



Published in final edited form as:

*Dent Mater.* 2016 February ; 32(2): 294–304. doi:10.1016/j.dental.2015.11.014.

## Novel self-healing dental resin with microcapsules of polymerizable triethylene glycol dimethacrylate and *N,N*-dihydroxyethyl-*p*-toluidine

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### Abstract

**Objectives**—Bulk fracture is one of the primary reasons for resin-based dental restoration failures. To date, there has been no report on the use of polymerizable dental monomers with acceptable biocompatibility to develop a resin with substantial self-healing capability. The objectives of this study were to: (1) develop a self-healing resin containing microcapsules with triethylene glycol dimethacrylate (TEGDMA)-*N,N*-dihydroxyethyl-*p*-toluidine (DHEPT) healing liquid in poly(urea-formaldehyde) (PUF) shells for the first time, and (2) determine the physical and mechanical properties, self-healing efficiency, and fibroblast cytotoxicity.

**Methods**—Microcapsules of polymerizable TEGDMA-DHEPT in PUF were prepared via an *in situ* polymerization method. Microcapsules were added into a BisGMA-TEGDMA resin at microcapsule mass fractions of 0%, 5%, 10%, 15% and 20%. A flexural test was used to measure

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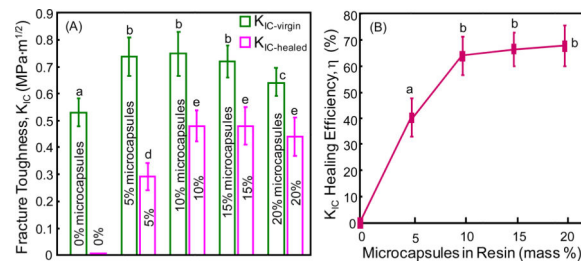
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composite strength and elastic modulus. A single edge V-notched beam method was used to measure fracture toughness  $K_{IC}$  and self-healing efficiency.

**Results**—Flexural strength and elastic modulus (mean  $\pm$  sd;  $n = 6$ ) of resin containing 5% to 15% microcapsules were similar to control without microcapsules ( $p > 0.1$ ). Adding microcapsules into the resin increased the virgin  $K_{IC}$ , which was about 40% higher at 15% microcapsules than that with 0% microcapsules ( $p < 0.05$ ). Specimens were fractured and healed, then fractured again to measure the healed  $K_{IC}$ . A self-healing efficiency of about 65% in  $K_{IC}$  recovery was obtained with 10–20% microcapsules. All specimens with 0–20% microcapsules had fibroblast viability similar to control without resin eluents ( $p > 0.1$ ).

**Significance**—Self-healing dental resin containing microcapsules with polymerizable TEGDMA-DHEPT healing liquid in PUF shells were prepared for the first time with excellent self-healing capability. These microcapsules and self-healing resins containing them may be promising for dental restorations to heal cracks/damage and increase durability.

### Graphical abstract



### Keywords

Self-healing dental resin; microcapsules; polymerizable healing liquid; mechanical properties; fracture toughness recovery; cytotoxicity

## 1. Introduction

Dental caries is a prevalent problem worldwide with a significant financial burden [1]. Resin composites are popular materials to fill tooth cavities due to their excellent esthetics and direct-filling capabilities [2,3]. However, the durability of these restorations is limited, with half of all restorations failing in less than 10 years, and with fracture as one of the primary reasons for failure [4,5]. It was reported that more than 25% of composite replacements were driven by some forms of fracture [6]. Indeed, fracture of restorations was the main reason for failure in composite restorations in large cavities after 5 years of use [7].

A main reason that composite restorations fail was suggested to be the formation and accumulation of micro-cracks, caused by factors including mastication forces and thermal stresses [8]. Efforts have been made to develop composites with improved resistance to fracture failures [9–13]. These efforts included optimizing the inorganic filler level, reducing filler size to nanoscale, adding different types of fillers such as fibers, whiskers and nanotubes, improving the polymer matrix and optimizing the polymerization reactions. These strategies have yielded composites with better mechanical performance and improved

longevity. Nonetheless, composites are still brittle and prone to fracture, especially in large-sized restorations in high load-bearing locations [3]. Therefore, there is a strong need to inhibit crack growth and fracture failures in dental resin-based restorations [14].

Self-healing polymers have the promise of autonomic repair to heal cracks and damage [15]. They have the built-in capability to repair damage and recover the load-bearing capability [16]. A promising method for providing self-healing capability is by embedding microcapsules into the composite [17]. Each microcapsule has an external shell that encapsulates a healing liquid inside. When the polymer experiences damage and cracking, the microcapsules could be ruptured by the damage. They release the healing liquid which flows into the crack planes and the damage site, exposing itself to the catalyst embedded in the polymer matrix. Self-healing then occurs due to the polymerization of the healing agent, which fills and bonds the crack together and inhibits the crack propagation [18]. In a pioneering study, dicyclopentadiene (DCPD) was encapsulated in a poly(urea-formaldehyde) (PUF) shell to form microcapsules [19]. Grubb's catalyst, a transition metal carbene complex, was used in an epoxy matrix to trigger the polymerization of the released DCPD, which achieved a good self-healing efficiency [19]. Since then, several other studies were reported on microcapsules of various shell and healing liquid compositions, with potential applications ranging from microelectronics to aerospace [20,21], as well as bone cement where effective rebonding of the crack was achieved, with the healed specimens reaching approximately 75% of the original fracture toughness [22].

For dental use, efforts were made to incorporate DCPD-containing microcapsules and Grubb's catalyst into a composite, achieving a recovery of 57% of the original fracture toughness of composite [23]. Another study tested the mechanical properties of dental resins with DCPD-containing microcapsules, showing that the use of microcapsules did not affect the mechanical performance of resin matrix [24]. However, literature search revealed no further report on the use of DCPD and Grubb's catalyst in dental materials, likely due to biocompatibility concerns. Toxicity from the self-healing agent inside the microcapsules as well as the catalyst present in the composite needs to be considered [14]. The DCPD toxicity [25], Grubb's catalyst toxicity, and their high cost [26] remain challenges in using them in dental composite. Another study developed nanocapsules with a polyurethane (PU) shell containing the triethylene glycol dimethacrylate (TEGDMA) liquid, demonstrating that the addition of nanocapsules into a dental adhesive increased the dentin bond strength [27]. However, these nanocapsules contained no catalyst for polymerization, and hence no self-healing effect on adhesive resin was reported [27]. To date, there has been no report on the use of polymerizable dental monomers as healing liquid with proven biocompatibility in dentistry to develop a resin demonstrating a substantial self-healing capability.

The healing liquid should have a relatively low viscosity to flow and fill the cracks in the resin matrix. TEGDMA is flowable and has been used as a dental monomer with acceptable biocompatibility. Furthermore, TEGDMA can form a polymer via free-radical initiation by using a peroxide initiator and a tertiary amine accelerator. A usual dental tertiary amine accelerator, *N,N*-dihydroxyethyl-*p*-toluidine (DHEPT), has good solubility and stability in TEGDMA. Therefore, the present study proposed to test DHEPT incorporation in TEGDMA to serve as the self-healing liquid inside microcapsules for the first time. In the

present study which was our first study, we focused on the synthesis and characterization of the self-healing microspheres, incorporation into resin, physical and mechanical properties, and fibroblast cytotoxicity. Then in our second study, we further added calcium phosphate and antibacterial monomer to the self-healing resin, and tested oral biofilm response [28].

Accordingly, the objectives of this study were to investigate TEGDMA-DHEPT as a self-healing liquid in PUF microcapsules for dental applications and to examine the mechanical properties and self-healing efficacy. The following hypotheses were tested: (1) The new TEGDMA-DHEPT-in-PUF microcapsules could be incorporated into a dental resin without decreasing the mechanical properties of the resin; (2) The microcapsule-containing resin would have a high self-healing capability after fracture; (3) The microcapsule-containing resin would have a low cytotoxicity against human fibroblasts.

