Multifunctional Polyesters for Bioartificial Vascular Prostheses

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Summary: Aliphatic polyesters of controlled molecular weight and low molecular weight distribution were prepared via anionic ring-opening polymerization using a multifunctional star-shaped initiator. Functionalization results in star-shaped functional polyesters bearing methacrylate end groups. Novel biodegradable polyester resins were prepared by photochemical crosslinking of the functional polyesters. Three-dimensional microstructuring via UV replica molding shows the potential of this material as substrate for biomedical devices.

Keywords: biodegradable resins; functional star-shaped biodegradable polyesters; photochemical crosslinking; UV replica molding

Introduction

The synthesis of new biodegradable polymers for biomedical applications is of increasing interest. Alongside with specific physical and chemical properties of these polymers, their processability into devices with controlled geometry at the microscale is emerging as an important request for the design of advanced tissue engineering and drug delivery systems. Microfabrication techniques offer the possibility of controlling the topography and size of features in the same scale of individual cells and have been recently applied to biodegradable materials for the fabrication of medical devices[1–3] including microfluidics vascular scaffolds.[4] Due to their good mechanical properties, biodegradability and biocompatibility, versatile polymers such as aliphatic polyesters prepared by anionic ring- opening polymerization of lactones are one of the most interesting and thus well reviewed materials for biomedical applications.[5,6] We have shown that inserting functionalities into these polymers will even increase their field of application due to the possibility of tuning their properties with the density of functional groups and the use of the groups for further processing and functionalization.[7] However, the synthesis of these materials is rather sophisticated and might limit their success. A more simple synthetic route towards multifunctional polyesters starts with multifunctional alcohols such as pentaerythritol, dipentaerythritol or star-shaped poly(ethylene glycol) and a lactone monomer using tin or zinc based catalysts.[8,9] By end functionalization of the resulting star-shaped polymers with acrylate,[10] maleate or itaconate[11] end groups the prerequisites for the preparation of photochemically[7,10,11,12] or thermally[11,12] crosslinked poly(ε-caprolactone)s is fulfilled. In this paper the focus lies on star-shaped PCLs with methacrylate end groups which are used for fabrication of 3D microstructured layers via replica molding. A long term goal for these substrates is the fabrication of bioartificial vascular prostheses.

Synthetic Strategy

Functional poly(ε-caprolactone) (PCL) can be obtained by functionalization of the end groups of the poly(caprolactone) chain. To

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achieve an adequate concentration of functional groups, star-shaped poly(caprolactone)s are synthesized using multifunctional initiators. These can be, for example, di(trimethylolpropane) or di(pentaerythritol) resulting in 4- or 6-arm star-shaped functional PCL or multifunctional polymers such as linear or branched polyglycidols resulting in functional bottle brushes.[13] We synthesized star-shaped PCL using di(trimethylolpropane) as multifunctional initiator and zinc 2-ethylhexanoate as catalyst. After functionalization by Schotten-Baumann reaction with methacryloyl chloride in absence of any base functional PCLs with methacrylate end groups (sPCL-MA) were obtained (Scheme 1).

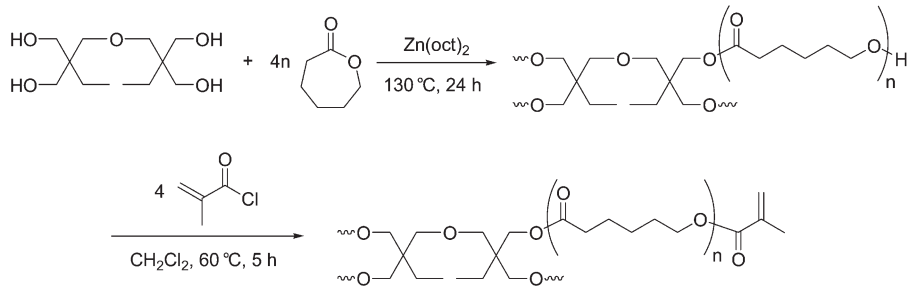
Star-shaped functional PCLs were synthesized with different molecular weights; work-up was performed by precipitation in hexane. The M_n values were determined via end-group analysis (comparison of the integrals of signals of the initiator and the repeating units); values of 2900, 5000 and 100200 g mol^{-1} were obtained, which correspond to a degree of polymerization of 20, 39 and 872. SEC analyses showed M_n values of 4300, 8900 and 135600 g mol^{-1}and molecular weight distributions of $M_w/M_n = 1.3$ to 1.4. The degree of functionalization of the hydroxyl groups determined by NMR spectroscopy is 100%. The polymer yields were > 99%, the ratios of CL repeating units to methacrylate groups are 5:1, 10:1 and 218:1, as determined from NMR.

