Liquid Injectable Polymers Based On Modified Caprolactone As Potential Drug Delivery Vehicles

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Statement of Purpose: The objective was to examine the potential of poly(5–ethylene ketal ε-caprolactone) (MCL) or its copolymer with D,L-lactide (DLLA) as a low viscosity, injectable polymeric delivery vehicle suitable for regio-specific drug delivery.

Methods: 5-ethylene ketal ε-caprolactone monomer was synthesized by oxidation of 1,4 cyclohexanedione monoethylene acetal with 3-chloroperoxybenzoic acid in anhydrous dichloromethane at room temperature for 24 hours.[1] The solution was frozen at -20°C, filtered and purified by column chromatography using silica gel and 25%, 30% and 40% EtOAc/hexane gradient as eluent[2]. Linear poly(5-ethylene ketal ε-caprolactone) and its copolymer with DLLA were prepared by ring-opening polymerisation at 110°C for 24 hours using tin octanoate as catalyst and octanol or methoxy polyethylene glycol (PEG 350) as initiator. The resulting polymer was purified by precipitation in methanol cooled using dry ice. The structure, purity and number average molecular weight of the polymers were determined by ^{1}HNMR recorded in DMSO-d6 at 400 MHz. The number average molecular weights were calculated by end group analysis from the signal intensity of the CH_3 group of octanol at 0.85 ppm, CH_3 group of PEG 350 at 3.23 ppm, the methylene group of MCL at 2.3 ppm and methine group of DLLA at 5.1 ppm. The thermal properties of the polymers were measured with a DSC 1 STAR^e system (Mettler Toledo). The samples were run at a rate of 10 °C/min using a cycle from +25 °C to -90 °C and -90 °C to +25 °C. The glass transition temperature (Tg) was obtained from the second heating cycle. The viscosity at temperatures ranging from 25°C to 50°C was determined using a TA AR 2000 rheometer. A parallel plate apparatus with cone stainless steel (0.5 DEG) attachment and 40 mm diameter was used. In vitro degradation of the polymers was undertaken (150 mg of the polymer in 1 ml of 0.1M phosphate buffer saline (PBS) at pH of 7.4 and temperature of 37°C) for 24 weeks. The change in mass, molecular weight, composition and T_g with time were measured (n=3). Cytotoxicity of the MCL monomer was assessed as follows. 20 mg of monomer was degraded in 2 mL of 8X Dulbecco's modified eagle's medium (DMEM) at pH 7.4 for 24 hours. The resulting solution was diluted 8 times with deionised water to make the solution isotonic and the pH adjusted to 7.4. The resulting solution was diluted with DMEM and added to 3T3 fibroblasts (passage 7) at varying concentrations. 100 µL of the resulting solution supplemented with 5% fetal calf serum (FCS) was added to each well. The cells were cultured for 24 hours, 10µL of cell proliferation reagent (WST-1) was added and incubated for 4 hours and the absorbance was measured at 440 nm (n = 4).

Results: The monomer was obtained with a yield of 61.6%. The monomer was homopolymerized and copolymerized with DLLA at 110°C by the cleavage of the acyl oxygen bond of the cyclic monomer. Figure 1 is the structure of the homopolymer initiated with PEG-350. The ^{1}H NMR spectra confirmed the major peaks associated with the backbone polymer and the end groups. The homopolymers and copolymers with DLLA have low Tg ranging from -20°C to -36°C, which imparted a low viscosity. The viscosity ranged from 3.0 Pa•s and 106.0 Pa•s at 37°C and thus the polymers are injectable through standard gage needles. The polymers initiated with PEG 350 were less viscous and degraded faster compared to polymers initiated with octanol. The copolymers with DLLA were more viscous but degraded faster than the homopolymers, regardless of initiator used. Moreover, the degradation products of the MCL monomer were non-toxic to 3T3 fibroblast cells, as shown in Figure 2.

Figure 1. Structure of poly(5–ethylene ketal ε-caprolactone) initiated with PEG 350.

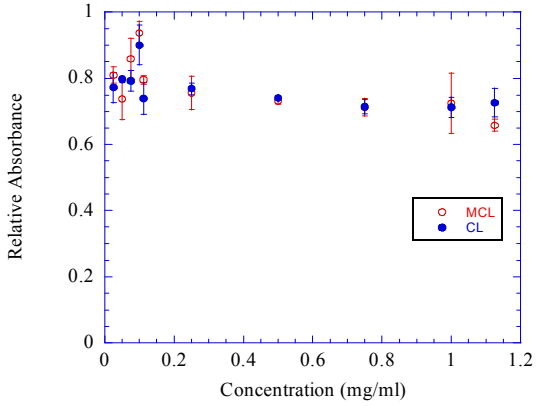

Figure 2. Cytotoxicity of MCL and CL on 3T3 fibroblast cells

Conclusions: This work demonstrates that an injectable polymer can be made from poly(5–ethylene ketal ε-caprolactone). The viscosity and degradation rate can be controlled by copolymerizing with DLLA and or by initiating with octanol or PEG 350. The monomer was nontoxic to 3T3 fibroblast cells.

References: (1) Tian D. Macromol, 1997; 30(3): 406-409. (2) Mecerreyes D. Macromol, 1999; 5175 – 5182.