## 2. Materials and methods

### 2.1. Synthesis of microcapsules

Microcapsules were prepared by *in situ* polymerization of formaldehyde and urea, following a previous study [29]. DHEPT (Sigma-Aldrich, St. Louis, MO) at 1% mass fraction was added to TEGDMA monomer (Esstech, Essington, PA). At room temperature, 50 mL of distilled water and 13 mL of a 2.5% aqueous solution of ethylene-maleic anhydride (EMA) copolymer (Sigma-Aldrich) were mixed in a 250 mL round bottom glass flask. The flask was suspended in a water bath on a hotplate (Isotemp, Fisher Scientific, Pittsburg, PA). The EMA solution was used as a surfactant to form an “oil-in-water” emulsion (“oil” being TEGDMA-DHEPT). Under agitation by a magnetic stir bar (diameter = 7.8 mm, length = 50 mm, Fisher Scientific) at 300 rpm, the shell-forming material urea (1.25 g), ammonium chloride (0.125 g) and resorcinol (0.125 g) (Sigma-Aldrich) were added into the solution. The resorcinol was added in the reaction of shell formation to enhance the rigidity of the shells [30]. The pH was adjusted to 3.5 via drop-wise addition of 1 M sodium hydroxide solution. Then, the agitation rate was increased to 400 rpm, and 30 mL of the TEGDMA-DHEPT liquid was added into the flask. A stabilized emulsion of fine TEGDMA-DHEPT droplets was formed after 10 min of agitation. Then, 3.15 g of a 37% aqueous solution of formaldehyde (Sigma-Aldrich) was added, and the flask was sealed with aluminum foil to prevent evaporation. The temperature of the water bath was raised to 55 °C and the shell material was isothermally polymerized for 4 hours (h) under continuous agitation [30]. In this process, ammonium chloride catalyzed the reaction of urea with formaldehyde to form PUF at the oil-water interface to develop the shell [30]. The microcapsules thus obtained were rinsed with water and acetone repeatedly, vacuum-filtered, and air-dried for 24 h in a hood.

### 2.2. Characterization of microcapsules

An optical microscope (TE2000-S, Nikon, Japan) was used to examine the microcapsules. The microcapsule diameters were measured using the optical microscope together with an image analysis software (Nis-Elements BR2.30, Nikon, Japan). In addition, the surface morphology of TEGDMA-filled microcapsules was examined with scanning electronic microscopy (SEM, Quanta 200, FEI, Hillsboro, OR). Microcapsules were spread onto an

adhesive tape and sputter-coated with gold. Some microcapsules were placed on an adhesive tape and cut open with a razor blade to facilitate the examination of the shell structure, following a previous study [29].

The ability of the encapsulated TEGDMA to polymerize was quantified by near-infrared (NIR) spectroscopy (Nicolet 6700, Thermo Scientific, Waltham, MA). A mixture of microcapsules with 0.5% by mass of benzoyl peroxide (BPO) initiator powder (the catalyst) (Sigma-Aldrich) were broken by manual spatulation and placed in a  $6 \times 3 \times 2$  mm Teflon mold. NIR spectra were acquired immediately after resin paste mixing and at 24 h post-cure in an FTIR spectrometer (Nicolet 6700, Thermo Scientific). The degree of vinyl conversion (DC) was calculated from the % change in the integrated peak area of methacrylate  $=\text{CH}_2$  absorption band, normalized by thickness of the specimen before and after curing, following a previous study [31].

The yield of microcapsules was calculated as the ratio of the dry weight of total microcapsules of each batch divided by the weight of the initial substances [29], i.e., urea, resorcinol, ammonium chloride, formaldehyde, TEGDMA and DHEPT. Microcapsules loaded with TEGDMA were dispersed in acetone and sonicated at 40Hz for 5 min (Branson, Fisher Scientific). This broke the microcapsules, and the TEGDMA and DHEPT were dissolved in the acetone solvent. After vacuum filtration and drying for 1 d, the undissolved microcapsule shell fragments were collected and weighed. The TEGDMA-DHEPT mass was calculated as the initial weight of the microcapsules minus the shell weight. The TEGDMA-DHEPT mass fraction in the microcapsules was calculated as the TEGDMA-DHEPT mass divided by the total mass of the microcapsules [27].

To assess the stability of the microcapsules, additional microcapsules were exposed to air at ambient temperature for 30 d. The TEGDMA-DHEPT mass fraction in the aged microcapsules was again calculated following the aforementioned procedures.

The thermal stability of the microcapsules was tested using differential scanning calorimetry (DSC, 2920MDSC, TA, New Castle, DE) to measure the heat flow. Five mg of microcapsules was placed in an air-tight aluminum pan and heated at a heating rate of  $10^\circ\text{C}/\text{min}$  from  $0^\circ\text{C}$  to  $350^\circ\text{C}$  in a nitrogen environment. The DSC diagram was recorded by the DSC analysis instrument. With the increase in temperature, any exothermic and endothermic events were recorded on the DSC diagram, thus providing information on how thermally stable the microcapsules were, and at what temperature they became unstable. All assessments were conducted using 6 batches of samples ( $n = 6$ ).

### 2.3. Fabrication of self-healing dental resin

Bisphenol A glycidyl dimethacrylate (BisGMA) (Esstech) and TEGDMA monomers were mixed at a 1:1 mass ratio. The mixture was rendered light-curable by adding 1% by mass of a photo-initiator, phenyl bis(2,4,6-trimethylbenzoyl) phosphine oxide (BAPO, Sigma-Aldrich). Then, 0.5% benzoyl peroxide (BPO) was also added to the monomer mixture as the self-healing initiator. BPO could react with DHEPT from the microcapsules in the case of microcapsule rupture to cause self-healing. The 0.5% of BPO was selected because it did

not decrease the mechanical properties of the resin and it was sufficient to trigger the free-radical polymerization in a preliminary test.

Microcapsules were mixed into the photo-activated BisGMA-TEGDMA monomers at the following mass fractions: 0%, 5%, 10%, 15% and 20%. Microcapsule mass fractions greater than 20% were not used because the mechanical properties of the resin were degraded in preliminary studies. For mechanical testing, each paste was placed in a stainless steel mold of  $2 \times 2 \times 25$  mm and covered with a Mylar strip. Each specimen was photo-cured (Triad 2000, Dentsply, York, PA) for 1 min on each open side of the mold. The specimens were demolded and stored in distilled water at 37 °C for 24 h prior to testing.

#### 2.4. Flexural testing

A computer-controlled Universal Testing Machine (5500R, MTS, Cary, NC) was used to fracture the specimens in three-point flexure using a span of 10 mm and a crosshead speed of 1 mm/min. Flexural strength  $S$  was measured as:  $S = 3P_{\max}L/(2bh^2)$ , where  $P_{\max}$  is the load-at-failure,  $L$  is span,  $b$  is specimen width and  $h$  is thickness. Elastic modulus  $E$  was measured as:  $E = (P/d)(L^3/[4bh^3])$ , where load  $P$  divided by displacement  $d$  is the slope in the linear elastic region of the load-displacement curve. The specimens were taken out of the water and fracture while being wet. Six specimens of each group were tested [32].

#### 2.5. Fracture toughness testing

Fracture toughness  $K_{IC}$  was measured via a single edge V-notched beam (SEVNB) method under mode I condition [33]. A notch with a depth of approximately 500  $\mu\text{m}$  was machined into a resin bar of  $2 \times 2 \times 25$  mm using a diamond blade with a 150  $\mu\text{m}$  thickness (Buehler, Lake Bluff, IL). Then, a 3- $\mu\text{m}$  diamond paste (Buehler) was placed into the notch tip, and a new sharp razor blade was used to cut the notch further to a total depth of about 700–800  $\mu\text{m}$ . According to previous studies using the same method, this produced a relatively sharp notch with a tip radius of approximately 20  $\mu\text{m}$  [33,34]. For each specimen, the notch length was measured using an optical microscope (TE2000-S, Nikon) on both sides of the specimen and then the notch length was averaged. The notched specimens were tested in the same three-point fixture with the notch on the tensile side, and the loading pin aligned with the notch under a 3x magnifier.  $K_{IC}$  was calculated following an established SEVNB method [34]. The photo-cured BisGMA-TEGDMA resins with 0% to 20% of microcapsules were tested. This yielded the original virgin  $K_{IC}$  of the specimens,  $K_{IC\text{-virgin}}$ .

