Degradation Characteristics of Novel In-Situ Crosslinkable Poly(Lactide-co-Glycolide-Ethylene Oxide-Fumarate) Copolymer Networks

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Statement of Purpose: Biocompatible polymeric materials with a wide spectrum of degradation characteristics which can be crosslinked *in situ* are required for minimally invasive procedures in tissue regeneration. Our laboratory has developed a novel class of in situ crosslinkable copolymers based on poly(lactide-co-glycolide-ethyleneoxide-fumarate) (PLGEOF) macromers consisting of ultra low molecular weight (ULMW) PLGA and PEO blocks linked by unsaturated fumarate units [1]. Hydrophobic solid, amphiphilic rubber, or hydrophobic gels can be fabricated by changing the ratio of ULMW PLGA to PEO in the copolymer. The network density can be controlled by the density of fumarate groups on the copolymer. The unsaturated fumarate groups in the macromer can be used to covalently attach biologically active peptide sequences to the network. PLGA and PEO are FDA approved and fumaric acid occurs naturally in the Kreb's cycle. The objective of this work was to determine the hydrolytic and enzymatic degradation characteristics of these networks.

Methods: The rate of *in situ* crosslinking and hardening of the network depends on the density of unsaturated fumarate groups in the macromer. High density of unsaturated groups can be obtained by using ultra-low molecular weight ULMW PLGA. ULMW PLGA was synthesized by ring opening polymerization of the lactide (L) and glycolide (G) monomers in a dry atmosphere with diethylene glycol (DEG) as the bifunctional initiator as described [1]. The M_n ranged from 1-2 kDa with polydispersity index of 1.1-1.3, respectively. PLGEOF was synthesized by condensation polymerization of ULMW PLGA and PEO with FuCl. The structure of PLGEOF was characterized by ^{1}H-NMR, ^{13}C-NMR and FTIR and chain length distribution was measured by GPC. For network formation, PLGEOF was mixed with NVP or peptide crosslinker and crosslinked with APS/TEMED (water soluble initiation system) or BPO/DMT (organic soluble initiator systems) or BAPO (UV initiator system). The mixture will be degassed, injected between two glass plates, and heated to 37°C for 15 min to crosslink. The disk-shaped samples were used for swelling and degradation studies. The amino acid sequence Lys-Ala-Ile-Gly-Glu-His-Lys with acrylate end-groups, synthesized in the solid-phase, was used as the enzymatically degradable peptide crosslinker [2]. The peptide crosslinker is degraded by MMP (collagenase type III; MMP-13) secreted by migrating BMS cells. Degradation of the samples was determined by measuring the weight loss as a function of incubation time in culture media only (NVP crosslinked samples) or MMP-13 solution (25 µg/ml; peptide crosslinked samples) at 37°C. Samples crosslinked with a mutant peptide (scrambled sequence of the same amino acids as in the peptide crosslinker) were used as the control

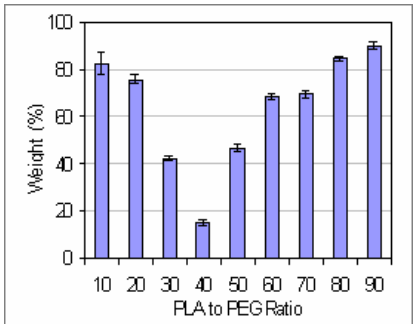

Fig. 1. Effect of PLA/PEG ratio on mass loss.

Results / Discussion: The degradation of PLEOF networks as a function of the ratio of lactide to ethylene oxide domains after 21 days are shown in Figure 1. PLEOF networks with 10-50% LA are water swellable gels, while samples with 60 and 70% are amphiphilic and samples with 80 and 90% LA are hydrophobic and water insoluble. Figure 1 demonstrates that degradation can be increased from <5% after 21 days for 90% PLA network to >80% with 40% PLA network. The effect of lactide to glycolide ratio on degradation is shown in Figure 2. The PLAF sample (blue) showed <10% degradation after 20 weeks while the PLGF sample (red) had >20% degradation after 2 weeks. The PLEOF sample with 90% lactide had 20% mass loss after 5 weeks while that of the PLGEOF completely degraded after 2 weeks. By incorporating enzymatically degradable peptide sequences in the network, the rate of degradation can also be accelerated from 20% after 15 days to >60%, as shown in Figure 3.

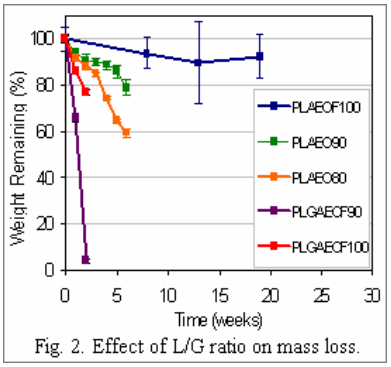

Fig. 2. Effect of L/G ratio on mass loss.

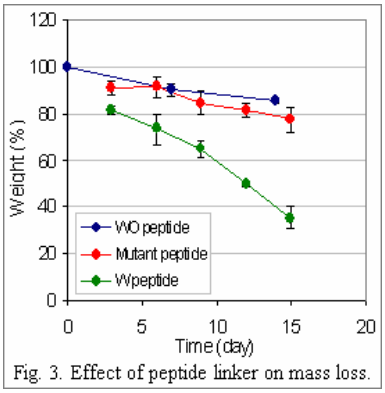

Fig. 3. Effect of peptide linker on mass loss.

Conclusions: PLGEOF networks have a wide range of degradation times. PLGEOF networks are useful for fabrication of tissue engineered scaffolds or fabrication of protein/gene delivery systems.

Reference:

[1] Jabbari E, He X. J. Mater. Sci. Mater. Med., in Press (2006).
[2] X. He, E. Jabbari, Protein Pept. Lett. 13 (2006) 715.