Development of Degradable Hydrogels for Growth Plate Regeneration

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Statement of Purpose: The growth plate, or epiphyseal plate, is the site of new bone growth at the ends of bones in growing children. The importance of this area to normal growth and development makes it especially prone to having lasting effects in the case of an injury. In many cases, an injury can result in formation of a bone bridge that can lead to growth arrest, which could eventually create angled growth and deformity. Approximately 18.5% of childhood fractures involve the growth plate [1]. Currently, several approaches have been made to fill the injury with fat, muscle, and bone cement in the hopes of preventing bony bar formation [2], however the results are far from ideal. Here, the goal is to develop a hydrogel construct that displays the mechanical properties inherent to the natural growth plate, as well as a degradation profile that would allow new tissue to form and repair the damaged physis.

Methods: A macromer was synthesized in an overnight condensation reaction between a diacrylate and amine as outlined in the literature [3]; free radical polymerization was used to create the hydrogel. Samples are named as in the original paper. All samples were made using diethylene glycol diacrylate, represented by the A and an amine, labeled as follows: 3-methoxypropylamine (1), isobutylamine (6), decylamine (7), and 3-morpholinopropylamine (11). Porous samples were created through several methods; in one, PMMA beads were sintered and the macromer was polymerized around the beads. Other pores were created using a fast degrading hydrogel system as the porogen with a longer degrading system polymerized around the particles. SEM imaging was used to characterize the porous systems made. Degradation was characterized by gravimetric analysis of samples immersed in 37°C PBS. Mechanical testing was carried out on hydrated samples using a BOSE ELF 3300 Mechanical Testing System with a 225 N load cell. Toxicity data was obtained by exposure of the final degradation products to D1 pluripotent mesenchymal cells followed by MTT assay.

Results: For all systems created, degradation, toxicity, and mechanical analyses were completed. It was found that with the same macromer chemistry the degradation time period and mechanical properties can be tuned by the ratios of diacrylate to amine in the macromer synthesis. Increasing this ratio decreases the chain length, thus creating a higher degree of crosslinking, resulting in slower degradation and increased mechanical properties. Porous systems created have interconnected pores with a controllable size as shown in Figure 1. The use of faster degrading polymers as the porogen allows for a controlled opening of pores over time, as well as potential for a multi-phase drug release system. The relative toxicities of all macromer systems have been studied in comparison

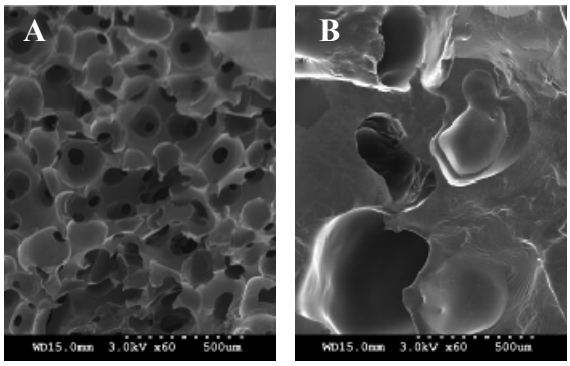

Figure 1: SEM images of porous hydrogels made with PMMA (A) and faster degrading hydrogels (B) as the porogen.

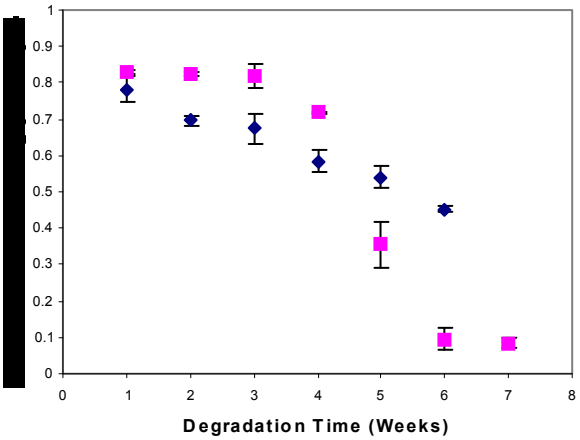

Figure 2: Degradation of A6 ◆ and A7 ■.

to that of PLGA using MTT analysis. It was found that the 50% toxic concentration values (TC_{50}) of the PLGA is approximately 1.8 mg/mL, as compared to the A6 system with a TC_{50}= 0.16 mg/mL, and A7 with TC_{50}=0.20 mg/mL. Based on our experience with other polymer systems, we expect that slow accumulation of byproducts over the the time period of degradation will allow the clearance of degradation products before these high values are reached. Degradation plots, like that shown in Figure 2, have been obtained. The compression modulus analysis with degradation closely follows that of mass loss during the degradation time.

Conclusions: Several hydrogel systems having tunable degradation, mechanical, and drug delivery properties were developed. These materials are being explored for use in regenerating damaged growth plate tissue.

References:

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