In order to test the self-healing efficacy, immediately following specimen fracture, the two halves of the specimen were placed back into the same mold which was labeled and was originally used to make the same specimen. This is similar to the case of a resin-based restoration in a tooth cavity, where the cracked restoration would stay in the tooth cavity to allow the released healing liquid to heal the crack. Because the fracture ruptured the microcapsules, the released TEGDMA-DHEPT from the microcapsules would react with the BPO in the resin matrix. This would cause the polymerization of the released liquid to heal and bond the two cracked planes into one cohesive specimen. This healed sample was placed in a humidior at 37 °C for 24 h. The notch length was again measured and made sure that it was the same as the virgin notch length of the same specimen. Then the healed bar was

tested again using the same flexural method to measure the  $K_{IC}$ . This yielded the healed value,  $K_{IC\text{-healed}}$ .

The self-healing efficiency ( $\eta$ ) was assessed following a previous study as [35]:  $\eta = K_{IC\text{-healed}}/K_{IC\text{-virgin}}$

The fractured surfaces of selected self-healed specimens were examined via SEM after sputter-coating with gold. In addition, the fractured and unhealed surfaces, which were rinsed with ethyl alcohol immediately after fracture to remove the released healing agent, were also examined for investigation of fracture mechanisms.

## 2.6. Cytotoxicity testing

The cytotoxicity of the five groups of resins containing 0%, 5%, 10%, 15% and 20% of microcapsules was examined by measuring cell survival and proliferation *in vitro* via a MTT assay [36]. To prepare resin specimens for cytotoxicity testing, the cover of a sterile 96-well plate was used as molds, following a previous study [36]. Fifty  $\mu\text{L}$  of resin paste of each group was placed into the bottom of the dent and covered with a Mylar strip, then light-cured for 30 s (Optilux VCL 401, Demetron Kerr, Danbury, CT). This formed a disk of about 8 mm in diameter and 0.5 mm in thickness. The disks were sterilized with ethylene oxide (Anprolene AN 74i, Andersen, Haw River, NC). Then, six disks of each group were immersed in 10 mL of a commercial fibroblast culture medium (ScienCell, San Diego, CA), referred to as FM. The medium was agitated for 24 h at 37 °C to obtain resin eluents, following a previous study [36]. The original extract solution was then serially diluted for the cytotoxicity test [36]. Three solutions were prepared at dilutions of 32-fold (1 part of original extract + 31 parts of fresh FM), 64-fold, and 128-fold, respectively, following a previous study [36]. The reason for choosing 128-fold dilution was that the amount of saliva flow for an average person is approximately 1000 to 1500 mL per day [37]. The 128-fold dilution yielded to a total solution volume of 1280 mL for the six resin disks. The 32-fold and 64-fold corresponded to a total solution of 320 mL and 640 mL respectively, which would be equivalent to 1/4 and 1/2 of the normal saliva amount per day, to take into account of reduced saliva production for some patients. The total resin volume of the six disks was 151  $\text{mm}^3$ . Hence, the resin volume divided by the total solution volume for the three solutions was 0.12, 0.24, and 0.47  $\text{mm}^3/\text{mL}$ , respectively. Fresh FM without any resin eluent (resin/solution volume ratio = 0  $\text{mm}^3/\text{mL}$ ) served as the control in cell culture.

Human gingival fibroblasts (HGF, ScienCell) were cultured in a growth medium consisting of FM supplemented with 2% fetal bovine serum, 100 IU/mL penicillin and 100 IU/mL streptomycin. They were seeded into the wells of 96-well micro-plates at a density of 4,000 cells/well [38]. After 24 h of incubation at 37 °C in a humid atmosphere with 5%  $\text{CO}_2$  in air, the culture medium in the 96-well microplates was removed and replaced with 100  $\mu\text{L}$  of the aforementioned resin extract solutions. Then the cells were cultured for another 48 h. To each well was added 20  $\mu\text{L}$  of (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (MTT, Sigma-Aldrich) solution at a concentration of 5 mg/mL [38]. After incubating in a dark room for 4 h, the unreacted dye was replaced by adding 150  $\mu\text{L}$ /well of dimethylsulfoxide (DMSO, Sigma-Aldrich). The plate was gently shaken until the crystals were completely dissolved. Then the absorbance of the solutions was measured

spectrophotometrically using a microplate reader (Spectra Max M5, Molecular Devices, Sunnyvale, CA) at 492 nm. Pure FM without any resin eluent was used as control to culture fibroblasts, and its absorbance was set as 100%. Cell viability was assessed as  $A_{\text{resin}}/A_{\text{control}}$ , where  $A_{\text{resin}}$  was the absorbance of cells cultured with resin eluents, and  $A_{\text{control}}$  was the absorbance of cells cultured in FM without resin eluents [38].

## 2.7. Statistical analysis

One-way analysis of variance (ANOVA) was performed to detect the significant effects of the variables. Tukey's multiple comparison test was used at a  $p$  value of 0.05.

## 3. Results

Fig. 1A shows a pile of the synthesized microcapsules which had the appearance of a white powder. Fig. 1B shows that the microcapsules had a black ring outside and a relatively bright area inside. This phenomenon was attributed to the two different refractive indices of the PUF shell and the healing liquid inside. This indicates that the TEGDMA was successfully encapsulated by the PUF shell. The SEM image in Fig. 1C showed the external surface of microcapsules. The diameters in two perpendicular directions were measured and averaged for each microcapsule. The microcapsules were measured to have an average diameter of  $70 \pm 24 \mu\text{m}$  ( $n = 200$ ). Higher magnification in Fig. 1D revealed details of the shell, showing numerous nanoparticles attaching to a smooth shell surface to form a rough shell. The smooth shell surface appeared to be dense without voids. Fig. 1E displayed the shell wall of a microcapsule at a high magnification. The thickness of the shell was estimated to be  $230 \pm 43 \text{ nm}$  (mean  $\pm$  sd;  $n = 6$ ). Crushed microcapsules with shell fragments and the released healing agent between two glass slides were displayed in Fig. 1F, further demonstrating the liquid filled structure of microcapsules.

Fig. 2 shows the NIR results of the microcapsules after they were fractured and the released TEGDMA-DHEPT was polymerized. The presence of the =CH overtone band at  $6165 \text{ cm}^{-1}$  indicated that TEGDMA was successfully encapsulated. Furthermore, after polymerization for 24 h, reduction in absorbance of this band signified that polymerization of TEGDMA occurred. The degree of conversion for the released TEGDMA-DHEPT polymerization was  $(67.2 \pm 0.6)\%$  (mean  $\pm$  sd;  $n = 3$ ). The analysis of the polymer products spectra after the microcapsules were crushed confirmed the reactivity of the microcapsules.

The synthesis yield of the microcapsules was calculated as the weight of the microcapsules of each batch divided by the weight of the initial substances used. This yield was measured (mean  $\pm$  sd;  $n = 6$ ) to be  $(76.8 \pm 3.7)\%$ .

The TEGDMA-DHEPT mass fraction in the microcapsules was calculated as the TEGDMA and DHEPT mass divided by the total mass of the microcapsules. This was measured (mean  $\pm$  sd;  $n = 6$ ) to be  $(70.8 \pm 5.4)\%$  at 1 d, and  $(66.9 \pm 4.6)\%$  after aging in air for 30 d. These two values are not significantly different from each other ( $p > 0.1$ ).

Fig. 3 displays a representative DSC diagram of the microcapsules. A typical exothermic peak and an endothermic valley appeared in the DSC curve at high temperatures. The



exothermic peak at 162 °C was due to the polymerization reaction of TEGDMA in the microcapsules, which was triggered by the high temperature. The endothermic valley at about 307 °C was because of the decomposition of the PUF shell [39]. These results demonstrate that the PUF shell-based microcapsules are chemically stable at temperatures of up to about 150 °C, which showed an excellent thermal stability.