Crosslinking and Microstructuring

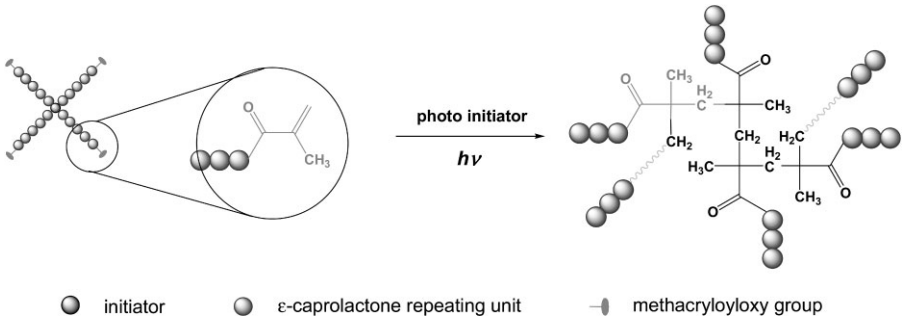
Novel biodegradable polyester resins were prepared by photocrosslinking reaction of the functional polyesters in the presence of a photoinitiator following the mechanism of a radical polymerization (Scheme 2).

Microstructured polymer films were prepared by UV replica molding on poly(dimethylsiloxane) (PDMS) masters. We chose replica molding as micropatterning technique because of the numerous advantages it offers: it is a relatively inexpensive technique fast and easy to execute, consisting only of three main steps: dispensing of the polymer solution, crosslinking by irradiation with UV light, and release of the replica (Scheme 3).

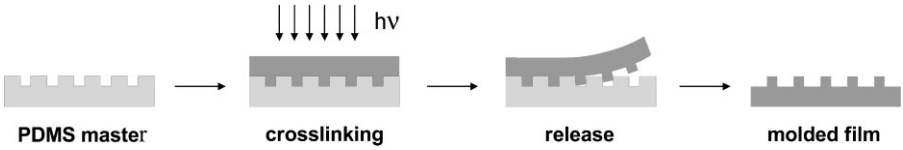
Large area resins were made from a solution of sPCL-MA (5:1 and 220:1) in dichloromethane (10 wt.-%) using Irgacure 819 (1 wt.-% with respect to sPCL-MA) as photoinitiator. After 2 h, in which the solvent evaporated, the polymer films were irradiated with UV light ($\lambda = 366$ nm, 1.0 mW/cm^2 at 5 cm distance) for 30 min. Replicas with pillars (10 μm diameter, 9 μm height and 20 μm interdistance) and ridges (5 μm grooves, 15 μm ridges) were prepared. On the same masters, also replica molding by solvent evaporation without any chemical crosslinking was performed, SEM images are shown in Figure 1. Replicas from both low and high molecular weight polymers were fabricated. In the case of the low molecular weight, only crosslinked films could be released from the



Scheme 1.
Synthetic pathway to star-shaped functional PCL.



Scheme 2.
Photocrosslinking of polyesters bearing methacrylate end groups.



Scheme 3.
Schematic representation of the UV replica molding process.

PDMS masters as self-supporting micropatterned substrates. In the case of the high molecular weight polymer, the fidelity of replication was higher (the surface was smoother) and both crosslinked and uncrosslinked films could be released from the masters and handled without problems.

DSC analysis of the resins shows that resins based on low molecular weight sPCL-MA have a low crystallinity, as observed from the low melting enthalpy ($\Delta H_m = 1.7\,J/g$). The resins prepared from high molecular weight sPCL-MA have higher crystallinity ($\Delta H_m = 70.3\,J/g$). The

