Journal of Applied Polymer Science

Shape-memory bioresorbable terpolymer composite with antirestenotic drug

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ABSTRACT: Shape-memory polymers (SMPs) that combine shape-memory, biodegradability, and controlled drug release properties are very promising for medical and pharmaceutical application. Moreover, incorporation of antirestenotic drug into SMP biodegradable stent seems to be an interesting solution because of possibility to combine the mechanical support that provides stent and also drug elution. The aim of our study was to analyze the effect of incorporation of sirolimus into poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) on physicochemical and mechanical properties, degradation, and shape-memory effect of the terpolymer. For this purpose, sirolimus was incorporated into the terpolymer by injection molding method. It has been demonstrated that drug-free terpolymer after injection molding characterized insignificant changes in terpolymer composition. Degradation of materials during processing was not observed. Incorporation of drug molecules did not change shape-memory properties of terpolymer. ^{1}H- and ^{13}C-NMR spectra of poly(lactide-*co*-glycolide-*co*-trimethylene carbonate) confirmed that changes during degradation were similar for terpolymer and terpolymer with sirolimus. Sustained and regular release of sirolimus was observed. The developed material presents potential for biomedical and pharmaceutical applications. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41902.

KEYWORDS: biodegradable; biomedical applications; drug delivery systems

Received 25 September 2014; accepted 18 December 2014
DOI: 10.1002/app.41902

INTRODUCTION

It is estimated that cardiovascular disease cause even one-third of human mortality throughout the world.[1] Drug-eluting stents (DESs) have been demonstrated to decrease clinical restenosis rates compared to bare-metal stents.[2] Even though polymer-coated metallic DESs have revolutionized the treatment of obstructive coronary disease, they do not represent an optimal solution, regarding the possibility of very late stent thrombosis (LST) due to impaired endothelialization, hypersensitivity reaction, inflammation, and vascular dysfunction. Once the drug is eluted completely from the surface of a DES there is no utility demonstrated for stents and their presence serves as a nidus for potential LST and chronic inflammation.[3] Therefore, biodegradable polymeric stents have recently attracted much attention as an alternative to metallic stents. They can provide delivery of the drug, as well as mechanical support of the vessel until restoration and complete dissolution of the stent.[2,4] Completely absorbable poly(L-lactide) stent eluting everolimus has recently entered the market.[5] The stent is balloon expandable and consists of a backbone of poly(L,L-lactide) (PLLA) coated with poly (D,L-lactide) (PDLLA) that controls the release of antiproliferative drug.[3] DES reduce restenosis via inhibition of smooth muscle cell proliferation. Paclitaxel and sirolimus are among the most often used antirestenotic drugs, because they can inhibit proliferation and migration of vascular smooth muscle cells (VSMCs), important factors in the development of neointima formation, thereby preventing restenosis.[2,6–8]

Commonly used bioresorbable devices are prepared with the aliphatic polyesters obtained by the ring-opening polymerization of lactones. They are versatile polymers possessing good mechanical properties, hydrolizability, and biocompatibility. The technique of the ring opening polymerization allows to obtain materials with controlled architecture, microstructure, and tailored properties. Proper control of composition, microstructure, molecular weight is crucial in a view of further medical applications.[9] Copolymerization of polyesters with polycarbonates allows to modify the polymeric microstructure, mechanical properties, degradation rate[10] so as to adjust the final material

to the requirements of the medical market. Polymers containing carbonate units are more flexible and its degradation products exhibit reduced acidity in comparison with aliphatic polyesters which are now applied in daily medical practice. It is important to mention that commercially available polyesters and polyester-carbonates are commonly synthesized using stannous compounds as initiators. However, they are relatively toxic.[9] Zirconium complexes are less toxic initiators and its low biological toxicity compared to stannous octanoate $Sn(oct)_2$ has been confirmed.[11]

Shape-memory polymers (SMPs) are stimuli-responsive compounds that can change their shape as a consequence of an external stimulus, such as variations of temperature, light, pH, etc. Thermoresponsive SMPs are processed to receive their permanent shape. Afterward, within a given temperature range, they can be easily deformed into a temporary shape that can be fixed by fast cooling and recover their permanent shape by reheating.[12] Usually, the temporary shape is obtained by deforming the polymer from its original shape above the transition temperature (T_{trans}), followed by cooling it to below T_{trans} value. Shape recovery occurs when polymer is reheated above the T_{trans} value and is returned to its original shape. The T_{trans} can be either a glass transition temperature (T_g) or a melting temperature (T_m) of the polymer.[13] Medical devices with shape-memory effect could be implanted with the minimal shape and recovery to its original shape when in the body.[14] Heat-induced SMPs have drawn the most attention because they can change shape by changing the temperature. They can recover to their permanent shape upon heat activation above their transition temperature. If the transition temperature is around body temperature, then it has promising potential for use in biomedical applications.[15]