Flexural strength and elastic modulus of resin with different microcapsule mass fractions are plotted in Fig. 4 (mean  $\pm$  sd;  $n = 6$ ). The flexural strength and elastic modulus of resins containing 0% to 15% microcapsules were not significantly different from each other ( $p > 0.1$ ). However, the mechanical properties of the resin with 20% microcapsules were significantly lower than the other groups ( $p < 0.05$ ).

The fracture toughness  $K_{IC}$  results are plotted in Fig. 5 (mean  $\pm$  sd;  $n = 6$ ). In (A), the virgin and healed  $K_{IC}$  of the resins are plotted vs. microcapsule mass fraction. Adding microcapsules into the resin increased the virgin  $K_{IC}$ , which was about 40% higher at 15% microcapsules than that at 0% microcapsules ( $p < 0.05$ ). For the healed  $K_{IC}$ , the specimen was completely fractured and then the two halves were placed back into the mold to allow self-healing to occur. The healed  $K_{IC}$  significantly increased, from no healing at 0% microcapsules to maximum healing at 10% and 15% microcapsules ( $p < 0.05$ ). The self-healing efficiency is plotted in (B). A self-healing efficiency of 64%-68% in  $K_{IC}$  recovery was obtained when the microcapsule concentration in the resin was 10%.

Representative fracture surfaces of self-healing resin are shown in Fig. 6. The example shown is for the resin containing 15% microcapsules. The initial virgin fractured surface of a specimen is shown in (A). Typical step tail patterns (arrows) following the crack propagation direction could be seen, with an example enlarged in the insert in (A). In (B), the specimen was fractured into two halves, and the two halves were placed into the mold for the released healing liquid to polymerize and heal the specimen. The healed specimen was re-fractured and examined in SEM. Many polymer films and layers (arrows) were visible on the healed surface in (B). These numerous irregularly-shaped films in many different locations on the fracture surface indicate the successful release of TEGDMA from microcapsules and polymerization to bond the cracked planes together. This is consistent with the measured relatively high recovery of the fracture toughness in Fig. 5.

Fig. 7 plots the results on human fibroblast cytotoxicity in vitro. Cell viability in fibroblast medium without any resin eluents was set as 100%. All five groups of resin specimens with 0%, 5%, 10%, 15% and 20% microcapsules had cell viability similar to that of FM control ( $p > 0.1$ ). Hence the incorporation of microcapsules into resin did not significantly compromise the cell viability.

#### 4. Discussion

The present study synthesized TEGDMA-DHEPT containing microcapsules, and the resin with these microcapsules demonstrated successful healing, with substantial recovery of load-bearing capability. Polymeric microcapsules are often prepared *via* emulsion polymerization techniques [40]. In the present study, microcapsules with a healing liquid of TEGDMA plus

1% DHEPT surrounded by a PUF shell, were manufactured through an *in situ* polymerization technology in an oil-in-water emulsion. A key requirement of the self-healing process is the rupture of the embedded microcapsules on crack intrusion. The roughness of the microcapsule wall with nanoparticle deposit (Fig. 1D) is of vital importance in obtaining a mechanical interlock between the microcapsule and resin matrix. An interlocking interface would help the microcapsule to be ruptured when a crack propagating in the resin matrix hits the microcapsule. In contrast, with a smooth interface without interlock, the resin matrix crack may go around the microcapsule and not rupture it, without releasing the healing liquid to heal the crack. The microcapsule wall thickness is another key issue. A thinner wall may be easily ruptured, and may be too fragile for handling and mixing of microcapsules into a resin matrix. On the other hand, microcapsule walls that are too thick may make the microcapsule difficult to be broken by the crack, thus failing to release the liquid to cause healing. Therefore, an optimal wall thickness for the microcapsules is vital. A previous study reported average wall thickness values of 160–220 nm [30]. In the present study, the TEGDMA-DHEPT-filled microcapsules with a PUF wall thickness of about 230 nm were shown to successfully heal the dental resin.

The microcapsule stability is another important issue, and the synthesis of stable microcapsules is a necessity to protect the encapsulated healing agent from premature polymerization [41]. The reactive liquid inside microcapsules must not diffuse out of the shell wall during its potentially long shelf-life. In the present study, the microcapsules were exposed to air at ambient temperature for 1 month, and the results suggested that the microcapsules were stable, with negligible permeability and negligible loss of the liquid TEGDMA through the PUF shell. Furthermore, the high temperature experiment of TEGDMA polymerization and PUF shell wall fragmentation with the DSC analysis showed a durable thermal property of PUF shell-based microcapsules up to 150 °C, which will not be experienced in the shelf or in the mouth. These results indicate that these microcapsules likely have a long shelf-life with good thermal stability; however, actual long-term tests need to be performed in further investigations.

Incorporating microcapsules into polymers can inevitably change the properties of the host polymer. The goal would be to obtain self-healing capability without decreasing the original mechanical properties of the resin. Decreasing the mechanical properties of dental polymer including flexural strength and fracture toughness can compromise the durability and reliability of the restoratives [42–44]. A previous study showed different results on the effect of incorporation of microcapsules on the mechanical performance of the host material [24]. Studies showed that the incorporation of microcapsules was accompanied with significant improvements in tensile strength [45] and flexural strength of the polymer matrix [46]. However, another study reported a continuous reduction in the strength of the resin with increasing microcapsule content [47]. In the present study, the flexural strength and elastic modulus of the resin were not significantly reduced or increased by the addition of 0% to 15% microcapsules. However, these properties were significantly decreased at 20% microcapsules. Therefore, whether the addition of microcapsules would affect the mechanical properties of the resin appears to depend on the microcapsule mass fraction.

Previous studies showed that after microcapsule incorporation, the fracture toughness of the polymer matrix generally increased [48–51]. In the present study, a nearly 40% increase in the original virgin  $K_{IC}$  was achieved when the microcapsule mass fraction was increased from 0% to 15%. Regarding the toughening mechanism, as shown in the fracture planes (Fig. 6A for virgin fracture surface), numerous step tails originating from the fractured microcapsules were present. This is consistent with the phenomenon reported earlier with self-healing polymers containing microcapsules [47]. It appears that the propagation of the crack tip became discontinuous in the presence of microcapsules, which caused an out-of-surface divergence in crack propagation [47]. After puncturing the microcapsule, the two cracks in different planes met together in order to obtain continuity, thus forming a step tail structure next to the microcapsule [47]. Therefore, the toughening mechanism appeared to be crack pinning and deflection caused by the microcapsules in the resin. In addition, the rupture of the PUF microcapsules, the interfacial debonding, and the liquid burst likely also consumed energy, interfered with the crack, and contributed to an increase in virgin  $K_{IC}$ .

The self-healing efficiency  $\eta$ , was measured to quantify the recovery of the original  $K_{IC}$ . The polymerized films on the fracture plane of the healed specimen (Fig. 6B) indicate that the healing agent containing the amine accelerator had the capability to react with the BPO initiator in resin bulk. The polymerization capability of the healing agent was also consistent with the result of NIR analysis. The self-healing efficiency increased to a recovery of about 65% in  $K_{IC}$  when the microcapsule mass fraction was increased from 5% to 10% and 15%. A lower recovery at 5% microcapsules was due to the insufficient dosage of the microcapsules, leading to insufficient quantity of the released healing agent to cover the broken planes. The better healing effect deriving from higher microcapsule concentrations may be explained by more healing agent release, resulting in re-bonding of the cracked planes. There was little difference in healing efficacy from a microcapsule concentration of 10% to 20%. This was likely because the healing agent released from the microcapsules was sufficient to completely cover the crack plane [52]. The self-healing efficiency of about 65% is consistent with previous studies reporting a 57% average recovery of the original fracture toughness [23], and a 75% recovery in toughness [19]. It should be noted that on the fractured, healed and refractured surfaces, some microcapsules in the surface did not undergo fracture. It appeared that the crack went through the microsphere-resin interface without rupturing the microsphere in some cases, hence the self-healing liquid was not released, and the self-healing effect of that microsphere was not utilized. It is possible that the healing efficacy could be further increased if more microspheres could be ruptured by the crack. Further study needs to investigate whether silanizing the microspheres to achieve microsphere-resin matrix bonding would lead to more microsphere rupture during fracture.

