Injectable Multiblock P(PF-co-CL) Copolymer and Dual Drug Delivery for Treatment of Bone Defects

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Statement of Purpose: The ideal bone tissue replacement should meet the three most important challenges: functioning as a backbone scaffold, enhancement of bone healing and prevention of infection. To function as an optimal backbone scaffold the novel synthetic tissue should mimic the mechanical properties of human bone at its best. Poly(propylene fumarate) (PPF) and polycaprolactone (PCL) have been studied extensively for this purpose and have proven themselves as excellent candidates with respect to mechanical stability as well as biocompatibility. Investigators in different studies have shown that bone tissue regeneration can be accelerated by application of several growth factors such as bone morphogenetic proteins (BMPs) or fibroblast growth factors (FGF). However, threatening infection of injury-site after surgical procedure cannot be completely ruled out even by meticulous surgical care and employment of additional adjunctive conventional treatment. Raising antibiotic resistance and biofilm producing bacteria make the bone graft a nidus for infection even if antibiotic is systemically administered leading to higher morbidity and poor outcome for the latter. In this work, our goal is to maximize local drug concentration by delivery of the antibiotic and the growth factors directly at the pathological site. We have investigated the feasibility of an injectable poly(propylene fumarate-co-caprolactone) copolymer with embedded poly lactic-co-glycolic acid (PLGA) and oligo(polyethylene glycol) fumarate (OPF) microspheres for simultaneous delivery of multiple drugs to bone defects.

Materials and Methods: Previously published methods were used for synthesis of P(PF-co-CL) copolymer and fabrication of PLGA and OPF microspheres.[1–3] Furthermore, scaffolds with different formulations were fabricated with incorporation of varying amounts of PLGA and OPF microspheres into the copolymer (10%, 20%, 30% w/w). To characterize release kinetics from scaffolds, the embedded microspheres were loaded with the model drug Texas red dextran (TRD) with MW of 40.000, which mimics the molecular weight of proteins. Mechanical and thermal properties of scaffolds were analyzed using dynamic mechanical analyzer (DMA) and thermal gravimetrical analyzer (TGA). Surface morphology of scaffolds was assessed using scanning electron microscopy (SEM). Moreover, the drug release was monitored over a 28-day period and analyzed by using a Spectrophotometer at 595 nm wavelength.

Results: SEM images show that we have successfully embedded PLGA and OPF (Fig.1) microspheres into the P(PF-co-CL) copolymer and that they are homogenously distributed in the matrix.

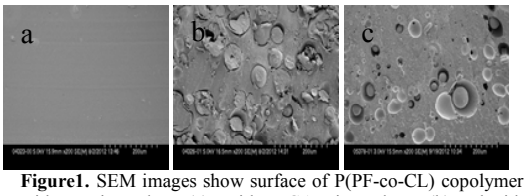

Figure1. SEM images show surface of P(PF-co-CL) copolymer without microspheres(a), with PLGA microspheres (b) and with both PLGA and OPF-microspheres (c).

Figure 2 shows TRD release from PLGA microspheres throughout the entire 28 day-period in all of polymer formulations. Moreover, we demonstrate that embedding the PLGA-microspheres in the copolymer significantly decreases TRD burst release.

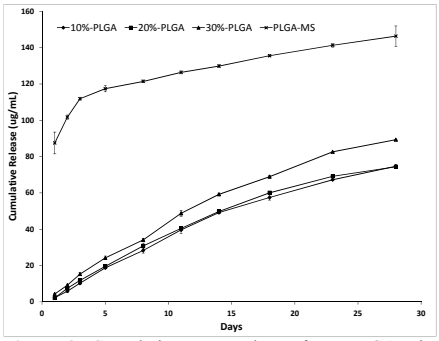

Figure 2. Cumulative TRD release from PLGA-microspheres embedded in copolymer over a period of 28 days.

Figure 3 demonstrates the release of TRD from OPF-microspheres embedded in copolymer containing 10% PLGA microspheres. It appears that TRD release increases with incorporation of OPF microspheres into copolymer.

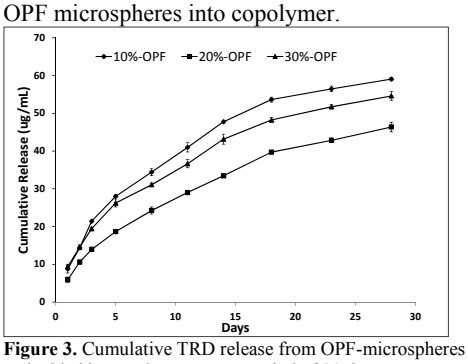

Figure 3. Cumulative TRD release from OPF-microspheres embedded in copolymer over a period of 28 days.

Conclusions: Our data reveal that PLGA- and OPF- microspheres could be embedded in P(PF-co-CL) copolymer and used for dual drug delivery applications. These scaffolds could be a potential candidate for delivery of growth factors and antibiotics to bone defects in vivo.

References: 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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