There have been developed terpolymers of L-lactide (LL), glycolide (GG), and trimethylene carbonate (TMC), obtained by the ring opening polymerization, initiated with low-toxic zirconium (IV) acetylacetonate $Zr(Acac)_4$, that recover their original shape at the human body temperature. Introducing three different units: LL, GG, and TMC into polymer chain makes it possible to modify T_g temperature of desired material so as to adjust the T_{trans} value that shape recovery occurs. As far as medical devices are concerned the appropriate T_{trans} value should be temperature of the human body. Therefore, the novel SMPs are proposed for practical medical applications as self-expanding stents, new tools for microinvasive surgery, or smart matrices for controlled drug release.[9] Development of multifunctional materials for biomedical applications that combine biodegradability, controlled drug release, and shape-memory capability would be advantageous.[16] In the previous study, we described not only the synthesis of poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate),[9] detailed analysis of its chain microstructure,[17] but also morphology and thermal properties after degradation *in vivo*.[18,19] The obtained polymers showed SMPs and what is particularly important they recovered the permanent shape near body temperature. The glass transition temperature of the LL, GG, and TMC terpolymers changed with unit composition and followed a trend based on the relative amount of the three units.[9] Lately, we presented further study on poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate).[20] We obtained a biocompatible and biodegradable polymeric material possessing good shape-memory behavior, which would be designed as medical implants. Selected terpolymers possessed 75% of LL, 10% of GG, and 15% of TMC with Mn range: 26,000–52,000. This composition of the units and concrete values of Mn ensured desired high mechanical strength, flexibility, and the recovery temperature close to the temperature of the human body. On the basis of our experience, we selected appropriate material for drug eluting stent.

Usually, DESs are composed of a stent platform, a drug-carrier, and an active drug.[21] However, incorporation of drug into stent seems to be an interesting solution because of possibility to combine the mechanical support that provides stent and drug elution from stent coating. The concept of incorporation of medicines into shape-memory stents was presented before.[16,22] Biodegradable stent with incorporated drug would possess improved functionality and less complicated production process. Controlled drug release has been studied for covalent SMP networks. The absence of any impact of drug incorporation on the thermal properties of the semicrystalline polymer network has clearly been shown for a library of PCGDMA-derived networks. However, it should be underlined very low drug-loading (<0.8 wt %) of this network which was obtained by the swelling technique.[23,24] The further step will be development of biodegradable shape-memory terpolymer with a drug, which could be used as biodegradable shape-memory drug eluting stent for significant reduction of restenosis. There have not been published data on shape-memory poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) with sirolimus. Therefore, the aim of our study was to analyze the effect of drug incorporation into poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) on physicochemical and mechanical properties, degradation, and shape-memory effect of the terpolymer. For this purpose, sirolimus was incorporated into poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) by injection molding method.

MATERIALS AND METHODS

Synthesis and Characterization of Terpolymer

Poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) (Ter) was used to prepare matrix with sirolimus (rapamycin) (Ter+Sir). Terpolymer were synthesized according to the method described previously.[20] Briefly, the synthesis was performed in bulk by ring opening polymerization (ROP) of glycolide (Purac), L,L-lactide (Purac), and TMC (Boehringer Ingelheim) at 120°C for 72 h at argon atmosphere. Zirconium (IV) acetylacetonate ($Zr(acac)_4$) (Aldrich) was used as a non-toxic initiator with an *I*/*M* molar ratio of 1/1200. The obtained materials were precipitated with methyl alcohol to remove unreacted monomers and then dried at 50°C under vacuum.

The polymers were characterized before and after processing as well as during degradation according to the following techniques:

Changes in the chain microstructure and in the terpolymer composition were monitored on the basis of ^1H- and ^{13}C-NMR spectroscopy. Spectra were recorded with Bruker-Avance II Ultrashield Plus spectrometer operating at 600 MHz (^1H) and

150 MHz (^{13}C), using $CDCl_3$ as a solvent. Spectra were obtained with 32 scans, 11 μs pulse width, and 2.65 s acquisition time for ^{1}H-NMR. For ^{13}C-NMR spectra were obtained with 20,000 scans, 9.4 μs pulse width, and 0.9 s acquisition time.

The molar mass and molar mass distribution of the obtained terpolymer were determined by gel permeation chromatography (GPC) with a Physics SP 8800 chromatograph (tetrahydrofuran was used as the eluent, the flow rate was 1 mL/min, and Styragel columns and Shodex SE 61 detector were used). The molar masses were calibrated with polystyrene standards.

Thermal properties were determined using TA DSC 2010 differential scanning calorimeter (DSC) (TA Instruments, New Castle, DE). The instrument was calibrated using high purity indium and gallium. The specimens were heated from −100 to 200°C under a nitrogen atmosphere (flow = 50 mL/min) at heating rate of 20 deg/min. The melting temperature (T_m) of the composites was determined from 1st heating run as the peak maximum of melting endotherm. The glass transition temperature (T_g) was determined as the midpoint of heat capacity change of amorphous sample obtained by quenching from melt to liquid nitrogen.

