Characterization and Release Kinetics of Calcium Silicate Cement as a Risedronate Delivery System

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Statement of Purpose: Injectable bone cements, like calcium phosphate cement (CPC) and poly (methyl methacrylate) (PMMA) cement, have been well studied and clinically applied in non-load bearing bone fixation and bone screw augmentation applications. However, their limitations, like low mechanical strength and heat generation, lead especially in patients with osteoporosis to worsening contact between implant and bone and, eventually, implant failure. Calcium silicate cement (CSC) is known to produce higher mechanical strength implants. To additionally promote osteoblast function and bone ingrowth, CSC was prepared containing additionally risedronate (RA), a third generation bisphosphonate. In this study material property changes by RA and the release kinetics of RA from hardened CSC samples in *ex vivo* environment are investigated.

Methods: Ground calcium silicate powder (C_2S:C_3S=1:1, Innovative BioCeramix Inc., Vancouver, Canada), was combined with 0.1, 0.5 and 1.0 weight% of risedronic acid. The cement pastes were molded into 17 mm × 2 mm (diameter × height) and 6 mm × 12 mm polystyrene cylinders for the testing of setting time and compressive strength, respectively, and stored in a 37 °C and 100% RH incubator. The cement setting time was determined in accordance with ASTM Standards Database (ASTM ID: C191-08). The compressive test was carried out at a crosshead speed of 2.54 mm/min on an INSTRON 3369 instrument equipped with a 50 kN load cell. High performance liquid chromatography (HPLC) was used to detect RA release in PBS. The mobile phase was an aqueous phosphate buffer solution (PBS, 1.5 mM Na_2EDTA, 11 mM sodium phosphate and 5 mM tetrabutylammonium bromide as an ion-pair reagent) and methanol (V:V = 88:12, pH = 6.75). The UV detection wavelength was 262 nm and column temperature was 25 °C. A Perkin Elmer Frontier/Spotlight 400 FTIR microscope (Shelton, CT, U.S.A.) was used to detect the RA distribution and possible interaction with CSC in hardened CSC samples.

Table 1: Setting time and compressive strength of calcium silicate cement with different risedronate concentrations

		CSC	CSC (0.1% RA)	CSC (0.5% RA)	CSC (1% RA)
Setting time (min)		56±8	56±6	84±2	96±8
Compressive strength (MPa)	3 Day	25.376±5.166	22.287±6.500	18.214±4.266	0.321±0.078
	7 Day	26.735±5.920	21.624±3.441	19.396±4.292	0.387±0.094

Results: Both setting time and compressive strength (Table 1) were adversely affected by the addition of RA beyond 0.5%. FTIR spectra (Fig. 1) reveal that the phosphonate group (POO^-) which stretches at 951 cm^{-1} and 887 cm^{-1} in RA, shifts to higher wavenumbers of 893 cm^{-1} and 999 cm^{-1} in calcium-RA complexes. In the 10% RA-CSC sample, POO^- stretches at 937 cm^{-1} and 879 cm^{-1} which points to the formation of RA calcium salts in hydrated cements. The FTIR microscope data indicate that risedronate is homogenously distributed within cement pellets (Fig. 1). The cumulative release profiles (Fig. 2) reveals that, in the long-term, RA continued to leach out from the cement pellets at a very slow rate, increasing only by 1% within 5 months.

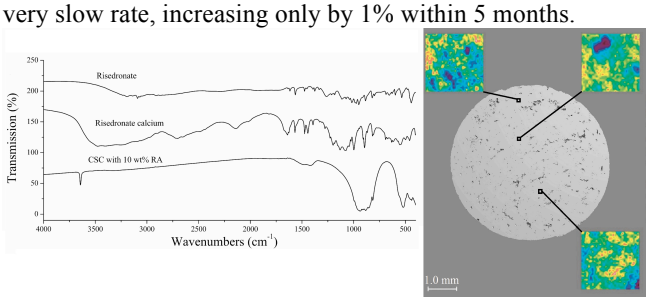

Figure 1: FTIR analyses of pure risedronate, risedronate calcium, CSC with 10wt% risedronate and FTIR microscope analysis of risedronate distribution within CSC

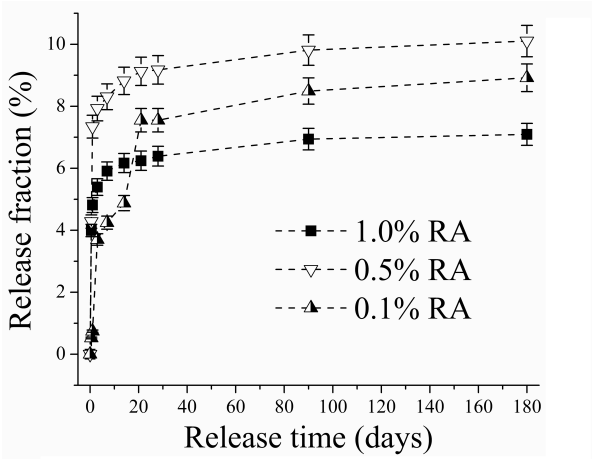

Figure 2: Risedronate fractional releases from different concentration-loaded CSC samples

Conclusions: The setting time and compressive strength results clearly demonstrate that RA modifies calcium silicate cement hydration mechanism, which is attributed to RA high affinity to calcium ions. The IR spectrum of the hardened CSC samples with 10% RA is notably different from that of pure RA or stoichiometric RA-calcium complexes implying the formation of risedronate calcium complexes in CSC, which is not a simple reaction with risedronate and $Ca(OH)_2$. These results indicate that progressively adsorbed onto CSH surfaces, RA is able to inhibit further growth and entanglement of CSH gels, resulting into the loss of mechanical strength. Based upon our study release profiles, CSC is capable of delivering RA in a sustained and controllable manner. CSC is thus able to double up as a slow-release drug delivery vehicle for the third generation bisphosphonate risedronate.

References: Gong TX et al. J Biomed Mater Res Part A. 2013, DOI: 10.1002/jbm.a.34908 (in press).

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