In Situ Setting Polymer/Ceramic Composite Bone Cements for Controlled Release of Simvastatin

Mark Fulmer[1], Xinyin Liu[1], Elliott Gruskin[1], Milvia Lepre[2]
[1]Synthes Inc. West Chester, PA
[2]Synthes Europe, Oberdorf, Switzerland

Statement of Purpose: In addition to their known benefits of lowing cholesterol and reducing heart attacks, [1] statins have also been reported to promote bone formation. However, the optimal dosing and delivery of statins has yet to be established. In theory, sustained local drug delivery offers better control of the dosages, optimizes therapeutic effects and minimizes systemic toxicity. In this study, we evaluated a novel polymer/ceramic composite that sets under physiological conditions for its potential use as bone void filler, as well as a carrier for the controlled local release of simvastatin.

Methods:

Sample Preparation: Poly (DL-lactide) (PDLLA, i.v. =0.49 dl/g) was dissolved in N-methyl pyrrolidone (NMP) at a weight ratio of 1:2 to form viscous gel. The gel was then mixed with a bioresorbable calcium phosphate cement (CPC) at 1:3 and 2:3 (PDLLA: CPC) ratios to form injectable pastes.

Mechanical Testing: The paste was injected into molds and cured into cylinders of 6 mm (D) x 12 mm (L) at 37°C in PBS (pH7.4). Compressive strength of the composites was determined using an Instron testing apparatus at a speed of 2.54mm/min.

Release Study: Simvastatin was mixed with the paste at a concentration of 3 % (w/w). The resultant mixture was injected into pre-wetted dialysis membrane tubing, and placed in PBS (pH 7.4) at 37°C. 2 mL of aliquots were taken at 1d, 3d, 4d, 5d and weekly up to 10 weeks. 2mL of fresh PBS was added back to each sample to maintain constant volume. The concentration of simvastatin was detected with HPLC at 238nm on a PDA detector.

Degradation Study: The composites incorporated with 3wt% simvastatin were placed in phosphate buffered saline (pH 7.4) at 37°C. At each week, samples were taken out of the buffer and freeze dried. The average molecular weight of the PDLLA at each time point was measured using gel permeation chromatography (GPC) with polystyrene as narrow standards.

Results / Discussion: The compressive strength of the composites was found to be between 3-5MPa after curing in PBS (pH 7.4) at 37°C for 24 hours. These values are comparable to the compressive strength of cancellous bone. In addition, the X-ray diffraction spectra of the composites showed that the CPC cured into hydroxyapatite with the presence of trace calcium carbonate.

In the release study, the initial burst release of simvastatin from the composite with 1:3 PDLLA: CPC was higher than the release from the composite of 2:3 ratio (Figure 1). However, after the initial burst release, both composites showed near linear release at comparable release rate for up to 10 weeks.

The average molecular weight of PDLLA in both composite formulations decreased ~ 11% during the 10 weeks of degradation study. There was no significant difference between the two formulations (Figure 2).

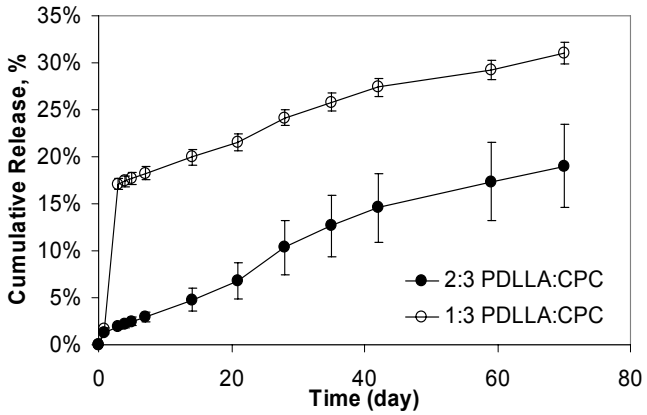

Figure 1. Cumulative release of simvastatin from composites in PBS (pH 7.4, 37°C) for 70 days (n=3).

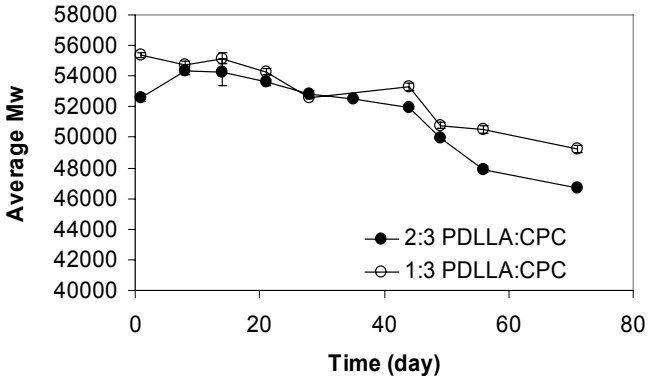

Figure 2. Degradation of PDLLA in the composites in PBS (37°C, pH 7.4) for 70 days (n=3).

Conclusions: The PDLLA/CPC composites solidified in contact with water due to the diffusion of NMP. The CPC component in the composites cured into hydroxyapatite as confirmed by XRD spectra. The compressive strength of the composites was found to be close to that of cancellous bone. Therefore, this composite system can serve as bone cements with the advantages of *in situ* setting. Furthermore, the system showed sustained release of simvastatin, a hydrophobic small molecule. Altogether, these data demonstrate that this composite system may have potential as both a bone void filler, and a carrier for the sustained local delivery of therapeutic agents.

References:

1. Mundy G et al, Science (1999) 286: 1946-1949