Published in final edited form as:

J Biomed Mater Res B Appl Biomater. 2015 February ; 103(2): 305–312. doi:10.1002/jbm.b.33199.

Extended fatigue life of a catalyst-free self-healing acrylic bone cement using microencapsulated 2-octyl cyanoacrylate

Alice P.W. Brochu¹, Oriana B. Matthys¹, Stephen L. Craig², and William M. Reichert^{1,*}

¹Department of Biomedical Engineering, Duke University, Box 90281, Durham, North Carolina 27708

²Department of Chemistry, Duke University, Box 90154, Durham, North Carolina 27708

Abstract

The tissue adhesive 2-octyl cyanoacrylate (OCA) was encapsulated in polyurethane microshells and incorporated into bone cement to form a catalyst free, self-healing bone cement comprised of all clinically approved components. The bending strength, modulus, and fatigue lifetime were investigated in accordance with ASTM and ISO standards for the testing of PMMA bone cement. The bending strength of bone cement specimens decreased with increasing wt% capsules content for capsules without or with OCA, with specimens of < 5 wt% capsule content showing minimal effect. In contrast, bone cement bending modulus was insensitive to capsule content. Load controlled fatigue testing was performed in air at room temperature on capsule free bone cement (0 wt%), bone cement with 5 wt% OCA-free capsules (5 wt% No OCA), and 5 wt% OCA-containing capsules (5 wt% OCA). Specimens were tested at a frequency of 1 Hz at maximum stresses of 90%, 80%, 70% and 50% of each specimen's bending strength until failure. The 5 wt% OCA exhibited significant self-healing at 70% and 50% of its reference strength ($p < 0.05$). Fatigue testing of all three specimen types in air at 22 MPa (50% of reference strength of the 5 wt% OCA specimens) showed that the cycles to failure of OCA-containing specimens was increased by two-fold compared to the OCA-free and capsule-free specimens. This study represents the first demonstration of dynamic, catalyst free self-healing in a biomaterial formulation.

Introduction

Self-healing materials (SHM) are designed to halt and repair microdamage accumulated during repetitive subcritical loading (e.g. fatigue). The first description of autonomous repair of polymer damage came from Dry in 1996 [1] who reported the incorporation of liquid resin filled fibers into polymer matrix. In this scheme a propagating crack causes fiber rupture, releasing resin into the crack plane where it cures and heals the crack. This approach somewhat mimics a network of blood vessels responsible for healing of damaged tissue [2]. The team of White, Sotos and Moore has reported extensively on a similar strategy where liquid monomer is contained in microcapsules that are distributed at 5–10 wt% in polymer matrix [3–10]. Again, capsule rupture by a propagating crack releases

*corresponding author.

monomer into the crack plane where the monomer is exposed to co-embedded catalyst, cures, and heals the crack.

The SHM field has been steadily growing over the past ten plus years, but with only minor extension into polymeric biomaterials [9-11]. This is in spite of the fact that numerous biomedical implants fail following the accumulation of microdamage during repetitive loading [9]. Current SHMs generally do not utilize materials that are acceptable for clinical use and any SHM formulation proposed for a biomedical application would need to be assessed using accepted ASTM and ISO standards for the mechanical and biocompatibility characterization of biomaterials.

Our goal has been to fabricate a self-healing biomaterial from materials that are currently in clinical use, and to do this in a manner that avoids the use of potentially toxic catalysts. PMMA bone cement is a simple two-component thermoset that has a long history of use in total joint replacement surgeries, does not require post-polymerization modifications, and is in need of improvement to its fatigue resistance. For these reasons, PMMA bone cement was an attractive option for the first self-healing biomaterial designed using the matrix repolymerization scheme [9, 12]. Our scheme is to encapsulate the water-reactive healing agent 2-octyl cyanoacrylate (OCA) tissue adhesive, commercially-known as Dermabond™, in polyurethane (PUR) microcapsules, and then disperse the capsules in a matrix of Palacos R PMMA bone cement [10]. This creates a catalyst-free self healing bone cement system is based on the matrix repolymerization scheme (Figure 1).

We recently reported the successful encapsulation of OCA in PUR microspheres and its incorporation into a Palacos R bone cement matrix [10]. Subsequently we characterized the tension, compression, fracture toughness, and cytotoxicity of the bone cement embedded with OCA-containing microcapsules using ASTM and ISO standards [13]. Results showed that 5 wt% was the maximum capsule content that could be used in the bone cement while still adhering to commercial requirements and reported values for sample stiffness, strength, and fracture toughness (5 wt% is a typical maximum capsule content used in the SHM field [14, 15]). Furthermore, the addition of OCA-containing capsules to the matrix was not found to affect the viability and proliferation of MC63 human osteosarcoma cells in elution cytotoxicity testing [15].

