Autonomic Healing of Acrylic Bone Cement

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Acrylic bone cement, consisting of poly(methyl methacrylate) (PMMA) beads embedded in a PMMA matrix, is commonly used as a grout-like material to secure a joint prosthesis to the bone in orthopedic joint surgeries. This material is widely used in the more than 700 000 knee and hip-replacement surgeries performed in the US alone. The number of these surgeries is expected to increase to over 2 million surgeries per year by 2015.[1] Many patients require revision surgeries about 10 years after the initial replacement surgery, primarily due to aseptic loosening of the implant.[2] This loosening may be due in part to the released debris during microcrack accumulation in the bone cement, which leads to bone resorption at the bone–cement interface.[3] Although acrylic bone cement has substantial limitations, no significant clinical modifications to the cement have been made since its introduction in the 1960s.[3,4] A number of approaches have been pursued to address problems with the cement including dispersing small quantities of reinforcing phases,[5–8] refinement of processing conditions,[9–15] and new chemical formulations.[16–19] Despite these efforts, the fundamental problems associated with commercial bone cement persist; namely, fatigue and fracture of the cement and the osteolytic response to particulate debris. If microcracking could be prevented or limited, the lifetime of the cement would be increased, and the need for these revision surgeries reduced. As bone cement is a biomaterial that replaces living tissue with its inherent ability to repair wounds, imparting self-healing functionality to a synthetic biomaterial like bone cement could address this persistent problem in joint replacement lifetime.

Developments in the field of self-healing materials present an attractive means of extending the lifetime of polymeric materials through microencapsulated healing agents.[20,21] Though the need for self-healing biomaterials is large, as recently addressed by Brochu et al.,[22] there have been only a few instances of work in this field. Among these studies, those relating to self-healing bone cement include the use of microencapsulated dicyclopentadiene and Grubb's catalyst[23] (where toxicity and high cost present an issue) and encapsulated cyanoacrylate.[24] Recently, a dual-capsule free-radical healing chemistry was demonstrated in a generic dental resin mimic (epoxy vinyl ester) and this system may also be applicable to other polymeric biomaterials.[25] Here, we present a novel thermoplastic solvent-healing method using a biofriendly microencapsulated solvent embedded in Simplex P bone cement. This single-capsule approach does not rely on chemical reactions or external stimuli, and can be added as an independent component to a bone cement formulation to be mixed directly into the cement during surgery.

Solvent bonding or welding has long been used to bond plastic fittings and joints, and repair of macroscopic cracks in thermoplastics such as PMMA.[25–30] Inspired by this technique, we developed our self-healing system for bone cement based on a solvent bonding mechanism. In this process, a solvent exposed to two polymer surfaces swells and dissolves the polymer chains, allowing the free chains of the two surfaces to be in contact in the presence of the solvent. As the solvent diffuses or evaporates from the matrix, the chains entangle and contract, bonding the two surfaces together. Solvents have been employed for healing epoxy thermoset materials that are undercured and possess latent reactivity,[31,32] but their use for autonomic healing of thermoplastics via solvent bonding has not been explored.

Solvents were screened for use in our self-healing system based on compatability with established encapsulation procedures, low toxicity, and their ability to solvent weld PMMA. A comparison of solvents considered in this study, along with lap shear bonding results, is shown in Table S1 and Figure S1 (Supporting Information). A good solvent for a polymer is implied by a small difference in the solubility parameter (based on chemical properties and structure of the molecule) of the solvent and the polymer. Anisole is an excellent solvent for PMMA with an identical solubility parameter (δ) of 9.5 $(\text{cal cm}^{-3})^{1/2}$ to that of PMMA,[33] and initial lap shear results showed good bonding of PMMA substrates with anisole as the solvent (Figure S1, Supporting Information). Anisole, with ties to the fragrance and flavoring industry, is an FDA approved food additive [Code of Federal Regulations, Title 21, Volume 3, (Rev. 04/01/13), CITE: 21CFR172.515] and is relatively nontoxic with an oral median lethal dose (LD50) of 3700 mg kg^{-1} in rats.[34] Due to the microliter-range in total volume that would be present as the liquid core in the microcapsules throughout the bone cement, the use of anisole should not present a toxicity hazard.

