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Biocompatible Nanocapsules for Self-Healing Dental Resins and Bone Cements

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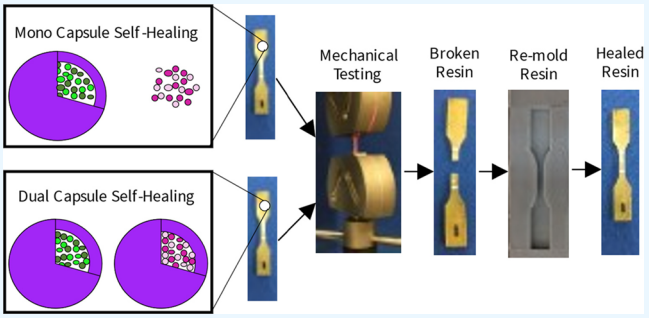
ABSTRACT: Bone cements and dental resins are methacrylate-based materials that have been in use for many years, but their failure rates are quite high with essentially all dental resins failing within 10 years and 25% of all prosthetic implants will undergo aseptic loosening. There are significant healthcare costs and impacts on quality of life of patients. Self-healing bone cements and resins could improve the lifespan of these systems, reduce costs, and improve patient outcomes, but they have been limited by efficacy and toxicity of the components. To address these issues, we developed a self-healing system based on a dual nanocapsule system. Two nanocapsules were synthesized, one containing an initiator and one encapsulating a monomer, both in polyurethane shells. The monomer used was triethylene glycol dimethacrylate. The initiator capsules synthesized contained benzoyl peroxide and butylated hydroxytoluene. Resins containing the nanocapsules were tested in tension until failure, and the fractured surfaces were placed together. 33% of the samples showed self-healing behaviors to the point where they could be reloaded and tested in tension. Furthermore, the capsules and their components showed good biocompatibility with Caco-2 cells, a human epithelial cell line suggesting that they would be well tolerated in vivo.



INTRODUCTION

Self-healing materials which can repair and recover functionality without human intervention have drawn significant interest for biomedical materials in the past 20 years.[1] The idea of self-healing materials stems from nature, specifically in the way living multicellular organisms are able to repair themselves without external intervention.[2] Self-healing materials could be exceptionally useful in methacrylate-based systems such as bone cements and dental resins. It is estimated that over 25% of all prosthetic implants will undergo aseptic loosening[3] which includes microcrack formation in bone cement. Aseptic loosening triggers inflammation and bone resorption and generally requires surgical revision.[3] Revision surgeries are technically demanding, expensive and result in low satisfaction rates among patients.[4] Meanwhile, dental diseases are the most prevalent chronic diseases worldwide and are costly burdens to health care services.[5] Tooth decay impacts close to 100% of the population.[6] Modern dental resins avoid the environmental and health concerns with mercury but have poor durability with posterior fillings lasting 3 to 10 years and large fillings lasting less than 5 years.[7]

Most methacrylate-based systems use capsules for self-healing properties. Capsules are easy to implement in both dental resins and bone cements because these systems often contain other filler particles to enhance the mechanical properties of the materials.[8] Initially, the self-healing capsules simply act as an additional filler. The capsules contain components encapsulated by shells[9] that break when a crack propagates through the material releasing components into the crack via capillary action that can then polymerize and heal the matrix.[10] Biocompatibility is essential for self-healing systems used in biomedical applications. One of the first capsule-based systems was a single capsule system containing dicyclopentadiene encapsulated in a poly(urea-formaldehyde) shell that formed a microcapsule (50−200 μm). Grubb's catalyst was used to initiate the polymerization of the dicyclopentadiene. A number of groups have looked at this system, and the mechanical properties of the repairs are good,[11] but high cost and toxicity concerns curbed this approach.[12,13] More recently, a number of groups have looked at triethylene glycol dimethacrylate (TEGDMA) liquid encapsulated in polymer shells. Poly(urea-formaldehyde) (UF) microcapsules with TEGDMA and *N,N*-dihydroxyethyl-p-toluidine (DHEPT)

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were mixed with benzoyl peroxide (BPO), the catalyst, freely added to the resin; self-healing efficiency showed that about 65% of the virgin fracture toughness could be achieved when using 15% microcapsules in a flexural test.[12] Dual UF microcapsule systems consisting of initiator capsules containing BPO and monomer capsules contained 4′-methylenebis-(*N*,*N*-dimethylaniline) (MBDMA) (the tertiary amine), trimethylol-propane ethoxylate triacrylate (TMPET) (an acrylate monomer), and bisphenol A ethoxy-late diacrylate (Bis-EMA) (an acrylate monomer) led to 75% of the fracture toughness in an epoxy matrix.[14] Because resin-composite restorations are in contact with saliva, an alternative approach using 2-octul-cyanoacrylate in urethane microcapsules has been explored which reacts without the addition of a catalyst and led to an increase in cycles to failure in a bending test.[15] Microcapsules of a solvent, anisole with polymethylmethacrylate (PMMA) were encapsulated in double walled polyurethane/urea-formaldehyde (PU/UF) shells.[16] 50−80% healed fracture toughness was seen in this system.

Polyurethane (PU) has been used in biomedical implants for many years[17] and shows excellent compatibility with blood.[18] Because of their block-copolymer character, PUs have a wide range of versatility in terms of their physical properties and ability to biodegrade. PU, through the years, has proven to be extremely biocompatible as well as thermally stable in the body.[17] TEGDMA is the monomer of choice. BPO is employed as the initiator. The self-healing aspect of the composite is composed of a two-part monomer-initiator polymerization system made solely from materials that are classified by the U.S. Food and Drug Administration as Generally Recognized as Safe (GRAS) to eliminate complications concerning biocompatibility.[12]

While all of these systems can lead to substantial self-healing, the long-term stability and biocompatibility are concerns. We focused on developing a system that would be biocompatible, easily blended into resins, minimally alter critical materials properties like the resin modulus, and provide self-healing behavior. To this end, we investigated single and dual nanocapsule systems based on PU nanocapsules containing nontoxic components. We hypothesized that nanocapsules would impact the mechanical properties of the resin less than larger particles and still lead to a robust self-healing process. To determine the impact of single and dual nanocapsules on self-healing of methacrylate resins, we synthesized PU nanocapsules encapsulating either the initiator or monomer and performed mechanical testing and biocompatibility analysis to determine the feasibility of this system as a self-healing additive for dental resins and bone cements.

MATERIALS AND METHODS

Materials. All materials were obtained from commercial suppliers and used without further purification. Sodium dodecyl sulfate (SDS) (BP166, Fisher Scientific) and 99% pure hexadecane (HD) (AC120465000, ACROS Organics) were the surfactant and costabilizer, respectively, used to form the PU nanocapsules. Isophorone diisocyanate (IPDI) 98% (AC427602500, ACROS Organics) and 1,6-hexanediol (HDOH) 97% (AAA1243930, ACROS Organics) were the reactants from which PU was formed. TEGDMA 95% (261548, Sigma Aldrich) was the monomer encapsulated in the PU nanocapsules. BPO (S25672, Fisher Scientific) was the initiator used in the self-healing reaction testing. Butylated hydroxytoluene, 99%, FCC (W218405, Fisher Scientific) was the stabilizer that was encapsulated with the initiator to prevent the BPO from reacting prematurely. The resin used was the West System epoxy resin; this resin was formed with 105 epoxy resin and 209 extra slow hardener. The West System 105 epoxy resin is based on bisphenol A diglycidyl ether, and it exhibits comparable properties to methacrylate-based bone cements and dental resins.