Preparation and Characteristic of Terpolymer Matrices

Drug-free matrices and matrices with 7 wt % of sirolimus (LC Laboratories) were prepared by injection molding method (Thermo Hake MiniLab extruder and MiniJet mini injection molder). Before injection, polymers were grinded and dried for a week at 23°C, 80 mbar. The polymers were processed at the melting temperature of terpolymer (117°C). The samples were formed in bone-shape bars ISO 527-2 (1BA) using MiniJet piston injection molding system (Thermo-Haake). The obtained polymer bars were analyzed by means of NMR, DSC, GPC. The mechanical properties of samples were determined using tensile testing machine Instron 4204, crosshead section rate was 20 mm/min. All the composites were tested at ambient temperature (+23°C).

Analysis of Shape-Memory Properties. The shape-memory behavior was tested by means of the following procedure of deformation and recovery. Recovery rate (R_r), was calculated from the following equation:

$$R_r(\%) = \left[\frac{L_m - L_r}{L_m - L_0}\right] \times 100,$$

where L_m is the length of maximally elongated sample; L_r is the length of the sample after shrinkage; L_0 is the length of the sample before deformation (elongation). First, the bone-shape bars ISO 527-2 (1BA) were stretched at 40°C up to 100% deformation by means of Instron dynamometer. The deformed sample at temporary shape was fixed by quenching the sample at −12°C. Then, the samples were placed in a water bath (37°C) and allowed to shrink (recover the permanent shape). At designated time intervals, the length of the samples was measured to determine the recovery rate.

Mechanical Analysis. The mechanical properties of the samples were determined using tensile testing machine Instron 4204, crosshead section rate was 20 mm/min. The samples were formed in bone-shape bars ISO 527-2 (1BA) using MiniJet piston injection molding system (Thermo-Haake). All composites were tested at ambient temperature (23°C). Respective values were calculated as average from five (tensile test) measurements.

Morphology Analysis. Materials were analyzed at magnification ×10 using optical microscope (OM) (bresser binolux microscope). The images were processed using "Makroaufmass programm" software.

In Vitro Degradation and Drug Release Study

Degradation of Ter and Ter+Sir bars (5 mm × 5 mm; 1.5 mm thick; ≈ 40 mg) was conducted in 3 mL of 0.01*M* phosphate buffered saline (PBS, pH 7.4) at 37°C for 15 weeks under continuous agitation at 240 rpm. Moreover, the Ter+Sir bars were subjected for real time (37°C) and accelerated release (70°C) study. The aim of accelerated release study conducted for 5 weeks was detailed analysis of the initial period of release process that may results in a burst effect. After sampling at the predetermined intervals, buffer was replaced to maintain the sink condition. The samples were collected for HPLC study to analyze the amount of released drug. The degradation rate was analyzed on the basis of weight loss [%]. The percentage of weight loss (W_L %) was calculated according to the following equation: $W_L\ (\%) = [(W_0 - W_{dry})\ /\ W_0] \times 100$, where W_0 is the initial weight and W_{dry} the residual weight of the films dried under vacuum. Additionally, degradation process was characterized by means of NMR and GPC.

RESULTS AND DISCUSSION

The analysis of sirolimus incorporation in poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) by injection molding method on physicochemical, mechanical properties, and shape-memory effect was conducted. Moreover, degradation of drug-free terpolymer matrix and matrix with sirolimus was compared. Changes of terpolymer composition and chain microstructure during degradation were analyzed in detail by means of NMR spectroscopy.

Table I. Characteristics of Drug Free Terpolymer (Ter) and Terpolymer with Drug (Ter+Sir) Before and After Processing

Kind of polymer	Mn (kDa)	*D*	F_{LL}	F_{GG}	F_{TMC}	T_g[a] (°C)	T_{m1}[b] (°C)	ΔH_{m1}[b] (J/g)	T_{m2}[b] (°C)	ΔH_{m2}[b](J/g)
Ter before processing	26	2	66.5	11.3	22.2	43	117	9.4	-	-
Ter processed	26	2	67.6	10.3	22.1	41	105	3.2	-	-
Ter+Sir processed	26	2	67.4	10.7	21.9	41	95	1.3	189	1.1

[a] Obtained by DCS (second heating).
[b] Obtained by DSC (first heating).
F_{LL}, F_{GG}, F_{TMC}, content of lactide, glycolide, or carbonate in terpolymer, respectively (molar percentage); M_n, number-average molar mass; *D*, molar-mass dispersity; T_g, glass transition temperature, T_m, melting temperature, ΔT_m, melting enthalpy.

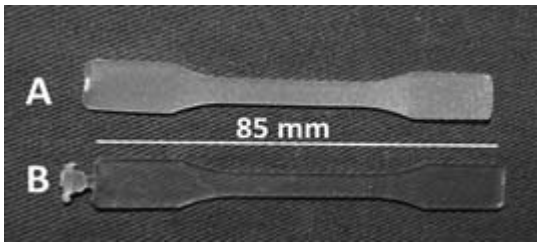

Figure 1. Comparison of tensile test bone-shape samples: (A) composite of terpolymer with 7% wt/wt sirolimus content, (B) neat terpolymer.