Double-shell wall pol(urethane)/urea-formaldehyde (PU/UF) microcapsules were produced based on a previously reported method.[35] Anisole was encapsulated successfully with this method due to the solvent's low water solubility and sufficiently high boiling point (150 °C). In addition to the anisole solvent,

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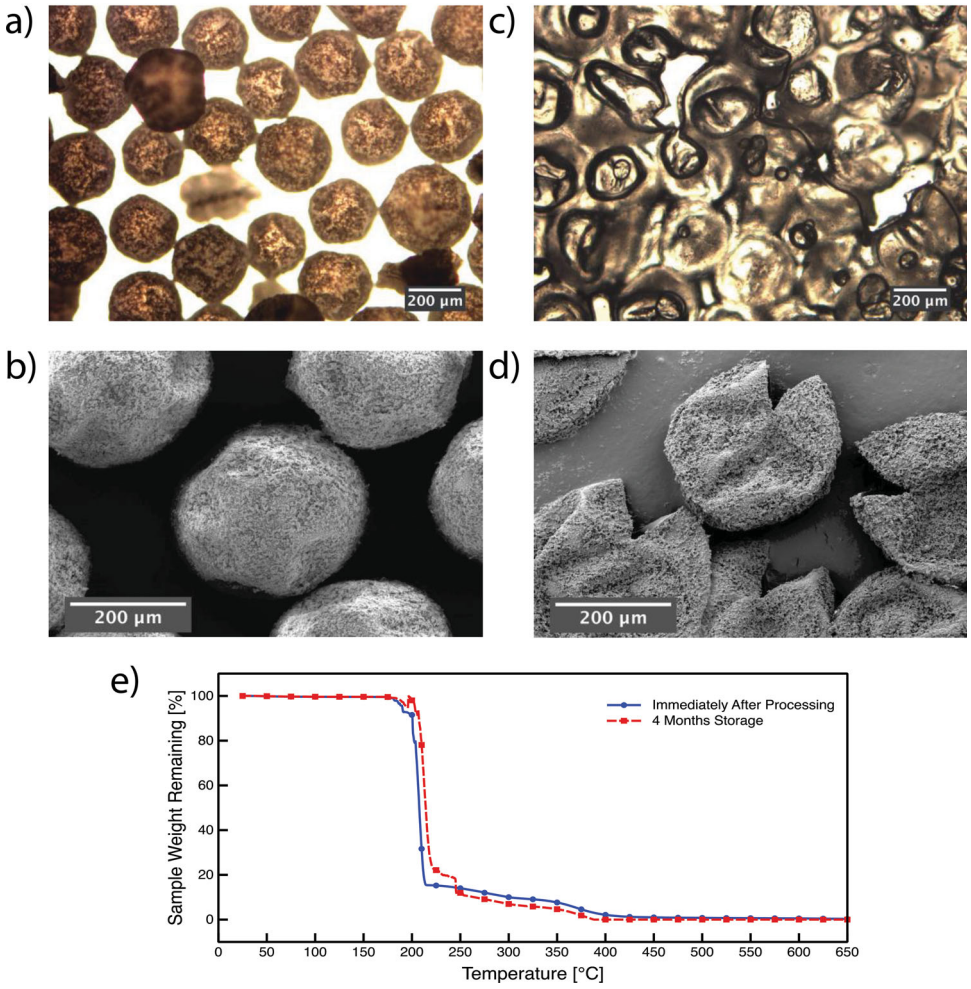

Figure 1. Microcapsules for self-healing bone cement. a) Optical image of poly(urethane)/urea-formaldehyde (PU/UF) shell wall capsules containing anisole solvent with 10 wt% dissolved PMMA polymer (350 kDa). b) Scanning electron microscope (SEM) image of the same capsules. c) Optical image of crushed capsules. d) SEM image of crushed capsules. e) TGA scans of microcapsules immediately after processing and after four months storage at ambient conditions.

