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Design and *in vivo* assessment of polyester copolymers based on trimethylene carbonate and ε-caprolactone

Chong Zhang, Danhua Liu, Xiaowei Zhang, Ping Wang, Zhu Zhen, Jianxin Li, Dongxu Yi, Ying Jin, Dan Yang

Department of Pharmaceutics, Liaoning Research Institute of Family Planning, Shenyang 110031, People's Republic of China

Chong Zhang was the designer of the experiment, an experimenter, and the author and reviser of this article. Xiaowei Zhang, Ping Wang, and Zhu Zhen were experimenters. Danhua Liu was an experimenter and a corrector of this article.

Correspondence to: D. Liu (E-mail: danhliu@163.com)

ABSTRACT: Poly(trimethylene carbonate-*co*-caprolactone) (PTCL) copolymers with various trimethylene carbonate ratios were synthesized by ring-opening polymerization and were used to prepare implants for an *in vivo* experiment. Medical silicone rubber was used as the control. Implants were prepared by compression molding with a laboratory instrument. The properties of these copolymer implants were investigated. PTCL implants and silicone rubbers were implanted subcutaneously in the dorsal region of New Zealand white rabbits. The assessment was performed 1, 2, 3, 4, 5, 6, 7, and 8 months postoperatively by the determination of the weight loss, water uptake, thermal behavior, molecular weight of the explanted implants, and histological examination. During the 8-month implantation, the value of maximum weight loss was found to be 25%. A continuous decrease in the molecular weight occurred. No remarkable tissue reactions were observed during degradation, and foreign-body reactions were similar to those of silicone rubbers, which are commercially available materials. In this study, we aimed to indicate the likely clinical behavior but good biodegradable properties of PTCL copolymers compared to those of silicone rubber. This may open a new avenue of application for them in the drug industry. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41815.

KEYWORDS: biocompatibility; biomedical applications; polyesters

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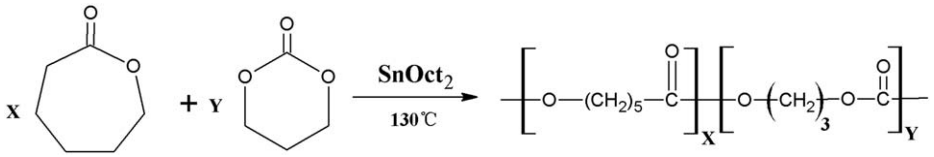
INTRODUCTION

Biodegradable polymers, such as polyglycolide,[1–3] polylactide,[4–7] poly(ε-caprolactone) (PCL),[8–10] and poly(trimethylene carbonate) (PTMC),[11–13] have attracted more attention during recent decades. These polymers have very promising applications in the biomedical field, including in tissue engineering, drug-controlled release, gene delivery, and suture materials. Polymers used in the biomedical field must generally meet strict requirements, and consequently, an improvement in their properties appears necessary to extend their application range.[14,15]

PTMC is an amorphous elastomer with a glass-transition temperature (T_g) at about −14°C. PTMC exhibits good mechanical performance,[16] including a high flexibility and high tensile strength. It degrades *in vivo* by surface erosion without the release of acidic species.[17] PCL has been used in several Food and Drug Administration approved products[18] because of its good solubility, excellent blend compatibility, relative nontoxicity, sufficient mechanical strength, and high permeability for many drugs; it offers promising potential for load-bearing applications in drug-delivery systems. However, because of its high crystallinity,[19,20] PCL degrades rather slowly and is less biocompatible with soft tissue, and this restricts its further clinical application.

The copolymerization of polyesters with polycarbonates is a means for adjusting the degradation rate and other properties.[21,22] 1,3-Trimethylene carbonate (TMC) has attracted much attention because it is used as a softening component together with glycolide to prepare copolymer sutures known as Maxon.[23–25] Various copolymers of lactide and TMC have been reported.[26–28] These carbonate–ester copolymers, with their outstanding tensile strength and flexibility, have been investigated for applications as heart constructs and nerve regeneration guides, cartilage implant and wound dressings, sustained drug release carriers, and stent covers. The characteristics of these candidates for medical applications can be tailored by the adjustment of the monomer ratio and the resulting sequences of TMC and other monomers. Therefore, TMC copolymers have found their place in the field of biomaterials.



Scheme 1. Reaction scheme for the synthesis of the PTCL copolymers.

In our previous work,[11,29,30] various polymers and copolymers were prepared by the variation of the chemical composition, catalyst ratio, and so on. However, no detailed study on the degradation properties and histological examination of various ratio poly(trimethylene carbonate-*co*-caprolactone) (PTCL) copolymers has been reported thus far.