While previous studies [19,23] used DCPD and Grubb's catalyst with toxicity concerns [25,26], the present study used dental monomers (TEGDMA, DHEPT, and BPO) for healing liquid polymerization; these components have already been used in commercial dental resins approved by the Food and Drug Administration. Indeed the cytotoxicity test (Fig. 7) showed similar results to culture medium without resin eluents. With good self-healing efficiency of the TEGDMA, DHEPT and BPO system, if the restoration experiences cracks in service, the ruptured microcapsules could deliver the healing agent in time to the damaged region for a recovery. Further study is needed to test the self-healing of dental restorations *in vivo*.

The effect of possible leakage of unreacted free formaldehyde from PUF shells on cytotoxicity needs to be determined [53]. To date, there has been no report and no data available on the biocompatibility of PUF-based microcapsule inclusion into a dental resin. The present study showed that the addition of microcapsules did not affect cell viability, compared to that without microcapsules, as well as to the control using commercial fibroblast medium without any resin eluents. The results showed that the amount of microcapsules (e.g., 15%) was enough to repair damage; however, it was rather a small amount and could well be below the toxicity threshold. Hence, the present self-healing resin containing microcapsules had minimal toxicity similar to cells in fibroblast medium without any resin eluents. Although there were limitations regarding the correlation between *in vitro* and *in vivo* testing, this result did provide insight into the potential promise of this healing system.

## 5. Conclusions

Novel self-healing dental resin containing microcapsules with polymerizable TEGDMA-DHEPT healing liquid in PUF shells were prepared via *in situ* polymerization, and exhibited a substantial self-healing capability. Once crack and damage ruptured the microcapsules, the released TEGDMA-DHEPT healing liquid could react with the BPO in the resin matrix and polymerize to bond the cracked planes together. The shell wall of the microcapsules had a proper thickness with a smooth surface roughened by nanoparticle deposits, which promoted micromechanical interlocking of microcapsules in the resin matrix.

The flexural strength and elastic modulus of the resin were not adversely affected when the microcapsule mass fraction was 15%. The inclusion of microcapsules increased the virgin fracture toughness of resin. The self-healing efficiency showed that about 65% recovery of the virgin fracture toughness could be achieved when using 15% microcapsules. The self-healing resin containing microcapsules appeared to have good cellular cytotoxicity *in vitro*. Therefore, the novel self-healing dental resin containing microcapsules with polymerizable TEGDMA-DHEPT liquid in PUF shells may be promising for crack-inhibiting and self-healing dental restorations to prolong the lifetime.

## Acknowledgments

We thank Esstech (Essington, PA) for kindly donating the BisGMA and TEHDMA monomers. This study was supported by NIH R01 DE17974 (HX) and a seed grant from the University of Maryland Baltimore School of Dentistry (HX).

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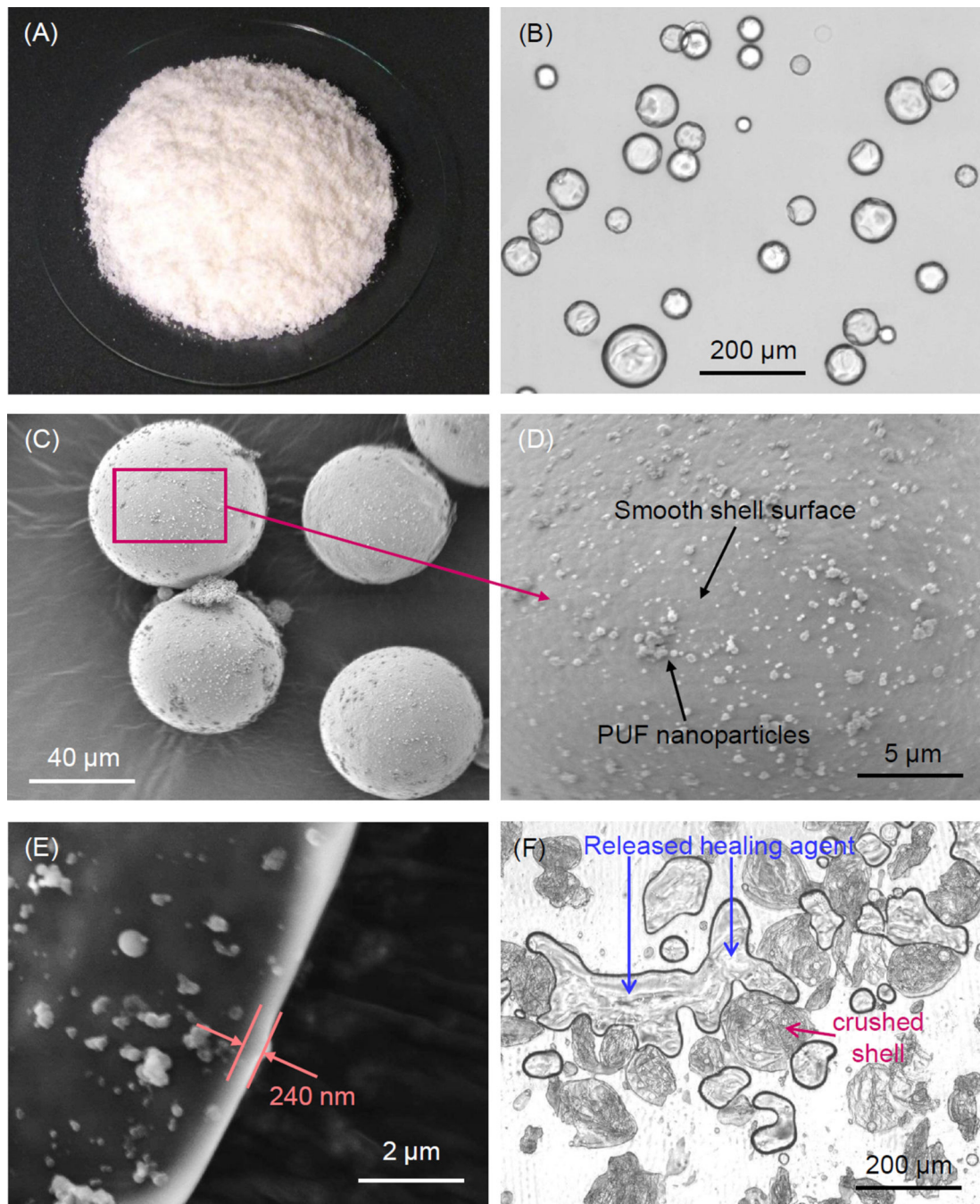
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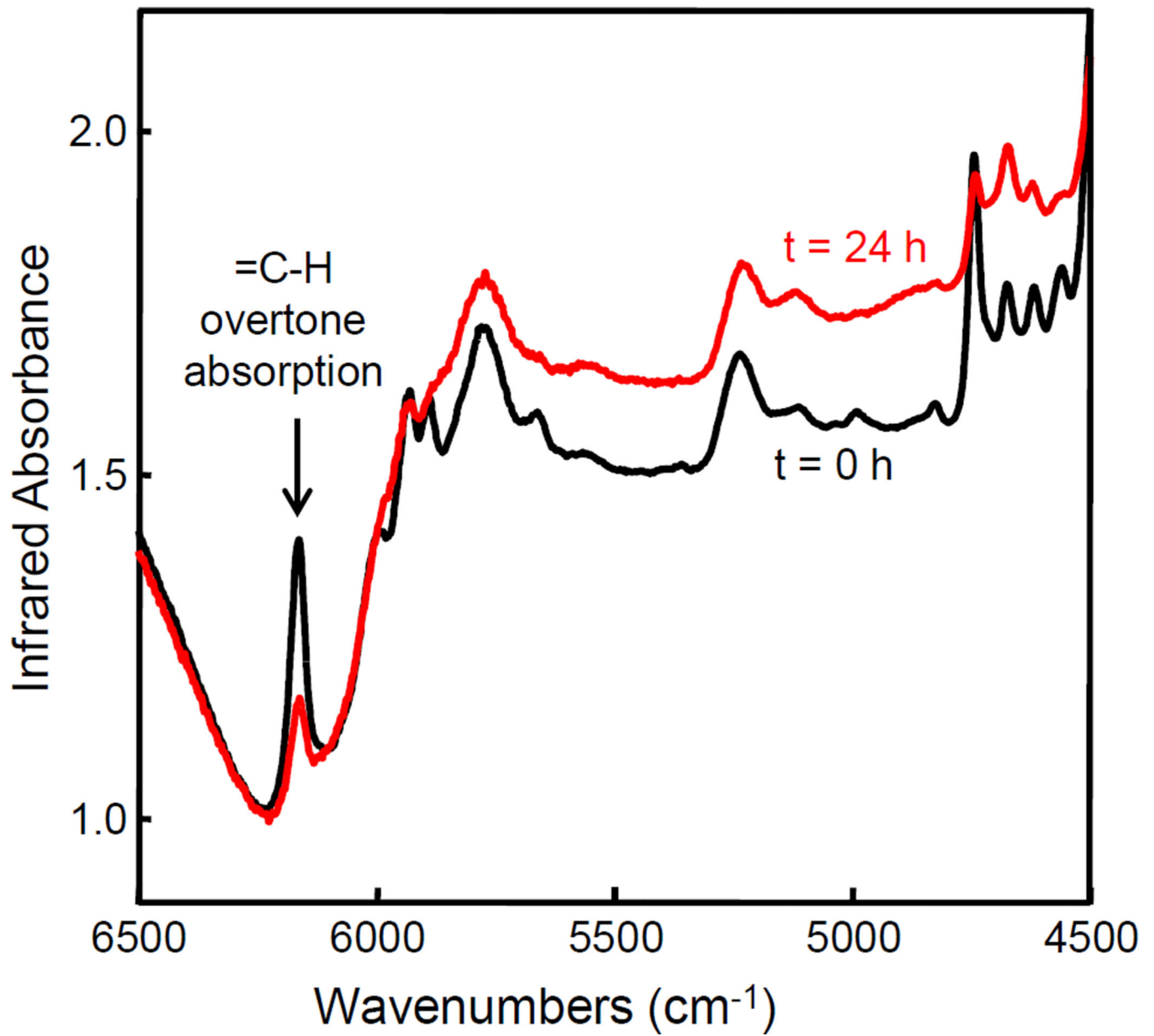
### Highlights