dissolved PMMA was incorporated into the liquid core of the microcapsules. The additional PMMA supplied to the crack plane from the microcapsules could potentially aid in filling and healing of the microcracks. Addition of 10 wt% PMMA of average molecular weight 350 000 Da was chosen based on solvent bonding tests with acrylic lap shear specimens (see Figure S2, Supporting Information). Optical and scanning electron micrograph (SEM) images, **Figure 1**, of the microcapsules show a wrinkled surface morphology (Figure 1a,b). Rupture of the capsules releases the liquid (anisole) core (Figure 1c). Thermogravimetric analysis (TGA) scans show microcapsule thermal stability is excellent with little mass lost up to 200 °C, (anisole bp = 150 °C). In addition, the capsules remain stable even after 4 months of storage in a closed vial at ambient conditions (Figure 1e).

To assess self-healing performance, we employ a test method and healing metric previously developed for a variety of self-healing polymers.[36,37] A tapered double-cantilever beam (TDCB) fracture specimen is used to propagate a controlled mid-plane crack through bone cement. The sample is then left to heal for a prescribed period of time with no external force applied, followed by reloading the sample until failure. Due to the geometry of the TDCB specimen, the stress intensity factor (K_I) is crack-length independent and the fracture toughness (K_{IC}) is calculated using the peak (critical) load at fracture (P_C) and knowledge of the geometry and stiffness of the specimen. Healing efficiency (η) is defined as the ratio of the healed fracture toughness to the virgin fracture toughness, which reduces to the ratio of the critical loads of the healed and virgin fracture tests.[36]

$$\eta = \frac{K_{IC}^{healed}}{K_{IC}^{virgin}} = \frac{P_C^{healed}}{P_C^{virgin}} \quad (1)$$

Microcapsules were incorporated into Simplex P bone cement at a variety of concentrations (0–10 wt%) during the mixing of the liquid (monomer and amine activator) and solid (polymer beads, benzoyl peroxide initiator, and barium sulfate radiopacifier) components of the cement. The dough-like mixture of the components is transferred to a TDCB mold and

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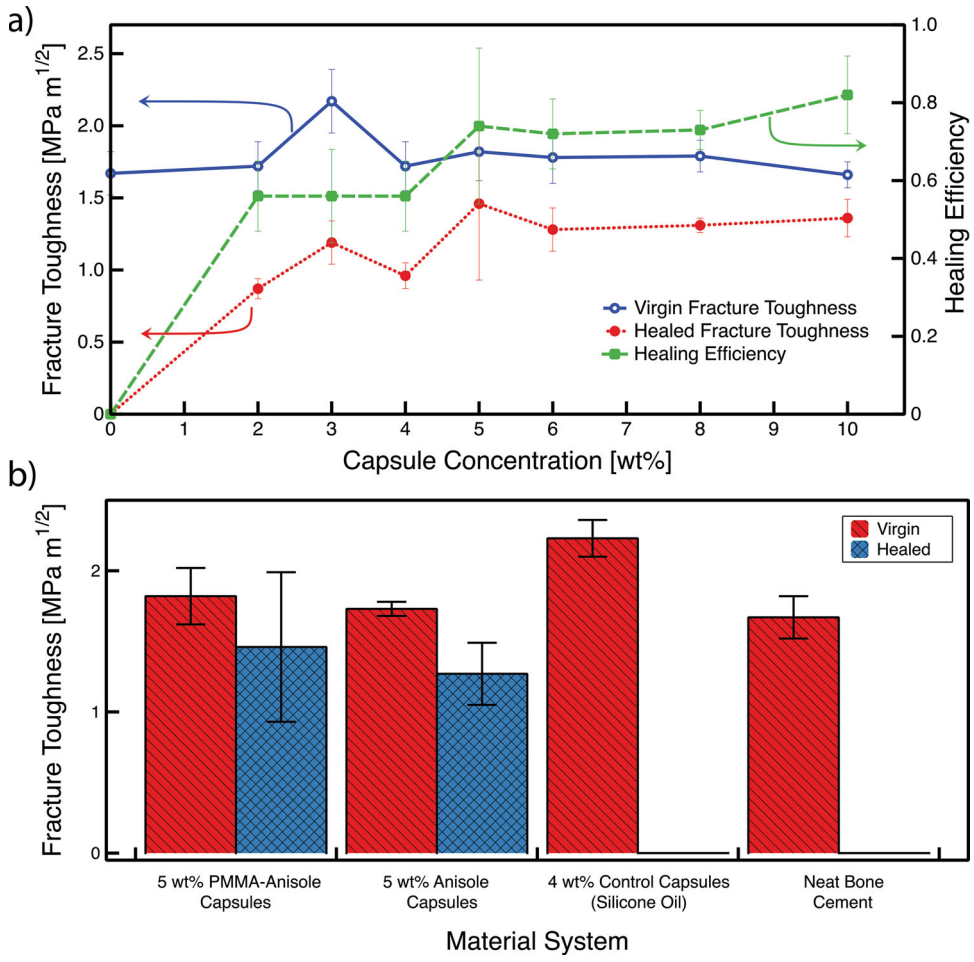

