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Shahriar Sharifi, Sébastien Blanquer, Dirk Grijpma. Polymeric microstructures with shape-memory properties for biomedical use built by stereolithography. *Journal of Applied Biomaterials & Functional Materials*, 2012, 10 (3), pp.280 - 286. 10.5301/JABFM.2012.10367 . hal-01833148

HAL Id: hal-01833148

<https://hal.science/hal-01833148>

Submitted on 10 Dec 2020

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Polymeric microstructures with shape-memory properties for biomedical use built by stereolithography

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ABSTRACT

Purpose: The aim of this study was to design and build porous microstructures with shape memory behaviour using biodegradable poly(D,L-lactide-co-trimethylene carbonate) dimethacrylate macromers. These microstructures could be advantageous for tissue engineering and other advanced biomedical applications.

Methods: Porous structures with a gyroid pore network architecture showing average pore sizes of 930 μm and complete pore interconnectivity were prepared by stereolithography. Built structures were characterized by micro-computed tomography ($\mu\text{-CT}$). Shape recovery and shape fixity of microstructures after 40% and 70% compression were evaluated.

Results: At 37 °C the flexible structures showed compression modulus values of 60 KPa and could be fully compressed. Thermal analysis showed that the built networks were amorphous with Tg values of 23 °C. After compression to 40 and 70%, shape fixity and shape recovery of the structures at respectively 0 °C and 37 °C was almost quantitative.

Conclusions: The well-defined pore network characteristics and the shape-memory properties of these structures allow their use as deployable tissue engineering scaffolds.

Key words: Biodegradable, Poly(D,L-lactide-co-trimethylene carbonate) networks, Shape-memory properties, Stereolithography

Accepted: October 25, 2012

INTRODUCTION

Building microstructures from shape-memory polymers could be advantageous for tissue engineering and other advanced biomedical applications. These porous materials display a unique combination of high surface area, high compressibility and shape-memory behavior that gives them a wide range of potential biomedical applications (1-3). These structures can be implanted in a compact form via minimally invasive surgeries and deployed to reach complex final shapes. For example, collapsible shape-memory tissue engineering scaffolds seeded with cells can potentially be implanted in a minimally invasive manner to initiate the repair or reconstruction of tissues or organs (4). Deployable shape-memory cellular structures can also be employed to allow cellular ingrowth or blood coagulation in an aneurysm sac to facilitate occlusion of the aneurysm (5).

Scientific literature on the preparation of microstructures from shape-memory polymers is scarce. The microstructures that have been described are mainly cellular solids based on epoxies or urethanes that have been obtained by conventional foaming processes, such as pro-

cesses involving chemical blowing agents, gas foaming or particulate leaching (1, 6-8). Although making 3-dimensional foams with good shape-memory properties is possible using these techniques, there is poor control over the architecture of the pore network and the pore interconnectivity.

Porosity, pore size and pore interconnectivity along with bioactivity and physical-mechanical properties of the matrix are the main design parameters when biomedical applications of these implants are considered. For example as tissue engineering scaffolds, the porosity of scaffolds plays a main role in determining oxygen and nutrient transport to the cells. Besides that, cell differentiation, ingrowth and integration with neighboring tissue are also strongly influenced by the porosity and microarchitecture of the scaffold (9, 10).

Fabrication of microstructures by solid freeform fabrication techniques, such as stereolithography (SLA), allows the production of structures with well-defined pore network architectures (11). In this study, porous structures showing shape memory behavior were precisely prepared by SLA using biocompatible and biodegradable poly(D,L-lactide-co-trimethylene carbonate) (P(DLLA-co-TMC))

dimethacrylate macromers. These copolymers and their networks have been used for a number of biomedical applications including tissue engineering (12-14). The structures obtained were characterized by thermal, mechanical and structural analyses, and their shape fixity and recoverability were evaluated as well. The biocompatibility of the prepared structures was evaluated by direct contact cell cultures using human adipose stem cells.