Bulk fracture is one of the primary reasons for resin-based dental restoration failures. This study developed a self-healing resin containing microcapsules with triethylene glycol dimethacrylate (TEGDMA)-*N,N*-dihydroxyethyl-*p*-toluidine (DHEPT) healing liquid in poly(urea-formaldehyde) (PUF) shells for the first time. Specimens were fractured and healed, then fractured again to measure the healed fracture toughness  $K_{IC}$ . A self-healing efficiency of about 65% in  $K_{IC}$  recovery was obtained with 10–20% microcapsules. In conclusion, self-healing dental resin containing microcapsules with polymerizable TEGDMA-DHEPT healing liquid in PUF shells were prepared for the first time with excellent self-healing capability. These microcapsules and self-healing resins containing them may be promising for dental restorations to heal cracks/damage and increase durability. The figure below shows: (A) fracture toughness, and (B) self-healing efficiency (mean  $\pm$  sd;  $n = 6$ ). 0% refers to resin containing 0% microcapsules, 5% refers to resin containing 5% microcapsules, and so on. Values with dissimilar letters are significantly different from each other ( $p < 0.05$ ).

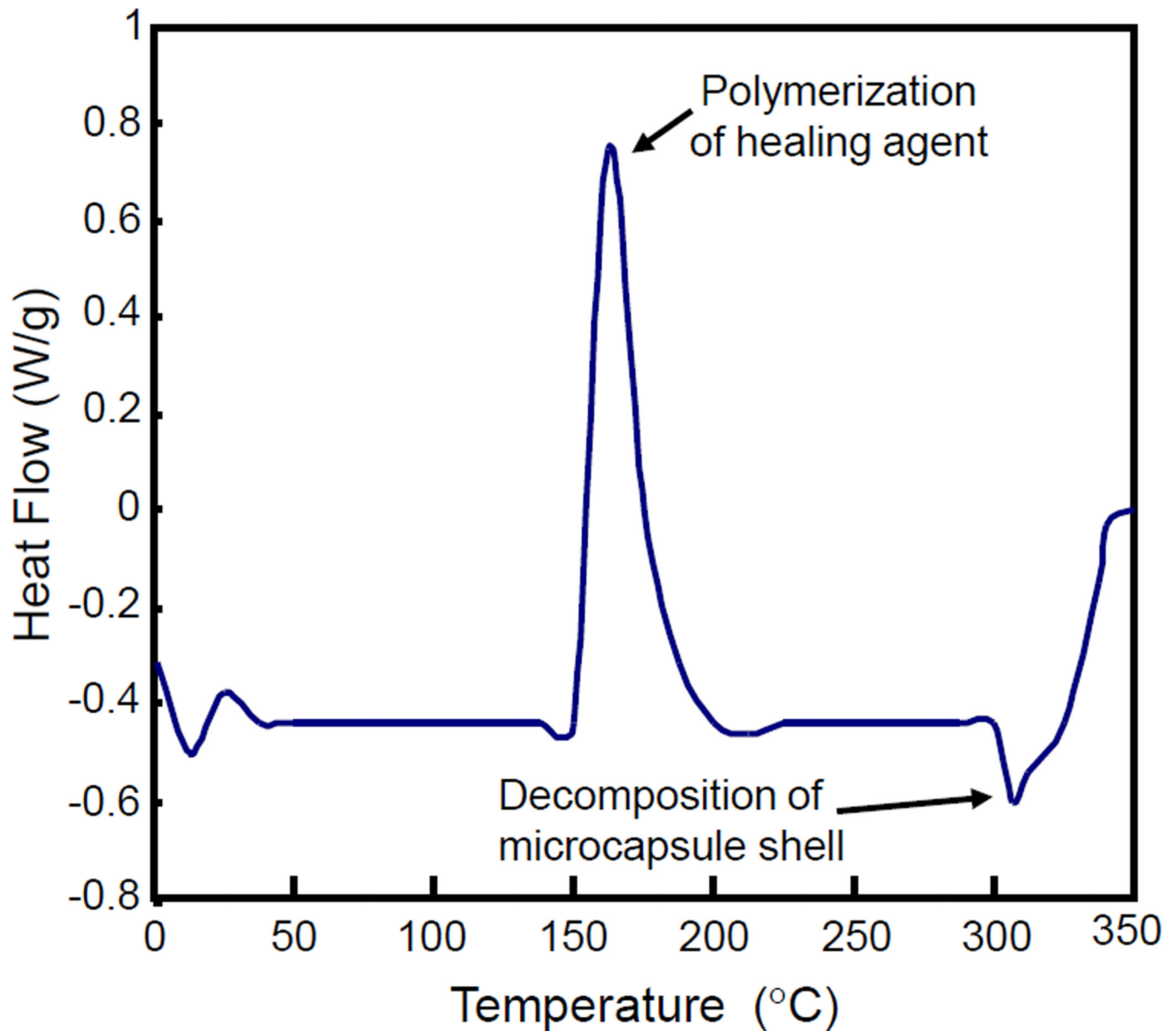




**Figure 1.** Microcapsules were prepared with polymerizable TEGDMA-DHEPT healing liquid inside PUF shells. (A) Photo showing a pile of the synthesized microcapsules. (B) Transmitting optical image showing the shell structure as a dark ring. (C) SEM image of typical microcapsules. (D) High magnification SEM image of the shell surface, showing nanoparticle deposits on an otherwise smooth shell surface. (E) High magnification SEM image indicating the shell thickness. (F) Optical image of crushed microcapsules showing the released healing liquid films.