The West System epoxy resin was used as a model of common bioinert biomaterials. Compared to commonly used bioinert biomaterials (such as bone cements), the West System epoxy resin has comparable physical properties. The West System epoxy resin has a density of 1.16 g/cm^3. The tensile strength, as defined by ASTM D-638, is 7300 psi. Finally, the tensile modulus, defined by ASTM D-638, is 3.98×10^5 psi for the West System epoxy resin. PMMA is used in total joint replacements to anchor implants to bone.[15] General purpose PMMA (AZO Materials) has a density of 1.18 g/cm^3, a tensile strength is 10,153 psi, and a tensile modulus is 4.21×10^5 psi. Likewise, PMMA bone cement has a tensile strength of 5105 psi and a tensile modulus of 3.70×10^5 psi.[19]

Preparation of Monomer Capsules. PU nanocapsules encapsulating TEGDMA were synthesized following procedures previously published in the literature.[20,21] PU nanocapsules were formed via polycondensation in a two-phase system through miniemulsions. In particular, HD and deionized (DI) water formed the two phases, an oil phase and an aqueous phase. SDS was used as the surfactant to confer colloidal stability. In this reaction, SDS helped to control the equilibrium between the rates of fusion and fission during sonication, which ultimately dictated the size of the droplets that form.[18]

Once 70 mL of DI water, 1.145 mL of HD, and 0.88 g of surfactant (SDS) were mixed together at 300 rpm and 40 °C for 1 h, 2.094 mL of IPDI and 6.1 mL of TEGDMA were slowly dripped into the mixture and stirred; this step began the synthesis of the nanocapsules. It is important to note that IPDI is hydrophobic. By dripping the IPDI and monomer into the solution, the IPDI was evenly distributed throughout the oil phase. As the IPDI and TEGDMA entered the pre-emulsification solution, the stirring speed was increased to 400 rpm. Once the IPDI and TEGDMA were fully injected into the beaker, the solution was left to mix at 400 rpm and 40 °C for 10 min. During this step, the solution turned opaque white. Next, the solution was sonicated with a 130-W Ultrasonic Processor with Thumb-actuated Pulser at an amplitude of 38% to break up any IPDI molecules that had aggregated. During this step, emulsions formed, and the solution looked like milk. While sonication was still progressing, an aqueous solution of 5.9 g of HDOH and 10 mL of DI water was dripped into the system. Because of the high reactivity of the isocyanate, the IPDI reacted immediately with the HDOH at the interface of the two phases.[21]

After sonication, the solution was left to react for 24 h at 40 °C and mixed at 300 rpm. After 24 h, much of the solvent had evaporated and a clear, viscous solution with a solid, white sphere was left in the beaker. The solution was washed to rid it of excess reactants or other contaminants. First, the solution was centrifuged in DI water at 4500 rpm and 4 °C for 30 min. After the centrifugation, a hard, white substance appeared at the bottom of the centrifuge tube, a small semitransparent layer was above the solid layer, and a cloudy, transparent water layer with an oily disk was on top. The disk and the water were removed, and fresh DI water was added to the centrifuge tube.

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The solution was vortexed and again centrifuged at 4500 rpm and 4 °C for 30 min. After the second wash, the solid, white pellet again appeared at the bottom of the centrifuge tube. The water layer was also present with a smaller oily disk on top. The water (supernatant) was again removed and replaced with fresh DI water. The solution was vortexed and centrifuged at 4500 rpm and 4 °C for 20 min. After this centrifugation, layers similar to those after the second wash appeared. The supernatant was removed, and new DI water was added. The solution was vortexed and centrifuged at 4500 rpm and 4 °C for 20 min for a fourth and final time. After this centrifugation, the centrifuge tube contained mostly clear water and a sticky, solid, white substance at the bottom. The supernatant (the water) was again removed, and the pellet was resuspended in fresh DI water; however, the pellet did not resuspend well. The partially resuspended pellet was then frozen in liquid nitrogen and lyophilized.

Preparation of Initiator Capsules. PU nanocapsules encapsulating BPO and butylated hydroxytoluene were synthesized referencing the same procedures previously published in the literature to encapsulate TEGDMA.[20,21] Again, the PU nanocapsules were formed via polycondensation in a two-phase system through miniemulsions. In particular, HD and DI water again formed the two phases, an oil phase and an aqueous phase. SDS was again used as the surfactant to confer colloidal stability.[21]

Once 70 mL of water, 1.145 mL of HD, and 1.1 g of SDS were mixed together at 300 rpm and 40 °C for 1 h, 0.05 g of BPO, and 0.005 g of butylated hydroxytoluene, resuspended in 2.094 mL of IPDI, were slowly dripped into the mixture and stirred; this step began the synthesis of the nanocapsules. By dripping the IPDI and initiator mixture into the solution, the IPDI was evenly distributed throughout the oil phase. As the IPDI solution entered the pre-emulsification solution, the stirring speed was increased to 400 rpm. Once the IPDI solution was fully injected into the beaker, the solution was left to mix at 400 rpm and 40 °C for 10 min. During this step, the solution remained clear. Next, the solution was sonicated with a 130-W Ultrasonic Processor with Thumb-actuated Pulser at an amplitude of 38% to break up any IPDI molecules that had aggregated. During this step, emulsions formed, and the solution looked like milk. While sonication was still progressing, an aqueous solution of 5.9 g of HDOH and 10 mL of DI water was dripped into the system. Because of the high reactivity of the isocyanate, the IPDI reacted immediately with the HDOH at the interface of the two phases.[21]

After sonication, the solution was left to react for 24 h at 40 °C, mixing at 300 rpm. After 24 h, much of the solvent had evaporated and a clear, viscous solution was left in the beaker. The solution was poured into a centrifuge tube and centrifuged with DI water for a total of five times at 10,000 rpm and 4 °C for 20 min each run. After each run, a distinct white pellet formed at the bottom of the tube. Additionally, after each run, the supernatant was discarded, new DI water was added to the tube, and the pellet was resuspended. After the fifth centrifugation period, the supernatant was again discarded, new DI water was added, and the pellet was then resuspended. The resuspended pellet was frozen in liquid nitrogen and lyophilized. When fully dry, the capsules appeared to be a white powder.

Characterization of Nanocapsules. *Capsule Morphology and Size.* A vacuum sputter coater (Denton Desk II) was used to deposit a 20 nm layer of gold palladium onto the nanocapsule samples placed on carbon tape on a specimen stub for scanning electron microscopy (SEM) imaging using the Nova NanoSEM 450 from FEI. The surface morphology of the capsules was examined as well as the diameters of the capsules. Transmission electron microscopy (TEM) imaging was performed using a FEI Morgagni M268 100 kV TEM equipped with a Gatan Orius CCD camera. To obtain TEM images, the capsule samples were loaded onto copper grids.

Capsule Size and Zeta Potential. A Malvern ZetaSizer (Nano ZS90) was used to determine the diameter and zeta potential of the nanocapsules via dynamic light scattering (DLS). The nanocapsules were placed in a 1 mg/mL solution of 190 proof ethanol for sizing. This solution was pipetted into a cuvette (14955129, Fisher Scientific) which was placed into the ZetaSizer. The capsules were placed in a 1 mg/mL solution of 10 mM potassium chloride (KCl) to determine the zeta potential. To measure the zeta potential, the solution was inserted into a folded capillary zeta cell (Malvern Store, DTS1070) which was placed in the ZetaSizer. Both the size and zeta readings were performed in triplicate.

