MECHANICAL PROPERTIES AND BIOCOMPATIBILITY OF POLY(METHYL METHACRYLATE) BONE CEMENT CONTAINING MICROENCAPSULATED TISSUE ADHESIVE

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ABSTRACT

One of the most broadly reported self-healing schemes is that pioneered by White and Sottos et al. in which a polymer matrix is co-embedded with a catalyst and microcapsules containing a reactive healing agent. Although this field has been steadily growing over the past 10 years, little discussion of extension into biomaterials has taken place and none of the existing systems employ materials acceptable for *in vivo* applications. Due to its long history of use, lack of post-polymerization modifications, and susceptibility to fatigue failure, poly(methyl methacrylate) (PMMA) bone cement is an attractive option for the first self-healing biomaterial designed utilizing the aforementioned embedded capsule and catalyst approach.

Interfacial polymerization of a polyurethane prepolymer with 1,4-butanediol was performed to encapsulate 2-octyl cyanoacrylate (OCA), an FDA-approved tissue adhesive, using an oil-in-water emulsion. The compressive, tensile, and fracture toughness properties of commercial PMMA matrices containing various wt% of capsules were investigated. The proliferation and viability of MG63 human osteosarcoma cells following various exposure times to extracts from OCA, capsule-embedded bone cement, and bone cement without capsules were also examined.

Incorporation of greater than 5 wt% capsules reduced the compressive and tensile strengths below commercially-accepted standards for bone cement. Fracture toughness, K, was increased by 13% with the inclusion of 3 wt% capsules but was decreased below the control value with contents of 15 wt% and higher. Additionally, cellular viability and proliferation were similar in cells exposed to media conditioned with commercial and capsule-embedded bone cements, suggesting the addition of capsules to the bone cement does not have a detrimental effect on the toxicity of the material.

1. INTRODUCTION

Numerous implants fail due to fatigue, wear, and environmental cracking following the accumulation of microdamage[1], marking these biomaterials as potential candidates for the introduction of self-healing biomaterials. PMMA bone cement is a space-filling matrix that forms mechanical interlocks between the metallic stem of a total joint replacement and the surrounding boney tissue, serving to transfer loads from the prosthesis to the bone[2]. Over time, microcrack formation within the bone cement matrix can lead to implant loosening and subsequent failure; development of a self-healing PMMA could significantly extend the functional lifetime of the implant.

2. MATERIALS

Unless otherwise specified, materials were obtained from commercial suppliers and used without further purification. OCA was generously donated by Ethicon, Inc. Methyl ethyl ketone, methyl isobutyl ketone, and cyclohexanone were used as solvents and 2,4-toluene diisocyanate and 1,4-butanediol were used to synthesize the polyurethane prepolymer following the protocol outlined by Yang et al. and reported by the authors previously[3, 4]. Pluronic F-68 was used as a surfactant. Para-toluenesulfonic acid was added to the organic phase as a stabilizer for the OCA monomer. Commercially-available Palacos R PMMA bone cement was used for all experiments reported herein.

3. METHODS

Interfacial polymerization of a polyurethane prepolymer with 1,4-butanediol was performed to encapsulate OCA using an oil-in-water emulsion[4]. Capsule-containing PMMA samples were fabricated following ASTM F451 and D638 for compression and tension, respectively. Fracture toughness was investigated using the tapered double-cantilever beam (TDCB) geometry described previously[5]. In all samples, the weight of particles (PMMA powder plus OCA-containing capsules) comprised 67% of the sample. Extracts from OCA and bone cement containing 0 or 10 wt% capsules were prepared in culture medium following the recommendations of ISO 10993. MG63 human osteosarcoma cells were cultured in these extract media to observe the effects on cellular proliferation and viability.

4. RESULTS

The minimum standard for the compressive strength of bone cement is 70 MPa[6]. Compressive tests of capsule-embedded bone cement specimens exceeded this criterion up to 5 wt% or less capsules (Figure 1A). However, a 20% decrease in ultimate compressive strength (UCS) occurred when the capsule content was increased to 10 wt%. Incorporation of more than 10 wt% capsules further decreased the compressive strength until 25 wt% capsules, where compressive strength leveled off. Furthermore, specimens containing 10 wt% or less capsules deformed plastically upon failure whereas specimens with higher capsule content fragmented upon failure (Figures 1B and C). The ultimate tensile strength (UTS) of the capsule-embedded specimens decreased monotonically with increasing wt% capsules, whereas the Young's modulus of capsule-containing samples appeared to drop sharply at 5 wt%

then decreased more slowly thereafter. Cements filled with 5 wt% or less capsules lie above the lower limit of the industry standard.

The inclusion of 3 wt% capsules resulted in a 13% increase in average K while inclusion of 5 wt% and 10 wt% capsules yielded K values approximately equal to that of control samples. Increasing capsule content to 15 and 20 wt% resulted in decreases of 26**%** and 47%, respectively when compared with capsule-free controls.