MATERIALS AND METHODS

Materials

Trimethylene carbonate (1,3-dioxan-2-one; TMC) was obtained from Boehringer Ingelheim, Germany. *D,L*-Lactide (DLLA) was obtained from Purac Biochem, The Netherlands. Stannous octoate (tin 2-ethylhexanoate; SnOct_2), 1,6-hexanediol (99%), triethyl amine (TEA), pentaerythritol triacrylate, anhydrous dichloromethane and methacrylic anhydride (MAA) were obtained from Sigma-Aldrich, USA. The reagents and solvents were of analytical grade and used as received.

Synthesis and characterization of *P*(DLLA-co-TMC) oligomers and macromers

P(DLLA-co-TMC) oligomer with a targeted number average molecular weight (M_n) of $30 \text{ kg}\cdot\text{mol}^{-1}$ and a TMC/DLLA molar ratio of 0.4:0.6 was synthesized by ring-opening polymerization of the corresponding monomers using 1,6-hexanediol as an initiator and SnOct_2 as a catalyst. TMC, DLLA and SnOct_2 (2×10^{-4} mole per mole of monomer) along with the initiator, were charged into a 3-necked round bottom flask, and the reaction was continued for 3 days at 130°C under nitrogen. Macromers were prepared by reacting the terminal hydroxyl groups of the hydroxyl group terminated *P*(DLLA-co-TMC) oligomers with MAA in the presence of TEA. The required amounts of the oligomers, MAA and TEA were measured out in 1:4:4 molar ratios and charged into a 3-necked flask. The reaction was allowed to proceed for 7 days at room temperature. The *P*(DLLA-co-TMC) dimethacrylate formed was then purified by precipitation in a cold excess of diethyl ether and stored at -20°C until used.

The monomer conversions, molecular weights (M_n) and degrees of functionalization were determined by high-resolution proton nuclear magnetic resonance spectroscopy ($^1\text{H-NMR}$; Varian Innova 300 MHz, USA) using CDCl_3 as a solvent (Merck, Germany).

The thermal properties of the oligomers and macromers were evaluated by differential scanning calorimetry (DSC) using a PerkinElmer Pyris DSC apparatus. Samples weighing 5-10 mg were heated to 100°C at a rate of $10^\circ\text{C}/\text{min}$, and then cooled to -50°C at rate of $5^\circ\text{C}/\text{min}$.

After 5 minutes at this temperature, a second scan was recorded from -50°C to 100°C at $10^\circ\text{C}/\text{min}$. The glass transition temperature of the specimens, T_g , was determined as the midpoint of the change in the heat capacity.

Formulation of stereolithography resins and building of shape-memory structures

To prepare resin formulations for SLA, *P*(DLLA-co-TMC) macromers were mixed with 50 wt% propylene carbonate as a nonreactive diluent (15). To this mixture, 5 wt% Lucirin TPO-L, 0.15 wt% Orasol Orange G and 5 wt% pentaerythritol triacrylate were added as photoinitiator, dye and cross-linking agent, respectively. Cylindrical 3-dimensional porous structures with a gyroid pore network architecture with an average pore size of $1,000 \mu\text{m}$ and a porosity of 70%, were designed using K3dSurf v0.6.2 (freeware from <http://k3dsurf.sourceforge.net>) and Rhinoceros 3D (McNeel, Europe) computer software. These structures were then built from the abovementioned resins by SLA using an EnvisionTec Perfactory Mini Multilens (Germany) SLA apparatus.

To precisely control the depth of cure in building the constructs, SLA working curves were first prepared to assess the curing behavior of the resin. Three-dimensional microstructure networks were then prepared in the SLA apparatus by photo-cross-linking subsequent layers of resin with thicknesses of $25 \mu\text{m}$, upon which a pixel pattern is projected. Each layer was illuminated at an intensity of approximately $1,000 \text{ mW}/\text{dm}^2$ for 30 seconds. After building, the structures were extracted for 72 hours with a 1:1 mixture of ethanol and water to leach out propylene carbonate. The final structures were obtained after 2 days drying at 40°C .