The current study represents the first demonstration of dynamic, catalyst-free self healing in a biomaterial formulation. Protocols established for testing of bone cement were used to measure the bending strength, bending modulus, and fatigue lifetime of the self-healing cement in accordance with the standards for the 4-point bending testing of bone cement [16, 17]. In-air fatigue testing at room temperature of 5 wt% OCA specimens clearly exhibited self-healing that was absent in 0 wt% specimens, and in 5 wt% No OCA specimens. The extent of self-healing increased with decreasing maximum load as the rate of microdamage accumulation decreased.

Experimental Section

Reagents

Materials were obtained from commercial suppliers and used without further purification. OCA was generously donated by Ethicon, Inc., Raleigh, NC. Methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), and cyclohexanone (Sigma Aldrich) were used as solvents and 2,4-toluene diisocyanate (TDI) and 1,4-butanediol (1,4-BD) (Sigma Aldrich) were used to synthesize the polyurethane prepolymer (pPUR) following the protocol outlined by Yang et al. and reported by the authors previously [10, 16]. Pluronic F-68 (Sigma Aldrich) was used as a surfactant. *Para*-Toluenesulfonic acid (Sigma Aldrich, PTSA) was added to the organic phase as a stabilizer for the OCA monomer. Commercially available Palacos R PMMA bone cement (Zimmer) was used for all experiments reported herein.

Microcapsule preparation

Microcapsules were prepared and characterized as described previously [10]. Briefly, at room temperature, Pluronic F-68 surfactant (1.84 g) was dissolved in deionized water (90 mL) in a 250 mL beaker. The solution was agitated for 1 h with a digital mixer (VWR PowerMax Elite Dual Speed Mixer) before beginning the encapsulation procedure. The aqueous phase was suspended in a hot water bath and heated to 50 °C prior to the addition of the organic phase and chain extender.

OCA (4 mL) was dissolved in MIBK (8 mL) and pPUR (3 g) were dissolved in MEK (10 mL) separately at room temperature. PTSA (1%) was added to the OCA-MIBK solution to further stabilize the OCA monomer. The pPUR- and OCA-containing solutions were then added simultaneously to the aqueous phase but not mixed prior to this addition. After the organic and aqueous phases were combined, the 1,4-BD (3 mL) chain extender was added dropwise to the stirring mixture via a syringe to form the segmented PUR shell material consisting of hard TDI-based segments and soft 1,4-BD segments. After a reaction time of 2 h at an agitation rate of 700 rpm, the mixer was switched off and the suspension of microcapsules rinsed with deionized water and vacuum filtered. Capsules were air-dried prior to use in the following experiments [10]. To manufacture OCA-free control capsules, the OCA was replaced with additional MIBK (4 mL) and the agitation rate reduced to 450 rpm; all other aspects of the encapsulation procedure were performed identically.

Microcapsules incorporation into bone cement matrix

Volume fraction is preferentially used to describe the dispersed phase content of in composite modeling; however, the SHM community exclusively describes capsule content using weight percent ($\text{wt}\% = 100 \times \text{mass fraction of capsules}$). We have chosen to adhere to the $\text{wt}\%$ convention in order to compare our results to the existing SHM literature. As such, the powder and liquid components of the bone cement were mixed according to the manufacturer's instructions [19]. Capsules were added to the slurry and the resultant dough was pressed into molds to form the desired rectangular specimens (see below). The amount of capsules in the bone cement composites in this study ranged from 0wt% to 15wt%, where the total $\text{wt}\%$ of particulates (capsules plus PMMA powder) was held constant at 5wt% in all specimens.

Bending tests

Following ISO 5833, rectangular bone cement samples were cured in rectangular silicone rubber molds for 1 h and then smoothed, producing specimens with dimensions of 10.0mm by 3.3mm by 75mm. 24 h post-manufacturing, specimens were subjected to 4-point bending at a crosshead speed of 5 ± 1 mm/min until failure using a Test Resources 840LE2 Electrodynamic tension-compression-flexural fatigue machine (Shakopee, MN). All tests were performed in air at room temperature.

