Absorbable, Injectable, Thermogelling Hydrogels of PCL-g-PEG

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Statement of Purpose: There is great interest in developing new absorbable polymers that can be used as matrices to promote controlled drug delivery and tissue healing. It is well known that biodegradable materials can have enormous advantages over nondegradable materials which are prone to infection and foreign body reaction.[1] There is recent interest in the formation of polymers that are water-soluble sols at low temperature and that can transform to gels by increasing the temperature.[2] The aqueous sols allow the facile incorporation of therapeutic drugs, cells, or particles at low temperature and their application *in-vivo* by minimally invasive injection. The gel state acts traps the therapeutics and promotes their function. The synthesis of water-soluble polymers that are thermogelling requires a balance between relative amounts of hydrophobic and hydrophilic domains. We report the development of thermogelling, PCL-g-PEG graft copolymers composed of a hydrophobic polycaprolactone (PCL) backbone and hydrophilic polyethylene glycol (PEG) grafts. The polymers and gels were characterized and used as a matrix to promote angiogenesis in rat calvarial defects.

Methods: Caprolactone (CL) and epoxy-terminated PEG (EPEG) were reacted by ring opening polymerization in toluene in the presence of an initiator (mono-PEG) and catalyst (stannous octoate) at 120°C. The polymers were purified and the polymer composition and molecular weight were characterized by nuclear magnetic resonance (NMR) and gel permeation chromatography (GPC). Gelation properties were studied by temperature-dependent dynamic rheology analysis. Gelation mechanisms were studied using uv-vis absorbance studies of hydrophobic dye solubilization, dynamic light scattering (DLS) and x-ray diffraction (XRD). *In-vitro* gel degradation studies were performed in the presence of a PBS eluting solvent at 37°C. The PCL-g-PEG sols were sterilized by filtration. VEGF or LPA containing sols were injected into rat calvarial defects and angiogenesis was studied by a novel magnetic resonance imaging (MRI) method.

Results: PCL-g-PEG polymers were soluble in water, were sols at low temperature, and transformed into gels with increasing temperature as shown in Figure 1. The gelation temperature decreased with increasing polymer concentration. The storage modulus (G') at 37°C varied from 0.2 to 5500 Pa with increasing concentration. The storage modulus was much higher than that for previously developed PLGA-PEG-PLGA and PLGA-g-PEG polymers.[3] Uv-vis studies showed that the polymer forms micelles in aqueous solution with a critical micelle concentration of 0.005 wt %. The micelles were ~15 nm in diameter and aggregated into larger structures with increasing temperature as determined by DLS. The polymer sol was noncrystalline and the gel was crystalline as determined by XRD. Degradation studies showed that the time for complete polymer degradation could be varied from one week to four months by the addition of varying amounts of the lipase enzyme and by incorporating various amounts of lactide (LA) into the PCL backbone, which increased degradation by hydrolysis. VEGF and LPA containing sols were injected into rat calvarial defects and showed stable depots. The controlled release of the growth factors promoted angiogenesis as evidenced by increasing blood perfusion rates over controls as determined by MRI.

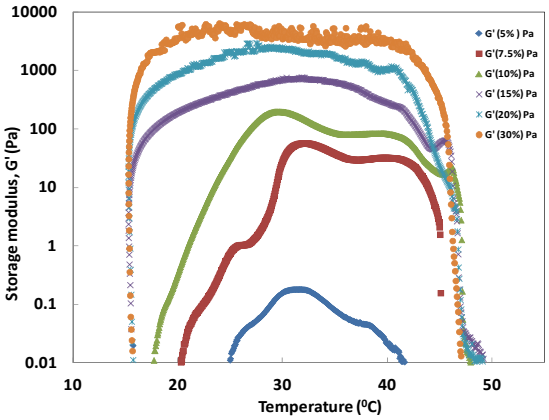

Figure 1. G' of PCL-g-PEG as a function of temperature and polymer concentration.

Conclusions: PCL-g-PEG polymers were synthesized, were water soluble, and exhibited thermoreversible sol-gel transitions. The mechanisms for gelation involved micelle aggregation and polymer crystallization. The polymer crystallization also contributed to the enhanced mechanical properties of the gels. The storage modulus of the gels could be varied over a four-fold range which is of interest for tissue engineering applications where matching the tissue mechanical properties is desirable. The degradation rate of the polymers could be varied over a wide temporal range. The use of the polymers for controlled release of growth factors for tissue healing was demonstrated in rat calvarial defects models.

References:

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