50b Synthesis and Characterization of Poly(L-Lactide) Networks as in-Situ Crosslinkable Scaffolds for Guided Tissue Regeneration

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Poly(lactic acid) (PLA) and its copolymers with glycolic acid (PLGA) are used in a variety of orthopedic applications as bone fixative, suture reinforcement, and as scaffolds for cell transplantation and guided regeneration. PLGA copolymers are semi-crystalline biocompatible copolymers and FDA approved for certain clinical applications. PLA and PLGA are generally used as preformed scaffolds or foams because casting from organic solvents or from melts at high temperature are required for fabrication. We have developed novel unsaturated PLA, PGA, and PLGA macromers to overcome the use of solvents or high temperature in fabrication of PLGA constructs. These novel macromers can be used as injectable in-situ crosslinkable scaffolds in a variety of applications in guided tissue regeneration.

Poly(L-lactide) unsaturated macromers were synthesized by condensation polymerization of fumaric acid, a substance that occurs naturally in the Kreb's cycle, with relatively short lactide or glycolide chains. Difunctional hydroxyl terminated short lactide or glyoclide chains were first synthesized by melt ring-opening polymerization of L-lactide (LA) or glycolide monomer with diethylene glycol (DEG) as the initiator and tin II-ethyl hexanoate as the catalyst. The molar ratio of LA to DEG was varied from 10 to 30 to produce low molecular weight PLA (LMWPLA) chains with number average molecular weights (M_n) in the range of 1000 to 4000 Dalton. The synthesized LMWPLA was characterized by ^{1}H-NMR, FTIR, and gel permeation chromatography (GPC). Next, the LMWPLA was condensed with fumaric acid to form unsaturated lactide-fumarate (PLAF) copolyesters. The PLAF macromer was characterized by ^{1}H-NMR, ^{13}C-NMR, FTIR, GPC, and differential scanning calorimetry (DSC). Molecular weight of PLAF depended on that of LMWPLA used in the synthesis. The M_n of PLAF increased from 4000 to 5200 Dalton as that of LMWPLA increased from 1000 to 2300. The polydispersity index of PLAF (2.5) was significantly higher than that of LMWPLA (1.6) for all molecular weights. Copolymerization with Fumaric acid did not significantly affect the degree of crystallinity of LMWPLA, as measured by WAXD. The melting point of the semi-crystalline PLAF, measured by DSC, depended on the molecular weight and fraction of glycolide in the synthesized low molecular weight PLGA polymer.

Injectable scaffolds were fabricated by free radical polymerization of PLAF with 1-vinyl-2-pyrrolidinone (VP) to facilitate crosslinking and sodium chloride (NaCl) crystals as porogen. Benzoyl peroxide and dimethyl toluidine were used as the free radical initiator and accelerator, respectively. The polymerizing mixture was injected into a mold, allowed to crosslink, and the porogen was leached out by soaking the scaffolds in distilled deionized (DI) water. Pore morphology was investigated with scanning electron microscopy (SEM). Cell behavior on PLAF surfaces was investigated with rat neonatal heart fibroblasts. Hearts were dissected, tissue was minced and digested with collagenase, and fibroblasts were purified by selective attachment to culture dishes. Fibroblasts showed significant adhesion to PLAF surfaces and the degree of attachment increased by coating the substrates with collagen, laminin, or fabronectin. Results demonstrate that the poly(lactide-fumarate) macromer is potentially useful for fabrication of in-situ crosslinkable scaffolds for guided tissue regeneration.