Controlling The In Vivo Degradation Rate of Poly(ethylene carbonate) Through Crosslinking

Laura Cornacchione, Brian Amsden.
Department of Chemical Engineering, Queen's University, Kingston, Ontario, Canada.

Statement of Purpose: Poly(ethylene carbonate) is a potentially interesting material for protein delivery and as a tissue engineering scaffold because it has a low glass transition temperature, is rubbery, and degrades in vivo without generating acidic degradation products. This degradation is primarily due to the local release of superoxide anion [1]. However, linear poly(ethylene carbonate) (PEC) degrades inappropriately fast in vivo for the indicated applications. To evaluate the hypothesis that the degradation rate of PEC can be prolonged and even tailored by the degree of crosslinking, PEC elastomers were prepared through photocrosslinking diacrylated low molecular weight prepolymers. The degradation of these elastomers in vitro under oxidative conditions and in vivo were then compared.

Methods: Linear poly(ethylene carbonate) (Mw = 60 kDa) was purchased from Empower Materials, Delaware. The 60 kDa PEC was depolymerized in the presence of tin(II)-2-ethylhexanoate and 5% ethylene glycol at 160ºC under vacuum for from 50 to 200 minutes to obtain the desired molecular weight. The polymers were purified by precipitation from dichloromethane into methanol cooled with dry ice. The polymer terminal hydroxyl groups were acrylated with acryloyl chloride in dry dichloromethane using 4-(dimethylamino)pyridine as a catalyst and triethylamine as a proton scavenger. The resulting prepolymer was precipitated in ethanol cooled with dry ice. The composition and number average molecular weight of the prepolymers was determined via ^{1}H-NMR in d6-DMSO. α,ω-diacrylate PEC with number average molecular weights of 2100, 6700 and 8100 Da were obtained. Elastomers were prepared from these prepolymers dissolved to 3 g/mL in dioxane in the presence of 1.5%(w/w) 2,2-dimethoxy-2-phenyl-acetophenone by exposure to 10 mW/cm^2 320-380 nm UV light in 1 mm thick glass molds covered with a glass coverslip. Following crosslinking, the dioxane was evaporated under vacuum for several days, and the sol removed by serial soaking in dichloromethane, followed by solvent evaporation. Coupons for testing were cut using a biopsy punch to produce discs approximately 5 mm in diameter and 0.9 mm thick. In vitro oxidation in triplicate was undertaken in a mixture of 0.01 M potassium superoxide (KO2) in anhydrous, inhibitor-free THF containing. 0.002 M 18-crown-6-ether. Discs were also implanted subcutaneously in the dorsa of male Wistar rats, following the guidelines of the Canadian Council on Animal Care. Discs of purified 60 kDa PEC were also implanted for comparison. Four discs were implanted per polymer per rat, and two rats per time point were used. At chosen times, two rats per group were sacrificed, and the discs explanted. The wet weight of the discs was immediately recorded, the discs dried, and the dry weight measured. Paired comparisons were made using a one-way ANOVA with a Bonferroni post-hoc test at a significance level of 99%.

Results: As has been shown previously,[2] linear PEC can be degraded by superoxide anion (Fig. 1). However, Fig. 1 also demonstrates that the rate of weight loss can be controlled by crosslinking the PEC; increasing the crosslink density retards the weight loss.

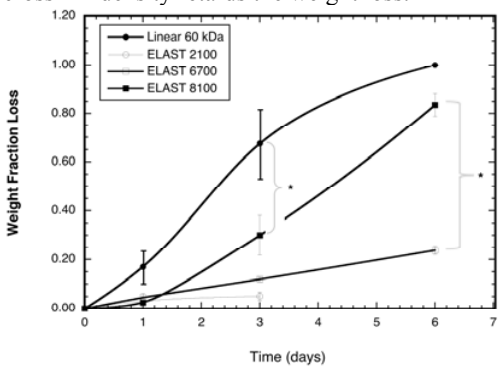

Figure 1. In vitro oxidative degradation of PEC and PEC elastomers (ELAST) at different crosslinking densities. Each point represents the average while error bars represent 95% confidence intervals. Data for 2000 MW elastomer at day 6 was excluded due to significant disc damage. * indicates that difference is significant.

Similar behavior was observed in vivo (Fig 2). Elastomers prepared with a prepolymer molecular weight of 6000 Da degraded notably slower than did linear 60 kDa PEC. The degradation rate of linear PEC was over 9 times greater than that of the PEC elastomer made from 6,000 Da PEC diacrylate (Elast 6000).

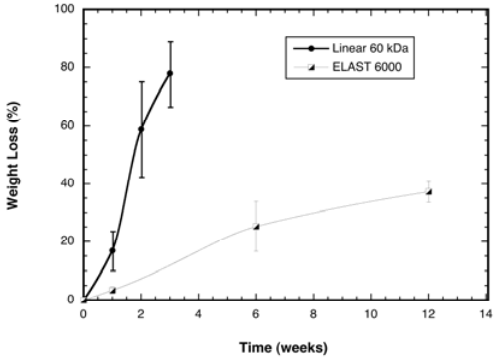

Figure 2. In vivo weight loss of linear 60 kDa PEC compared to that of a PEC elastomer prepared with 6000 Da PEC diacrylate.

Conclusions: In vitro oxidative degradation of elastomers prepared from PEC diacrylate suggested that degradation rate could be effectively controlled through manipulating crosslink density. This hypothesis was confirmed in vivo by following weight loss of PEC both crosslinked and noncrosslinked after subcutaneous implantation in rats.

References: 1. Acemoglu M,. J. Control. Release 1997;49:263-276. 2. Dadsetan M, . J Control Release 2003;93:259-270.