The purpose of this research was to evaluate the material–tissue response of various random copolymers in a rabbit implantation model compared to silicone rubber as control. We incorporated PCL segments into the PTMC backbone to produce PTCL random copolymers. Stannous octoate ($SnOct_2$) was used as catalyst. $SnOct_2$ is the most commonly used initiator in the polymerization of cyclic esters because of its nontoxicity and high efficiency.[31,32] $SnOct_2$ was approved by the Food and Drug Administration as a food additive.[33] We considered that the incorporation of PCL segments into the PTMC backbone would not only modify the chemical nature of the polymer but also hinder the crystallinity of the PCL segments and, therefore, control the degradation rate of the copolymer. Copolymer implants with a series of compositions were characterized. Finally, PTCL copolymers derived from the ring-opening polymerization of corresponding cyclic monomers were found to be good materials for their favorable biocompatibility, low toxicity, and biodegradability. Degradable biomaterials do not need subsequent surgical removal after they are implanted in bodies; this a feature superior to nondegradable biomaterials such as silicone rubber. The polyester copolymers constitute a new class of biomaterials, which will attract growing interest for biomedical applications, especially for controlled drug-delivery systems.

EXPERIMENTAL

Materials

ε-Caprolactone (CL; Alfa Aesar) was purified by drying over CaH_2 (Sinopharm Chemical Reagent Co., Ltd., China) and distilled under reduced nitrogen pressure. Polymer-grade TMC (Jinan Daigang Biomaterial Co., Ltd., China) was used without further purification. Formaldehyde and toluene were purchased from Sinopharm Chemical Reagent Co., Ltd. (China). Toluene was refluxed over sodium benzophenone and distilled under nitrogen before use. $SnOct_2$ (Sigma-Aldrich) was used as received. A toluene solution of $SnOct_2$ (1.0 mol/L) was prepared. Medical silicone rubber was received from Jinan Chensheng Medical Silicone Rubber Product Co., Ltd. (China). All other reagents were high performance liquid chromatography (HPLC) or analytical grade.

Synthesis of the PTCL Copolymers

The PTCL copolymers were synthesized by a ring-opening polymerization method, as previously described.[11,29,30] Briefly, the polymerizations were conducted in evacuated and sealed glass ampules with a toluene solution of $SnOct_2$ as a catalyst. Polymerizations were carried out for 24 h at 130 ± 2°C (Scheme 1). At monomer/catalyst molar ratios of 5000, 4000, and 3000, PTCL copolymers with TMC molar contents ranging from 70 to 90% were synthesized. The resulting PTCL copolymers were first dissolved in chloroform and reprecipitated from the filtrate with excessive cold methanol. After they were washed in methanol several times, the polymers were dried under reduced pressure until a constant weight was reached.

Preparation of the Copolymer Implants

The PTCL copolymers were melt-pressed with a laboratory instrument (XLB, Third Qingdao Rubber Machinery Factory, China) at 140°C to form implants with a dried mold, into which a predetermined size of polyimide film had been placed. A kind of mold with six cavities was used in this research. Each cavity, with dimensions of 42 × 3 × 1.5 mm^3, was used to prepare the implants. The implants were cooled to room temperature under pressure and then cut to a designated length of 40 mm for *in vivo* testing. We created different implants (C1, C2, and C3) by changing the molar ratio of TMC to CL (Table I).

Implantation

New Zealand white rabbits weighting about 2 kg were used in this study. All of the rabbits were housed in sterilized cages with sterile food and water and filtered air in the animal house of our institution. After shaving and disinfection, subcutaneous pockets were made to the right and left of four 1-cm midline incisions on the back of the rabbit. A single implant was placed in each pocket. Implants were sterilized by incubation in 70 vol % ethanol solution for 15 min followed by two rinsing steps of 5 min in sterile water before operation. After surgery, the animals were housed in a temperature- and humidity-controlled room with 12-h light/dark cycles, and they had access to water and standard rabbit food *ad libitum*. At 1, 2, 3, 4, 5, 6, 7 and 8 months after implantation, three rabbits were sacrificed each time. Three of each implant were removed from the rabbits. For the 8 months, the rabbits were weighted at each time point. All experiments were approved by local Ethics Committee for Animal Research and were performed according to Guidelines for the Care and Use of Laboratory Animals.