The Influence of Processing and Incorporation of the Drug Molecules on Terpolymer

Poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) has been selected for the study because of biodegradation, biocompatibility, and shape-memory effect.[9] This is an interesting material for self-expanding drug eluting stent. However, the effect on drug incorporation must be evaluated. Table I presents characteristics of poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) (Ter) before and after injection molding process. The comparison of drug-free terpolymer (Ter before processing, Ter processed) and terpolymer with initial concentration of 7% weight of sirolimus (Ter+Sir) allows to analyze two effects: processing and drug incorporation.

Drug-free terpolymer after injection molding characterized insignificant changes in terpolymer composition (decrease of glycolidyl units and increase of lactidyl and carbonate units) and thermal properties (decrease of glass transition temperature and melting temperature). Degradation of materials during processing was not observed, so molar mass (M_n) and molar mass dispersity (D) was unchanged. It was reported in the literature that encapsulation of the drug or other additives may cause plasticization of polymers.[25] The same effect was observed in the present study. Incorporation of low molecular weight sirolimus particles into poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) chain resulted in lowering the T_m value. It weakens the intermolecular interactions between molecules of polymers by separating them from one another in space.

Comparison of terpolymer before and after processing is presented in section below (Thermal and mechanical characterization).

Morphology. Testing bars made of the terpolymer and its composite with sirolimus (Figure 1) were analyzed with optical microscopy technique (Figure 2). Microscopic analysis revealed that sirolimus was not dissolved in polymer matrix during its thermal processing. The ×10 pictures magnification of the obtained composite showed particles of sirolimus existing in composite as aggregated crystals (Figure 2). The material was processed at the T_m of terpolymer (117°C); however, the melting point of sirolimus is much higher (189°C), which caused the formation of the composite.

Thermal and Mechanical Characterization. Morphology analysis of terpolymer bars using optical images revealed two phases: the crystals of sirolimus and terpolymer matrix. This structure was also proven by DSC thermal analysis (Table I). At the 1st run of thermal analysis of the composite, two melting endotherms were observed: $T_{m1} = 95°C$ ($\Delta H = 1.3$ J/g) and $T_{m2} = 189$ ($\Delta H = 1.1$ J/g). The second endotherm correlated with temperature of melting and endotherm of pure sirolimus. Polymer with drug was processed below melting temperature of sirolimus, therefore composite structure was expected. The 2nd run of thermal analysis revealed that the value of glass transition temperature (T_g) of the composite and neat terpolymer was in the same temperature region. This result suggested the absence of interaction between substrates. Apparently, sirolimus and terpolymer are immiscible in prepared ratio. The values of stress and strain at the break were lower in case of composite [Figure 3(A,B)]. Although stress value of the composite decreased, the stiffness for the composite and neat polymer was comparable [Figure 3(C)]. The explanation of this result could be the notch effect caused by filler aggregation which was observed using optical microscopy.

Shape-Memory Properties. The shape-memory properties were compared for neat polymer and it's composite with sirolimus. It was determined that incorporation of drug molecules (7 wt %) did not change shape-memory properties of terpolymer. Figure 4 presents percentage recovery rate of both materials. The purpose of the experiment was to analyze the effect of addition of the drug on the shape-memory properties of poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate). Therefore, we conducted the measurements at the temperature slightly lower than the midpoint of terpolymer T_g range, which slowed down the process of recovery of the permanent shape and allowed to determine the differences between these two materials. Actually, rapid permanent shape recovery is preferred in medical application (in a time frame of seconds), which was confirmed for

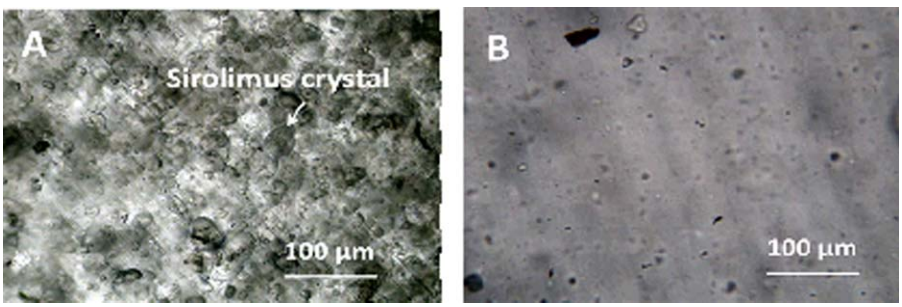

Figure 2. Optical microscopy images of (A) composite of terpolymer with 7% wt/wt sirolimus content—magnitude 10×, (B) neat terpolymer—magnitude 10×. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