Figure 2. Self-healing bone cement test results. a) Virgin and healed fracture toughness and healing efficiency as a function of microcapsule concentration. Note: in all cases, samples were allowed to heal for 7 d at ambient conditions. b) Virgin and healed fracture toughness for self-healing and control samples.

cured, leaving hardened bone cement embedded with microcapsules (see Experimental section for details). The testing, healing, and subsequent retesting were carried out at ambient conditions, allowing 7 d for healing to take place.

Figure 2a shows the results of this series of tests. Successful self-healing in Simplex P was demonstrated with healing efficiencies up to 0.80. The healed fracture toughness increases with capsule concentration until about 5 wt% capsule loading, when the toughness values generally plateau. The incorporation of microcapsules up to 10 wt% shows no detrimental effect on virgin fracture toughness. The healing efficiency increases with increased capsule concentration up to 5 wt% capsule loading, after which there is no substantial benefit with additional microcapsules. Samples containing 5 wt% microcapsules provided the highest healing efficiency at the lowest microcapsule concentration, and this concentration was selected for further studies. This value appropriately corresponds to the minimum predicted loading of microcapsules required to fill the crack plane. With an average of 15 μm crack separations observed for bone cement TDCB fracture specimens, and based on an average microcapsule diameter of 300 μm, we calculated that 4.2 wt% of microcapsules is required to effectively fill the crack volume, based on the predictive calculation developed by Rule et al.[37]

We also tested self-healing bone cement containing microcapsules with a neat anisole core along with a variety of controls. Microcapsules with a pure anisole core were fabricated in an identical manner as the PMMA–anisole microcapsules and were then incorporated into bone cement samples at 5 wt%. While the virgin toughness is relatively unaffected, the addition of 350 kDa PMMA to anisole increases the healed fracture toughness from 1.27 MPa $m^{1/2}$ to 1.46 MPa $m^{1/2}$ and the healing efficiency from 0.73 to 0.80 (Figure 2b). Aside from observing zero healing in cases where no capsules were present in the bone cement, we also produced control microcapsules containing a non-solvent (silicone oil) in their core to ensure that the anisole solvent was responsible for healing and not simply the presence of a liquid in the crack plane. Tested in a similar manner, the control microcapsules showed no healing in the 7 d allotted, as expected.

To understand how self-healing bone cement may perform in a biological setting, fracture tests were conducted at different time intervals of healing, both at room temperature and body temperature (37 °C). Healing intervals of 4, 24, 72, and

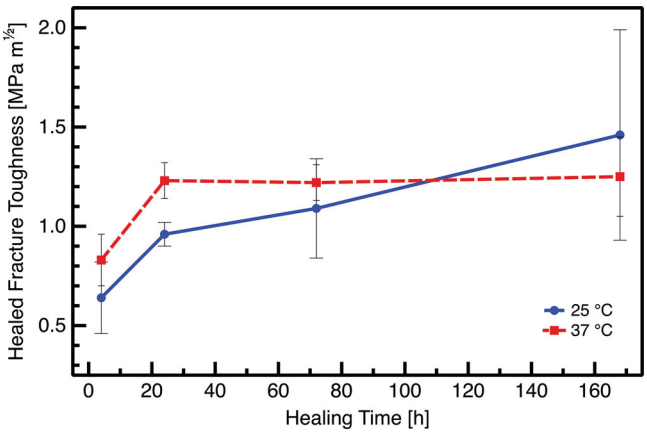

Figure 3. The effect of healing time on healed fracture toughness at room temperature (25 °C) and body temperature (37 °C). All specimens contained 5 wt% microcapsules containing PMMA–anisole core.

