A room-temperature autonomically-healing PMMA bone cement: influence of composition on fatigue crack propagation rate

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ABSTRACT: Purpose: To test two hypotheses. First, autonomic healing is achievable in a commercially available poly (methyl methacrylate) bone cement brand that is widely used to anchor total joint replacements. Secondly, in this self-healing cement, the fatigue crack propagation (FCP) rate is critically dependent on the relative amount of the mass of the healing agent (endo-isomer of dicyclopentadiene [DCPD] embedded in poly (urea-formaldehyde) [PUF] microcapsules (diameter = 226 ± 51 μm)) (M_{d2}) to that of the catalyst (a first-generation Grubbs’ catalyst) (M_{c1}). (Note that, in this work, the term, “autonomic healing” or “self-healing”, refers to the ability of the material, after having been damaged during service, due to formation of cracks, for example, to restore its initial mechanical performance without the need for any external intervention).

Methods: The strategy that was developed by White et al. for room-temperature autonomic healing of a neat polymeric material was used. The DCPD-filled PUF microcapsules and the catalyst were blended with the cement’s powder in a mortar bowl using a polymeric spatula, and the blended powder mixture and the cement’s liquid monomer were mixed under a partial vacuum. FCP tests were performed on specimens of seven study groups: the control cement (CMW™1), four sets having different values of M_{d2}/M_{c1}, one set in which only the DCPD-filled microcapsules were blended with the CMW™1 powder, and one set in which only the Grubbs’ catalyst was blended with the CMW™1 powder.

Results: An index of the self-healing achieved, as computed using the estimated FCP rates, was within the range reported in the literature for autonically-healing neat polymeric materials. Furthermore, the variation of the estimated FCP rate with M_{d2}/M_{c1} suggests that changes in this rate is critically dependent on change of M_{d2}/M_{c1}.

Conclusion: The results supported both of the study hypotheses (Journal of Applied Biomaterials & Biomechanics 2009; 7: 90-6).

KEY WORDS: Poly(methyl methacrylate) bone cement, Self-healing, Fatigue crack propagation

INTRODUCTION

Strategies that are currently available for achieving in situ self-healing functionality in neat polymers and polymer-based composite materials may be grouped into three categories: healing with an embedded liquid-phase healing agent; thermally-activated solid-phase healing; and healing of projectile puncture (1). (Note that the sense in which the term, “self-healing,” is used in this work is explained in the Abstract.) To date, the bulk of the work reported in the literature has been on the first-mentioned category, within which a variety of methods for delivering the healing agent to the advancing cracks in the component/structure have been described, such as use of a microcapsule/ring-opening metathesis polymerization (ROMP) system, hollow glass fibers, and a microvascular network (1-3). Autonomic healing may be regarded as a special case of in situ self-healing. The principle of the most popular way of achieving self-healing in a polymeric material may be summarized thus. Particles of a ruthenium-based (Grubbs’) catalyst and a small volume of poly(urea-formaldehyde) (PUF) microcapsules (filled with a compound that serves as the healing agent; namely, endo- or exo-stereoisomer of dicyclopentadiene, DCPD) are randomly dispersed in the matrix of the material (2). When a component/structure, fabricated from such a polymeric material, is subject to cyclical loads in service, the growing cracks penetrate the microcapsules, releasing the DCPD into the crack plane (by capillary action). The DCPD then reacts with the catalyst to trigger a ROMP of the DCPD, which leads to the production of a tough, highly-crosslinked polymer that seals the face of the growing crack; therefore, the crack growth is halted (2) (Fig. 1).

Aseptic loosening is the most common cause for revision of cemented total joint replacements (TJRs); i.e.
replacements that are anchored to the contiguous bone in a bed of poly(methyl methacrylate) (PMMA) bone cement (4, 5). The critical role played by fatigue microcrack initiation and propagation within the bone cement zones in this phenomenon is well known (6, 7). Therefore, improving the fatigue crack propagation (FCP) resistance of a PMMA bone cement may contribute to an increase in the in vivo longevity of cemented TJRs.