Capsule Molecular Components and Structures. Fourier-transform infrared (FT-IR) (PerkinElmer Frontier Optica) spectroscopy was used to produce spectrum to identify the molecular components and structures within the capsules. Gel permeation chromatography (GPC) (Viscotek, VE 2001) was used to measure the molecular weight of the PU in the capsules. The GPC column (PL1110-6504) is of the Agilent Plgel MIXED family. Its phase is MIXED-D, its inner diameter is 7.5 mm, its length is 300 mm, and its particle size is 5 μm. To measure the molecular weight of PU, the capsule samples were first crushed via a mortar and pestle. Then, 10 mg of the crushed sample was resuspended in 1 mL of tetrahydrofuran. This solution was filtered with PTFE membrane syringe filters (Fisher, 09-720-002) into GPC vials (VWR, 89239-024) which were placed in the GPC for characterization. Hydrogen-1 nuclear magnetic resonance (^{1}H-NMR) spectroscopy was used to further determine the structures of the capsules and the encapsulated contents. To perform this NMR, the capsule samples were resuspended in deuterated dimethyl sulfoxide at a concentration of 1 mg/mL.

Preparation of Resins. *West System Epoxy Resin.* To prepare the epoxy resin, a 4:1 ratio of 105 epoxy resin part 1 was added to the 209 extra slow hardener and mixed together in a paper cup. Then, the monomer capsules were added. The total capsule mass was 3 wt % of the 105 epoxy resin. The capsules were resuspended in 190 proof ethanol in order for the capsules to be well dispersed throughout the resin. The mixture was then poured into dog bone molds and heated with a heat gun. The resin was allowed to dry for 24 h. At that point, the dog bones were removed from the mold and placed in an oven at 200 °C for 20 min to further harden the resin by removing the ethanol from the resin through evaporation.

Blank West System Epoxy resins were also prepared in order to compare the resins with capsules. To prepare the epoxy resin, a 4:1 ratio of 105 epoxy resin part 1 was added to the 209 extra slow hardener and mixed together in a paper cup. 190 proof ethanol was also added to the mixture to create the same consistency as the resin with capsules. The mixture was then poured into a dog bone mold and heated with a heat gun. The resin was allowed to dry for 24 h. At that point, the dog bones were removed from the mold and placed in an oven at 200 °C for 20 min to further harden the resin by removing the ethanol from the resin through evaporation.

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ACS Omega 2022, 7, 31726−31735

For self-healing efficiency testing, West System Epoxy resins were created with the monomer capsules and BPO. To create these resins, a 4:1 ratio of 105 epoxy resin part 1 was added to the 209 extra slow hardener and mixed together in a paper cup. Then, the capsules were added. The total monomer capsule mass was 3 weight percent of the 105 epoxy resin. The capsules were resuspended in 190 proof ethanol in order for the capsules to be well dispersed throughout the resin. Finally, 0.5 g of BPO was added to the mixture. The mixture was then poured into the dog bone molds and heated with a heat gun. The resin was allowed to dry for 24 h. At that point, the dog bones were removed from the mold and placed in an oven at 200 °C for 20 min to further harden the resin by removing the ethanol from the resin through evaporation. A total of four of these samples containing monomer capsules and BPO were created.

A total of six other samples were made for self-healing testing. These samples were prepared the exact same way that the four resins with monomer capsules and BPO; however, in these resins, the initiator capsules were used in place of BPO. The total initiator capsule mass was 3 wt % of the 105 epoxy resin.

Control samples were made. To make the control resins, a 4:1 ratio of 105 epoxy resin part 1 was added to the 209 extra slow hardener and mixed together in a paper cup. Then, 1.5 g of TEGDMA was added. The mixture was then poured into the dog bone molds and heated with a heat gun. The resin was allowed to dry for 24 h. At that point, the dog bones were removed from the mold and placed in an oven at 200 °C for 20 min to further harden the resin. A total of 12 of these control samples were created.

Polishing the Dog Bones. Before fracturing the dog bones, the surface defects in the samples were removed to ensure that the samples did not fracture prematurely. First, the samples were milled to smooth the convex sides of the samples. The samples were then polished using 320, 600, 800, and 1200 grit SiC paper (Allied High Tech Products) on a polishing table. The sanding paper was waterproof, and polishing was performed with water flowing. Polishing was performed with increasing grit because the higher grit created finer and finer scratches which caused less damage to the sample but also removed less impurities.

Fracturing the Capsules. *Tension Test.* The tension test is one of the most fundamental and common types of mechanical testing. This test applies a pulling force to a material with an axial force until the sample breaks and measures the specimen's response to the stress.[19] The tension test was performed on a universal testing instrument (Instron electromechanical universal testing system, 3300 series) using a strain rate of 10^{-3} s^{-1}. A complete profile of tensile properties was obtained. These data resulted in a stress/strain curve which revealed the point of failure, the modulus of elasticity, yield strength, the ultimate tensile stress (UTS), and strain to fracture.

To perform the test, the dimensions of the gauge region of the dog bone sample were first determined. Then, reflective tape was placed at the edge of the gauge region. The reflective tape was used to measure length of the gauge region. Then, the sample was placed in the grips of the machine. During the testing, the grips moved apart until the sample snapped. A laser extensometer performed the strain and elongation measurements during the testing.

Determining Self-Healing Efficiency. *Tensile Test.* During this test, the monomer capsules was placed in the resin with the BPO initiator. The test proceeded as described above; however, when the resin broke, the two halves were placed back into the dog bone mold and left for 48 h to heal. Then, a second tensile test was performed on the healed resin samples.

Determining Biocompatibility. *Cell Culture.* The Caco-2 cells (a line of human epithelial colorectal cells) used were obtained from ATCC. The cells were cultured in Minimum Essential Medium−Alpha modification (MEM-α), supplemented with 20% fetal bovine serum (FBS), with both the MEM-α and the FBS having been purchased from ThermoFisher. Cells were grown in an incubator at 37 °C in a 5% CO_2 atmosphere.

Live/Dead Assay. The assay was performed using the LIVE/DEAD Viability/Cytotoxicity Kit, for mammalian cells, purchased from ThermoFisher. Calcein-AM was used as the live stain, with live cells appearing green, while ethidium homodimer-1 (EthD) was used as the dead stain, with dead cells being stained red. Images of the cells were taken using an IX81 Olympus fluorescence microscope. The cell count was 350,000 cells/mL, and the cells were mixed thoroughly before being spread out evenly over all 24 wells, leading to a count of 14,500 cells per well. After seeding, the cells were allowed to adhere for 23 h, after which point the testing and control conditions were created. Eight conditions were tested, with each condition having 600 μL of media (80% MEM-α and 20% FBS) present. Three wells contained 1 mg of BPO, three wells contained 10 mg of butylated hydroxytoluene (BHT), and three wells contained 10 mg of TEGDMA. These wells comprised the conditions that were intended to examine cell viability in the presence of the materials encapsulated by the PU nanocapsules. As for examination of cell viability in the presence of the PU nanocapsules themselves, there were three wells in which 10 mg of monomer nanocapsules (capsules with TEGDMA) were present, three wells in which 1 mg of initiator nanocapsules (capsules with BPO and BHT) were present, and three wells in which 10 mg of monomer nanocapsules created with 59 g of HDOH and 20.94 mL of IPDI (10× the usual amount) were present. Finally, there were two control conditions tested, with three wells having just 600 μL of media in them (a live control) and three wells having 100 μL of 10% ethanol present (a dead control). The cells were exposed to each condition for 1 or 24 h, after which point the nanocapsules, the encapsulated materials, and the media were all removed from the wells. The cells in each well were then washed with 650 μL of Gibco HBSS purchased from ThermoFisher. Following removal of the HBSS, 600 μL of fresh media was added to each well. Once fresh media were present in each well, 25 μL of stain was added to each well. The stain was prepared by mixing 8 μL of EthD with 4 μL of calcein and 1 mL of PBS. Following addition of the stain, the cells were allowed to incubate for 45 min at 37 °C in a 5% CO_2 atmosphere. After the incubation period had passed, the cells were imaged using the IX81 fluorescence microscope.