The bending strength, B , was calculated using Equation 1 where F is the force at break (in N), b is the average measured width of the specimen (10 mm), h is the average measured thickness (3.3 mm), and a is the distance between the inner and outer loading points (20 mm).

$$B = \frac{3Fa}{bh^2} \quad (1)$$

Equation 2 was used to determine the bending modulus, E , where f is the difference in the deflection under the loads of 15N and 30N (in mm), b is the average measured width of the sample (10mm), h is the average thickness (3.3mm), l is the distance between the outer loading points (60mm), ΔF is the load range over which the deflection was measured (15N), and a is the distance between the inner and outer loading points (20mm). The commercial requirements for B and E as stipulated by ISO 5833 are 50 and 1800MPa, respectively.

$$E = \frac{\Delta Fa}{4fbh^3} (3l^2 - 4a^2) \quad (2)$$

Fatigue tests

Following the protocols of Kuehn et al. [16] and Soltesz et al. [17], the ISO 5833 4-point bending standard was used for fatigue testing of bone cement specimens. Rectangular specimens were prepared as described for the bending tests. Based on the current bending test results, and on previous studies of the static mechanical properties of capsule-containing PMMA samples [13], three types of specimens were employed for fatigue tests: capsule-free specimens (0wt%), specimens containing 5wt% OCA-filled capsules (5wt% OCA), and specimens containing 5wt% capsules that contained no OCA (5wt% No OCA).

All samples were tested 1 day after manufacturing in air at room temperature. The samples were cycled to failure under load control using a Test Resources 840LE2 Electrodynamic tension-compression-flexural fatigue machine. The bending strengths determined for each of the three specimen types were used as the reference strengths for the fatigue tests. As recommended in the bone cement literature [17, 20-22], 10 samples ($n=10$) of each specimen type were subjected to load-controlled fatigue testing at a loading ratio R ($\sigma_{\min}/\sigma_{\max}$) of 0.05 and a frequency of 10 Hz. Ten samples of each specimen type were subjected to a $\sigma_{\max}$ of 90%, 80%, 70% or 50% of the specimen's reference strength. These data were used to generate stress vs. number of cycles to failure (S-N) graphs [23].

Weibull analysis

Probability-of-failure curves, $P(N_f)$, were generated from the S-N data using Equation 3 where N_f is the number of cycles to failure, and M and G are the failure order number and the total number of specimens tested, respectively [22, 24]. The failure order number is defined as the number assigned to an N_f value to denote its position within a list of G values arranged in ascending order of magnitude, $M=1,2,3...G$.

$$P(N_f) = (M - 0.3) / (G + 0.4) \quad (3)$$

For a given stress level, the N_f results were fitted to the linearized form of the 3-parameter weibull equation in Equation 4 where N_0 is the minimum or guaranteed fatigue life (i.e. the number of cycles below which no samples will fail), N_a is the characteristic fatigue life (i.e. the characteristic number of cycles to failure), b is the Weibull slope (a measure of the spread of the data), and N_0 is the number of cycles below which 63.2% of the N_f values. N_0 , N_a , N_f and b were all determined from plots of $\ln(N_f)$ vs. $\ln \ln[1/(1-P(N_f))]$ for each specimen type and applied stress level [22, 25, 26].

$$\ln \ln \left[\frac{1}{(1 - P(N_f))} \right] = b \ln(N_f - N_0) - b \ln(N_a - N_0) \quad (4)$$

The Weibull mean, N_{WM} , also called the index of fatigue performance, was calculated using Equation 4.

$$N_{WM} = N_a \sqrt{b} \quad (4)$$

Statistical analyses

All average values were reported as $\pm$ standard error of the mean. Independent two-sample t -tests were used to compare the average number of cycles to failure of the three specimen types at various load levels as well as the individual capsule compressive strengths of samples taken from each treatment at a given time point. The level of statistical significance was set at $p < 0.05$.

Results

Capsule morphology

OCA-containing capsules fabricated at an agitation rate of 700 rpm, and OCA-free capsules fabricated at an agitation rate of 450 rpm, both exhibited uniform spherical morphologies. Table 1 lists the average diameters and shell thicknesses of the capsules prepared in these studies. These results were consistent with previously reported data on capsule fabrication [10, 13].

Bending tests

Figures 2A and 2B contain the bending strength B and bending modulus E , respectively, of Palacos R bone cement as a function of wt% of capsules containing OCA (OCA) and without OCA (No OCA). The horizontal lines are the minimum values of bending strength (50MPa) and bending modulus (1800MPa) required of commercial bone cements. The bending strength and bending modulus of the capsule-free bone cement were both well above the minimum values and were similar to those reported in the literature for Palacos R bone cement [16, 21]. Bending strength decreased monotonically with increasing OCA-containing (OCA) and OCA-free (No OCA) capsule content (Figure 2A), and exceeded the commercial minimum for specimens containing 2 wt% OCA capsules and 10wt% for No OCA specimens. In contrast bending modulus was largely insensitive to capsule content (Figure 2B) and exceeded the minimum requirement for all capsule contents tested.