Weight Loss and Water Uptake

The percentage weight loss of the degraded copolymer implants was calculated from the weights before and after degradation according to the following equation:

$$W_{\text{loss}}\ \% = \frac{W_{\text{before}} - W_{\text{after}}}{W_{\text{before}}} \times 100\% \quad (1)$$

where W_{loss} is the percentage weight loss of the degraded copolymer implant, W_{before} represents the weight of the pristine

Table I. Characterization of the Copolymer Implants

Copolymer	Implant	TMC/CL (mol %)	$M_n \times 10^{-5}$ (g/mol)	Polydispersity index	$[\eta]$ (dL/g)
PTCL	C1	90:10	243,264	1.11	3.2
	C2	80:20	248,832	1.11	4.1
	C3	70:30	237,270	1.12	3.12

η = intrinsic viscosity.

copolymer implant before implantation, and W_{after} represents the remaining weight of the implant after drying.

The water uptake ($W_{water\text{-}uptake}$) was defined as follows:

$$W_{water\text{-}uptake}\ \% = \frac{W_{wet} - W_{after}}{W_{after}} \times 100\% \quad (2)$$

where W_{wet} represents the weight of the wet implant after blotting.

Histological Evaluation

The specimens, including the surrounding tissue, were harvested from the surgical sites, and the tissue was fixed in 4% buffered formalin. Subsequently, the tissue was embedded in paraffin. The paraffin sections were stained with haematoxylin eosin and investigated with light microscopy. The evaluation of the tissue reaction was mainly based on the presence of foreign-body giant cells.

Gel Permeation Chromatography Analysis

The molecular weight of the implants and their distribution (polydispersity index) were measured by gel permeation chromatography with a Waters model 1515 isocratic HPLC pump with a Waters model 2414 refractive-index detector at a flow rate of 1.0 mL/min (eluent: tetrahydrofuran, 35°C). Polystyrene standards (Waters) were used for calibration. The polydispersity index is a measure of the width of the molecular weight distributions.

Differential Scanning Calorimetry (DSC)

Thermal analysis was conducted with a DSC 200 F3 Maia thermal analyzer (Netzsch, Germany). The weight of all of the samples was maintained between 5 and 6 mg. The reference material was a blank aluminum pan. The thermal properties of all of the samples were characterized at temperatures of −100 to 100°C under a nitrogen atmosphere at a heating rate of 10°C/min. The melting temperature was taken as the maximum of the endothermic melting peak from the heating scans.

RESULTS AND DISCUSSION

Macroscopic Observations

For all of the animals, no detectable hyperemia phenomenon, infection, or exudate was found after surgery; this indicated that the copolymer implants and medical silicone rubber exhibited good biocompatibility with the tissue. Also, no significant difference in appetite change at each time point was observed before and after surgery. The skin wounds of the rabbits were healed within 7 days, as shown in Figure 1. Figure 2 shows the weight curves of the rabbits as a function of time. We found that the weight of the rabbits increased gradually with increasing time up to 8 months. The results show that these materials *in vivo* had no effect on the animals' normal life.

Weight Loss and Water Uptake

The weight loss and water uptake were analyzed, and the results are shown in Figures 3 and 4, respectively. Figure 3 shows that the degradation process was pronounced. The curves show a continuous weight loss after surgery. The weight loss of the copolymer implants decreased during the first 6 months and, by 6 months, decreased slowly. The maximum value of the weight loss, as obtained from all of the copolymer implants, was 25% for the 8-month degradation process. Simultaneously, the number-average molecular weight (M_n) of all of the PTCL

Figure 1. Wound healing of a New Zealand rabbit after 7 days of implantation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

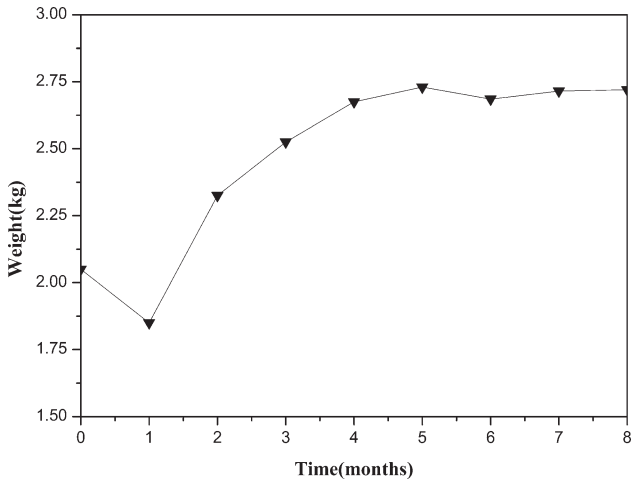


Figure 2. Weight data for rabbits over 8 months.