We present two hypotheses. The first was that autonomic healing through room-temperature ROMP of DCPD aided by a first-generation Grubbs' catalyst would be achieved in a commercially available PMMA bone cement brand that is widely used in TJRs, when DCPD-filled PUF microcapsules and Grubbs' catalyst were blended with the cement powder. Secondly, in such an autonomically-healing cement, the FCP rate was critically dependent on the relative masses of the DCPD-filled PUF microcapsules and the Grubbs' catalyst used. Results from this study should aid in developing a methodology for optimizing the composition of an autonomically-healing PMMA bone cement.

MATERIALS AND METHODS

Materials

The cement brand used in this work was CMW™2 (DePuy-CMW, Blackpool, UK). See Table I for compositions of the powder of this cement brand. The healing agent and first-generation Grubbs' catalyst used were the endo-isomer of DCPD (95% purity; Sigma Aldrich, St. Louis, MO, USA) and bis(tricyclohexyl-phosphine)benzylidine ruthenium (IV) dichloride (RuCl2(=CHPh)(PCy3)2) (Acros Organics, Morris Plains, NJ, USA), respectively.

Microencapsulation of the DCPD

The method used to encapsulate the DCPD in the PUF microcapsules - in situ polymerization in an oil-in-water emulsion - was that presented by Brown et al (8), with a few modifications. The reaction mixture (200 mL of deionized water and 50 mL of 2.5 wt.% aqueous solution of ethylene maleic anhydride copolymer) was manually mixed, in ambient laboratory air conditions (22 ± 1 °C), in a beaker (1000 mL) that was suspended in a temperature-controlled oil bath that was itself positioned on a programmable hot plate (Barnstead Thermolyne SuperNuova® Model Sp133835Q; Barnstead International, Dubuque, IA, USA). The next four steps were conducted under continuous mixing, at a rotational speed (ω) of ~420 rpm, using a digital mixer (General Series Lightnin® Model DS3004; Lightnin, Rochester, NY, USA) that drove a propeller that was positioned ~10 mm above the bottom of the beaker. First, urea (5.00 g), ammonium chloride (0.50 g), and resorcinol (0.50 g) were dissolved in the solution and its pH was then increased to ~3.50. Secondly, a stream of DCPD (60 mL) was very slowly added to the solution to form an emulsion, which was allowed to stabilize for 10 min. Thirdly, a 37 wt.% aqueous solution of formaldehyde (12.67 g) was added to the emulsion, yielding a 1.0:1.9 molar ratio of formaldehyde to urea. Fourthly, the emulsion was covered and heated, at 1 °C min⁻¹, to 55 °C. At the end of

**TABLE I - COMPOSITIONS OF THE POWDERS IN THE STUDY GROUPS**

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Study group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control A</td>
</tr>
<tr>
<td>Poly (methyl methacrylate) beads (g)</td>
<td>35.54</td>
</tr>
<tr>
<td>Barium sulfate (g)</td>
<td>3.64</td>
</tr>
<tr>
<td>Benzoyl peroxide (g)</td>
<td>0.82</td>
</tr>
<tr>
<td>Microcapsules containing the DCPD (wt./wt.%a)</td>
<td>0.00</td>
</tr>
<tr>
<td>Grubbs' catalyst (wt./wt.%a)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Expressed as % of the total mass of the powder*
the fourth step, the mixing continued for 4 hr, after which the mixer and the hot plate were switched off. The emulsion was allowed to cool to ambient air temperature and then the suspension of microcapsules was separated using an aspirator pump (Model 177001; Boekel Scientific, Feasterville, PA) that was fitted with a coarse-fritted filter. The microcapsules were rinsed with deionized water (~380 mL) and then dried, for ~24 hr, using an aspirator pump (Boekel Scientific™ Model 177001; Boekel Scientific, Feasterville, PA, USA). Post-drying separation of the microcapsules was performed using a sonic sifter (Advantech Model L3P; Advantech Manufacturing, New Berlin, WI, USA) with USA standard testing sieves.