168 h (7 d) are compared for the two healing temperatures in **Figure 3**. As expected, the healed fracture toughness increases more rapidly and stabilizes more quickly for 37 °C healing compared to 25 °C healing, presumably due to enhanced healing kinetics and efficacy. Fast healing kinetics can occur as a result of increased diffusivity of anisole in PMMA, as well as decreased surface tension and viscosity of anisole solutions. These mechanisms increase diffusion and solvation of anisole with the acrylic bone cement, and improve wetting and capillary action in the crack plane. The viscosity of anisole has been shown to decrease from 1.52 cP to 0.78 cP with a 15° increase in temperature (15 °C to 30 °C)[38] and experiments show that the contact angle of anisole on PMMA substrates decreases moderately at body temperature versus room temperature (Figure S4 and Figure S5, Supporting Information). Both temperature conditions reach an equivalent level of healed fracture toughness within experimental scatter.

Morphological differences in fracture surfaces between different healing systems and conditions are revealed in the SEM images in **Figure 4**. The neat Simplex P sample (no microcapsules) in Figure 4a shows a roughened morphology with fracture of the embedded polymer beads apparent. Circular-shaped holes are voids caused by entrapped air during processing. In the control microcapsule case (Figure 4b), no healing was observed and a thin, flaky surface morphology is the result of residual silicone oil coating the fracture surface. In the 5 wt% PMMA-anisole capsule healing cases (Figure 4c,d), solvated surfaces are apparent, and an increase in healing time from 1 to 7 d shows an increase in the macroscopic smoothness of the surface. This morphological change is attributed to the new PMMA deposited on the surface of the healed crack in combination with the solvation of the PMMA matrix and beads present in the bone cement.

We have demonstrated a microencapsulated self-healing system in Simplex P bone cement using a non-toxic solvent approach. Healing efficiencies up to 0.80 were achieved under quasi-static fracture and the incorporation of microcapsules did not reduce the inherent fracture toughness of the cement. Given the relevance of cyclic loading for orthopedic bone cement, future studies are planned to investigate this loading regime. Importantly, there is an abundance of prior studies demonstrating excellent fatigue performance[39–41] in other microcapsule-based healing systems. Future studies for this self-healing system include in vitro and in vivo assays to evaluate the healing efficacy and biocompatibility of the microcapsules. Long-term stability of the microcapsules in the biological environment is also of great importance. This self-healing