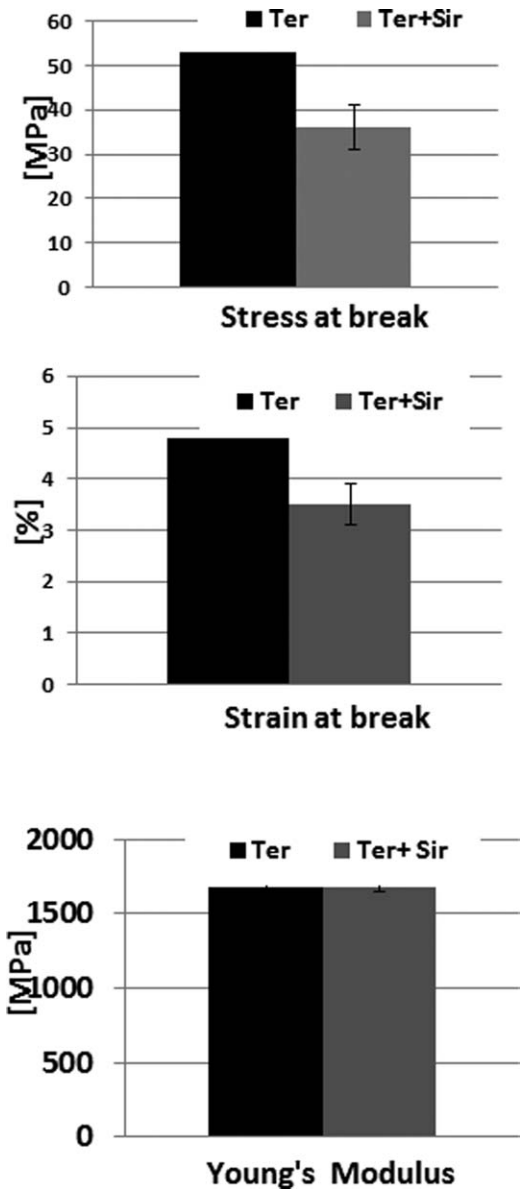

Figure 3. Mechanical properties of obtained composite: (A) The comparison of stress at the break values of neat terpolymer (Ter) and its composite with sirolimus (Ter+Sir), (B) The comparison of strain at the break values of neat terpolymer (Ter) and its composite with sirolimus (Ter+Sir), (C) The comparsion of Young's Modulus values of neat terpolymer (Ter) and its composite with sirolimus (Ter+Sir).

poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) in the previous study.[9] Figure 4 demonstrates similar shape-memory properties of Ter and Ter+Sir at 37°C, with R_r of 100%, and shape recovery within 40 min. It is worth noting the high reproducibility of the results—there were not observed significant differences between samples.

In Vitro Degradation and Drug Release Study

Degradation process of materials *in vitro* (neat terpolymer and its composite with sirolimus) was conducted in PBS (pH 7.4, 37°C) for 15 weeks. The changes in the polymer during 15 weeks of degradation are presented in Table II and discussed below.

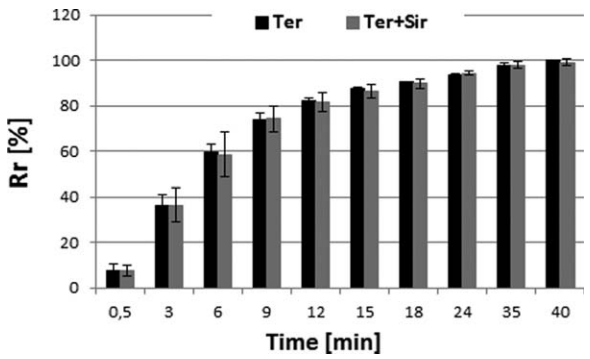

Figure 4. Comparison of recovery rate of neat terpolymer and its composite with sirolimus (Ter+Sir) (Data represent mean value ± S.D., $n = 5$).

NMR Analysis of Polymer Chain Microstructure During Degradation. On the basis of poly(lactide-*co*-glycolide-*co*-trimethylene carbonate) ^{1}H-NMR spectra, (Figures 5 and 6) changes of the monomer units distribution in Ter and Ter+Sir during degradation were evaluated. Signals in the NMR spectra were assigned to the appropriate sequences in the polymer chain according to previously described procedure.[17]

Ter and Ter+Sir initially contained predominant amount of the lactidyl units for both materials (above 67 mol %) as well as low amount of the glycolidyl (~10 mol %) and the trimethylene carbonate units (~21 mol %). Ter and Ter+Sir chain microstructures consists of long lactidyl ($L_{LL} = 10.14$ and 10.19) and short glycolidyl microblocks ($L_{GG} = 1.96$ and 1.93). In the case of composite (Ter+Sir), the length of the carbonate microblocks was slightly higher.

During degradation process, lactidyl units content slightly decreased and carbonate units content increased for both shape-memory materials. Changes were stable and proceeded evenly. Amount of glycolidyl units exhibited insignificant fluctuations (Figure 7).

On the basis of poly(lactide-*co*-glycolide-*co*-trimethylene carbonate) ^{13}C-NMR spectra (Figures 8 and 9), changes in the chain microstructure were observed.

The changes of average length of microblocks during degradation of Ter and Ter+Sir are presented in Figure 10. Average length of lactidyl microblocks of Ter+Sir increased from 10.19 at the beginning of the degradation process to 13.15 after 15 weeks of degradation. In the case of Ter the same phenomena was observed: average length of lactidyl microblocks increased from 10.14 at the beginning of the degradation process to 13.04 after 15 weeks. Simultaneously, carbonate microblocks increased for both materials (from 4.81 to 6.21 for Ter+Sir and from 3.74 to 6.38 for Ter). No significant changes during degradation were observed for average length of glycolidyl unit.

