Evaluation of *in situ* setting calcium phosphate cements as carrier materials for antibiotics

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Statement of Purpose: Sustained local release of antibiotics offers an effective way for treatment or prophylaxis of bone and soft tissue infections [1]. However, the release of antibiotics from traditional antibiotic impregnated polymethylmethacrylate (PMMA) beads and cement is often incomplete [2], and requires additional surgeries to remove the non-biodegradable implant in order to prevent buildup of bacteria resistance at the implant site [3]. In this study, bioresorbable calcium phosphate cement (CPC) and calcium phosphate cement incorporated with biodegradable polymer fibers (FCPC) that set under physiological conditions were evaluated as carriers for release of gentamicin sulfate.

Methods: CPC and FCPC were first mixed into paste, and then 0.5wt% and 1wt% of gentamicin sulfate was mixed into the paste. The resultant mixture was cured into cylinders of 6 mm (D) x 12 mm (L) at 37°C. The release study was performed in PBS (pH 7.4) at 37°C for 8 weeks. 2 mL of aliquots were taken at 1, 4, 8 hours, everyday in the first week, and then weekly up to 8 weeks. Fresh PBS was changed at each sampling time. The concentration of gentamicin was detected using fluorescence polarization immunoassay (FPIA) technique. Setting time of the cements was determined with modified Gillmore needle method at 10, 11 and 12 minutes after curing at 37°C. Compressive strength of the cement was tested on the cylinders cured for 24 hours. CPC and FCPC with no gentamicin sulfate added were used as controls for all testing.

Results / Discussion: The indentation load detected in the modified Gillmore needle method for all samples was above 90 lbf (i.e. 400 N) at three testing points: 10, 11 and 12 minutes, indicating the cements set ~ 10 minutes despite the addition of gentamicin sulfate. However, the presence of antibiotic did decrease the load of the cements. For CPC samples, the load decreased by 10% and 47% with the addition of 0.5wt% and 1wt% gentamicin sulfate, respectively. For FCPC, the load decreased by 22% and 42% with the addition of 0.5wt% and 1wt% gentamicin sulfate.

The compressive strength of CPC cements decreased slightly with the presence of gentamicin sulfate. No significant differences were observed for gentamicin impregnated FCPC cements (Figure 1).

For all samples, the release of gentamicin showed initial burst, which was followed by near linear release for up to 14 days (Figure 2). The release was slowed down after the first two weeks, and reached equilibrium ~ 28 days, after which slight increase of release was observed until the end of the 56-day study. FCPC samples showed faster release than CPC samples for both 0.5wt% and 1wt% of drug loading.

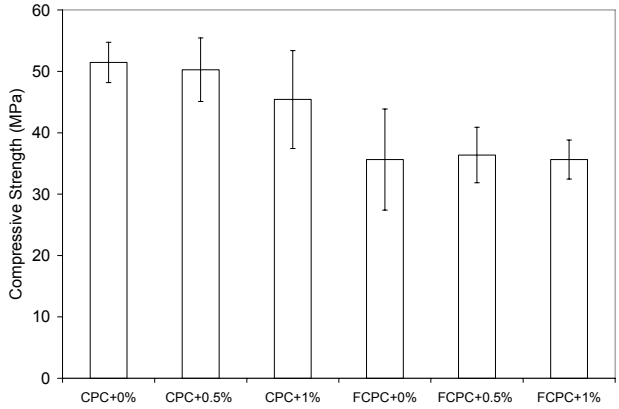

Figure 1. Compressive strength of gentamicin impregnated CPC and FCPC samples compared to the controls (n=6).

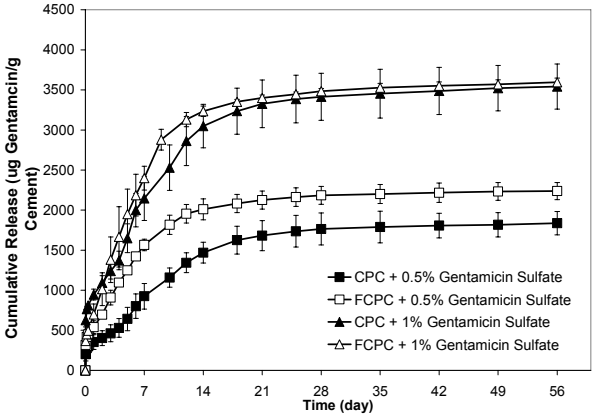

Figure 2. Cumulative release of gentamicin from CPC and FCPC in PBS (pH 7.4, 37°C) for 56 days (n=3).

Conclusions: The release of gentamicin from CPC and FCPC both increased with increasing initial drug content. Even though the indentation load decreased in presence of gentamicin sulfate, the cements impregnated with the antibiotic could still set ~10 minutes under physiological conditions. The compressive strength of cured CPC and FCPC was not statistically affected by the various amounts of gentamicin added in the cements. Altogether, the two calcium phosphate cements evaluated in this study showed their potentials as carriers for controlled local delivery of antibiotics.

References:

1. Wininger, D. et al. Antimicrobial Agents and Chemotherapy (1996) 40(12): 2675-2679.
2. DiCicco M. et al. J. Biomed. Mater. Res. Part B: Appl. Biomater. (2003) 65B: 137-149
3. Neut D et al. Biomaterials (2003) 24: 1829-1831