Fatigue tests: percentage of specimen-specific reference stress

The ISO 5833 4-point bending standard was used for fatigue testing of bone cement specimens that was either void of capsules (0wt%) or were filled with 5wt% of either OCA-free capsules (5wt% No OCA) or OCA-containing capsules (5wt% OCA). Load-controlled tests were performed until specimen failure for 90%, 80%, 70% and 50% of the specimen reference stress. Reference stress values used were the 4-point bending strengths listed in Table 2 for each specimen type.

Figure 3A is the S-N fatigue plot (applied stress v. cycles to failure) for bone cement specimens that either lacked capsules (0wt%) or were filled with 5wt% of either OCA-free capsules (5wt% No OCA) or OCA-containing capsules (5wt% OCA). Figure 3B compares the average cycles to failure of the three specimen types at each applied percent reference stress. Overall, the average cycles to failure, also referred to as the fatigue life, increased with decreasing percent reference stress applied to the specimens. The cycles to failure for all specimen types were grouped at 90% and 80% of the reference stress; however, the cycles to failure of 5wt% OCA specimens were significantly longer at 70% and 50% of the specimen reference stress, with the 50% data set showing the most dramatic increase.

Figure 4 contains the probability of failure plots where the least (30%) and the greatest (50%) extension of cycles to failure were observed for 5 wt% OCA specimens. The three failure curves for 90% reference stress trials were essentially indistinguishable, whereas the failure curve at 50% reference stress for the 5 wt% OCA specimens was shifted to much higher cycles to failure, or a significantly extended fatigue life, compared with 0 wt% and 5 wt% No OCA specimens.

Table 3 lists the average cycles to failure measured experimentally for the 50% reference stress trials, and the Weibull parameters for these data sets. For the measured values the 5wt% OCA specimens exhibited a 22-fold increase in fatigue life over 0wt% specimens, and a 15-fold increase in fatigue life over 5wt% No OCA specimens. The corresponding differences for the fitted Weibull mean fatigue life (N_{WM}) were 26-fold and 18-fold respectively. The minimum fatigue life (N_0) predicted that the 5wt% OCA specimens would

experience 9-fold and 7-fold, respectively, more cycles without any incidence of failure compared 0 wt% and 5 wt% No OCA specimens.

Fatigue tests: 50% reference stress of 5wt% OCA specimen

Because 5 wt% OCA had a lower reference stress than the other two specimen types (Table 1), the fatigue tests were repeated for all specimen types at the 50% reference stress of the 5wt% OCA specimens, or 22MPa. This allowed a normalized comparison under loading conditions where the greatest extension of fatigue life was observed.

Table 4 and Figure 5 show that the 5wt% OCA specimens again exhibited significantly higher cycles to failure compared to the other specimen types. For the measured values, the 5wt% OCA specimens exhibited 2-fold increases in fatigue life over 0wt% specimens and the 5wt% No OCA specimens. The corresponding differences for the fitted Weibull mean fatigue life (N_M) were 2.4-fold and 2.0-fold, respectively. The minimum fatigue life (N_0) of 5wt% OCA was 1.3-fold longer than that predicted for 0wt% specimens, but was only 3% different than that predicted for 5wt% No OCA.

Discussion

A variety of schemes have been developed to allow for the autonomous healing of polymers employing both nonreversible and reversible chemistries, which we recently reviewed through the lens of developing self-healing biomaterials [9]. Self-healing thermosets and thermoplastics are designed to resist failure by repairing microcracks before they accumulate into propagating cracks. The most widely employed self-healing scheme for thermoplastics and thermosets involves co-embedding a polymer matrix with catalyst and a reservoir of liquid healing agent, either in hollow fibers or microcapsules [1,5]. Microcracks formed during mechanical perturbation cause the fiber or capsule rupture, thus releasing healing agent that fills the crack plane, and cures in the presence of the co-embedded catalyst.

In the current study, the microcapsule approach was investigated for developing self-healing bone cement. Palacos R PMMA bone cement was embedded with FUR microcapsules containing OCA tissue adhesive. All three materials are widely used in biomedical applications. Because OCA curing is initiated by moisture, our formulation also eliminated the need for a potentially toxic catalyst.