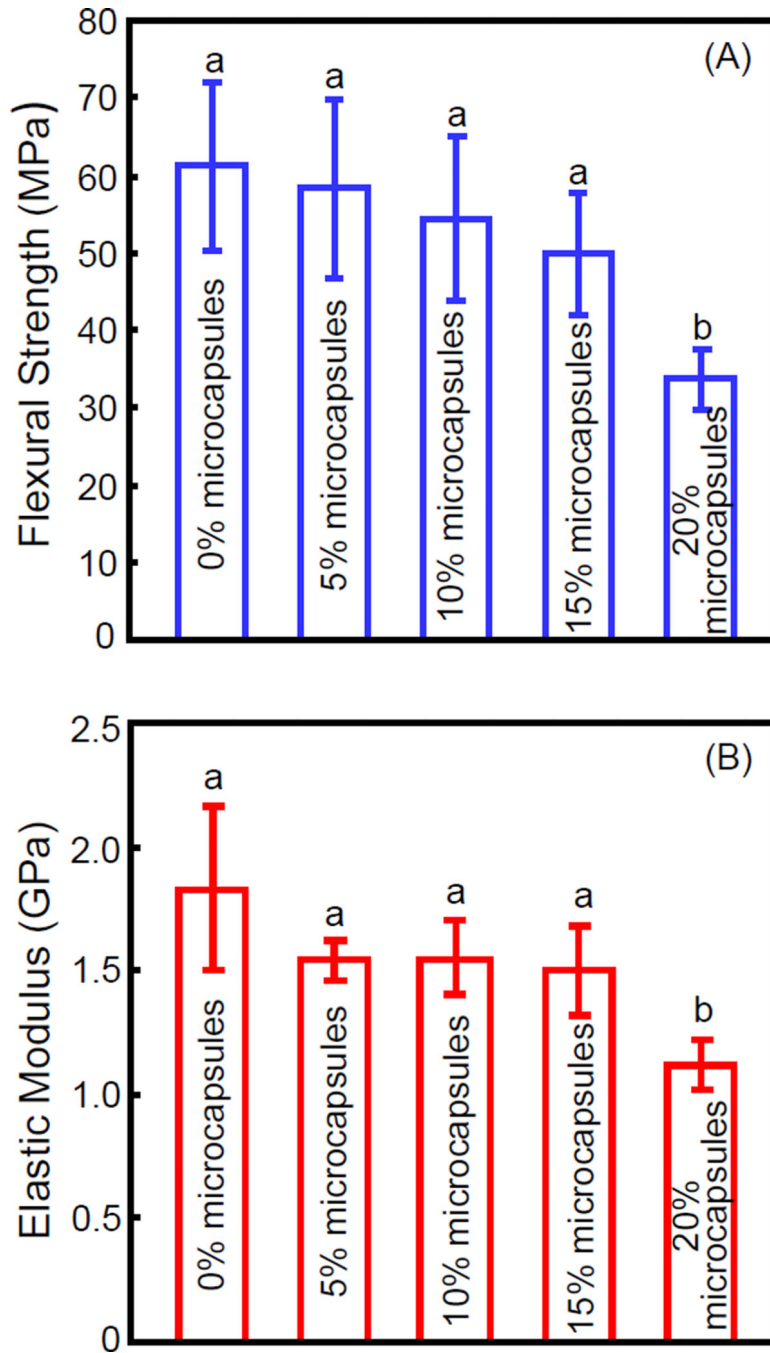


**Figure 2.** NIR spectra of microcapsules consisting of TEGDMA-DHEPT healing liquid inside PUF shells. Appearance and absorption of vinyl peak at  $6165\text{ cm}^{-1}$  verified the successful process of encapsulation and excellent polymerizable ability of these microcapsules.