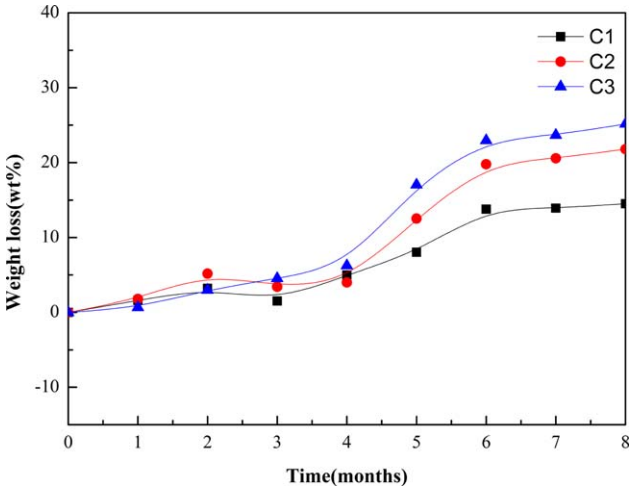


Figure 3. Weight loss of the PTCL implants as a function of the degradation time. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

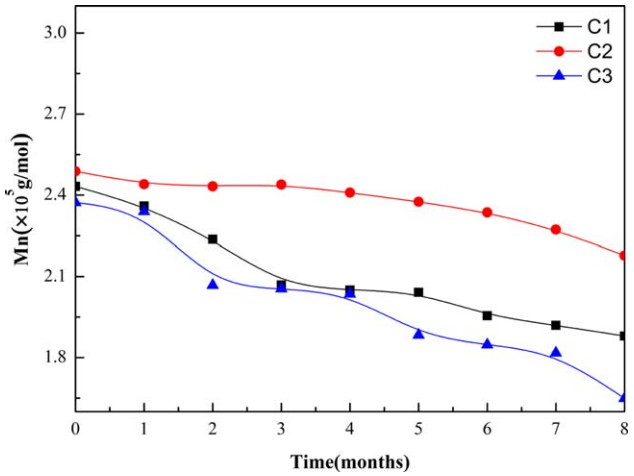


Figure 5. Molecular weight loss of the PTCL implants as a function of the degradation time *in vivo*. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

implants decreased slowly with degradation time, as shown in Figure 5. The decrease in the molecular weight began immediately after implantation.

The water absorption capacity and the degradability are the most important properties for biodegradable materials. One of the major drawbacks in the use of a material is its water absorption tendency. The diffusion of water into the implants resulted in increased degradation. The hydrophilicity or hydrophobicity of the material determines the water absorption, which is a key factor in regulating the rate of degrading materials, such as aliphatic polyesters. The water absorption increased over time and was similar in the different implants up to 8 months, at lower than 4%.

All of the copolymers exhibited both a low water absorption and a remarkable weight loss over the 8 months. No changes occurred in silicone rubber because of its nondegradable properties.

Thermal Properties

During the degradation process, no melting peak was found in the DSC curves. However, the T_g was pronounced. As expected, the PTCL copolymer implants showed decreasing T_g when the CL ratio increased from 10 to 30% before implantation, as shown in Figures 6–8. When the CL content in the initial copolymer implants increased, its T_g approached that of the PCL homopolymer, which usually shows a T_g −60°C.[34–36]

The value of T_g decreased slightly for all of the copolymer implants after degradation over 8 months, as shown in Figures 6–8. The phenomenon of decrease occurred because of the internal plastication effect of low-molecular substances resulting from degradation. When the low-molecular substances

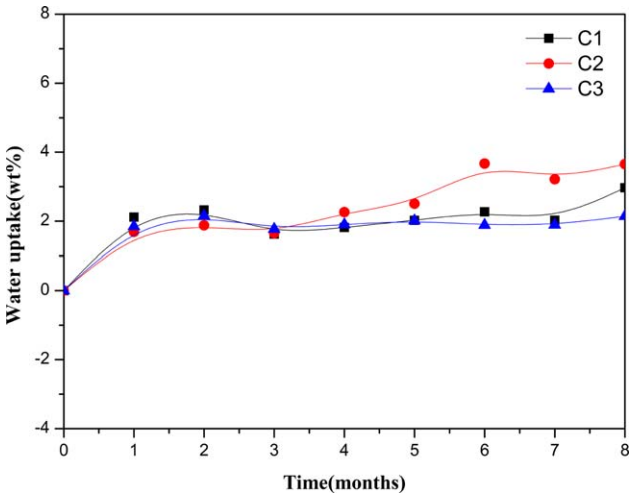


Figure 4. Water uptake during the degradation of the PTCL implants. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