For the OCA-containing bone cement specimens tested here, acceptable bending strength was maintained at capsule contents of 5wt% or less (Figure 2A). This observation was expected as we already reported that 5wt% capsular content was the upper limit for acceptable PMMA bone cement compression, tension, and fracture toughness properties [13]. Interestingly, the bending modulus E remained nearly constant regardless of capsule content in OCA and No OCA samples (Figure 2B).

The bending strength B is a function of F , the force at break, whereas the bending modulus E is a function of the specimen deflection f between specific load levels. The remaining terms in Equations 1 and 2 are experimental and geometric constants. The force at break is the load at which the specimens become so strained that crack propagation occurs to

specimen failure. This value was clearly affected by the presence of capsules with and without OCA (Figure 2A). It is well-established that particles in a polymer matrix can serve as sites for crack initiation and preferred paths for crack propagation if adhesion between particle and matrix is poor [27], which is probably the case with our formulation. In contrast, the bending deflection was measured within in the elastic region of the specimens where cracks are less likely to have formed. E was therefore dominated by the modulus of the PMMA matrix that made up 85-100% of the weight of the specimens tested. Based on the above bending strength results, and the recently reported mechanical testing of our formulation [13], it was concluded that 5wt% capsular content had only minimal impact on the mechanical properties of PMMA bone cement. A 5wt% capsule content is a standard loading threshold that is widely used throughout the SFM literature [14, 15].

PMMA bone cement utilized in load bearing implants does not fail under constant strain rate until failure; rather, it suffers from fatigue caused by repetitive subcritical loading [28]. Therefore, the next step was to measure the self-healing capacity of bone cement embedded with 5wt% OCA-containing capsules under dynamic loading conditions. Load-controlled 4-point bending fatigue tests were conducted with bone cement specimens containing 0wt% capsules, with 5wt% OCA-free capsules, and 5wt% OCA-containing capsules. Self-healing would be evident if the specimens containing OCA-filled capsules exhibited increased cycles to failure compared to the other specimen types. These studies were conducted on specimens stored in air at room temperature over a range of applied stresses that were percentages of each specimen's bending strength (Table 2).

The lower the percentage reference tested, the higher the number of cycles to failure for all specimen types (Figure 3 and 4). Most importantly, the presence of OCA-filled capsules (5wt% OCA) extended the fatigue life of bone cement specimens at 70% and 50% reference stress that did not occur for capsule-free bone cement (0 wt%) or bone cement filled with OCA-free capsules (5wt% No OCA). Encapsulated OCA also extended bone cement fatigue life by 2-fold compared to the other specimen types when all three specimen types were tested at the 50% reference stress of 5wt% OCA (Figure 5). Testing at the same reference stress clearly normalized the comparison; however, the normalized self-healing effect was less than what we would have predicted based on the non-normalized results.

The OCA-containing specimens tested at 90% and 80% of the reference stress did not exhibit self-healing. In spite of OCA's relatively rapid reaction kinetics, we hypothesize that the rate of damage accumulation in the specimens tested at 90% and 80% of reference strength was higher than the rate of OCA release and curing; whereas the rate of damage accumulation was sufficiently slow at 70% and 50% reference strength conditions to allow for self-healing by OCA release and curing.

It is important to note that all of the applied stresses in the fatigue tests exceeded the loads experienced during normal ambulation. For example, each step places approximately 2 times body weight distributed over the femoral head surface area of 2in^2 , which for a 150lb person is approximately 225psi, or 1.6 MPa. Assuming that each hip is loaded at $\sim 1\text{ Hz}$, normal walking corresponds to applied loads of 1.6MPa/cycle. In contrast, our most mild fatigue testing condition was 22MPa at 5Hz, or 4.4MPa/cycle at 5 times the cycling rate. Therefore

the lowest loading per cycle tested here was nearly three-fold higher at 5 times the duty cycle than that experienced during normal ambulation. We hypothesize that the lower loading during walking would result in a slower rate of microcrack accumulation and thus be more conducive to self-healing of bone cement by OCA release and curing.

Other water-reactive healing agents have been proposed for various self-healing applications [29, 30]. These composites were intended to react with ambient humidity upon damage, yielding stable healing that was not dependent on the released healing agent encountering catalyst in the damage plane. Garcia et al. developed a self-healing anticorrosive organic coating based on the polymerization of water-reactive octyl dimethylsilyloleate, a silyl ester encapsulated in the urea-formaldehyde capsules utilized by White et al. for numerous self-healing systems [5, 29]. This monomer and encapsulation procedure utilized materials unacceptable for *in vivo* applications, but demonstrated effective healing of a surface defect in a thin film resulting from monomer exposure to ambient humidity and its subsequent polymerization. Additionally, a self-healing concrete was developed wherein microcrack formation exposed dry cement depots within the concrete to water and carbon dioxide; the reaction formed a calcium carbonate “seal” within the concrete that filled microcracks to halt propagation and increase the concrete’s strain at failure [30].