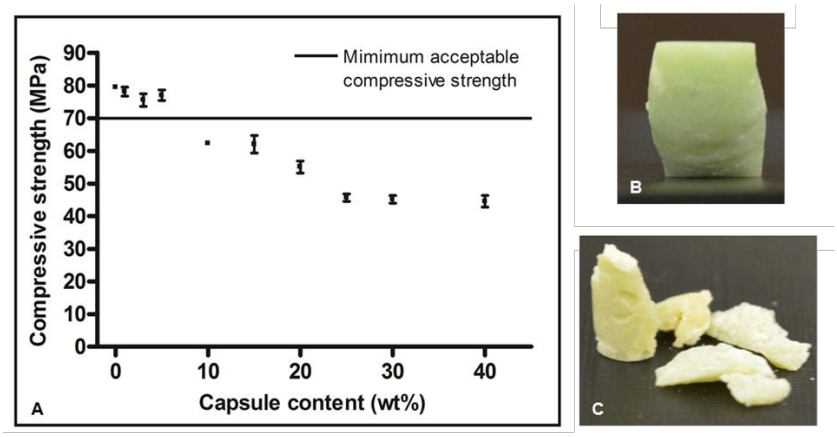

Figure 1: (A) Relationship between capsule content and the ultimate compressive strength of bone cement (average ± SEM, n=3 with 5 replicates per group). Photographs of samples containing (B) 0 wt% and (C) 40 wt% capsules post-compression testing.

The effects of bone cement extract on MG63 proliferation over 24, 48, and 72 h are shown in Figure 2A-C. While proliferation in cells treated with commercial and capsule-embedded (SH) bone cement extracts was significantly reduced with respect to control samples, the addition of capsules did not significantly affect proliferation at 24, 48, or 72 h with respect to samples of bone cement without capsules.

The effects of OCA extract on cellular proliferation over 24, 48, and 72 h are presented in Figure 2D-F. A significant decrease in the proliferation of cells exposed to OCA extract-containing medium diluted to 50% (50% OCA) with respect to control was observed at each time point; the large decrease observed after 48 h suggests the OCA has a delayed effect on proliferation. However, some proliferative recovery is noted after 72 h.

5. CONCLUSIONS

The effects of capsule incorporation on the compressive, tensile, and fracture toughness properties of bone cement showed that inclusion of greater than 10 wt% capsules resulted in the decrease of UCS and UTS below the commercially-required levels; the fracture toughness was improved with the incorporation of 3 wt% capsules but declined as content was increased above 15 wt%. The effects of extract from a capsule-embedded bone cement on the proliferation and viability of MG63 human osteosarcoma cells indicated the addition of capsules did not significantly affect the response of the cells to the PMMA. The effects of both capsule-embedded bone cement and OCA extracts were found to be mediated through dilution of the extract.

Cells also demonstrated the potential to regain proliferative ability with increasing exposure time.

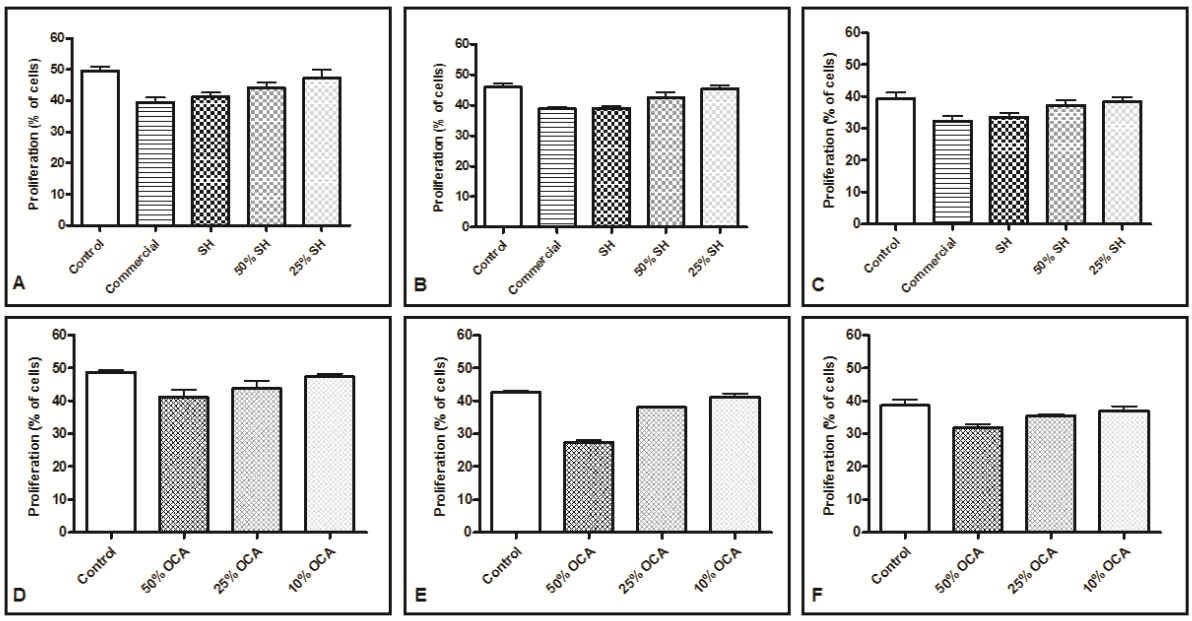

Figure 2: Proliferation of MG63 human osteosarcoma cells in response to growth in extract from (A,B,C) bone cement and (D, E, F) OCA after (A, D) 24, (B, E) 48, and (C, F) 72 h (average ± SEM, n=4).

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