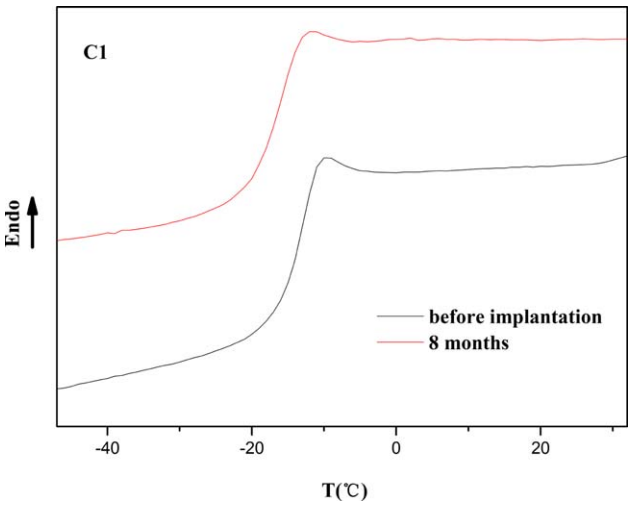


Figure 6. T_g of implant C1 before implantation and at 8 months (T = temperature). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

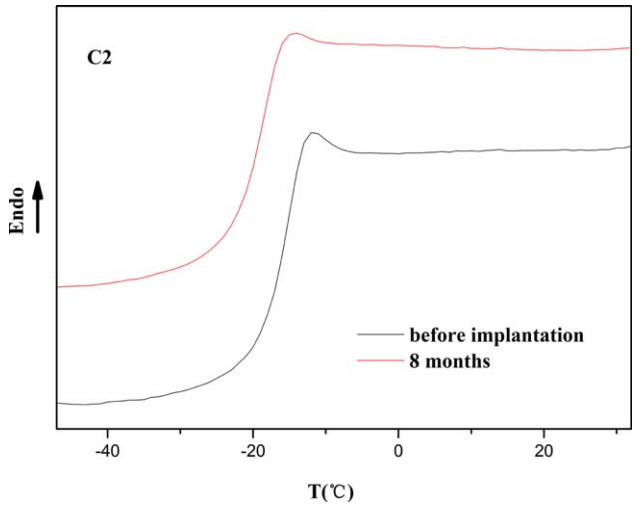


Figure 7. T_g of implant C2 before implantation and at 8 months (T = temperature). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

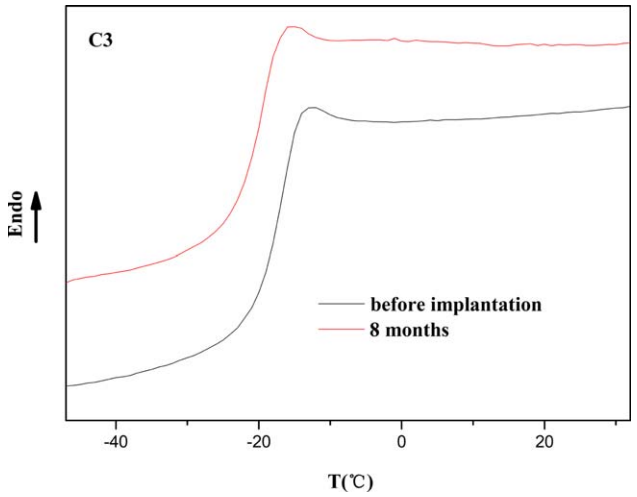


Figure 8. T_g of implant C3 before implantation and at 8 months (T = temperature). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

increased, the macromolecular chain presented better flexibility and mobility, and the intermolecular interaction decreased. On the other hand, degradation occurred mainly in the amorphous area[37–39] because of the inability of water and enzymes to penetrate the crystal zone of the copolymer implant. The random scission of the ester bonds by hydrolysis and enzymatic degradation caused a reduction in the molecular weight. Smaller chains were produced, which dissolved more easily and diffused through the copolymer carriers. This led to macromolecular segment rearrangement and an increase in the crystallinity. There were more caprolactone segments, and this resulted in a decrease in the T_g values of the copolymer implants.

Histological Evaluation

During the experiment, all of the rabbits remained in good health. No acute inflammation or necrosis and adverse tissue reactions were identified at any time period at the implant sites.