Finally, the team of White, Sottos, and Moore has begun adapting their repolymerization schemes to formulate self-healing bone cements and dental resins. This group recently presented the encapsulation of low toxicity organic liquids to induce self-healing by solvent welding of PMMA following capsule rupture [31]. They have also reported the self-healing of dental resin mimics that employ the free radical polymerization where the acrylate monomer and peroxide initiator occupied separate capsules [11]. In both cases the healing efficiency was determined by measuring the fracture toughness of the virgin matrix, and then immediately re-apposing the fractured pieces to allow the released healing agent to cure in the crack plane. The healed specimen was then tested to determine the fractional recovery of the original virgin fracture toughness. The dental resin exhibited >70% self-healing efficiency, including following immersion in buffered saline at 37 °C; however all specimens were singularly macro-fractured, physically immobilized, and then subjected to prolonged curing times (e.g. 24h).

The current study represents the first demonstration of dynamic, catalyst-free self-healing in a biomaterial formulation. Well-established bone cement testing protocols for 4-point bending strength, stiffness and fatigue life were employed. In our opinion, prolongation of specimen fatigue life was a more functionally appropriate means of demonstrating self-healing in bone cement than was fracture toughness, although the fracture toughness of our system has been reported [11]. However, all tests were conducted in air at room temperature.

One of the key tradeoffs associated with capsule-based SHMs is that increasing the wt% of healing agent containing capsules on one hand decreases the intrinsic mechanical strength of the matrix material, while on the other hand increases the material’s self-healing capacity. For applications in total joint replacements, where the intrinsic properties of PMMA far exceed the loads experienced *in vivo*, it could be argued that reductions in intrinsic tensile, compressive, and bending strengths are worth the tradeoff for a significant increase in

fatigue lifetime. The current and previous studies on our OCA-PMMA system have shown this tradeoff occurs around 5 wt% capsules.

That said, the functional lifetime of the encapsulated OCA, compared with that of commercial acrylic bone cement needs further study to determine its clinical usefulness. Given the modes of bone cement failure *in vivo*, more complex and biomimetic loading strategies and testing in simulated body fluid at 37 °C will be necessary. *In vivo* bone tissue compatibility studies are also required. Expansion of testing into more biomimetic realms may also require optimization of the capsule shell material to improve the long-term stability of PUR in PMMA. Potential solutions involve functionalizing the capsule shell to improve its hydrophobicity and protect the OCA core; additionally, functionalizing with chemistries that more closely resemble the PMMA matrix and may improve adhesion at the capsule/matrix interface. Alternative capsule materials, such as urea-formaldehyde or silica, may also improve this self-healing system.

Conclusions

Capsule inclusion at or below 5wt% resulted in a bending strength at or above commercial standards, while the bending stiffness was maintained above commercial standards at all capsule contents tested. Bone cement with 5wt% OCA containing capsules displayed dynamic self-healing properties at lower load levels when compared with capsule-free specimens, and those containing 5wt% OCA-free capsules. These results clearly demonstrate the feasibility of developing a self-healing bone cement based on encapsulated OCA tissue adhesive.

Acknowledgments

The authors would like to thank Ethicon, Inc. for the generous donation of 2-octyl cyanoacrylate tissue adhesive. The authors also gratefully recognize the contributions of Duke University colleague Steven Owen for specimen mold manufacturing, Gregory Evans for sample fabrication, Zachary Keen for polymer synthesis, and Charles Wallace and Matthew Novak for assistance with statistical analysis. This research was supported by NIH grant EB 013874 (WMR).