**Morphology of the DCPD-filled PUF microcapsules**

The morphology of these microcapsules was obtained, in triplicate, using a scanning electron microscope (JEOL JSM-6490LV, Tokyo, Japan) operated at an acceleration voltage of 5 kV.

**Preparation and characterization of the blended cement powder mixture**

The DCPD-filled PUF microcapsules and the Grubbs’ catalyst were very carefully but thoroughly blended with the cement powder in a mortar bowl using a polymeric spatula. Table I gives the concentrations of these two constituents in the cement powders of the study groups. The compositions of the cements in the groups were carefully selected in order to investigate the influence of the mass of the Grubbs’ catalyst (M_{Gr}) for a fixed mass of the DCPD-filled microcapsules (M_{micro}) (groups A, B, and C); and the influence of M_{micro} for a fixed M_{Gr} (groups C and D). Groups E and F were included to represent cases where the conditions necessary for self-healing did not exist.

The particle diameter distribution and morphology of the blended cement powder mixture, for each of the groups A-F, were determined using a laser diffraction system (Sympatec Particle Size Analyzer, Model HDD200; Sympatec GmbH, Golar, Germany) and an environmental scanning electron microscope (Model XL30; Philips, The Netherlands) operated at an acceleration voltage of 15 kV, respectively. For each blended powder mixture, each analysis was run in triplicate.

**Preparation of fatigue crack propagation test specimens**

For the preparation of the test specimens, the blended cement powder mixture and the cement’s liquid monomer were mixed in a vacuum mixer (Stryker MixEvac® II High vacuum mixer; Stryker, Kalamazoo, MI, USA; partial vacuum = 70 ± 2 kPa). (For all the study sets, the same liquid monomer was used, being that in CMW™1; therefore, the composition of the liquid monomer was 18.22 g of methyl methacrylate monomer, 0.15 g of N,N-dimethyl-p-toluidine, and 25 ppm of hydroquinone.) Once a homogeneous mixture was obtained, it was poured into a syringe (Stryker bone cement syringe; Stryker) from which it was injected (Stryker 206-600 Dual speed cement injector; Stryker) into a stainless steel mold, whose cross-sectional shape and dimensions corresponded to those of the ASTM D 5045 fracture toughness test specimen (9) (Fig. 2). Weights (of 100 N) were placed on top of the mold, which was then stored in ambient laboratory air conditions (temperature and relative humidity of 21 ± 1 °C and 54 ± 2%, respectively). After ~1 hr, the cement specimen was removed from the mold. The dimensions of all the specimens were carefully measured, and only those for which each dimension was within 1% of the nominal value (Fig. 2) were retained. All these retained specimens were then very carefully examined visually for surface porosities. Only those specimens that had no visible surface pores were accepted. These specimens were then stored in phosphate buffered saline, at 37 °C, for 5 days, and specimens were selected at random from this group and used in the FCP tests. Prior to each of these tests, the tip of the molded starter notch in a selected specimen was sharpened with a razor blade (by gently rubbing the blade back-and-forth into the notch six times), as is commonly done in these tests (10).