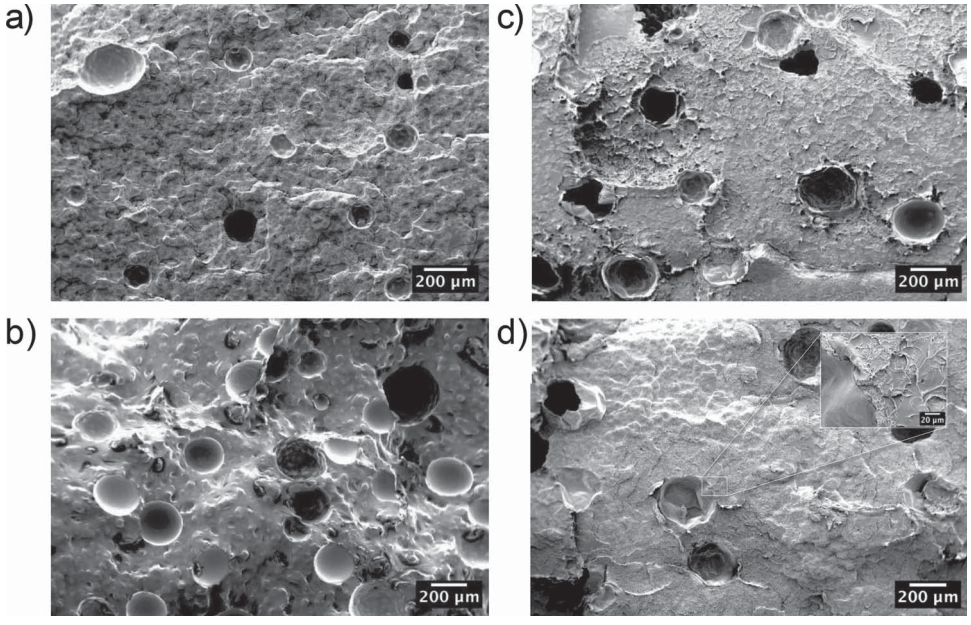

Figure 4. SEM images of fracture surfaces. a) Neat bone cement (no microcapsules). b) Bone cement containing 4 wt% capsules containing silicone oil (control). c) Bone cement containing 5 wt% capsules containing PMMA–anisole core after 24 h healing at room temperature. d) Bone cement containing 5 wt% capsules containing PMMA–anisole core after 7 d of healing at room temperature.

system could be employed in other biomaterials such as dental resins and cements used in spinal and skull surgeries, as well as engineering thermoplastics used in structural applications. The costs and number of joint replacement surgeries are expected to significantly increase over the next few decades and self-healing bone cement could benefit patients, as well as the healthcare industry, by extending the lifetime of acrylic bone cement.

Experimental Section

Microcapsule Preparation: Poly(urethane)/urea-formaldehyde (PU/UF) microcapsules containing anisole (Sigma-Aldrich) with 10 wt% dissolved PMMA (average $M_w \approx 350\,000$ Da; Sigma–Aldrich) were prepared as previously described[35] with the following changes: 4 g of PU prepolymer was dissolved in 60 mL of core solution (10 wt% PMMA and 90 wt% anisole) and added to the mixing vessel containing double the UF reaction components, stirring at 500 RPM. Microcapsules were then dried and size-selected using sieves to obtain microcapsules between 250 and 355 μm in diameter. Pure anisole core microcapsules and control microcapsules (containing silicone oil) were fabricated in an identical manner.

Microcapsule Thermal Stability: Microcapsules were tested for thermal stability using TGA, performed on a MettlerToledo TGA851. Intact capsules were inserted into an alumina crucible and heated at a rate of 10 °C min^{-1} under nitrogen flow. The mass loss over time was recorded and compared for microcapsules tested immediately after processing, as well as microcapsules stored for 4 months at ambient conditions.

Fracture Specimen Preparation and Testing: To conserve the amount of bone cement used in each TDCB fracture sample, a localized short-groove TDCB technique was used. Localized TDCB fracture specimens were prepared using machined Teflon molds. A machined acrylic TDCB shell was inserted into the mold, with a hollow center region for molding of the bone cement. As the bone cement is composed primarily of PMMA, the bone cement bonds well to the acrylic shell and allows the crack to propagate through the bone cement along a molded groove at the centerline of the specimen. The Simplex P bone cement components were kept at a 2:1 ratio of solid (including microcapsules at loadings 0–10 wt%) to liquid, and hand-mixed for 30 s. The bone cement was poured into the mold in the central region of the acrylic shell and allowed to cure at ambient conditions for 30 min. The TDCB sample was then removed from the mold and a diamond saw used to prepare the center region for precracking. Twenty-four hours after the initial curing, the sample was precracked with a razor blade and immediately tested in an Instron load frame using pin loading under displacement control at a rate of 50 μm s^{-1}. The crack was allowed to propagate approximately 10–15 mm, after which the sample was unloaded at the same rate, removed from the frame, and allowed to heal at different temperatures (25 °C or 37 °C) and/or time periods (4 h–7 d). Samples healed at 25 °C were stored at ambient conditions in the laboratory while samples healed at 37 °C were stored in an environmentally controlled warm room designed for biological research. An environmental scanning electron microscope was used to take images of the fracture surfaces on a Philips XL30 ESEM-FEG instrument after sputtercoating with a gold-palladium source.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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