Changes of terpolymer composition and copolymer chain microstructure during degradation were stable and even for both materials. Average length of lactidyl and glycolidyl

Table II. Characteristic of Drug Free Terpolymer (Ter) and Terpolymer with Drug (Ter+Sir) Before Degradation and After 2, 5, and 15 Weeks of Degradation

Sample	Degradation time (week)	Mass (%)	M_n $\times 10^3$	F_{LL} (%)	F_{GG} (%)	F_{TMC} (%)	L_{LL}	L_{GG}	L_{TMC}
Ter+Sir	0	100.0	26.0	67.4	10.7	21.9	10.2	1.9	4.8
Ter+Sir	2	100.0	17.0	66.6	10.9	22.5	10.5	2.0	5.0
Ter+Sir	5	97.8	8.0	66.3	11.1	22.6	11.2	1.9	5.6
Ter+Sir	15	57.7	1.8	64.8	7.8	27.5	13.2	2.1	6.2
Ter	0	100.0	26.0	67.6	10.3	22.1	10.1	2.0	3.7
Ter	2	97.8	17.0	66.5	10.9	22.6	9.7	2.0	4.9
Ter	5	96.8	6.0	66.2	11.0	22.9	10.7.	1.5	5.6
Ter	15	47.9	1.5	65.7	6.6	27.7	13.0	2.1	6.4

M_n, number-average molar mass, F_{LL}, F_{GG}, F_{TMC}, content of lactide, glycolide, or carbonate in terpolymer, respectively; L_{LL}, L_{GG}, L_{TMC} the average length of lactidyl, glycolidyl, carbonate microblocks, respectively.

microblocks for Ter and Ter+Sir exhibited similar values and length of carbonate microblocks was slightly higher for Ter+Sir.

Weight Loss and Water Absorption Study. The progress of the degradation of both tested materials was analyzed on the basis of weight loss and water absorption. Weight loss was very similar for both polymeric materials (Table II). For the first 5 weeks of degradation weight loss was negligible. Significant change was observed after 15 weeks of degradation: about 50% weight loss (57.7% for Ter+Sir and 47.8 for Ter). Faster degradation for polymer without sirolimus was noticeable.

Although changes in weight loss between Ter and Ter+Sir were observed, M_n changes were very similar for both materials. From the beginning of degradation, regular M_n loss was observed. After 15 weeks of degradation, only 6% of the initial value of M_n remained. The process of M_n decrease was slightly faster for polymer without sirolimus.

Drug incorporation into polymeric chain caused changes in hydrophilicity of the obtained material. Sirolimus exhibits a hydrophobic character what influenced slower degradation rate of the composite, observed in the present study.

Drug Release Study. The *in vitro* process of sirolimus release from poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) in first weeks of incubation was conducted in real-time at 37°C and at elevated temperature (70°C). The accelerated *in vitro* studies performed at elevated temperatures has been gaining popularity as a means of shortening long-term release studies that normally take several months.[26] We analyzed the initial period of drug release because of the biggest risk of burst effect. Adsorption of drug substance on the surface of matrix is considered as major reason of rapid initial release.[27] In case of polymer-drug composite, burst effect may be caused by release of drug cluster located at the surface or close to surface of matrix. The amount of released drug was analyzed by means of HPLC. According to the obtained results, drug release from poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) was very slow and sustained without rapid release (Figure 11), which is recommended for long-term application. After 5 weeks of degradation in real-time release study performed at 37°C, only 2% of sirolimus was released (S.D ± 0.08, $n = 3$), which correlated with degradation data. Much faster degradation and drug release is expected *in vivo*, because poly(trimethylene carbonate) undergoes enzymatic degradation.[28,29] Moreover, the material is developed for stent that is significantly thinner, which enables faster external fluid inflow and acceleration of diffusion of drug. The diffusion of water from the release medium into the polymer matrix is essential to initiate drug release.[16] Slightly faster

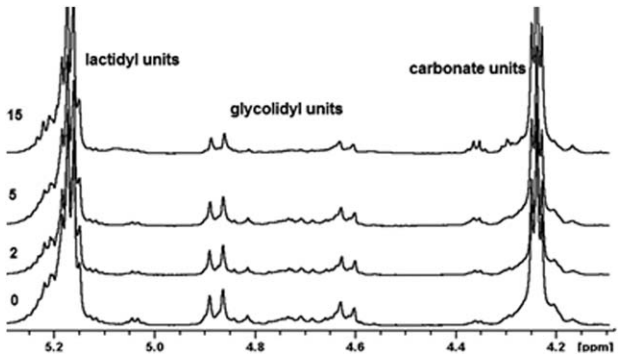

Figure 5. ^{1}H-NMR spectra (600 MHz, CDCl3) of Ter after 0, 2, 5, 15 weeks of degradation. Methine proton region of lactidyl units and methylene proton region of glycolidyl and carbonate units.

