolymer SMP material after different periods of in vitro degradation

Degradation period weeks	Temp. of glass transition	Temp. of melting (1st melting peak)	Enthalpy of melting (1st melting peak)	Enthalpy of recrystallization	Temp. of melting (2nd melting peak)	Enthalpy of melting (2nd melting peak)
	T_g, °C	T_{m1}, °C	ΔH_{m1}, J·g^{-1}	ΔH_r, J·g^{-1}	T_{m2}, °C	ΔH_{m2}, J·g^{-1}
0	43.7	–	–	4.4	127.6	4.4
8	40.2	76.0	10.9	9.2	127.3	10.1
10	36.3	75.0	15.9	13.6	125.5 / 130.7	15.9
18	19.3	70.4	1.7	–	105.7	41.7

127.5 °C decreases with an increased time of degradation, while the enthalpy of melting increased to 41.7 J·g^{-1} (see Table 1). This may suggest a larger number of less perfect crystals that can be melted at lower temperatures. Moreover, the discussed melting peak (especially visible for the sample degraded for 10 weeks) exhibits characteristic splitting, which can be evidence of less perfect crystallites. The temperature range of this peak indicates that the effect of this change is assigned to the melting of the crystallites within lactide blocks.

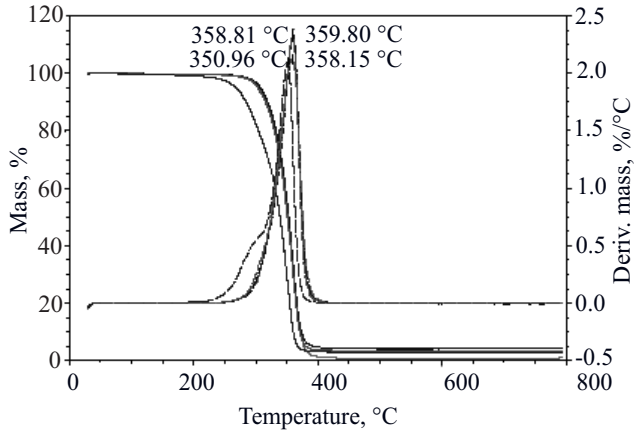

Fig 5. TG and DTG curves of material before and during the degradation process for 4—10 weeks

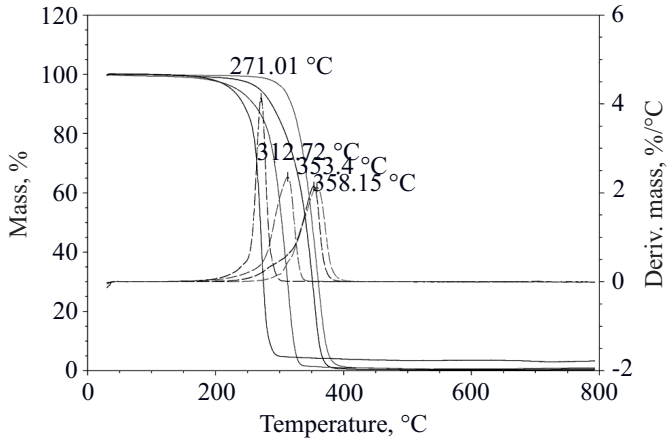

Fig. 6. TG and DTG curves of material before and during the degradation process for 12—18 weeks

TG analysis confirms the conclusions derived from DSC studies. The maximum of the DTG curves, assigned to maximum rate of mass loss, changes slightly from 358.2 °C to 351.0 °C for samples degraded below the T_g (Fig. 5), and then from 12 weeks of degradation. For samples degraded at temperatures above the T_g, the maximum rate of mass loss clearly decreases to 271.0 °C (Fig. 6).

The results from DSC, SEM and mass loss analysis are confirmed by the WAXS method. Results of WAXS measurements were analyzed with respect to the crystalline structure of polylactide as the dominant phase. Before the in vitro degradation process, the crystallinity of polymeric staple was relatively low.

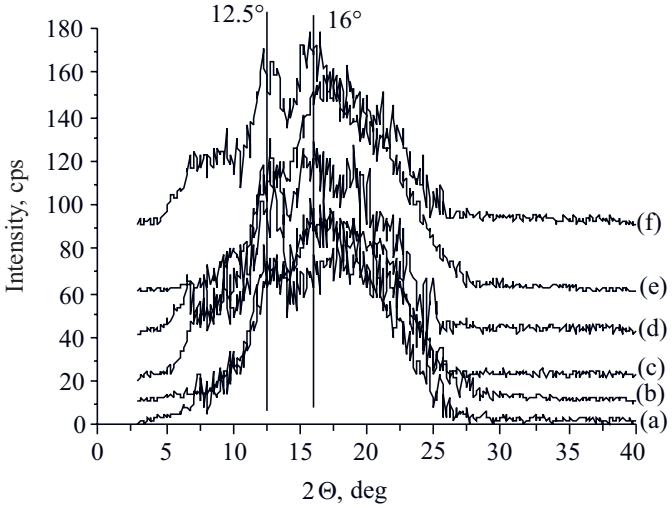

Fig. 7. WAXS patterns of terpolymer SMP material before and during the degradation process respectively: (a) — before degradation, (b) — after 2 weeks, (c) — after 4 weeks, (d) — after 6 weeks, (e) — after 8 weeks, (f) — after 10 weeks of degradation