References

1. Dry C. Procedures developed for self-repair of polymer matrix composite materials. *Composite Structures*. 1996; 35:263–9.
2. Tooley KS, Sottos NR, Lewis JA, Moore JS, White SR. Self-healing materials with microvascular networks. *Nature Materials*. 2007; 6:581–5.
3. Kessler MR. Self-healing: a new paradigm in materials design. *Proceedings of the Institution of Mechanical Engineers Part G-Journal of Aerospace Engineering*. 2007; 221:479–95.
4. Kessler MR, Sottos NR, White SR. Self-healing structural composite materials. *Composites Part a-Applied Science and Manufacturing*. 2003; 34:742–52.
5. White SR, Sottos NR, Geubelle PH, Moore JS, Kessler MR, Sriram SR, et al. Autonomic healing of polymer composites. *Nature*. 2001; 409:794–7. [PubMed: 11236987]
6. Andersson, HM.; Keller, MW.; Moore, JS.; Sottos, NR.; White, SR. Self-Healing Polymers and Composites.. In: Zwaag, Svd, editor. *Self Healing Materials: an Alternative Approach to 20 Centuries of Materials Science*. Springer: AA Dordrecht, The Netherlands; 2007. p. 19–44.
7. Kessler MR, White SR. Self-activated healing of delamination damage in woven composites. *Composites Part a-Applied Science and Manufacturing*. 2001; 32:63–99.

8. Bergman, SD.; Wuld, E. Remendable Polymers.. In: Zwaag, Svd, editor. Self Healing Materials: an Alternative Approach to 20 Centuries of Materials Science. Springer; AA Dordrecht, the Netherlands; 2007. p. 45-68.
9. Eroch ABW, Craig SL, Reichert WM. Self-healing biomaterials. Journal of Biomedical Materials Research Part A. 2011; 91A:492–506. [PubMed: 21171168]
10. Brochu ABW, Chyalla WJ, Reichert WM. Microencapsulation of 2-octylcyanoacrylate tissue adhesive for self-healing acrylic bone cement. Journal of biomedical materials research Part B, Applied Biomaterials. 2012; 100B:176–72.
11. Dailey MMC, Silvia A V, McIntire PJ, Wilson GO, Moore JS, White SR. A self-healing Biomaterial based on free-radical polymerization. Journal of Biomedical Materials Research Part A. 2013:n/a–n/a.
12. Lewis G, Wellborn B, Jones L II, Biggs T. A room-temperature autonomically-healing PMMA bone cement: influence of composition on fatigue crack propagation rate. Journal of Applied Biomaterials & Biomechanics. 2009; 1:90–6. [PubMed: 20799168]
13. Brochu ABW, Evans GA, Reichert WM. Mechanical and cytotoxicity testing of acrylic bone cement embedded with microencapsulated 2-octyl cyanacrylate. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2013:n/a–n/a.
14. Browne EN, White SR, Sottos NR. Retardation and repair of fatigue cracks in a microcapsule toughened epoxy composite - Part I: Manual infiltration. Composites Science and Technology. 2005; 65:2466–73.
15. Browne EN, White SR, Sottos NR. Retardation and repair of fatigue cracks in a microcapsule toughened epoxy composite - Part II: In situ self-healing. Composites Science and Technology. 2005; 65:2474–80.
16. Kuehn KD, Ege W, Gopp U. Acrylic bone cements: mechanical and physical properties. Orthopedic Clinics of North America. 2005; 36:29–41. [PubMed: 15542120]
17. Soltesz U, Schäfer R, Jaeger R, Gopp U, Kühn K-D. Fatigue Testing of Bone Cements - Comparison of Testing Arrangements. Journal of ASTM International. 2005:2.
18. Yang JL, Keller MW, Moore JS, White SR, Sottos NR. Microencapsulation of Isocyanates for Self-Healing. Polymers. Macromolecules. 2008; 41:5550–5.
19. Palacos R Instructions for use. Zimmer Surgical, inc.; Dover; 2012.
20. Jeffers JT, Browne M, Jenson AB, Prendergast PJ, Taylor M. Cement mantle fatigue failure in total hip replacement: Experimental and computational testing. Journal of Biomechanics. 2007; 40:1525–33. [PubMed: 17070816]
21. Soltesz U. The influence of loading conditions on the lifetimes in fatigue testing of bone cements. Journal of Materials Science-Materials in Medicine. 1994; 5:654–6.
22. Lewis G. Fatigue testing and performance of acrylic bone-cement materials: State-of-the-art review. Journal of Biomedical Materials Research Part B- Applied Biomaterials. 2003; 66B:457–86.
23. Kuehn, K-D. Bone Cements. Up-to-Date Comparison of Physical and Chemical Properties of Commercial Materials. Springer; Heidelberg; 2000.
24. Lewis G, Austin GE. Mechanical properties of vacuum-mixed acrylic bone cement. Journal of Applied Biomaterials. 1994; 5:307–14. [PubMed: 8180537]
25. Lewis G, Janna S, Bhattarain A. Influence of the method of blending an antibiotic powder with an acrylic bone cement powder on physical, mechanical, and thermal properties of the cured cement. Biomaterials. 2005; 26:4317–25. [PubMed: 15635656]
26. Lewis G, Janna SI. Effect of fabrication pressure on the fatigue performance of Cemex XL acrylic bone cement. Biomaterials. 2004; 25:1415–20. [PubMed: 14643616]
27. Fu S-Y, Feng X-Q, Lauke B, Mai Y-W. Effects of particle size, particle/matrix interface adhesion and particle loading on mechanical properties of particulate-polymer composites. Composites Part B: Engineering. 2008; 39:933–61.
28. Perek J, Pilliar RM. Fracture toughness of composite acrylic bone cements. Journal of Materials Science-Materials in Medicine. 1992; 3:335–44.