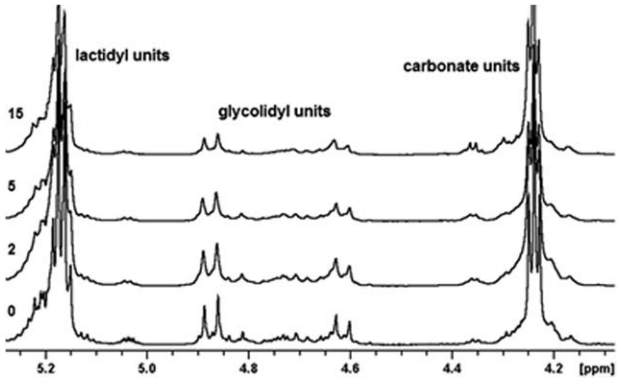

Figure 6. ^{1}H-NMR spectra (600 MHz, $CDCl_3$) of Ter+Sir after 0, 2, 5, 15 weeks of degradation. Methine proton region of lactidyl units and methylene proton region of glycolidyl and carbonate units.

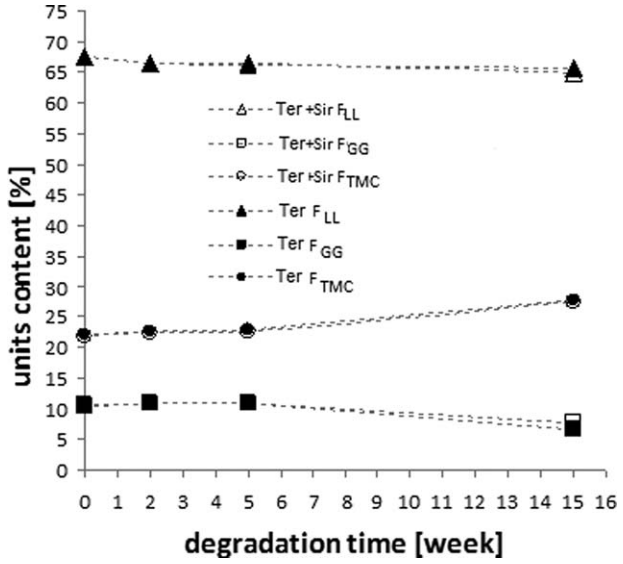

Figure 7. Changes of units content during degradation of Ter and Ter+Sir.

release of another hydrophobic drug—paclitaxel from the same kind of terpolymer was observed for thinner matrices.[19] Much faster release was shown at 70°C as a result of faster degradation. However, it should be underlined that even at elevated temperature, the drug release rate and profile was sustained without rapid burst of drug. Both, the real-time and accelerated experiment confirmed usefulness of poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) for sirolimus release.

CONCLUSIONS

Incorporation of antirestenotic drug into SMP biodegradable stent seems to be an interesting solution because of possibility to combine the mechanical support that provides stent and also drug elution. In the present study, sirolimus was incorporated into poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) by injection molding method and the effect on drug incorporation has been evaluated. Poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) has been selected for the study because of biodegradation, biocompatibility, and shape-memory effect. Drug-free terpolymer after injection molding characterized insignificant changes in terpolymer composition. Degradation of materials during processing was not observed. The influence of processing on physicochemical, mechanical properties, and shape-memory effect was studied: the mechanical test of terpolymer revealed that addition of the sirolimus influenced polymer strength; stress value of the composites decreased, the stiffness for composite and neat polymer was comparable. It could be explained by the notch effect caused by filler aggregation which was observed using optical microscopy. On the other hand, incorporation of drug molecules did not change shape-memory properties of terpolymer: similar shape-memory property of Ter and Ter+Sir were observed at 37°C, with R_r of 100%. Additionally, degradation of drug-free terpolymer matrix and matrix with sirolimus was compared. On the basis of poly(lactide-*co*-glycolide-*co*-trimethylene carbonate) ^{1}H- and ^{13}C-NMR spectra changes of the monomer units distribution and changes in the chain microstructure during Ter and

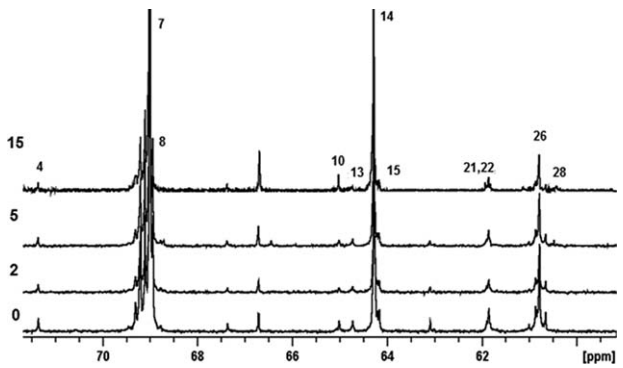

Figure 8. ^{13}C-NMR spectra (150 MHz, $CDCl_3$) of Ter during 0, 2, 5, 15 weeks of degradation. Methine carbons region of lactidyl units and methylene carbons region of glycolidyl and carbonate units. 4-TLLLL+TLLLT, 7-LLLL, 8-LLGG, 1-TTG+GGTGG+TGTGG,13-GGTGT+TTL+LTT,14-TTT+TTT+TTG, 15-TTGG, 21-GGTT, 22-GGTGT+GGTGG, TGTGG+TGTGT, 24-TGGGG+TTGG, 25-TGGT, 26-GGLL, 27-GGGG, 28-LGL.