Characterization of built porous structures

The gel contents of the porous structures built were determined by conducting swelling studies using dichloromethane as a swelling agent. The extracted samples were weighed and immersed in excess dichloromethane for 48 hours. Then the swollen specimens were dried in a vacuum oven at 40°C until constant weight, and weighed again. From these values the gel fraction was determined (16).

The thermal properties of the structures built were determined by DSC, using a similar method to that used for the oligomers and macromers. Elastic moduli of the structures were determined by compressive testing using a Zwick Z020 (Germany) tensile tester. Compression tests were carried out at room temperature, physiological temperature (37°C) and at 0°C at a crosshead speed of $50 \text{ mm}/\text{min}$.

Values of the onset strain of densification were determined by plotting the energy efficiency parameter as a function of the compressive strain (17). The efficiency

parameter is defined as the ratio of the absorbed energy up to strain (ϵ) divided by the stress itself:

$$E = \frac{\int_0^\epsilon \sigma(\epsilon) d(\epsilon)}{\sigma(\epsilon)} \quad [1]$$

The onset strain of densification was determined as the strain at which the energy efficiency reaches a maximum value.

Micro-computed tomography (μ -CT) (GE eXplore Locus SP μ -CT scanner with a spatial resolution of 7 μ m) was employed to visualize the porous structures built by SLA. Scanning was done applying an X-ray tube voltage of 80 kV, a current of 80 μ A and an exposure time of 3,000 milliseconds. No filter was applied. After reconstruction using the Feldkamp algorithm, thresholded isosurface images were obtained (GE MicroView software). Porosities, pore size distributions and average pore sizes of the structures prepared by SLA were assessed from the μ -CT data.

Shape-memory properties

Cylindrical scaffolds with gyroid pore network architectures (diameter 12 mm, height 14 mm) were immersed in a basin of water of 37 °C and compressed into a temporary shape (40% and 70% compression) at 10% per minute. Fixing of the shape was done by decreasing the temperature to 0 °C while maintaining the compressive strain. To ensure uniform heating, the specimens were kept at the test temperature for 10 minutes. To evaluate shape recovery, the sample with the fixed temporary shape was again immersed in water at 37 °C until the specimen returned to its permanent shape. Quantitative shape-memory properties were evaluated using a digital camera to record the changes in shape of the specimens.

The shape fixity (R_f) and the shape recovery (R_r) were calculated using the following formulas:

$$R_f(\%) = \frac{l_u}{l_i} \times 100 \quad [2]$$

$$R_r(\%) = \frac{l_p - l_r}{l_p} \times 100 \quad [3]$$

In Equation 2, l_i and l_u , respectively, represent the height of samples after compression (to 40% or 70%) and cooling, and the height of the cooled and compressed samples after unloading. In Equation 3, l_r represents the recovered height of the sample after warming up to 37 °C, while l_p represents the original height of sample at room temperature. These experiments were repeated using 3 samples. The porosities, pore size distributions and aver-

age pore sizes of the structures in their temporary shape (at 40% and 70% compression) and after their shape recovery were evaluated by μ -CT as described in a previous section.