RESULTS

Optimization of Reaction Characteristics for Nanocapsules. *PU Reaction.* To optimize the monomer and initiator capsules, first the reaction to form PU was optimized. PU is formed by the chemical reaction between a di/

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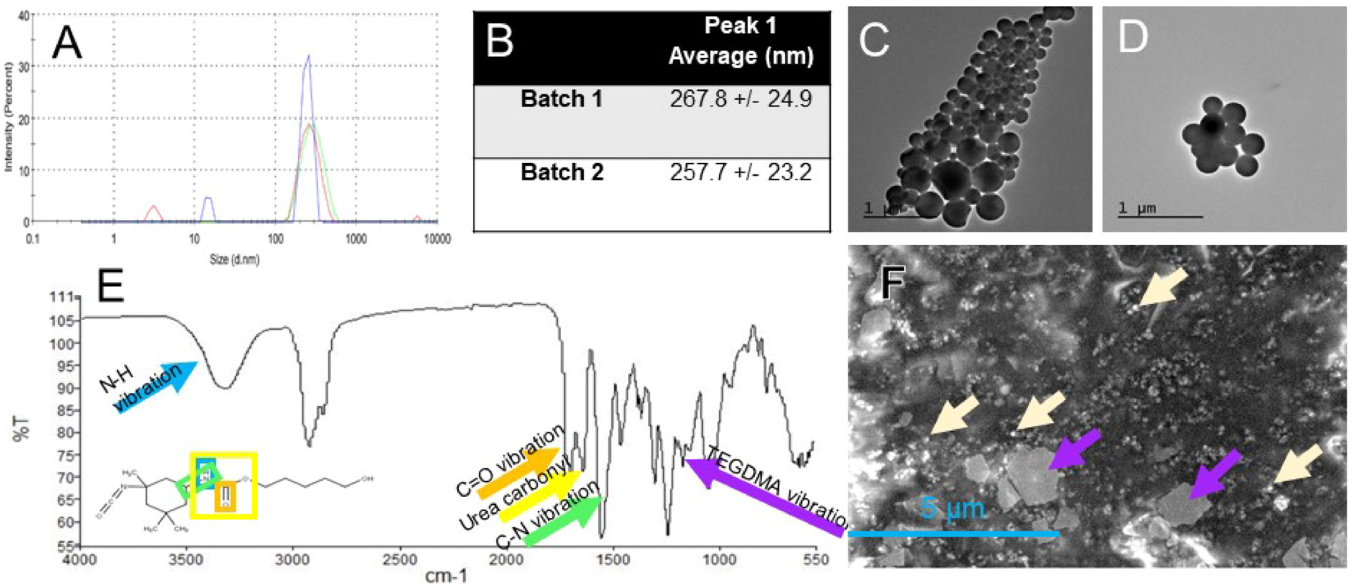
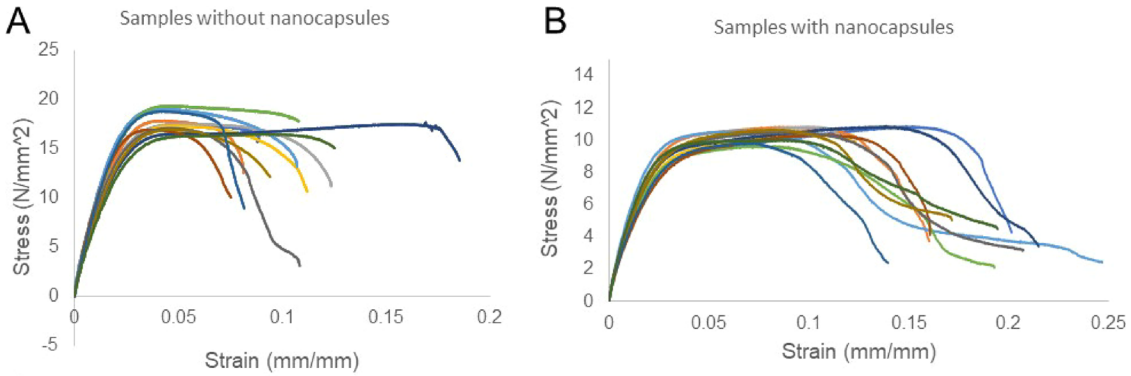


Figure 1. (A) DLS of TEGDMA nanocapsules. (B) Diameter of nanocapsules was consistent batch to batch. (C, D) TEM images of nanocapsules. (E) FT-IR demonstrating the presence of the PU as well as the TEGDMA. (F) SEM showing the nanocapsules (tan arrows) and residual TEGDMA. Not all of the TEGDMA was encapsulated in this formulation.



C

	Elastic Modulus (N/mm^2)	Yield Stress (N/mm^2)	UTS (N/mm^2)	Strain to Fracture (mm/mm)
Samples without nanocapsules	833.7 +/- 80.4	12.4 +/- 1.1	17.7 +/- 0.9	0.107 +/- 0.03
Samples with nanocapsules	422.2 +/- 41.3	7.4 +/- 0.6	10.5 +/- 0.4	0.177 +/- 0.04

Figure 2. Incorporating nanocapsules into the matrix. (A) Stress–strain curves for the epoxy resin without nanocapsules (n = 12). (B) Stress–strain curves for samples with nanocapsules (n = 12). (C) Table comparing critical features from these two groups. Adding nanocapsules impacts the mechanical properties of the resin, as expected.

polyisocyanate and a diol or polyol; this reaction forms repeating urethane groups.[17]

To form the PU nanocapsules, a 5:1 ratio of HDOH to IPDI was used to ensure that end capping of the IPDI occurred during the reaction. To minimize the size distribution of the PU nanocapsules in the system, the amount of surfactant was varied. For SDS, the critical micelle concentration is 6 to 8 mM. This is the concentration of SDS in a bulk phase, in this case water, above which micelles start to form. In this particular formulation, with a total of 80 mL of DI water, this means that a mass of 0.138 g of SDS or greater must be added in order to form micelles. Guo et al. in "The Role of Surfactant and Costabilizer in Controlling Size of Nanocapsules Containing TEGDMA in Miniemulsion" stated that a typical procedure to obtain PU nanocapsules encapsulating TEGDMA included 0.88 g of SDS and 0.88 g of HD.[21] Torini et al. reported preparing the miniemulsions with 0.66 g of SDS and 0.66 g of HD.[20] The basic procedure for the preparation of miniemulsions is based on the dispersion of HD in the aqueous phase with the surfactant, SDS; however, the amount of HD and surfactant must be varied depending on what is being encapsulated.[20]

In the reaction, the surfactant was anionic and provided stable miniemulsions.[20] The costabilizer allowed for the buildup of an osmotic pressure in the droplets which provided stability against Ostwald ripening.[20] During the reaction, to form both the monomer and initiator nanocapsules, a stable miniemulsion was first obtained when the IPDI was added to the pre-emulsification solution and sonicated. Then, the HDOH was dissolved in the external phase and added to the

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ACS Omega 2022, 7, 31726–31735

miniemulsion. This addition leads to the reaction between the IPDI and HDOH at the interface of the two nonmiscible phases (the water and oil phases).[20]

Capsule Characteristics. PU capsules that encapsulate TEGDMA and BPO/butylated hydroxytoluene were synthesized via a polycondensation in a two-phase system through miniemulsions. The capsules are parts of dual- and monocapsule self-healing systems. It was determined that 0.88 g of SDS is the optimal amount of surfactant needed to form nanocapsules near the 200 nm size range with a low polydispersity index (PDI) (Figure 1). The monomer capsules can be synthesized with consistency in size, zeta potential, and chemical composition over multiple batches; however, the samples contained excess TEGDMA. While the excess could be minimized by washings, subsequent adjustments in the protocol to increase the amount of IPDI and HDOH 10-fold essentially eliminated excess TEGDMA.