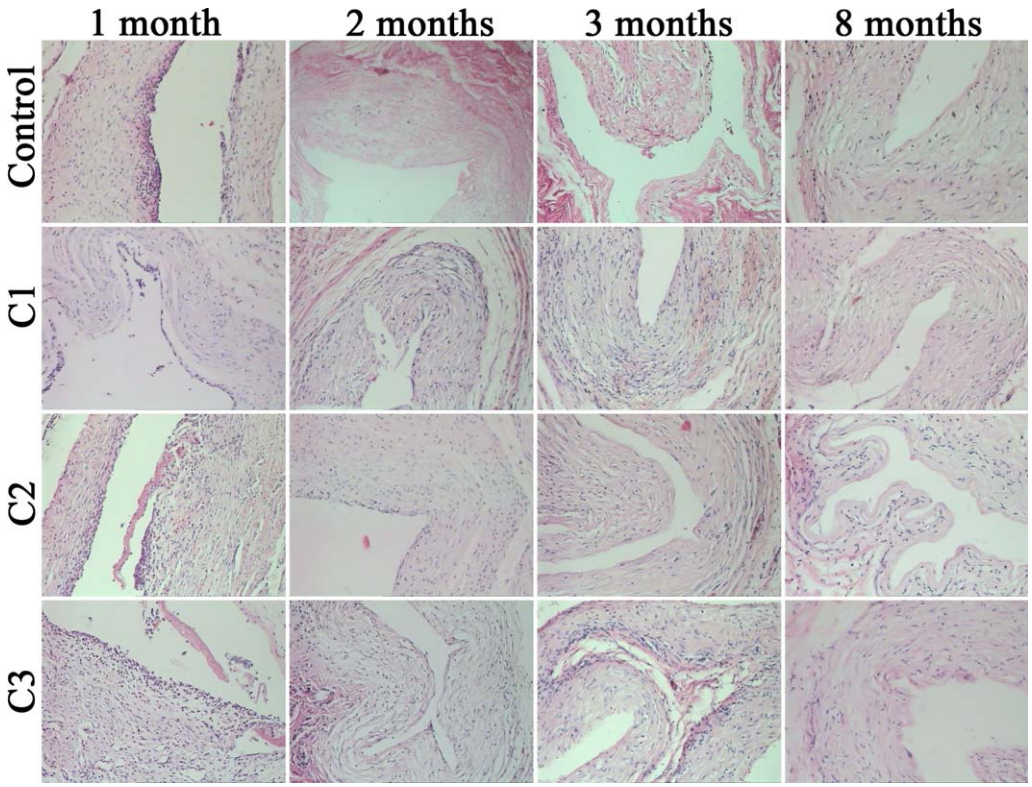


Figure 9. Histological micrographs of the implants with haematoxylin and eosin staining at 1, 2, 3, and 8 months. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 9 illustrates the optical microstructure of the interfaces between the implants and tissues stained by haematoxylin and eosin after 1, 2, 3, and 8 months of implantation. Histological observation showed that fibrous encapsulation occurred for all types of copolymer implants; this resulted from some degradation debris.

One month postoperation, no neutrophils were observed around the silicon rubber implants; this indicated that no obvious acute inflammation occurred. Some multinucleated foreign-body cells gathered around the copolymers and silicon rubbers (Figure 9). We reported that as a consequence of macrophage/biomaterial interaction, there was a fusion of adherent macrophages; this led to the formation of multinucleated foreign-body cells on the biomaterial surfaces. Fibroblasts in a particular orientation can be observed in the surrounding tissue; this illustrated that the fibrosis/fibrous capsule formed. Few neutrophils were observed around the copolymer implants at 1-month postimplantation. The inflammatory phase is a necessary prerequisite for healing. Therefore, it was difficult to assess whether the mild inflammatory response was due to the normal healing process or to the material's effect during the early stage of wound healing. However, not a large number of cells assembled at the surface of the materials; this could have shown that the materials studied had good biocompatibility *in vivo* with a mild inflammatory response.

After degradation for 2 months, multinucleated foreign-body cells disappeared at the material surface (Figure 9). No neutrophils were observed around the four kinds of materials, and this indicated that no obvious acute inflammation occurred.

In the tissue section images at 3 and 8 months after subcutaneous preparation, C1, C2, and C3 appeared similar to silicone rubber. All of the tissues were normal during the degradation process, and this indicated that the copolymer exhibited good biocompatibility with the surrounding tissues.

Inflammation and fibrous tissue encapsulation are normal host defense mechanisms to a foreign-body response.[40,41] The extent of the mild inflammatory response in this study may have depended on the type of injury; the size, shape, and the rate of copolymer degradation; and the chemical and physical properties of the copolymer.[42–45] The results clearly show that materials in this study were suitable for using *in vivo*.