Biocompatibility

The biocompatibility of the porous structures built was assessed using adipose stem cell culturing in direct contact with the surface of the materials. First, the scaffolds were sterilized by immersing in ethanol 70% for 30 minutes, followed by several washing steps with sterile phosphate-buffered saline (PBS). Human adipose stem cells (passage 7) were seeded into and onto the built porous P(DLLA-co-TMC) structures in wells of cell-adherent polystyrene tissue culture plates at a concentration of 2.5×10^5 cells per scaffold. After 3 hours of preincubation, the wells were filled with 3 mL medium and incubated for 2 weeks, replenishing the medium every 2 days. Cell viability was evaluated using a methylene blue assay. Briefly, the medium was aspirated from the wells, and the scaffolds were washed once in PBS. Then, the scaffolds were incubated in 10% paraformaldehyde fixative solution (Sigma Aldrich, USA) for 20 minutes and washed with PBS. An amount of 100 μ L of methylene blue solution was dropped onto the scaffolds; after 3 minutes they were washed several times with PBS until no blue staining came out of the scaffold. The stained cell-seeded cell-containing scaffolds were then visualized by optical microscopy.

RESULTS

Synthesis and characterization of P(DLLA-co-TMC) oligomers and macromers

Using hexanediol as a bifunctional initiator, a mixture of D,L-lactide and TMC was polymerized by ring opening polymerization to yield telechelic oligomeric diols. The number average molecular weight of the oligomers determined by $^1\text{H-NMR}$ was $28 \times 10^3 \text{ g} \cdot \text{mol}^{-1}$. The TMC/DLLA molar ratio in the oligomers calculated from the ratio of the integral values of CH_2OCOO of TMC at 4.08-4.39 ppm and of $-\text{CHCOO}$ of lactide at 1.42-1.85 ppm was found to be 58.3:41.7. End functionalization of the oligomers to form P(DLLA-co-TMC) dimethacrylate was confirmed by the appearance of protons of vinyl groups at 5.6 and 6.2 ppm and of the methylene protons of the methacrylate groups at 1.95 ppm in the $^1\text{H-NMR}$ spectra. The degree of functionalization (DF) of macromers was determined from the peak areas corresponding to the methacrylate protons (5.6 and 6.2 ppm) and the hexanediol $-\text{CH}_2\text{O}-$ protons (1.2 ppm). A DF of 70% was obtained for the macromers.

DSC analysis showed that the oligomers and the mac-

Fig. 1 - Porous structures designed with gyroid pore network architecture and made by stereolithography (SLA) using P(DLLA-co-TMC) dimethacrylate-based resins. A) Computer-aided design of the porous structure. B) Micro-computed tomography image of the structure. C) Photographic image of the structure after extraction. Scale bar is equal to 2.5 mm.

romers were completely amorphous, they showed T_g values of 13.0°C and 13.2 °C, respectively.

Preparation of porous structures and their characterization

The porous structures with gyroid pore network architecture made from shape-memory macromers by SLA were characterized by analysis of their microarchitecture, mechanical testing and swelling studies. First μ -CT was employed to assess the porosity and the pore network characteristics of the scaffolds built. Figure 1 shows computer-aided designs (CADs) of the porous structures with gyroid pore network architectures and the corresponding μ -CT images of the structures built. As can be seen in the figure, the structure was accurately built as it very closely resembles the design. The porosity of the architecture was 70% with an average pore size of 1,000 μ m. According to the μ -CT data, the structures built had a porosity of 70.9% and an average pore size of 931 μ m. The pore network is fully interconnected.

Water ethanol mixtures which are used for the extraction of the propylene carbonate diluent are poor solvents for the unreacted macromers. The unreacted macromer was extracted from the built structures with dichloromethane, which is a good solvent for the P(DLLA-co-TMC) macromers. The scaffolds built were found to have high gel contents of 88% as determined in swelling experiments. According to DSC, the network structures were amorphous with T_g values of 23 °C. These values were somewhat higher than those of the macromers and oligomers, as could be expected.

Figure 2 shows the compression stress-strain curves of the structures built, at 0 °C, at room temperature and at physiological temperatures of 37 °C. As also is the case with foamed materials, the 3 stages of deformation: bending, buckling and densification are evident in this figure, especially regarding the porous specimen compressed at room temperature. At this temperature, the onset of densification can be determined to be approximately 46% compression; at 37

Fig. 2 - Compression behavior of 70% porous structures designed with gyroid pore network architecture and prepared from P(DLLA-co-TMC) macromers at different temperatures. The networks had a glass transition temperature of 23°C.