The initiator capsules were synthesized using the same protocol and were composed of PU and encapsulated BPO and butylated hydroxytoluene. It was determined that 1.1 g of SDS is the optimal amount of surfactant needed to form nanocapsules with around the 300 nm size range with a low PDI (via DLS).

Mechanical Testing. The West System Epoxy resin was used as a matrix for testing the impact of the TEGDMA and BPO nanocapsules because the properties of the resin are well known and consistent. The mechanical properties of the resin with the monomer capsules were compared to those of blank resins in order to determine how the capsules affect the resin properties.

Incorporation of nanoparticles into matrices is known to impact the mechanical properties of many systems (Figure 2).[22] Not surprisingly, the nanocapsules studied here impacted the mechanical properties of the matrix. The addition of 3 wt % nanocapsules significantly impacted the mechanical properties. The modulus of the composite was half of that of the matrix alone. Likewise, the nanocapsules impacted the yield stress and the UTS of the resins. The nanocapsules did not impact the strain to fracture values. None of this is unexpected with the addition of nanocapsules to an epoxy resin. In a dental resin or bone cement, there are a number of fillers and other additives. Exchanging one of the fillers for a self-healing component could achieve the desired mechanical properties while adding the self-healing feature.

Following fracture, samples were put back together in the molds to see if there was any self-healing with just monomer capsules. As expected, no self-healing was seen. Following mechanical testing, the fracture surfaces were analyzed using SEM.

SEM revealed that the monomer capsules broke during mechanical testing. Figure 3A,B shows the resin alone. Figure 3C shows the resin with monomer capsules (the very small dots scattered through the fracture surface.) Higher resolution images show that the capsules have broken. Broken capsules can be seen in Figure 3D−F. Larger capsules appear to break more readily than smaller capsules with some smaller capsules still intact on the fracture surfaces.

Self-Healing Efficiency. The goal of this work was to determine if incorporating nanocapsules filled with TEGDMA, the monomer, and BPO, the initiator could promote self-healing following fracture.

West System Epoxy resins were prepared with monomer capsules and BPO. The BPO was added directly to the resin and not encapsulated in these experiments. Tensile tests were performed on these samples.

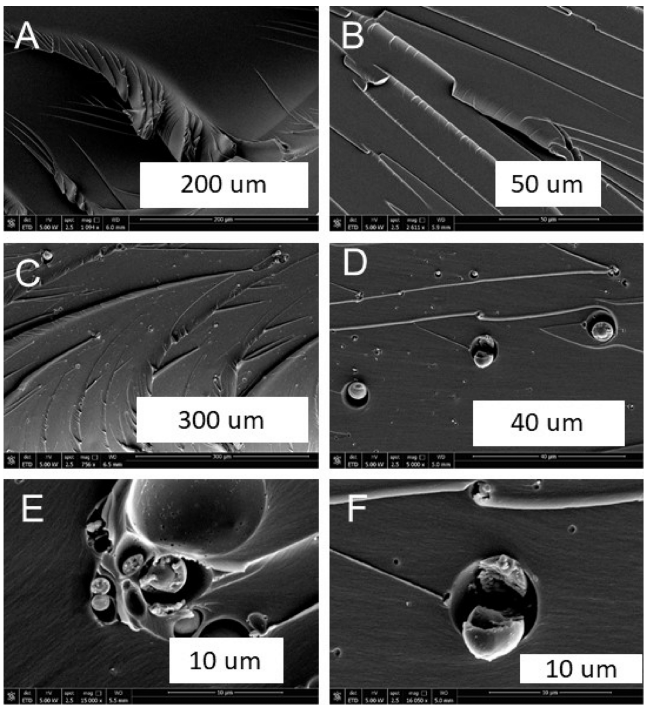

Figure 3. Images show the fracture surface on samples of West System epoxy resin. (A) This image shows the area at which the fracture occurred in a sample without monomer capsules. (B) This SEM image presents a zoomed in image of another fracture site in the resin. (C) This SEM image shows the fracture surface from a sample with monomer capsules. The capsules, especially larger capsules, are evident in the surface and cause a rougher surface. (D) These SEM images show fracture surfaces another sample with monomer capsules at a higher magnification. In these images, it is evident that some of the larger capsules have cracked. The white dots in these images are the nanocapsules. (E, F) These SEM images focus on the monomer capsules in the resin. These images show fractured capsules in the resin.

The samples underwent strain to fracture. The elastic moduli, yield stress, and UTS were similar to the previously tested samples. All of the samples were then placed back together in the molds in which the dog bones were cast. After 48 h, two of the four samples exhibited self-healing and could be tested again. Not surprisingly, the self-healed system showed smaller stress−strain curves. Figure 4A shows the stress−strain curves for the samples during the initial tests (R1 and R2) and the stress−strain curves following self-healing (Healed R1 and Healed R2). Figure 4C shows the values for the modulus, yield stress, UTS, and strain to fracture for the as-made versus self-healed samples. While the modulus is maintained or increased for the samples, the yield stress and UTS are significantly decreased.

Nonetheless, even with the BPO initiator just mixed into the resin, the system exhibited self-healing in some of the samples. As a control, based on this, epoxy resins with TEGDMA (n = 12) were prepared as controls to determine if unencapsulated TEGDMA in the resin has any self-healing effect. These samples were tested with a tensile test. None of the samples showed a self-healing effect confirming that the presence of TEGDMA in capsules is essential for self-healing to occur.

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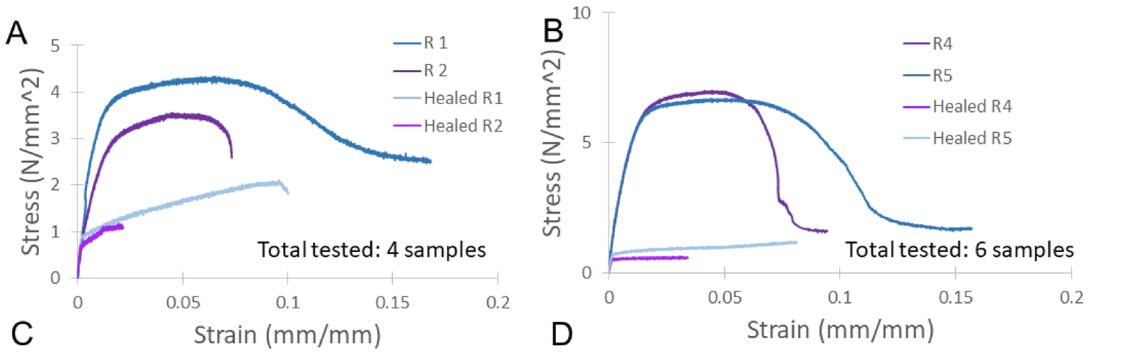
ACS Omega 2022, 7, 31726−31735