**Fatigue crack propagation tests**

In these tests, the test specimen (Fig. 2) was cyclically loaded, in ambient laboratory air, under load control, at a frequency of 2 Hz, using a servohydraulically-actuated materials testing machine (858 Bionix Test System; MTS, Eden Prairie, MN, USA). The load was controlled by commercially available software (TestStar Ilm Station Manager V 3.3B 1205 with remote station control option; MTS).
The specimens were loaded in tension-tension using a sinusoidal wave function (minimum force = 10 N; maximum force = 170 N). The length of the initial crack (a) was monitored as a function of time, using two crack propagation gages (Model #TK-09-CPA01-005/DP; Vishay Measurements Group, Inc.; Malvern, PA, USA) arranged in a circuit that contained a precision constant-current supply (BK Precision Single Output DC Power Supply Model #1621A; BK Precision, Yorba Linda, CA), a connector block (BNC-2110 Shielded Connector Block; National Instruments, Austin, TX) and an amplifier. The raw data acquired - voltage and time - were sent to a data acquisition system (LabVIEW 8.0; National Instruments, Austin, TX, USA) that converted them to a and number of cycles (N), respectively. For each of the study groups, five specimens were tested.

The FCP rate was estimated as being equal to the slope of the a-N curve at the start of the “heel” section of the curve, this being the point at which fast fracture was deemed to commence.

**Statistical analysis**

The estimated FCP rates were statistically analyzed using ANOVA, with the Bonferroni correction, using the 95% confidence limits approach, and the Kruskal-Wallis test (SAS® Version 9.1; SAS Institute Inc., Cary, NC, USA). Significant difference was taken at the 5% level.

**RESULTS**

The diameter of the DCPD-filled PUF microcapsules (d) was 226 ± 51 µm, which is within the range reported in the literature. For example, Maudlin et al (11) reported d to be 180 ± 40 µm, while White et al (2), Brown et al (8), Brown et al (12), and Kessler et al (13) found the mean d to be 220 µm (when ω = 454 rpm), 280 µm (when ω = 400 rpm), 180 µm, and 166 µm, respectively. As for the morphology of the DCPD-filled microcapsules, they were spherical (Fig. 3).

For both the particle size distribution and the morphology of the blended cement powder mixture (cement powder + DCPD-filled PUF microcapsules + Grubbs’ catalyst), there was very little variation among study groups A-F (mean particle diameter = 40.56 ± 0.55 µm). Figure 4 gives the sample results for these characteristics for the group C mixture. These results suggest that the blending method produced mixtures of consistent homogeneity.

Figure 5 presents the sample a-versus-N results obtained using specimens in the control cement and study group C, with the estimated FCP rates being given in Table II. For a cement in any of the study groups A-D, FCP rate was significantly lower than for the control cement (Pr > χ² = 0.019-0.022; and Table III). As for groups E and F, each of the estimated FCP rates is not significantly different from that for the control group (Pr > χ² = 0.442 or 0.551; and Table III).

With regard to the self-healed groups, the values of the mass ratio of the in situ self-healing agents (ie M_{DM}/M_{GC}) were 1.0, 4.0, 8.0, and 14.0, for groups A, B, C, and

<table>
<thead>
<tr>
<th>Study group</th>
<th>FCP rate (10⁻⁴ mm cycle⁻¹)</th>
<th>Self-healing efficiency(%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30.30 ± 3.00</td>
<td>–</td>
</tr>
<tr>
<td>A</td>
<td>18.40 ± 6.60</td>
<td>39.3</td>
</tr>
<tr>
<td>B</td>
<td>11.20 ± 3.18</td>
<td>63.0</td>
</tr>
<tr>
<td>C</td>
<td>4.00 ± 1.45</td>
<td>86.8</td>
</tr>
<tr>
<td>D</td>
<td>9.10 ± 2.80</td>
<td>70.0</td>
</tr>
<tr>
<td>E</td>
<td>26.88 ± 6.89</td>
<td>NAb</td>
</tr>
<tr>
<td>F</td>
<td>29.48 ± 8.15</td>
<td>NAc</td>
</tr>
</tbody>
</table>

a Magnitude of (mean FCP rate of self-healing cement - mean FCP rate of control cement)/ (mean FCP rate of control cement).

bSelf-healing efficiency cannot be calculated for these groups because the conditions necessary for self-healing did not exist in these groups.
Self-healing bone cement

The variation of the estimated FCP rate with $M_{DM}/M_{GC}$ does not follow a monotonic trend but, rather, the results of the statistical analyses of the estimated FCP rates show that a significant change in this rate occurs when the change in $M_{DM}/M_{GC}$ exceeds 4 but is less than 14 (Tabs. I, III).