°C the onset of densification is at approximately 55% compression.

In agreement with the thermal analysis, the 70% porous scaffolds exhibited typical rubbery behavior at room temperature and at 37 °C, with elastic modulus values of 2,540 kPa and 60.4 kPa, respectively. These structures prepared from P(DLLA-co-TMC) dimethacrylate-based resins were more rigid glassy materials at 0 °C and had an elasticity modulus of 20,900 kPa.

Shape-memory properties

In Table I the results of the shape fixity and shape recovery of the prepared porous structures after compression to 40% and 70% at 37 °C are presented. Also the corresponding average pore sizes are given.

Upon unloading, after being compressed to 40% and 70%, the prepared porous structures did not show spontaneous shape recovery at 0 °C. This indicates excellent shape fixity of the materials. For both compression levels, a high value of recovery was observed at 37 °C; however, the rates of shape recovery for specimens compressed to 40% were lower than those for specimens compressed to 70% (data not shown).

In Figure 3, images of the porous structures with gyroid pore network are shown in their original (permanent) shape and in their temporary, compressed state. Also indicated is the pore size distribution of the pores in the corresponding states as determined by μ -CT. Upon increasing the temperature from 0°C to 37°C, the P(DLLA-co-TMC) structure deployed from its temporary shape to its original permanent dimensions and shape. In the uncompressed original state, pores

Fig. 3 - Shape recovery of porous structures designed with gyroid pore network architecture, upon heating and with corresponding changes in pore size and pore size distribution. The P(DLLA-co-TMC) structures had a glass transition temperature of 23 °C. A) Temporary shape of the structure (70% compressed) at 0 °C. B) Transient shape of the structure upon heating to 37 °C; at this point the compression is approximately 40%. C) Structure completely recovered to its original permanent shape. Scale bar is equal to 2.5 mm.

TABLE I - SHAPE FIXITY (R_f) AND SHAPE RECOVERY (R_r) OF PREPARED POROUS STRUCTURES AFTER 40% AND 70% COMPRESSION AT 37 °C

Compression (%)	R_f (%)	R_r (%)	Average pore size* (μm)
0	--	--	931
40	99 $\pm$ 1	95 $\pm$ 1.3	718
70	99 $\pm$ 2	98 $\pm$ 1.1	577

Shape fixity and shape recovery were determined at 0 °C and 37 °C, respectively. Data are presented as means $\pm$ standard deviation. The corresponding average pore sizes in the temporary state at 0 °C are presented as well.

*Single determinations.

in the porous structures ranging in size from 886 to 1,172 μm made up more than 86% of the pore volume. Upon being compressed to 40% and 70%, the (average) pore sizes of the structures can be seen to decrease significantly.

The proliferation of adipose stem cells seeded into and onto the scaffolds is shown in Figure 4. The images correspond to cell culturing periods of 1 day and 7 days.

DISCUSSION

Photo-cross-linkable P(DLLA-co-TMC) macromers can be conveniently prepared by ring-opening polymerization of TMC and *D,L*-lactide initiated by hexane diol and subsequent functionalization in a reaction with methacrylic anhydride. Depending on the monomer composition, poly(*D,L*-lactide-co-trimethylene carbonate)s can

Fig. 4 - Optical microscopy images of methylene blue-stained adipose stem cells seeded into and onto the P(DLLA-co-TMC) scaffolds prepared by stereolithography. Images were taken after 1 day (A) and after 7 days (B) of cell culturing (scale bar = 1 mm).