C

	Elastic Modulus (N/mm2)	Yield Stress (N/mm2)	UTS (N/mm2)	Strain to Fracture (mm/mm)
R1 as made	217.2	2.8	3.6	0.0733
R2 as made	408.8	3.3	4.3	0.168
R1 post healing	615.5	0.7	1.2	0.0118
R2 post healing	508.1	0.9	2.1	0.100

D

	Elastic Modulus (N/mm2)	Yield Stress (N/mm2)	UTS (N/mm2)	Strain to Fracture (mm/mm)
R4 as made	506.2	5.8	7.0	0.0943
R5 as made	505.3	5.7	6.7	0.156
R4 post healing	421.5	0.5	0.6	0.0341
R5 post healing	516.8	0.7	1.2	0.0812

Figure 4. (A) This figure depicts the stress/strain curves from two of the four samples of resin with the monomer capsules and BPO after self-healing. These samples were prepared at the same time and with the same conditions. The properties of the original resins (R1 and R2) are also displayed for comparative purposes. (B) Stress−strain curves from 2 of the six samples of resin with the monomer capsules and initiator capsules after self-healing. These samples were prepared at the same time and with the same conditions. The properties of the original resins (R4 and R5) are also displayed for comparative purposes. (C) Mechanical properties of R1 and R2, which exhibited self-healing as made and after the self-healing reaction. (D) Mechanical properties of the dual-capsule system as made and after self-healing for the two samples of six that exhibited self-healing.

Epoxy resins with monomer capsules and initiator capsules were also prepared. These samples underwent tensile tests. All of the samples exhibited mechanical properties similar to the monomer capsule-alone samples. Of the six samples tested, two exhibited self-healing after 48 h. The stress−strain curves for the as-made (R4 and R5) and healed samples (Healed R4 and Healed R5) are shown in Figure 4B.

Similar to the samples where the initiator, BPO, was dissolved in the resin, the dual nanocapsule systems that exhibited self-healing maintained their modulus but showed substantial drops in the yield stress and UTS. The values for the modulus, yield stress, UTS, and strain to failure are summarized in Figure 4D.

Researchers have proposed multiple definitions of healing efficiencies. We will measure healing by defining a recovery ratio (R). The recovery ratio is shown in eq 1, where f is the partially healing material property and $f\infty$ is the virgin state material property.[23]

$$R(f) = \frac{f}{f_{\infty}} \tag{1}$$

Using this equation, we get the recovery ratios shown in Table 1.

As expected, while the modulus was maintained in the self-healed samples, the yield stress, UTS, and strain to fracture all dropped for both the system with the initiator mixed directly in the resin (R1 and R2) and for the dual initiator and monomer capsule system.

The tensile test is an excellent test for looking at whether a self-healing system works, but it would be relatively rare for a dental resin or bone cement to be in tension under normal conditions. It is more common that in use, a resin or cement would experience crack propagation. Having a system that can promote self-healing, even if the original yield stress or UTS are compromised would still be very valuable.

Table 1. Recovery Ratio for Each Property Examined for the Resin Samples after Self-Healing

	elastic modulus	yield stress	UTS	strain to fracture
R1	2.833	0.262	0.333	0.161
R2	1.243	0.279	0.488	0.595
R4	0.833	0.094	0.086	0.362
R5	1.023	0.130	0.179	0.520

Biocompatibility. This self-healing system was built around materials that are designed to be extremely biocompatible. To test whether the biocompatibility was achieved in the practical system, we performed a series of live-dead assays on the components and nanocapsules. The results of the biocompatibility studies are presented in Figure 5 as well as Figure S2.

Figure S2 demonstrates the biocompatibility of the compounds contained within the PU nanocapsules. The compounds chosen for this system were already characterized as GRAS (generally recognized as safe), but a live/dead assay was performed using these materials to see how the viability of the cells in the presence of these compounds compared to the viability of the cells in the presence of the nanocapsules in which these materials are contained. Caco-2 cells were chosen because epithelial cells are the first likely to come into contact with these materials in a dental resin, and they are sensitive to their environment.

Figure 5 depicts the results of the live/dead assay performed using the Caco-2 cell line with nanocapsules containing either the monomer or BPO. The images were taken after the cells had been exposed to the nanocapsules and the various encapsulated materials for 1 h. Live cells, stained by calcein-AM, appear green. Dead cells, stained by ethidium homodimer-1, appear red. Quantification of the results of the live/dead assay can be seen in Figure 5F. These can be compared to the free compounds tested in Figure S2.

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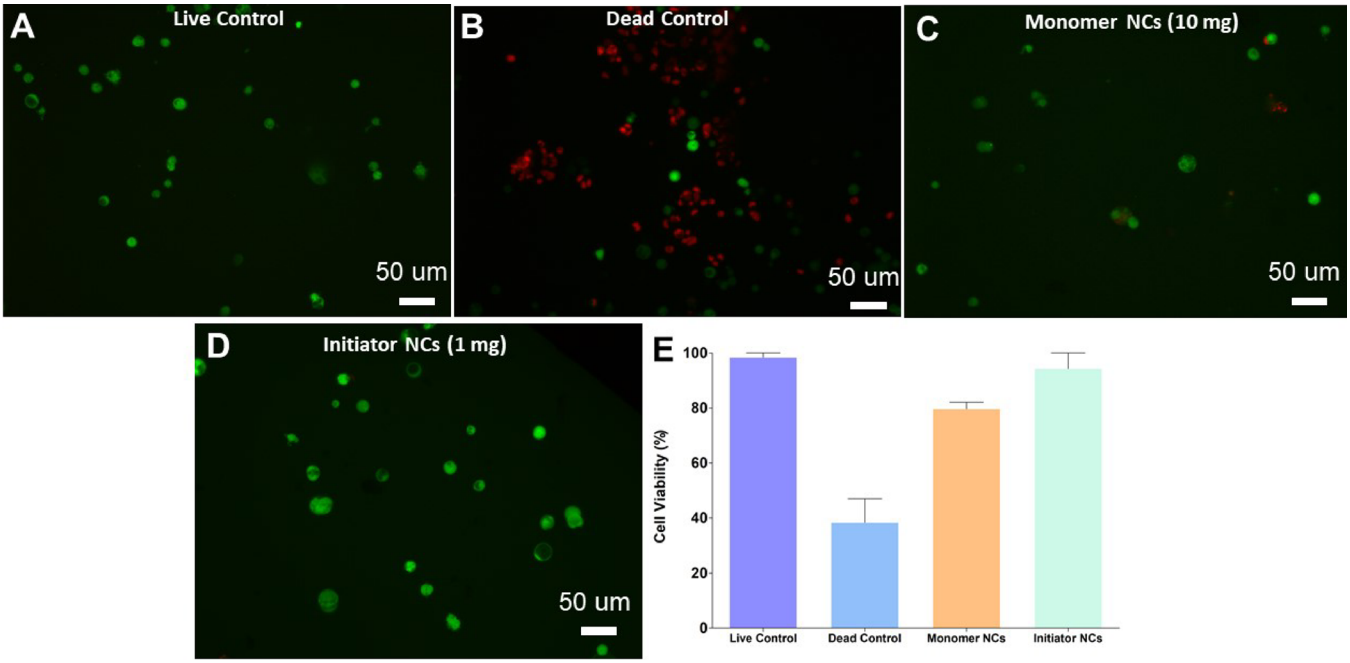

Figure 5. Live-dead assay with Caco-2 cells. Images 1 h postexposure to nanocapsules and controls. (A) Live control. Cells with no additional components. (B) Dead control. Cells were incubated for 1 h with 10% ethanol. (C) Monomer nanocapsules containing TEGDMA (10 mg). (D) Initiator nanocapsules containing BPO and BHT (1 mg). (E) Quantification of live-dead assay results.