**DISCUSSION**

The estimated FCP rates for groups A-D (Tab. II) indicate that room-temperature in situ self-healing was achieved in these groups in that, with the exception of group A, the computed self-healing efficiency was within the range reported for an autonomically-healing neat polymer (10).

It is pointed out that various definitions of room-temperature autonomic healing efficiency have been used in literature reports; examples being definitions that are based on fracture toughness (2, 12, 13) and on strain energy (11, 14). As for groups E and F, no self-healing occurred because of the absence of the minimum conditions for this phenomenon; i.e. inclusion of both DCPD-filled PUF microcapsules and Grubbs' catalyst in the cement powder. The small amount of FCP retardation seen in the specimens in study groups E and F is similar to the FCP retardation provided by BaSO$_4$ particles (the radiopacifier) in a plain PMMA cement brand (Surgical Simplex®P), relative to its radiolucent counterpart, for which a longer crack path in the radiopaque cement has been identified as a possible contributing factor (15).

**TABLE III - RESULTS OF THE ANOVA, WITH BONFERRONI POST HOC, TESTS ON THE ESTIMATED FCP RATES**

<table>
<thead>
<tr>
<th>Study group pair</th>
<th>Difference between means</th>
<th>Simultaneous 95% confidence limits</th>
<th>Outcome$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A vs. Control</td>
<td>-11.85 x 10$^{-4}$</td>
<td>-22.63 x 10$^{-4}$; -1.07 x 10$^{-4}$</td>
<td>S</td>
</tr>
<tr>
<td>Group B vs. Control</td>
<td>-19.07 x 10$^{-4}$</td>
<td>-29.85 x 10$^{-4}$; -8.29 x 10$^{-4}$</td>
<td>S</td>
</tr>
<tr>
<td>Group C vs. Control</td>
<td>-26.32 x 10$^{-4}$</td>
<td>-37.10 x 10$^{-4}$; -15.54 x 10$^{-4}$</td>
<td>S</td>
</tr>
<tr>
<td>Group D vs. Control</td>
<td>-21.17 x 10$^{-4}$</td>
<td>-31.95 x 10$^{-4}$; -10.39 x 10$^{-4}$</td>
<td>S</td>
</tr>
<tr>
<td>Group E vs. Control</td>
<td>-3.39 x 10$^{-4}$</td>
<td>-14.17 x 10$^{-4}$; 7.39 x 10$^{-4}$</td>
<td>NS</td>
</tr>
<tr>
<td>Group F vs. Control</td>
<td>-0.80 x 10$^{-4}$</td>
<td>-11.58 x 10$^{-4}$; 9.98 x 10$^{-4}$</td>
<td>NS</td>
</tr>
<tr>
<td>Group A vs. Group B</td>
<td>7.22 x 10$^{-4}$</td>
<td>-3.56 x 10$^{-4}$; 18.00 x 10$^{-4}$</td>
<td>NS</td>
</tr>
<tr>
<td>Group A vs. Group C</td>
<td>14.47 x 10$^{-4}$</td>
<td>3.69 x 10$^{-4}$; 25.25 x 10$^{-4}$</td>
<td>S</td>
</tr>
<tr>
<td>Group A vs. Group D</td>
<td>9.32 x 10$^{-4}$</td>
<td>-1.45 x 10$^{-4}$; 20.10 x 10$^{-4}$</td>
<td>NS</td>
</tr>
<tr>
<td>Group B vs. Group C</td>
<td>7.25 x 10$^{-4}$</td>
<td>-3.53 x 10$^{-4}$; 18.03 x 10$^{-4}$</td>
<td>NS</td>
</tr>
<tr>
<td>Group B vs. Group D</td>
<td>2.10 x 10$^{-4}$</td>
<td>-8.68 x 10$^{-4}$; 12.88 x 10$^{-4}$</td>
<td>NS</td>
</tr>
<tr>
<td>Group C vs. Group D</td>
<td>-5.14 x 10$^{-4}$</td>
<td>-15.92 x 10$^{-4}$; 5.63 x 10$^{-4}$</td>
<td>NS</td>
</tr>
</tbody>
</table>