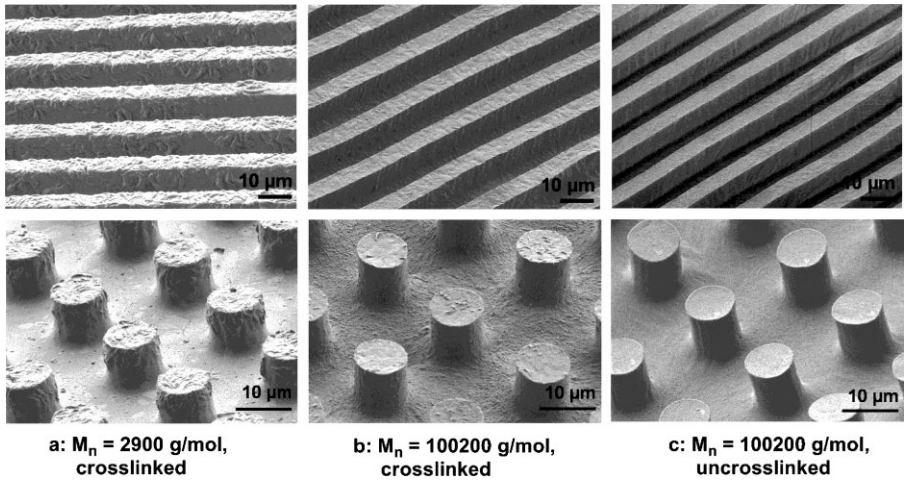


Figure 1.
Large area patterns of the polyesters. SEM images of low (a) and high (b) molecular weight crosslinked sPCL-MA and high molecular weight uncrosslinked sPCL-MA (c).

quality of the replica is related to the crystallinity of the material, higher crystallinity resulting in more defined features. Differently from the results we obtained with linear functional polyesters,[7] the crosslinking density does not significantly influence the fidelity of the replica, although the consequent disturbance of large crystallites in the material results in a slight deterioration of the micro-features as shown in Figure 1 in the case of replicas from high molecular weight polymers.

Conclusion

Star-shaped functional poly(ε-caprolactone)s were synthesized with different molecular weights and a molecular weight distribution of 1.3 to 1.4. The efficiency of functionalization was 100% resulting in biodegradable polyester bearing a methacrylate group at the end of each arm. This material was structured by photochemical crosslinking using UV replica molding resulting in 3D patterned resins. Crosslinking of high molecular weight sPCL-MA results in pillars and ridges of higher accuracy than crosslinking of low molecular weight sPCL-MA. The replicas of highest quality with very smooth surfaces were obtained with uncrosslinked high molecular weight sPCL-MA. The large area patterns can be used as substrates for biomedical devices.

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[1] C. J. Bettinger, E. J. Weinberg, K. M. Kulig, J. P. Vacanti, Y. Wang, J. T. Borenstein, R. Langer, *Adv. Mater.* **2006**, *18*, 165.
[2] R. Langer, D. A. Tirrell, *Nature* **2004**, *428*, 487.
[3] G. J. Slavik, G. Ragetly, N. Ganesh, D. J. Griffon, B. T. Cunningham, *J. Mater. Chem.* **2007**, *17*, 4095.
[4] Y. Wang, G. A. Ameer, B. J. Sheppard, R. Langer, *Nat. Biotechnol.* **2002**, *20*, 602.
[5] T. Biela, A. Kowalski, J. Libiszowski, A. Duda, S. Penczek, *Macromol. Symp.* **2006**, *240*, 47.
[6] H. Keul, H. Höcker, *Macromol. Rapid Commun.* **2000**, *21*, 869.
[7] C. Vaida, P. Mela, H. Keul, M. Möller, *J. Polym. Sci. Part A: Polym. Chem.* **2008**, *46*, 6789.
[8] K. R. Gorda, D. G. Peiffer, *J. Appl. Polym. Sci.* **1993**, *50*, 1977–1983 .
[9] M. A. R. Meier, U. S. Schubert, *E-Polymers* **2005**, no. 085.
[10] H. Kweon, M. K. Yoo, I. K. Park, T. H. Kim, H. C. Lee, H. S. Lee, J. S. Oh, T. Akaike, C. S. Cho, *Biomaterials* **2003**, *24*, 801–808.
[11] M. P. K. Turunen, H. Korhonen, J. Tuominen, J. V. Seppala, *Polym. Int.* **2002**, *51*, 92–100.
[12] C. Vaida, P. Mela, K. Kunna, H. Keul, K. Sternberg, M. Möller, *Macromolecular Bioscience* **2010**, DOI: 10.1002/mabi.201000023.
[13] H. Keul, M. Möller, *J. Polym. Sci. Part A: Polym. Chem.* **2009**, *47*, 3209.

