Dual Growth Factor Delivery from Injectable P(PF-co-CL) Copolymers for Bone Regeneration

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Statement of Purpose: Bone is, after blood, the most commonly transplanted tissue worldwide. Current clinical methods of treating skeletal defects include autologous bone, allograft bone, and synthetic bone substitute. Autologous bone is the "gold standard" and provides all the essential elements of effect bone healing. For bone tissue engineering, the synthetic biodegradable polymers should facilitate the natural bone-healing process by serving as scaffolds with similar mechanical properties as human trabecular bone, and carriers for controlled delivery of growth factors for bone regeneration. Poly(propylene fumarate) (PPF) and polycaprolactone (PCL) have both been systemically investigated for their crosslinking characteristics, mechanical properties, and biocompatibility, and have been proved as excellent candidates for bone scaffolds. In this study, we have investigated the properties of an injectable multiblock poly(propylene fumarate-co-caprolactone) copolymer P(PF-co-CL) with embedded poly(lactic-co-glycolic acid (PLGA) and oligo(poly(ethylene glycol) fumarate (OPF) microspheres. We will encapsulate both angiogenic and osteogenic growth factors, i.e. vascular endothelial growth factor (VEGF) and bone morphogenetic protein-2 (BMP-2) into the OPF and PLGA microspheres, respectively. The sequential, dual growth factor delivery is expected to promote local bone healing at defect sites. We will optimized the loading of both types of microspheres in the injectable P(PF-co-CL) composite and determine the release kinetics of the both growth factors.

Methods: P(PF-co-CL) copolymer synthesis and PLGA and OPF microsphere fabrication (with loaded growth factors) were based on previously published methods[1-3]. Eight polymer composite groups with different compositions were prepared: 100% copolymer (no microspheres), 20% PLGA-0% OPF, 20% PLGA-10% OPF, 20% PLGA-20% OPF, 20% PLGA-30% OPF, 30% PLGA-0% OPF, 30% PLGA-10% OPF, 30% PLGA-20% OPF. The composites were crosslinked via radical polymerization to form 3D composite scaffolds using benzoyl peroxide as initiator and N-vinyl pyrrolidinone as crosslinker. Mechanical properties of the crosslinked scaffolds were analyzed using dynamic mechanical analyzer (DMA). Surface morphology of scaffolds was assessed using scanning electron microscopy (SEM). Accelerated degradation of the scaffolds in NaOH (1M) was assessed for 5 weeks.

Results and Discussion: The compressive modulus of our materials was shown to increase when the loading of PLGA microsphere increased in the composites. When OPF microspheres were increased, the compressive modulus of the composition decreased (Figure 1). Increasing PLGA and OPF microspheres accelerated weight loss of the copolymer scaffolds in the accelerated degradation study (Figure 2). We had investigated that incorporation of PLGA and OPF microspheres into the P(PF-co-CL) copolymer significantly decreased Texas red dextran (TRD) burst release. TRD was released form both microspheres in a timely manner (no published data). We further demonstrated that the concentration of these two microspheres could change the mechanical properties of the composite. In an ongoing work, these microspheres are separately loaded with BMP-2 and VEGF and their release profile is being investigated.

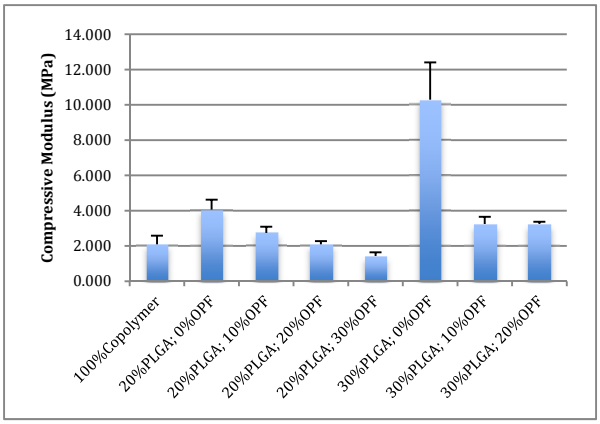

Figure 1. Compressive modulus increased when PLGA microspheres increased, and decreased when OPF microspheres increased.

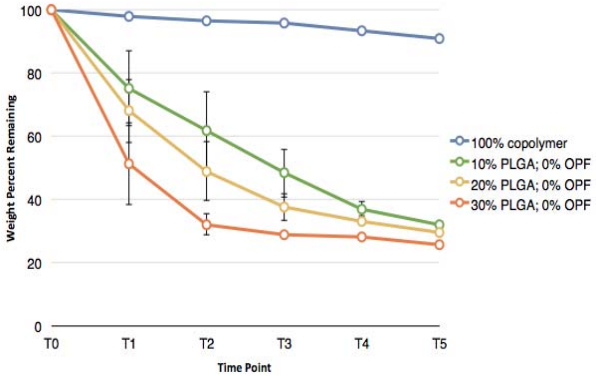

Figure 2. Weight percent remaining in a period of 5 weeks accelerated degradation test in NaOH (1M).

Conclusions: Our data suggest that properties of this composite material could be influenced by different concentration of incorporated PLGA and OPF microspheres. These scaffolds have the potential for dual drug delivery to the bone defects.

Reference: [1] Wang s. et al. Macromolecules 2005;38:7358-7370; [2] Jo S. et al. Biomacromolecules 2001;2:255-261; [3] Lu L. et al. Journal of biomedical materials research 2000;50:440-451.

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