Development of a Shape Memory Patch for Minimally Invasive Repair of Vascular Rupture

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Statement of Purpose: It is challenging and surgically risky to treat vascular injuries such as strokes and aneurysms, especially ruptures of small diameter blood vessels, through currently available therapeutic approaches. To address these issues, a vascular patch made of biodegradable shape memory polymers (SMPs) can be deployed to the injured or ruptured site in a minimally invasive manner via a laparoscope. SMPs are capable of achieving minimally invasive implantation and repair vascular injuries because they can be *fixed* into a temporary shape (i.e. an injectable shape for placement through a laparoscope) and *recover* their original, permanent shape (i.e. a ruptured tissue-specific shape) when triggered by an external stimulus such as heating above its melting temperature (T_m). Poly(ε-caprolactone) (PCL) is a biocompatible, biodegradable polymer that can be modified to form a chemically cross-linked polymer film with excellent shape memory properties[1]. However, its T_m (45-60°C) is too high for physiological applications. In this study, the T_m was tuned near body temperature (37°C) by copolymerizing ε-caprolactone (CL) with α-allyl carboxylate-ε-caprolactone (ACCL). When polymerized, the pendant double bonds from the allyls enable formation of chemical cross-links that are essential for fixing and recovery of shape. UV cross-linking of *x%*PCL-*y%*ACPCL (*x* and *y*: molar ratio) produced polymer films with tunable shape memory properties, suggesting these novel SMPs offer promise in treating vascular injuries in a minimally-invasive way.

Methods: ACCL was first synthesized by adopting the method for α-benzyl carboxylate-ε-caprolactone[2]. A series of *x%*PCL-*y%*ACPCL copolymers (*y* = *6*, *11*, and *15%*) were synthesized by ring-opening polymerization of ACCL and CL. Polymers and 2,2-dimethoxy-2-phenylaceto-phenone were solubilized in dichloromethane and irradiated with a 260 nm UV collimated beam. Differential scanning calorimetry was performed to determine thermal properties[3]. Shape memory properties of cross-linked films were characterized on a TA Instruments Q800 dynamic mechanical analyzer (DMA). Rectangular strips (~20mm x ~3.0mm x ~0.3mm) were loaded onto a tension clamp and subjected to three of the following thermomechanical cycles. Equilibrated at T_m+~15°C, films were subjected to tensile stress (0.004 MPa/min to 0.039 MPa) as shown in (1) of Figure 1. Films were then cooled (10°C/min to 0°C) (2), yielding the strain at the maximum stress $\varepsilon_l(N)$, before unloading the stress (0.004 MPa/min to 0 MPa) (3) and recording strain as $\varepsilon_u(N)$, the temporary shape. Finally, the films were heated (2°C/min to T_m+~15°C) (4) to recover the permanent shape $\varepsilon_p(N)$. The shape memory effect was quantified by shape fixity (R_f) and shape recovery (R_r). Shape fixity defines the ability to maintain a programmed shape induced by mechanical deformation, while shape recovery describes how well $\varepsilon_p(N)$ is recovered from the beginning of the Nth cycle (ε_p(N-1)):

$$R_f(N) = \frac{\varepsilon_u(N)}{\varepsilon_l(N)};\quad R_r(N) = \frac{\varepsilon_u(N) - \varepsilon_p(N)}{\varepsilon_u(N) - \varepsilon_p(N-1)}.$$

Results: To successfully repair vascular tissue, SMPs should demonstrate a T_m = ~37°C with R_f and R_r = ~100% after mechanical deformation into an injectable shape. T_m's of 44.6, 38.0, and 29.7°C for *y* = *6*, *11*, and *15%* copolymer films, respectively, suggest that shape recovery can be achieved in the body for *y* = *11* and *15%* without the need for additional heating that could damage tissue and cause inconsistencies in shape recovery. All polymers demonstrated R_f>99% after large (>30%) strains, indicating that the films can be programmed and fixed into a shape such as a long thread that can fit through a laparascope. Furthermore, R_r>99% was accomplished after repeated cycling, implying that a ruptured tissue-specific shape can be fully recovered if heated beyond the T_m~37 °C.

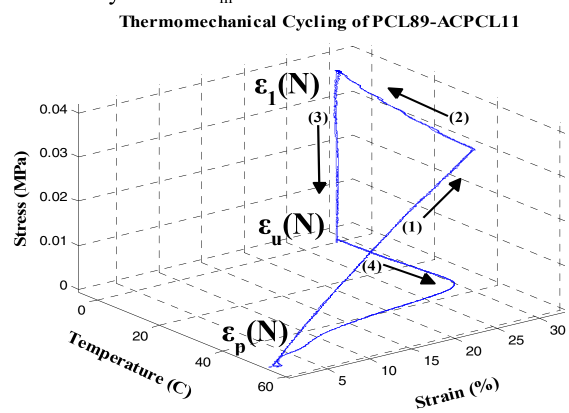

Figure 2. Initially at 0 MPa and 55°C, *y* = *11%* was subjected to 0.004 MPa/min to 0.039 MPa (1), cooled (2), unloaded of tensile stress (3), and heated to recover shape (4). The cycle was repeated three times.

Conclusions: A new class of SMPs, PCL-ACPCL, was synthesized and characterized in order to develop a minimally invasive vascular patch for injuries of small diameter blood vessels to which proximal access is difficult (e.g., strokes). T_m's near 37°C were achieved for 89%PCL-11%ACPCL and 85%PCL-15%ACPCL, indicating that shape recovery is possible for these polymers without implementing any risky heating procedures. Stress-controlled thermomechanical cycling demonstrated that these SMPs have an excellent ability to be programmed into an injectable shape for minimally invasive deployment to the site of injury as R_f was >99% for all films. R_r was also >99% after repeated cycling, suggesting these polymers can potentially assume a ruptured tissue-specific shape after implantation. PCL-ACPCL films will be tested in an *in vitro* vascular injury model.

References:

[1] Neuss S. Biomaterials 2009;30:1697-1705.
[2] Mahmud A. Macromolecules 2006;39:9419-9428.
[3] Guo B. Biomacromolecules 2011;12:1312-1321.