29. Garcia SJ, Fischer HP, White PA, Marquet J, Gonzalez-Garcia Y, Mol JMC, et al. Self-healing anticorrosive organic coating based on an encapsulated water reactive silyl ester: Synthesis and proof of concept. *Progress in Organic Coatings*. 2011; 70:142–9.
30. Yang YZ, Lepech MD, Yang EH, Li VC. Autogenous healing of engineered cementitious composites under wet-dry cycles. *Cement and Concrete Research*. 2009; 39:382–90.
31. White JR.; Gladman, AS.; Celestine, AD.; Moore, JS.; Sottos, NR. Self-healing PMMA biomaterials.. 4th International Conference on Self-Healing Materials.; Ghent, Belgium. 2013; Ghent University; Delft University of Technology;

FIGURE 1.
Schematic illustration of self-healing bone cement formulation.

FIGURE 2.

Bending strengths (A) and bending moduli (B) for specimens embedded with OCA-containing and OCA-free capsules (average 6 SEM, n 5 5). Note that the variance in each measurement was so small that the error bars were often smaller than the symbol size.

FIGURE 3.

The number of cycles to failure for each specimen type recorded at 90%, 80%, 70% and 50% of the applied reference stresses (A) (n = 5-10). The average numbers of cycles to failure were significantly higher in the OCA-containing specimens at 70% and 50% of the applied reference strengths compared to the other two specimen types (B).

FIGURE 4.

Probability of failure curves for samples tested in air indicate that specimens loaded to 90% of their reference strength underwent similar numbers of cycles to failure regardless of specimen type. When tested to only 50% of their reference strength, OCA-containing samples demonstrated prolonged lifetime when compared with the OCA-free specimens.

FIGURE 5.

Average number of cycles to failure for each specimen type when tested at 50% of the OCA-containing reference strength of 22 MPa (n = 5). OCA-containing specimens exhibited approximately two times as many cycles to failure.

Table 1

Average capsule diameter and capsule shell thicknesses (n=3)

	Diameter (μm)	Shell thickness (μm)
OCA-containing capsules	132 $\pm$ 29	2 $\pm$ 0.5
CCA-free capsules	59 $\pm$ 15	3 $\pm$ 0.7

Table 2

Bending strength and bending modulus (n=5).

	0 wt%	5 wt% No OCA	5 wt% OCA
Bending strength (MPa)	74.6 ± 1.2 (±1.6%)	65.7 ± 2.2 (±1.6%)	44.2 ± 1.5 (±3.4%)
Bending modulus (MPa)	3047 ± 56 (±1.8%)	2932 ± 41 (±1.4%)	3078 ± 31 (±1.0%)

Table 2

Experimental and Weibull fitted fatigue life of capsule-filled and capsule-free bone cements tested at 50% of specimen reference strength

Condition	0 wt%	5 wt% No OCA	5 wt% OCA
Measured average fatigue life (cycles)	24598 ± 4508 (±18%)	35991 ± 6011 (±16%)	552167 ± 105125 (±19%)
Characteristic fatigue life, N_a (cycles)	24389	32199	532698
Minimum fatigue life, N_m (cycles)	9897	11199	84966
Weibull slope, b	0.7323	0.6105	0.6025
Weibull mean, N_{wm} (cycles)	20871	30852	544661

Table 2

Experimental and Weibull fitted fatigue life of capsule-filled and capsule-free bone cements tested at 50% of the reference strength of 5 wt% OCA (22 MPa)

Condition	0 wt%	5 wt% No OCA	5 wt% OCA
Average fatigue life (cycles)	287646 ± 57503 (±20%)	252263 ± 55124 (±22%)	552167 ± 40878 (±7%)
Characteristic fatigue life, N_m (cycles)	332521	273447	532698
Minimum fatigue life, N_o (cycles)	64786	87750	84966
Weibull slope, b	0.6823	0.6556	0.6025
Weibull mean, N_{wm} (cycles)	274667	223405	544661