

Reconfigurable Biodegradable Shape-memory Elastomers using “click” Chemistry

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Statement of Purpose: Endovascular embolization of intracranial aneurysms is a minimally-invasive treatment in which an implanted material forms a clot to isolate the weakened vessel. Wide-neck intracranial aneurysms, with their challenging vessel geometry, are more susceptible to herniation of the embolization agent and usually require the help of permanent stenting devices. There is a need for fabrication of an endovascular device to prevent coil herniation, reduce risk of vasospasm, and ultimately biodegrade in a tractable manner. Soft biodegradable elastomers are a class of materials that have potential utility as endovascular devices due to their combination of biocompatibility and mechanical compliance. However, currently available elastomeric materials are not optimal for this application due to the difficulty in processing fully degradable products into complex three-dimensional geometries. To overcome this limitation, our approach is to synthesize soft covalent networks based on biodegradable poly(glycerol-co-sebacate) (PGS) coupled with multifunctional maleimide precursors using Diels-Alder cycloaddition chemistry. These elastomers can be processed into complex three-dimensional geometries using mild crosslinking conditions. Furthermore, cycloaddition reactions can obviate the formation of aliphatic domains to achieve total bioabsorption.

Methods: PGS pre-polymer was synthesized according to previous published methods¹. Furan modification of PGS was achieved via acrylation with furoyl chloride. The network was formed through coupling with bi-functional maleimide groups at 92 °C for 3-9 days, depending on the degree of furan substitution. The network is called PGSF-DPBM. To fabricate complex helix geometry, a four-step process was employed (Figure 1). In the first step, precursors were melt-processed into a flat crosslinked film (1). Next, the crosslinked network was stressed and shaped into desired configuration at room temperature (2). In the third step, the retro Diels-Alder reaction was induced by subjecting the stressed network at 120 °C for 24 hours (3). Finally, cooling the material to 92 °C for another 24 hours induced the forward crosslinking to form a new permanent shape (4). The kinetics of network formation, thermo-mechanical properties, degradation profile and in vitro biocompatibility were also studied.

Results: The incorporation of furan groups was confirmed by the appearance of the peaks at $\delta 6.55$, $\delta 7.25$, and $\delta 7.65$ on ¹H NMR spectrum. Three degrees of substitution, on a sebacic acid basis, were used for further characterization (22%, 38%, 45%). Furan conjugation of PGS also resulted in the appearance of the band at ~ 1010 cm⁻¹ on ATR-FTIR spectrum, corresponding to the furan C-O-C ether stretch. Upon melt mixing PGSF and DPBM at high temperature to induce the crosslinking reaction, the =C-H bending of the maleimide group was visible at 690 cm⁻¹. Also visible was the appearance of a new peak at 1459 cm⁻¹, corresponding to the C=C in DA adduct². During curing at 92 °C, evolution of the 1010 cm⁻¹ furan

peak was monitored every 24 hours, showing a decrease over time. The gel point (p_g) of 45% network can be estimated using Flory–Stockmayer equation³ to be 0.18. Experimental results from rheometry, where the gel point was defined as the point at which the loss tangent $\tan\delta$ is temporarily frequency independent, combined with IR data showed the same p_g . The relaxation exponent was calculated to be 0.77, in agreement with the predicted value from percolation theory (0.7)⁴. Young’s modulus of PGSF-DPBM ranged from 4MPa (22%) to 11MPa (45%), indicating that DA cycloaddition reactions can produce mechanically robust networks. The T_g of PGSF-DPBM films ranged from -10 °C to 6 °C, indicating that PGSF-DPBM is an elastomeric material at room temperature. Samples with helical geometry were fabricated according to previously described process (Figure 1). On going degradation study shows that $\sim 75\%$ of the original mass remained after 20 effective days incubated in Sodium Acetate buffer at 37 °C.

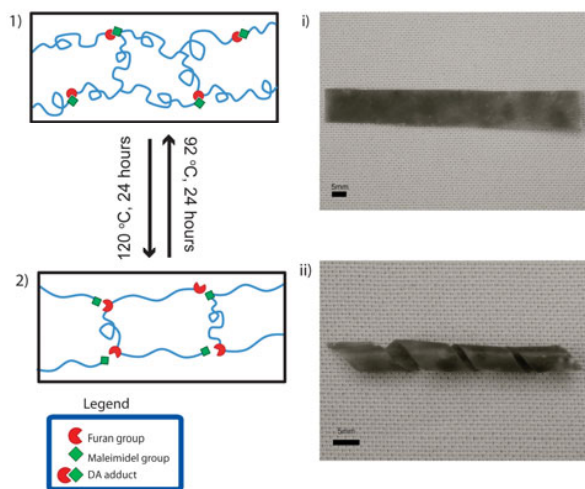


Figure 1. 1) Network crosslinked by forward DA, 2) Retro DA, i) Flat crosslinked film, ii) Helix geometry fabricated utilizing reversible chemistry

Conclusions: We have described the fabrication of a new biodegradable elastomer crosslinked based on Diels-Alder cycloaddition reactions. These materials exhibit thermo-mechanical properties, biocompatibility and degradation profiles that suggest it may serve as a suitable material candidate for applications in temporary mechanically compliant medical devices. Furthermore, the reconfigurability of DA chemistries, using relatively mild crosslinking conditions, affords additional capabilities including shape-memory and the formation of complex geometries.

References: (1) Wang, Y. *Nature biotech.* 20, 602-606 (2002). (2) Nimmo, C. M. *Biomacromolecules* 12, 824-830 (2011). (3) Adzima, B. J. *Macromolecules* 41, 9112-9117 (2008). (4) Martin, J. E. *Physical Rev. Let.* 61, 2620-2623 (1988).