Doing a comparison of the monomer nanocapsules and the monomer compound (TEGDMA), one can see that there is a slightly higher viability when cells are exposed to 10 mg of the monomer nanocapsules than when they are exposed to 10 mg of TEGDMA (83% viability in the presence of the monomer nanocapsules (Figure 5) vs 75% in the presence of the TEGDMA (Figure S2)). In contrast, the initiator nanocapsules and the initiator compound (BPO) both displayed comparably high levels of cytotoxicity, with 50% or fewer of the cells living after 1 h of exposure to 10 mg of the initiator nanocapsules or to 10 mg of free BPO. This necessitated using smaller quantities of the materials for live/dead assays. At a quantity of 1 mg, 100% cell viability was seen for both the initiator nanocapsules and BPO. We know from previous work with the nanocapsules that compounds like fluorescein can be within the shell of the nanocapsules,[24] and there is a high probability of that happening in this case such that some of the BPO is not within the core of the nanocapsules but near the surface of the shells.

■ DISCUSSION

TEGDMA was chosen as the monomer because it has a long shelf-life yet polymerizes quickly.[25] It is important for the healing liquid to have a relatively low viscosity to flow and fill the cracks of the resin matrix; TEGDMA is able to flow and has previously been used as a dental monomer with acceptable biocompatibility.[12] Additionally, TEGDMA can form a polymer via free-radical initiation by using a peroxide initiator (and a tertiary amine accelerator to speed the reaction).[25]

The novelty of this system lies in the use of all GRAS approved components and the extensive biocompatibility of the self-healing systems created. To stabilize the BPO to ensure free radicals are not formed prior to its release from the capsule, BHT was used. This compound scavenges the free-radical species that are responsible for peroxide formation and acts as an effective suppressor to peroxide formation.[26] The use of BPO and BHT in the initiator component of a dual-capsule-based self-healing system further extends the novelty of the study as well as the likelihood that this system would be stable over time. While over the short term, mixing BPO in the matrix does work to promote self-healing in some of the samples, having a dual-capsule system with BPO mixed with BHT increases the stability of the system.

One of the exciting findings in this work was that the nanocapsules did fracture. For a capsule-based self-healing system to be effective, the capsules must break as a crack propagates through the resin. If the shell is too thick, the capsules will not rupture when a crack propagates; however, if the shell is too thin, the capsules will be too fragile.[27] These capsules are stable and do fracture appropriately. However, only a fraction of the samples exhibited self-healing following fracture. One of the most significant challenges we encountered with the nanocapsule system was obtaining good mixing of nanocapsules so that they were well dispersed in the system. Beyond this, loading the nanocapsules into this matrix was challenging. We were limited to 3 wt % capsules in the matrix. This is in contrast to other work which looked at 5 wt % of particles.[12] Higher loading may be possible in different resin systems. Nonetheless, the healing efficiency with lower concentrations of nanocapsules is still comparable. The 5 wt % system exhibited healing efficiencies on the order of 35%.[12] We achieved efficiencies consistent with this, but of course, only in a fraction of the samples tested. To move this technology into an application, the mixing issue will have to be considered carefully to make this system more reproducible.

The degree of biocompatibility of the self-healing system is worth noting. The majority of studies involving the use of nanocapsules test cell viability in the presence of microgram quantities of a given biomaterial.[28] The results of the live-dead assays presented in this work demonstrate that one can achieve 80% cell viability or greater even when cells are directly exposed to as much as 10 mg of the monomer nanocapsules or

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ACS Omega 2022, 7, 31726−31735

1 mg of the initiator nanocapsules. Given that the capsules only make up 3 wt % of the dog bone samples used in the tensile tests, it is highly unlikely that a quantity greater than 1 mg of the nanocapsules would ever be needed, let alone 10 mg.

CONCLUSIONS

By embedding PU nanocapsules encapsulating TEGDMA in an epoxy resin and comparing these resins to blank resins, the effects the monomer capsules have on the mechanical properties of a resin were determined. Tensile testing was used to determine the properties of both resin systems; the resin without monomer capsules proved to be stronger than the resin with the monomer capsules when the elastic modulus, yield stress, UTS, and strain to fracture in both types of resins were compared. However, it is important to note that the monomer capsules did indeed crack during the resin fracture. This ultimately proved that the capsules have potential to have a self-healing effect in a resin when a crack propagates through the resin. If such a crack were to occur and result in free nanocapsules entering the GI tract, the health of the patient would not be jeopardized, with the results of the live-dead assays demonstrating that a biocompatible self-healing system has been developed. Furthermore, after examining the self-healing capacity of resins with the monomer capsules and unencapsulated BPO and the monomer capsules and initiator capsules, a small degree of self-healing was present within the resins. Further testing must be pursued to fully understand the degree of self-healing possible in this dual-capsule system.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02080.

Supplemental information is included in order to better describe the monomer and initiator capsule characteristics in addition to increase the comprehension of the self-healing reaction. Additionally, the supplemental information contains more details from the mechanical tests performed (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. S.M. and J.L. contributed equally.

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Notes

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ABBREVIATIONS

PU, polyurethane; GRAS, generally recognized as safe; TEGDMA, triethylene glycol dimethacrylate; BPO, benzoyl peroxide; SDS, sodium dodecyl sulfate; HD, hexadecane; HDOH, 1,6-hexanediol; IPDI, isophorone diisocyanate; ASTM, American Society for Testing and Materials; DI, deionized; SEM, scanning electron microscopy; DLS, dynamic light scattering; FT-IR, Fourier-transform infrared spectroscopy; GPC, gel permeation chromatography; NMR, nuclear magnetic resonance; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; UTS, ultimate tensile strength; PDI, polydispersity index

REFERENCES

(1) Van Tittelboom, K.; De Belie, N. Self-Healing in Cementitious Materials—A Review. *Materials* **2013**, *6*, 2182.

(2) Cremaldi, J. C.; Bhushan, B. Bioinspired self-healing materials: lessons from nature. *Beilstein J. Nanotechnol.* **2018**, *9*, 907−935.

(3) Wooley, P. H.; Schwarz, E. M. Aseptic loosening. *Gene Ther.* **2004**, *11*, 402−407.

(4) Apostu, D.; Lucaciu, O.; Berce, C.; Lucaciu, D.; Cosma, D. Current methods of preventing aseptic loosening and improving osseointegration of titanium implants in cementless total hip arthroplasty: a review. *J. Int. Med. Res.* **2018**, *46*, 2104−2119.

(5) *Dental Diseases and Oral Health, Organization*, W. H., 2003. http://www.who.int/oral_health/publications/en/orh_fact_sheet.pdf (accessed April 28, 2018).