CONCLUSIONS

The synthesis of PTCL copolymers was carried out by ring-opening polymerization at 130°C. The feed monomer composition of the synthesized copolymers was 90:10, 80:20, and 70:30.

A minimal inflammatory response was evoked by copolymer implants, and this gradually decreased with time as the fibrous rim matured and was similar to that of silicon rubber, which revealed highly satisfactory biocompatibility results for these materials for clinical use. As shown in the histological micrographs, residual copolymer was observed at all four time points because of the ongoing degradation process. As the degradation time increased, the weight loss and molecular weight curves provided information that the overall tendency of the synthesized biodegradable polymers was to degrade gradually during the observation period from 1 to 8 months. The maximum value of weight loss as obtained for all of the copolymer implants was 25% for the 8-month degradation process; this was a favorable result for long-term usage in biomedical fields. Because of the incorporation of caprolactone, the degradation rate of the TMC–CL copolymers was greatly different from that of TMC[17] or CL homopolymers[46] after several months of implantation; this indicated that the degradation rate could be tuned.

Additionally, these materials may have been broadly applicable to many therapeutic approaches, such as tissue engineering applications and so on.

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REFERENCES

1. Montes de Oca, H.; Ward, I. M. *Polymer* **2006**, *47*, 7070.
2. Takashima, K.; Nishioka, E.; Hoshino, M.; Uesugi, K.; Yagi, N.; Imai, T.; Nakahira, A.; Kohzuki, M.; Osumi, N.; Onodera, H. *Neurosci. Res. Suppl.* **2011**, *71*, e308.
3. Shum, A. W. T.; Mak, A. F. T. *Polym. Degrad. Stab.* **2003**, *81*, 141.
4. Torres-Giner, S.; Gimeno-Alcaniz, J. V.; Ocio, M. J.; Lagaron, J. M. *J Appl. Polym. Sci.* **2011**, *122*, 914.
5. Li, X. Y.; Zhou, Q.; Yang, K. K.; Wang, Y. Z. *Chem. Pap.* **2014**, *68*, 1375.
6. Pilarek, M.; Grabowska, I.; Senderek, I.; Wojasinski, M.; Janicka, J.; Janczyk-Ilach, K.; Ciach, T. *Bioprocess. Biosyst. Eng.* **2014**, *37*, 1707.
7. Toncheva, A.; Spasova, M.; Paneva, D.; Manolova, N.; Rashkov, I. *Int. J. Polym. Mater. Polym. Biomater.* **2014**, *63*, 657.
8. Bender, E. A.; Adorne, M. D.; Colome, L. M.; Abdalla, D. S. P.; Guterres, S. S.; Pohlmann, A. R. *Int. J. Pharm.* **2012**, *426*, 271.
9. Gaharwar, A. K.; Mukundan, S.; Karaca, E.; Dolatshahi-Pirouz, A.; Patel, A.; Rangarajan, K.; Mihaila, S. M.; Iviglia, G.; Zhang, H. B.; Khademhosseini, A. *Tissue Eng. Part A* **2014**, *20*, 2088.
10. Pant, H. R.; Neupane, M. P.; Pant, B.; Panthi, G.; Oh, H. J.; Lee, M. H.; Kim, H. Y. *Colloids Surf. B* **2011**, *88*, 587.
11. Yang, D.; Zhang, C.; Li, M.; Zhang, W.; Guo, J.; Guan, Y.; Li, J. *Polym. Mater. Sci. Eng.* **2010**, *26*, 24.
12. Kluin, O. S.; van der Mei, H. C.; Busscher, H. J.; Neut, D. *Biomaterials* **2009**, *30*, 4738.
13. Papenburg, B. J.; Schüller-Ravoo, S.; Bolhuis-Versteeg, L. A. M.; Hartsuiker, L.; Grijpma, D. W.; Feijen, J.; Wessling, M.; Stamatialis, D. *Acta Biomater.* **2009**, *5*, 3281.
14. Qin, H.; Sun, C.; He, C.; Wang, D.; Cheng, C.; Nie, S.; Sun, S.; Zhao, C. *J. Membr. Sci.* **2014**, *468*, 172.
15. Lu, D.; Yang, L.; Zhou, T.; Lei, Z. *Eur. Polym. J.* **2008**, *44*, 2140.