have widely differing glass transition temperatures, elastic moduli, tensile strengths and degradation. This makes these tailorable materials suitable for a variety of biomedical applications (18). In this work we employed P(DLLA-co-TMC) network materials with a DLLA to TMC molar ratio of 0.6:0.4, because this polymer is amorphous with a glass transition (after photo-cross-linking of the macromers) at close to room temperatures. In addition, the macromers with relatively high molecular weights of 30 $\text{kg}\cdot\text{mol}^{-1}$ were used for photo-crosslinking. We found in preliminary work (data not shown) that increasing the molecular weight of the macromers resulted in significant improvement of the mechanical properties (strength, resilience and toughness) of the networks formed. This makes these networks especially attractive for use in preparing minimally invasive surgically implantable medical devices and tissue engineering scaffolds. Such devices could be implanted in a temporary shape below T_g that, after

implantation and warming up to body temperature, would expand to their permanent shape to perform a specific desired function.

With SLA, it was possible to prepare complex structures from these P(DLLA-co-TMC) macromers that possess shape-memory properties. As an example of a complex device, a cylindrical porous structure with a gyroid pore network architecture was built. The gyroid pore network has an infinitely connected triply periodic minimal surface with a large specific surface area and high pore interconnectivity. These architectures could therefore be of great interest for tissue engineering scaffolds or other volume-filling applications (19).

As our results confirm, the SLA technique allowed for the precisely controlled preparation of structures with designed (and desired) pore characteristics. The results provide information regarding the shape fixity and shape recovery of the structures built. Excellent shape fixity and near complete recovery of the specimens can be expected from the large difference in elasticity moduli of the specimens below and above the glass transition temperature, as illustrated in Figure 2.

Porous polymeric shape-memory materials are usually prepared by foaming techniques using supercritical carbon dioxide or gas-blowing methods. These foams usually have very broad pore size distributions (1). Since the gyroid pore network architecture is a designed structure that contains fully connected regular channels throughout the structure, the pore size distribution is quite low (Figs. 3 and 4).

In microporous structures prepared from shape-memory polymers, the number, size and location of struts and walls between the pores play an important role in determining the compressibility and the shape recovery after deformation of the structures. During the deformation process, the porous structure deforms by bending of the cell walls (closed-cell foams) or cell edges (open-cell foams) (20). Figure 2 shows the strain-stress curves of the P(DLLA-co-TMC) structures. When the network is in the glassy state at 0 °C, the structure deforms elastically in a uniform way. At room temperature, which is close to T_g of the network, the specimen first uniformly deforms elastically until a stress plateau is reached. At this point, μ -CT results in Figure 3 show that there is a significant decrease in pore size. Figure 2 shows that at 37 °C after approximately 50%-60% compression, densification can be observed. Here, the compressive stress increases significantly with the applied strain, due to contacting of the cell walls. This onset of densification is in correspondence with the previously calculated value of 55% compression. Because the gyroid pore network consists of many regular struts with no clear boundaries between the pores, collapse of the pore network due to compression occurs elastically, and complete shape recovery is still possible even after 70% compression, which is well above the onset of densification.

The cell culture study using adipose stem cells clearly demonstrates the biocompatibility of the built structures. The very open architecture can be advantageous in tissue engineering, specifically when large tissues are to be engineered, as the diffusion of nutrients and oxygen to the cells will not be hampered.

CONCLUSIONS

Porous structures were prepared by SLA using P(DLLA-co-TMC) macromers containing 40 mol% TMC. Porous structures with high interconnectivity were obtained. These structures showed good shape-memory properties in terms of shape fixity at low temperatures and excellent recovery upon heating to 40 °C. Structures did not show any adverse cytotoxicity when cultured with human adipose stem cells. The results here indicate the feasibility of making complex structures with shape-memory properties to fulfil several needs in the biomedical field.

Financial support: This research forms part of the Project P2.01 IDiDAS of the research program of the BioMedical Materials Institute, cofunded by the Dutch Ministry of Economic Affairs, Agriculture and Innovation. The financial contribution of the Dutch Arthritis Foundation is gratefully acknowledged.

Conflict of interest: The authors declare no conflict of interest.

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