(6) Petersen, P. E.; Bourgeois, D.; Ogawa, H.; Estupinan-Day, S.; Ndiaye, C. The global burden of oral diseases and risks to oral health. *Bull. World Health Organ.* **2005**, *83*, 661−669.
(7) Manhart, J.; Chen, H.; Hamm, G.; Hickel, R. Buonocore Memorial Lecture. Review of the clinical survival of direct and indirect restorations in posterior teeth of the permanent dentition. *Oper. Dent.* **2004**, *29*, 481−508.
(8) (a) Fugolin, A. P. P.; Pfeifer, C. S. New Resins for Dental Composites. *J. Dent. Res.* **2017**, *96*, 1085−1091. (b) Kenny, S. M.; Buggy, M. Bone cements and fillers: A review. *J. Mater. Sci.: Mater. Med.* **2003**, *14*, 923−938.
(9) Yuan, L.; Liang, G.-Z.; Xie, J.-Q.; He, S.-B. Synthesis and characterization of microencapsulated dicyclopentadiene with melamine−formaldehyde resins. *Colloid Polym. Sci.* **2007**, *285*, 781−791.
(10) White, S. R.; Sottos, N. R.; Geubelle, P. H.; Moore, J. S.; Kessler, M. R.; Sriram, S. R.; Brown, E. N.; Viswanathan, S. Autonomic healing of polymer composites. *Nature* **2001**, *409*, 794−797.
(11) (a) Wertzberger, B. E.; Steere, J. T.; Pfeifer, R. M.; Nensel, M. A.; Latta, M. A.; Gross, S. M. Physical characterization of a self-healing dental restorative material. *J. Appl. Polym. Sci.* **2010**, *118*, 428−434. (b) Biggs, P.; Jones, L.; Wellborn, B.; Lewis, G. A Self-healing PMMA Bone Cement: Influence of Crystal Size of Grubbs' Catalyst. In *25th Southern Biomedical Engineering Conference 2009, 15−17 May 2009, Miami, Florida, USA, Berlin, Heidelberg, 2009//*, 2009; McGoron, A. J., Li, C.-Z., Lin, W.-C., Eds.; Springer Berlin Heidelberg, 147−150.
(12) Wu, J.; Weir, M. D.; Zhang, Q.; Zhou, C.; Melo, M. A.; Xu, H. H. Novel self-healing dental resin with microcapsules of polymerizable triethylene glycol dimethacrylate and N,N-dihydroxyethyl-p-toluidine. *Dent. Mater.* **2016**, *32*, 294−304.
(13) Caruso, M. M.; Delafuente, D. A.; Ho, V.; Sottos, N. R.; Moore, J. S.; White, S. R. Solvent-Promoted Self-Healing Epoxy Materials. *Macromolecules* **2007**, *40*, 8830−8832.
(14) Dailey, M. M. C.; Silvia, A. W.; McIntire, P. J.; Wilson, G. O.; Moore, J. S.; White, S. R. A self-healing biomaterial based on free-radical polymerization. *J. Biomed. Mater. Res. A* **2014**, *102*, 3024−3032.
(15) Brochu, A. B. W.; Matthys, O. B.; Craig, S. L.; Reichert, W. M. Extended fatigue life of a catalyst free self-healing acrylic bone cement using microencapsulated 2-octyl cyanoacrylate. *J. Biomed. Mater. Res. B Appl. Biomater.* **2015**, *103*, 305−312.
(16) Gladman, A. S.; Celestine, A.-D. N.; Sottos, N. R.; White, S. R. Autonomic healing of acrylic bone cement. *Adv. Healthc. Mater.* **2015**, *4*, 202−207.
(17) Santerre, J. P.; Woodhouse, K.; Laroche, G.; Labow, R. S. Understanding the biodegradation of polyurethanes: From classical implants to tissue engineering materials. *Biomaterials* **2005**, *26*, 7457−7470.
(18) Srinivasan, P. K.; Sperber, V.; Afify, M.; Tanaka, H.; Fukushima, K.; Kögel, B.; Gremse, F.; Tolba, R. Novel synthetic adhesive as an effective alternative to Fibrin based adhesives. *World J. Hepatol.* **2017**, *9*, 1030−1039.
(19) Lee, C. The Mechanical Properties of PMMA Bone Cement. In *The Well-Cemented Total Hip Arthroplasty: Theory and Practice*; Springer: Berlin Heidelberg, 2005; 60−66.
(20) Torini, L.; Argillier, J. F.; Zydowicz, N. Interfacial Polycondensation Encapsulation in Miniemulsion. *Macromolecules* **2005**, *38*, 3225−3236.
(21) Guo, J.; Pan, Q.; Huang, C.; Zhao, Y.; Ouyang, X.; Huo, Y.; Duan, S. The role of surfactant and costabilizer in controlling size of nanocapsules containing TEGDMA in miniemulsion. *J. Wuhan Univ. Technol.-Mater. Sci. Ed.* **2009**, *24*, 1004−1006.
(22) (a) Kaizer, M. R.; Almeida, J. R.; Goncalves, A. P.; Zhang, Y.; Cava, S. S.; Moraes, R. R. Silica Coating of Nonsilicate Nanoparticles for Resin-Based Composite Materials. *J. Dent. Res.* **2016**, *95*, 1394−1400. (b) Li, L.; Zuo, Y.; Zou, Q.; Yang, B.; Lin, L.; Li, J.; Li, Y. Hierarchical Structure and Mechanical Improvement of an n-HA/GCO-PU Composite Scaffold for Bone Regeneration. *ACS Appl. Mater. Interfaces* **2015**, *7*, 22618−22629. (c) Mohr, R.; Kratz, K.; Weigel, T.; Lucka-Gabor, M.; Moneke, M.; Lendlein, A. Initiation of shape-memory effect by inductive heating of magnetic nanoparticles in thermoplastic polymers. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 3540−3545.
(23) Wool, R. P.; O'Connor, K. M. A theory crack healing in polymers. *J. Appl. Phys.* **1981**, *52*, 5953−5963.
(24) Menikheim, S.; Leckron, J.; Bernstein, S.; Lavik, E. B. On-Demand and Long-Term Drug Delivery from Degradable Nanocapsules. *ACS Appl. Bio Mater.* **2020**, *3*, 7369−7375.
(25) Diesendruck, C. E.; Sottos, N. R.; Moore, J. S.; White, S. R. Biomimetic Self-Healing. *Angew. Chem., Int. Ed.* **2015**, *54*, 10428−10447.
(26) Yehye, W. A.; Rahman, N. A.; Ariffin, A.; Abd Hamid, S. B.; Alhadi, A. A.; Kadir, F. A.; Yaeghoobi, M. Understanding the chemistry behind the antioxidant activities of butylated hydroxytoluene (BHT): A review. *Eur. J. Med. Chem.* **2015**, *101*, 295−312.
(27) Keller, M. W.; Sottos, N. R. Mechanical Properties of Microcapsules Used in a Self-Healing Polymer. *Exp. Mech.* **2006**, *46*, 725−733.
(28) (a) Ouyang, X.; Huang, X.; Pan, Q.; Zuo, C.; Huang, C.; Yang, X.; Zhao, Y. Synthesis and characterization of triethylene glycol dimethacrylate nanocapsules used in a self-healing bonding resin. *J. Dent.* **2011**, *39*, 825−833. (b) El-Ansary, A.; Al-Daihan, S.; Bacha, A. B.; Kotb, M. Toxicity of novel nanosized formulations used in medicine. *Methods Mol. Biol.* **2013**, *1028*, 47−74. (c) Picheth, G.; Houvenagel, S.; Dejean, C.; Couture, O.; Alves de Freitas, R.; Moine, L.; Tsapis, N. Echogenicity enhancement by end-fluorinated polylactide perfluorohexane nanocapsules: Towards ultrasound-activable nanosystems. *Acta Biomater.* **2017**, *64*, 313−322. (d) Montigaud, Y.; Ucakar, B.; Krishnamachary, B.; Bhujwalla, Z. M.; Feron, O.; Préat, V.; Danhier, F.; Gallez, B.; Danhier, P. Optimized acriflavine-loaded lipid nanocapsules as a safe and effective delivery system to treat breast cancer. *Int. J. Pharm.* **2018**, *551*, 322−328.

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