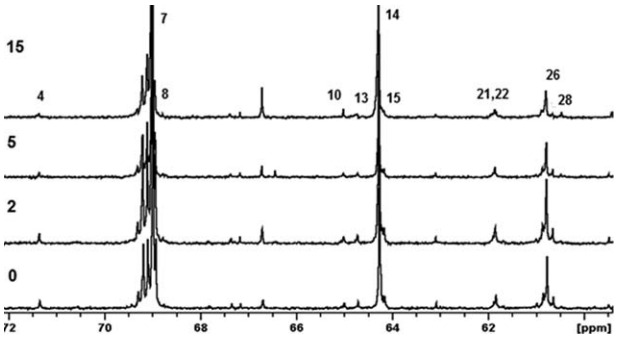

Figure 9. ^{13}C-NMR spectra (150 MHz, $CDCl_3$) of Ter+Sir during 0, 2, 5, 15 weeks of degradation. Methine carbons region of lactidyl units and methylene carbons region of glycolidyl and carbonate units. 4-TLLLL+TLLLT, 7-LLLL, 8-LLGG, 1-TTG+GGTGG+TGTGG,13-GGTGT+TTL+LTT,14-TTT+TTT+TTG, 15-TTGG, 21-GGTT, 22-GGTGT+GGTGG, TGTGG+TGTGT, 24-TGGGG+TTGG, 25-TGGT, 26-GGLL, 27-GGGG, 28-LGL.

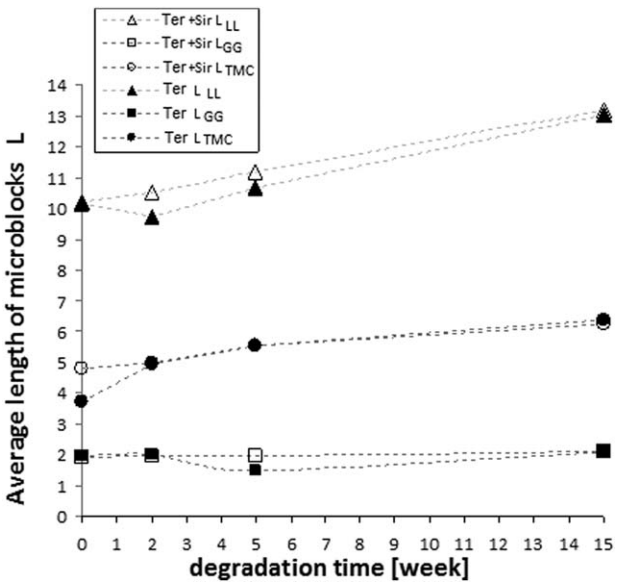

Figure 10. Changes of average length of microblocks during degradation of Ter and Ter+Sir.

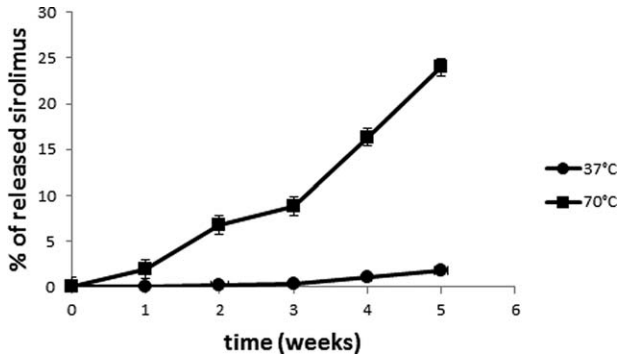

Figure 11. Cumulative release profiles of sirolimus from poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) during 5 weeks of degradation at 37°C and 70°C ($n = 3$).

Ter+Sir degradation were evaluated. During degradation process, lactidyl units content slightly decreased and carbonate units content increased for both shape-memory materials. Changes were stable and even. Average length of lactidyl microblocks of Ter+Sir and Ter increased. Simultaneously, carbonate microblocks appeared longer for both terpolymers. Changes during degradation were stable and even for both materials. Weight loss and M_n changes were very similar for both polymeric materials. In the last measured period of experiment after 15 weeks of degradation, about 50% weight loss was observed and only 6% of the initial value of M_n remained. The drug release process proceeded in sustained and regular manner.

The analyzed shape memory of poly(L-lactide-*co*-glycolide-*co*-trimethylene carbonate) with sirolimus presents potential for medical or/and pharmaceutical applications, however further study is needed, especially presenting biological activity, both, *in vitro* on cell culture and *in vivo*.

ACKNOWLEDGMENTS

This study was financially supported by grant of Polish Ministry of Science and Higher Education No N N405 682340

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