Long Term In Vivo Tissue Response and Degradation Behavior of Photo-Cross-Linked Star-Poly(ε-Caprolactone-co-D,L-Lactide Elastomeric Networks.

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Statement of Purpose: Synthetic biodegradable elastomers based on aliphatic polyesters are potentially useful materials for many biomedical applications, as they are resorbable and can be prepared with properties close to that of native tissue. We are currently examining the potential of a photo-cross-linkable elastomer as a protein delivery vehicle. We recently reported on the *in vivo* degradation of the photo-cross-linked elastomers in rats, where rods of two different crosslink densities having diameter of 1.8-2.0 mm and length of 1 cm were implanted subcutaneously for a period of 12 weeks. The results of that study indicated that the degradation mechanism depended on the crosslink density of the elastomer; as the crosslink density increased, the elastomer degraded in a manner consistent with surface degradation. In this study, we investigate longer term *in vivo* degradation and tissue response of rods of smaller diameters (0.67 mm), implanted subcutaneously in rats for a period of 30 weeks. The objectives were to determine the influence of diameter on the degradation rate, and to confirm the mechanisms of degradation.

Methods: Star-copolymer macromers of molecular weights of 1250 and 7800 Da were prepared by ring opening bulk polymerization at 140ºC for 48 hrs, using 50:50 molar ratios of ε-caprolactone and D,L-lactide. Stannous octoate was used as a catalyst/co-initiator and glycerol as the initiator. The terminal hydroxyl groups were acrylated to incorporate alkene functional groups. The macromers were UV photocrosslinked using 2,2-dimethoxy-2-phenyl-acetophenone to yield elastomer rods with diameters and lengths of approximately 0.67 mm and 15 mm. After sol extraction and sterilization with ethanol, four rods/rat were implanted subcutaneously dorsally into male Wistar rat. At given time points, extending up to thirty weeks, the rods were harvested and their mass, sol content, and mechanical and thermal properties measured. Histology of the surrounding tissue was performed to determine the tissue response.

Results/Discussion: The most significant finding of this study is the ability of crosslink density to control the rate of degradation and tissue response of the elastomers. Elastomers made of 7800 Da macromer degraded in a similar manner as high molecular weight linear aliphatic polyesters; swelling and a burst of acidic degradation products were observed, leading to the formation of a thick capsule around the implants. On the other hand, elastomers made of 1250 Da macromer, which have 6.5 times higher crosslink density, degraded predominantly by surface erosion; rod swelling and the release of of acidic degradation products were reduced significantly. Elastomers made of 7800 Da macromer behaved like a rubber in tension and had a starting Tg of -2^{o}C, Young's modulus of 0.98 MPa, stress at break of 5.41 MPa and strain at break of 5.53. By week 14, they had lost 96% of their initial strength, and by week 20 the remaining elastomer had a Tg of -15^{o}C and had become a paste surrounded by a thick fibrous capsule. By week 26, these elastomers were totally absorbed (Fig 1), and by week 30 the capsules had disappeared and the sites were almost healed. Elastomers made of 1250 Da macromers behaved like a plastic. Before implantation, they had a Young's Modulus of 57.3 MPa, stress at break of 19.7 MPa, strain of 2.1, yield stress of 10.44 MPa, and yield strain of 0.25. By week 14 they had lost 88% of their initial strength, due mainly to cracks being developed in the structure of the elastomer. The Tg was initially 17^{o}C, then fluctuated between 22^{o}C and 12 ^{o}C, being 21^{o}C at week 26 and 21^{o}C at week 30. Swelling and sol content of these highly crosslinked elastomers remained below 20% during the degradation period. The fibrous capsule surrounding these implants was signficantly thinner. This difference in capsule thickness was attributed to the slower degradation rate of the highly crosslinked elastomers, which results in a lower local concentration of acidic degradation products. Reducing the diameter of implants of high crosslink density yielded an elastomer with a higher Tg, consequently reducing the rate of degradation. However, no significant change in the properties of the low cross-link density elastomer with respect to diameter was observed.

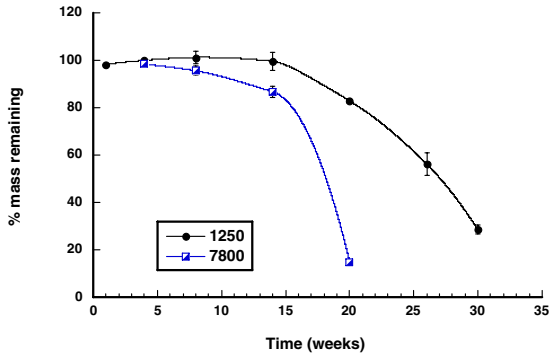

Fig 1. Remaining mass of explanted elastomers. Each point represents the average and the error bars represent the standard deviation of 3 samples. The average initial mass of the implants was 6 mg.

Conclusions: The implanted elastomers were well-tolerated in the subcutaneous site. The rate of degradation of the elastomers can be tailored by adjusting their crosslink density and diameter. Dense networks restrict the diffusion of water, thus reducing the rate of ester chain scission and release of low molecular weight degradation products. For highly crosslinked networks, reducing the diameter of the implant slowed its degradation rate.