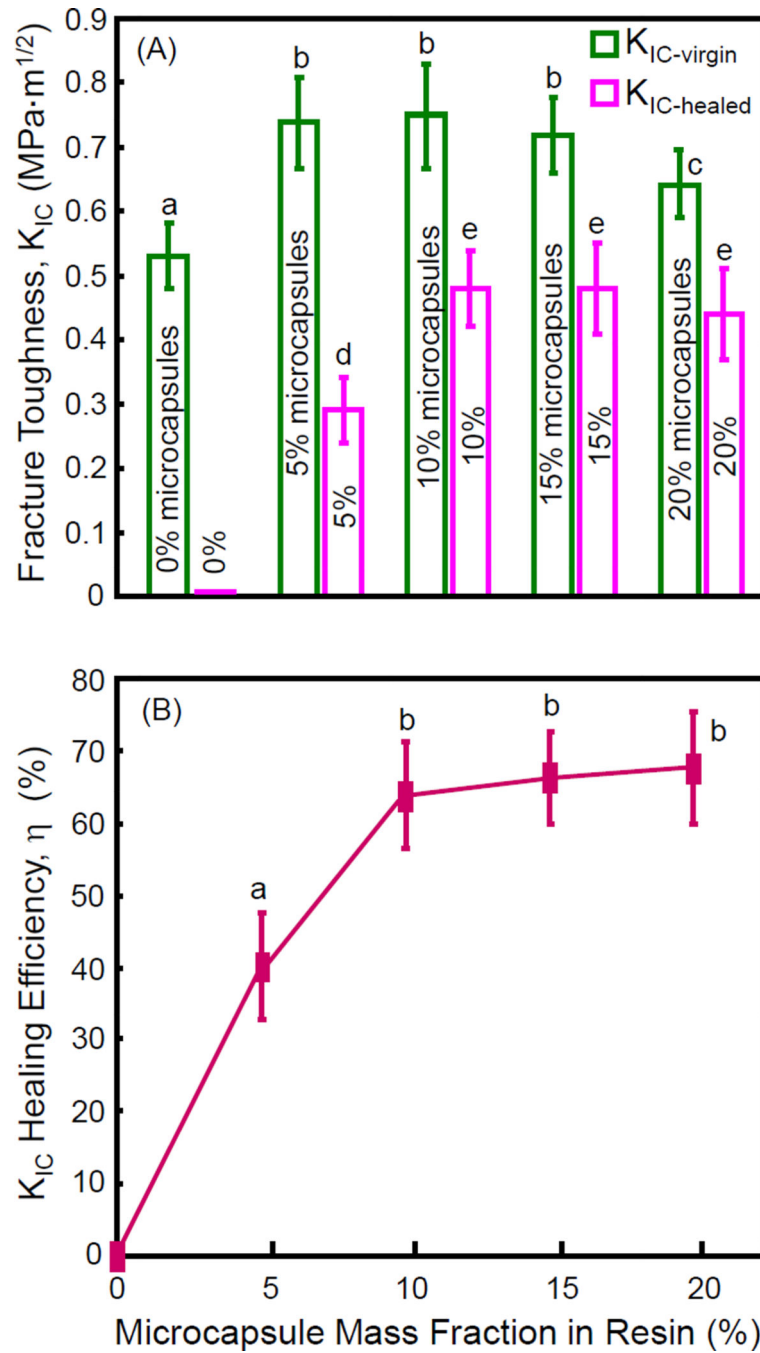


**Figure 3.**

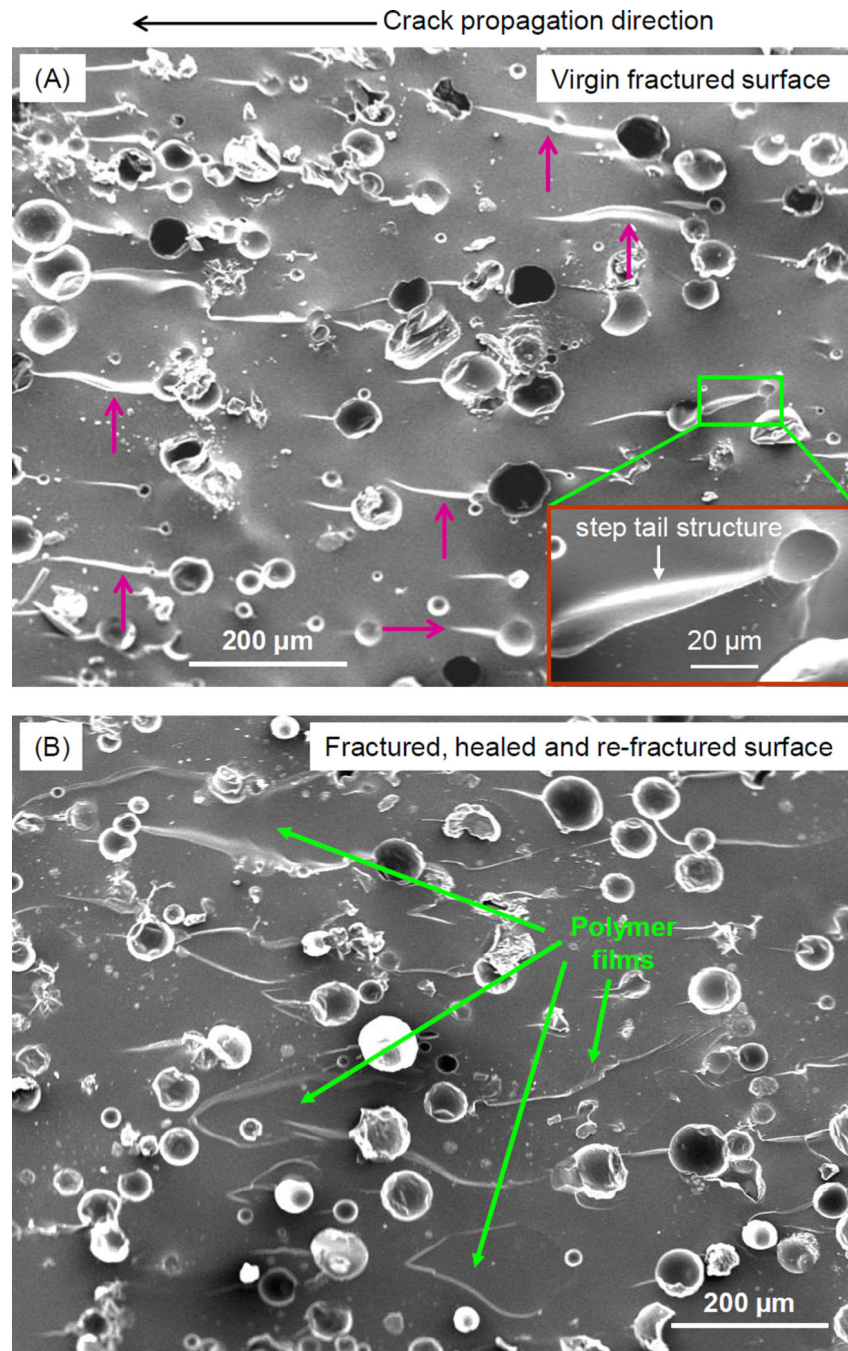
DSC diagram of microcapsules containing TEGDMA-DHEPT healing liquid inside PUF shells. The exothermic peak at 162 °C was due to polymerization of TEGDMA by the high temperature. The endothermic valley at 307 °C was related to PUF shell decomposition. These microcapsules were stable up to 150 °C, indicating suitability for use at temperatures in vivo in dentistry.



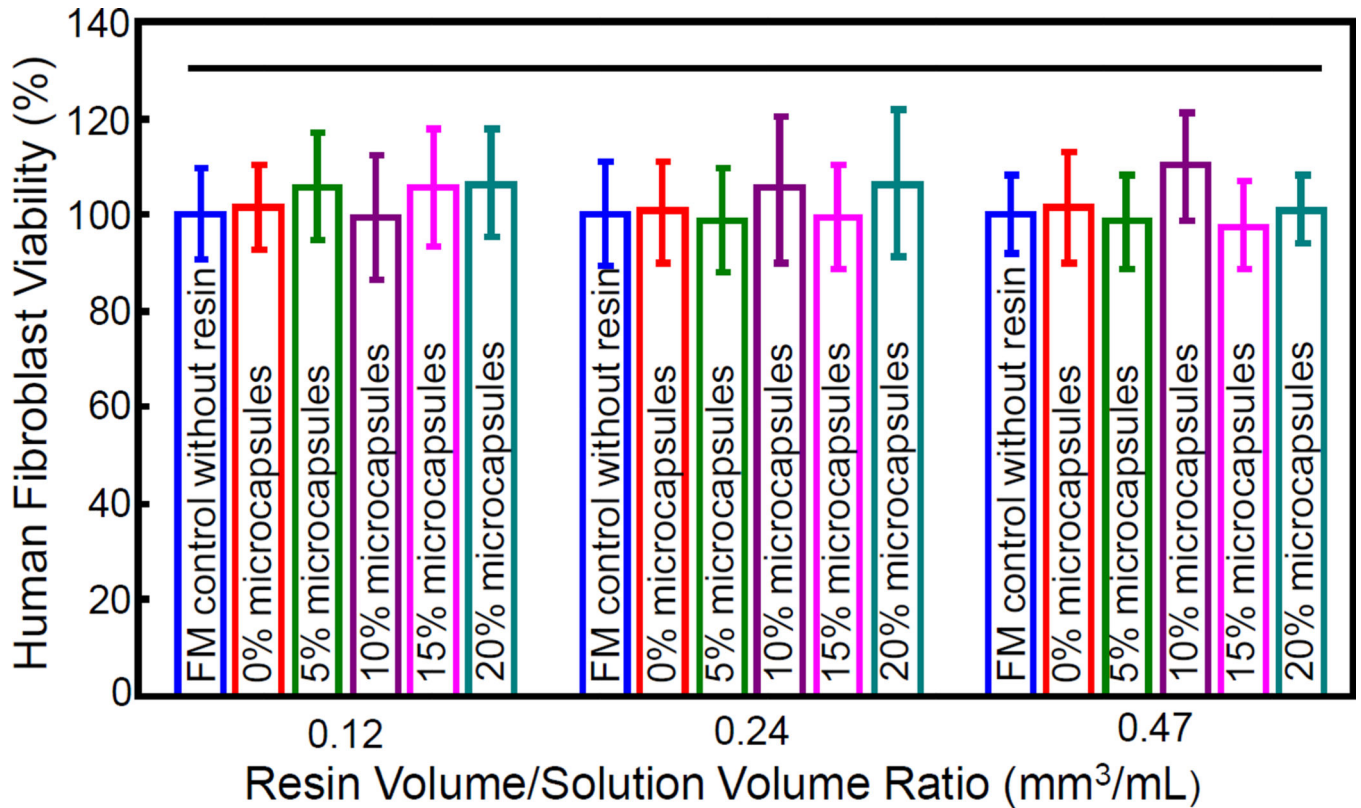
**Figure 4.** Mechanical properties of resin containing microcapsules of various concentrations: (A) flexural strength, and (B) elastic modulus (mean  $\pm$  sd;  $n = 6$ ). 0% refers to resin containing 0% microcapsules, 5% refers to resin containing 5% microcapsules, and so on. Addition up to 15% of microcapsules resulted in no significant decrease in strength and elastic modulus of the resin. In each plot, values with dissimilar letters are significantly different from each other ( $p < 0.05$ ).



**Figure 5.** Self-healing of resin containing microcapsules: (A) fracture toughness, and (B) self-healing efficiency (mean  $\pm$  sd;  $n = 6$ ). 0% refers to resin containing 0% microcapsules, 5% refers to resin containing 5% microcapsules, and so on. In each plot, values with dissimilar letters are significantly different from each other ( $p < 0.05$ ).



**Figure 6.** Representative SEM images of the fractured planes from the specimens containing 15% microcapsules. (A) The initial virgin fracture surface of the resin specimen revealing the step tail structure. The inset in (A) shows a higher magnification of a step tail structure. (B) The healed and re-fractured surface of the resin specimen displaying the presence of released and polymerized healing liquid films.



**Figure 7.**

Human gingival fibroblast cytotoxicity in vitro (mean  $\pm$  sd;  $n = 6$ ). “FM” refers to the cell culture group in fibroblast medium without any resin eluents. 0% refers to resin containing 0% microcapsules, 5% refers to resin containing 5% microcapsules, and so on. All groups had cell viability matching that of FM group, exhibiting a good biocompatibility. The 128-fold dilution (resin/solution volume ratio of  $0.12\text{mm}^3/\text{mL}$ ) yielded a total solution volume comparable to the daily saliva volume of 1000 mL –1500mL *in vivo*. Horizontal line in the plot indicated values that are not significantly different from each other ( $p > 0.1$ ).