There are no interference effects of ordered structures at the atomic level besides the weak signal at the 2θ ≈ 12.5°, Fig. 7, which is according to further studies related to the ordering of polylactide segments. The first change of the character of the diffraction pattern is observed after 10 weeks of in vitro degradation at a temperature above the T_g of the degraded polymer (due to decreasing of T_g

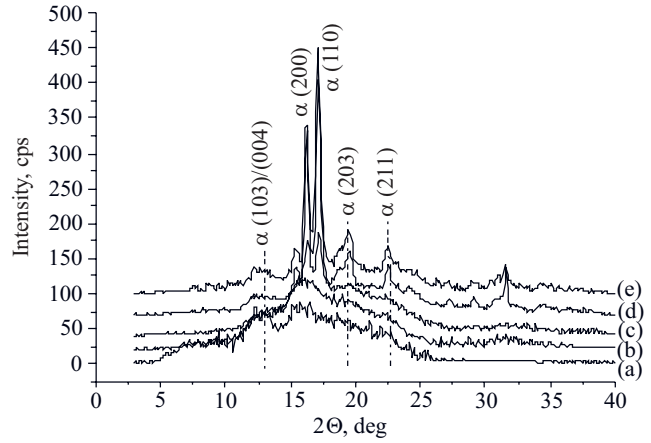

Fig. 8. WAXS diffraction patterns of staples during the degradation process: (a) — after 10 weeks, (b) — after 12 weeks, (c) — after 14 weeks, (d) — after 16 weeks, (e) — after 18 weeks of degradation

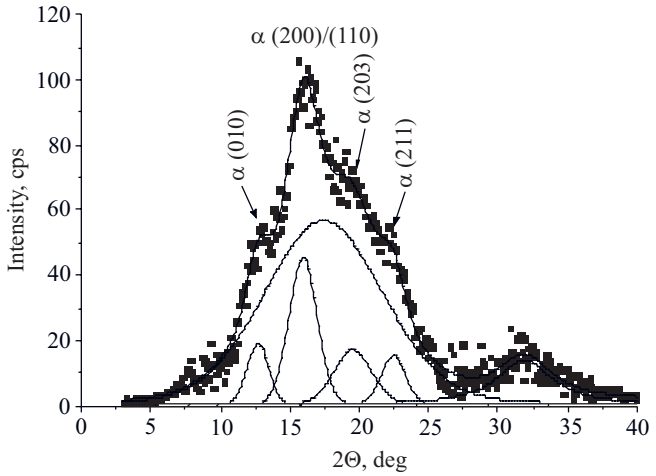

Fig. 9. WAXS pattern of sample subjected to degradation for 12 weeks

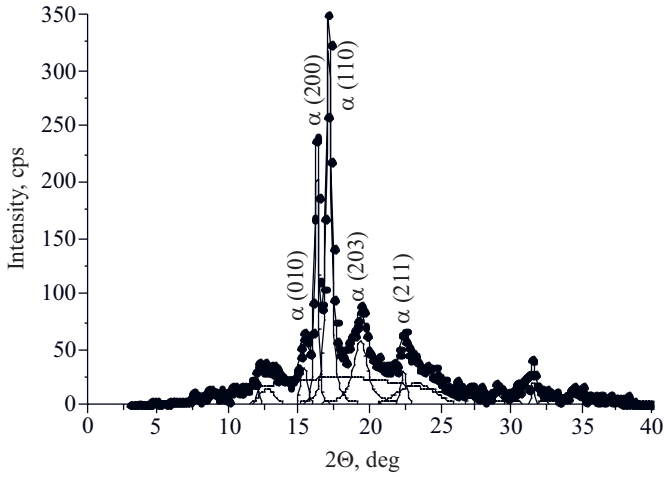

Fig. 10. WAXS pattern of sample subjected to degradation for 18 weeks

during degradation), then two distinct peaks at 2θ ≈ 12.5° and 2θ ≈ 16° appear (Fig. 8, Fig. 9).

T a b l e 2. Crystallinity index and sizes of crystallites of terpolymer SMP sample subjected to degradation for 10—18 weeks

Degradation period weeks	Crystallinity index	Sizes of crystallites, nm			
	%	$D_{(200)}$	$D_{(110)}$	$D_{(203)}$	$D_{(211)}$
10	34	3.7		1.8	3.7
12	35	5.0		2.8	4.3
14	36	16.8	17.0	4.1	5.5
16	60	27.8	24.8	9.9	20.4
18	62	23.8	22.8	7.9	19.1

The longer the biodegradation time, the more ordered is the supermolecular structure that is observed (Fig.10, Table 2). In this case hydrolysis of amorphous regions is preferable, leading to recrystallization and increase of crystallinity, and it is a well known phenomenon for semicrystalline polymers.

CONCLUSIONS

The supermolecular structure of our surgical staples made from a terpolymer SMP, studied over an 18 week in vitro degradation process, exhibited a number of characteristics dependent on the conditions of the degradation process. Changes were observed both in microstructure and supermolecular structure. The dynamics of the structural changes depends strongly on the temperature range of the degradation process and differed greatly when the degradation is conducted at temperatures above the T_g of the polymer. We could define two characteristic stages of the degradation process. The stability of the polymer up to 10 weeks of the in vitro biodegradation process should be confirmed by in vivo methods. It would be beneficial to compare the results of in vitro and in vivo experiments to find out how much the biological environment of tissue affects the structure and properties of the implanted material. SEM analyses revealed heterogeneities in the volume of samples and the progressive erosion of the material through the degradation process. Based on the DSC and WAXS studies, we observed an increase in the crystalline fraction of lactidyl blocs in the degraded material.

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