16. Zhao, B.; Hu, X. L.; Lu, C. R. J. *Appl. Polym. Sci.* **2011**, *120*, 2693.
17. Zhang, Z.; Kuijer, R.; Bulstra, S. K.; Grijpma, D. W.; Feijen, J. *Biomaterials* **2006**, *27*, 1741.
18. Woodruff, M. A.; Hutmacher, D. W. *Prog. Polym. Sci.* **2010**, *35*, 1217.
19. Miao, H.; Fan, Y.; Liu, Y.; Liu, Y.; Hao, J.; Deng, X. *Eur. Polym. J.* **2007**, *43*, 1055.
20. Choi, W. Y.; Lee, C. M.; Park, H. *J. LWT—Food Sci. Technol.* **2006**, *39*, 591.
21. Saha, S. K.; Tsuji, H. *React. Funct. Polym.* **2006**, *66*, 1362.
22. Dash, T. K.; Konkimalla, V. B. *J. Controlled Release* **2012**, *158*, 15.
23. Noorsal, K.; Mantle, M. D.; Gladden, L. F.; Cameron, R. E. *J Appl. Polym. Sci.* **2005**, *95*, 475.
24. Wada, A.; Kubota, H.; Taketa, M.; Miura, H.; Iwamoto, Y. *J Hand Surg. Br. Eur. Vol. B* **2002**, *27*, 329.
25. Zurita, R.; Franco, L.; Puiggali, J.; Rodriguez-Galan, A. *Polym. Degrad. Stab.* **2007**, *92*, 975.
26. Poirier, V.; Roisnel, T.; Sinbandhit, S.; Bochmann, M.; Carpentier, J. F.; Sarazin, Y. *Chem.—Eur. J.* **2012**, *18*, 2998.
27. Wang, L. F.; Kefalidis, C. E.; Sinbandhit, S.; Dorcet, V.; Carpentier, J. F.; Maron, L.; Sarazin, Y. *Chem.—Eur. J.* **2013**, *19*, 13463.
28. Chen, F.; Hayami, J. W. S.; Amsden, B. G. *Biomacromolecules* **2014**, *15*, 1593.
29. Zhang, C.; Zhang, X.; Yang, D.; Wang, P. J. *Appl. Polym. Sci.* **2013**, *130*, 3800.
30. Zhang, C.; Yang, D.; Li, M. *Mod. Chem. Ind.* **2012**, *69*.
31. Nalampang, K.; Molloy, R.; Punyodom, W. *Polym. Adv. Technol.* **2007**, *18*, 240.
32. Davachi, S. M.; Kaffashi, B.; Roushandeh, J. M. *Polym. Adv. Technol.* **2012**, *23*, 565.
33. Fernández, J.; Meaurio, E.; Chaos, A.; Etxeberria, A.; Alonso-Varona, A.; Sarasua, J. R. *Polymer* **2013**, *54*, 2621.
34. Woo, H. J.; Majid, S. R.; Arof, A. K. *Mater. Chem. Phys.* **2012**, *134*, 755.
35. Fernández, J.; Etxeberria, A.; Sarasua, J.-R. *J. Mech. Behav. Biomed. Mater.* **2012**, *9*, 100.
36. Shi, G.; Cooper, D. G.; Maric, M. *Polym. Degrad. Stab.* **2011**, *96*, 1639.
37. Deschamps, A. A.; van Apeldoorn, A. A.; Hayen, H.; de Bruijn, J. D.; Karst, U.; Grijpma, D. W.; Feijen, J. *Biomaterials* **2004**, *25*, 247.
38. Hou, Y.; Chen, J.; Sun, P.; Gan, Z.; Zhang, G. *Polymer* **2007**, *48*, 6348.
39. Jiang, N.; Jiang, S.; Hou, Y.; Yan, S.; Zhang, G.; Gan, Z. *Polymer* **2010**, *51*, 2426.
40. Qin, Z.; Kim, H. J.; Hemme, J.; Blankenstein, T. *J. Exp. Med.* **2002**, *195*, 1479.
41. Lin, P.; Lin, C.-W.; Mansour, R.; Gu, F. *Biosens. Bioelectron.* **2013**, *47*, 451.
42. Franz, S.; Rammelt, S.; Scharnweber, D.; Simon, J. C. *Biomaterials* **2011**, *32*, 6692.
43. Parent, M.; Nouvel, C.; Koerber, M.; Sapin, A.; Maincent, P.; Boudier, A. *J. Controlled Release* **2013**, *172*, 292.
44. Weiler, A.; Hoffmann, R. F. G.; Stähelin, A. C.; Helling, H.-J.; Südkamp, N. P. *Arthroscopy* **2000**, *16*, 305.
45. Li, G.; Yang, P.; Guo, X.; Huang, N.; Shen, R. *Cytokine* **2011**, *56*, 208.
46. Ma, G.; Song, C.; Sun, H.; Yang, J.; Leng, X. *Contraception* **2006**, *74*, 141.