$^a$Difference between means is significant
The significantly lower FCP rates in the specimens in groups A-D, compared to the rate for the control cement, may be attributable to two crack-tip shielding mechanisms that have been postulated to operate in autonomically-healed neat polymeric materials; namely, 1) retardation of crack growth when the viscous DCPD flows into the growing crack plane, and 2) prevention of unloading of the crack tip, which, it has been suggested, is a consequence of adhesive and crack-closure effects that stem from the polymerization of the DCPD (16).

The observation that a significant change in the estimated FCP rate occurs when the change in $M_{DM}/M_{GC}$ exceeds 4 but is less than 14 suggests that an optimum $M_{DM}/M_{GC}$ may exist for CMW™1 cement. If this is so, that would be consistent with the findings of Maudlin et al (11) on in situ self-healing of an epoxy resin using DCPD-filled PUF microcapsules and Grubbs’ catalyst. For that system, the maximum energy-to-failure of the autonomically-healed material was obtained with 1.00 wt.% (overall) of embedded wax microspheres loaded with 10 wt.% first-generation lyophilized Grubbs’ catalyst, for a fixed concentration of exo-isomer of DCPD (encapsulated in PUF microcapsules) (11). As far as the material system used in this study is concerned, estimated FCP rates for more experimental groups comprising more combinations of $M_{DM}$ and $M_{GC}$ (to give a wide array of the ratio, $M_{DM}/M_{GC}$) would be needed to be made and the results analyzed before any definitive statement can be made about the existence of an optimum $M_{DM}/M_{GC}$ for this cement. Although this was outside the scope of this study, our approach and the attendant results suggest a methodology that may be used to optimize the composition of a self-healed PMMA bone cement.

This study 1) demonstrated proof of the concept of room-temperature in situ self-healing of a commercially available PMMA bone cement brand that is widely used in cemented TJRs through utilization of the DCPD/Grubbs’ catalyst system; and 2) indicated a methodology that may be used to optimize the composition of this self-healed material. A TJR anchored in the contiguous bone using an autonomically-healed acrylic bone cement would be expected to have a significantly lower FCP rate than when a conventional bone cement is used. However, since it is unknown if DCPD and Grubbs’ catalyst are biocompatible, this aspect should be investigated, and, if it is shown that these materials are not biocompatible, future work should focus on developing healing agents and catalysts that are. Once that is achieved, autonomically-healing PMMA bone cements could then be considered viable for use in cemented TJRs. Then further research and development studies can be performed, such as 1) the investigation of the feasibility of encapsulating the healing agent in nanocapsules (3), as a way of increasing the FCP resistance of the cement, and 2) determination of the influence of $M_{DM}/M_{GC}$ on properties of the cement relevant to its use in cemented TJRs, examples being setting time, doughing time, and compressive creep resistance.

CONCLUSIONS

There are two main conclusions of the study. First, the index of self-healing computed based on the estimated FCP rate results indicate that room-temperature autonomous healing was achieved in a commercially available PMMA bone cement brand. Secondly, in an autonomously-healing variant of this cement brand, the ratio of the mass of the DCPD-filled PUF microcapsules to that of the Grubbs’ catalyst is a very important variable in that a change in the computed cement FCP rate appears to be critically dependent on a change of this ratio. The study results thus provide support for the two hypotheses.

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