Polymer Degradation and Stability 163 (2019) 87–99

Contents lists available at ScienceDirect

Polymer Degradation and Stability

journal homepage: www.elsevier.com/locate/polydegstab

Development of a new class of self-healing and therapeutic dental resins

Junling Wu [a, *], Xianju Xie [b, c], Han Zhou [b], Franklin R. Tay [d], Michael D. Weir [b], Mary Anne S. Melo [b], Thomas W. Oates [b], Ning Zhang [b, c, **], Qiang Zhang [e, ***], Hockin H.K. Xu [b, f, g]

[a] Shandong Provincial Key Laboratory of Oral Tissue Regeneration, Department of Prosthodontics, School of Stomatology, Shandong University, Jinan, 250012, China
[b] Department of Advanced Oral Sciences and Therapeutics, University of Maryland Dental School, Baltimore, MD, 21201, USA
[c] Department of Orthodontics, School of Stomatology, Capital Medical University, Beijing, 100050, China
[d] Department of Endodontics, Dental College of Georgia, Augusta University, Augusta, GA, USA
[e] Oral Implantology Center, Jinan Stomatological Hospital, Jinan, 250001, China
[f] Center for Stem Cell Biology & Regenerative Medicine, University of Maryland School of Medicine, Baltimore, MD, 21201, USA
[g] Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, 21201, USA

ARTICLE INFO

Article history:
Received 25 December 2018
Received in revised form
8 February 2019
Accepted 18 February 2019
Available online 22 February 2019

Keywords:
Self-healing
Dental resins
Polymerizable healing liquid
Antimicrobial
Remineralization
Mechanical property recovery

ABSTRACT

Bulk fracture and secondary caries are the two main problems causing failures and shortening the lifetime of dental resinous restorations. This article reviews recent research on self-healing dental and biomedical materials. This includes the development of self-healing dental resin composites and adhesives, combining self-healing with calcium phosphate nanoparticles in the resins for tooth lesion remineralization, and adding antibacterial monomer into self-healing resins to suppress oral biofilm grows and acid production. Furthermore, since the oral environment experiences saliva and drinks, this paper also reviews research on the self-healing of dental resins while being submerged in an aqueous environment, and the effect of long-term water-aging time from 1 day to 6 months on the self-healing capability. The new class of materials have demonstrated excellent self-healing efficacy in various material systems including bonding agents, composites and cements. They could heal cracks, regain load-bearing ability, inhibit oral pathogens, reduce or eliminate biofilm acids, raise biofilm pH to protect the teeth, and regenerate lost tooth minerals. Furthermore, their effects were indicated to be durable and long-lasting. While most of the recent publications on self-healing dental resins are from our group, this article also reviews publications from other researchers. The novel class of dental materials with triple benefits of self-healing, antibacterial and remineralization capabilities offer the much-needed improvements to address the two main reasons for restoration failures: fracture and secondary caries. They are expected to have potential for a wide range of dental and biomedical applications to overcome the current challenges and prolong the restoration life.

Contents

* Corresponding author.
** Corresponding author. Department of Advanced Oral Sciences and Therapeutics, University of Maryland Dental School, Baltimore, MD, 21201, USA.
*** Corresponding author.
E-mail addresses: doctorwujunling@163.com (J. Wu), dentistzhang112@163.com (N. Zhang), dentistzhangli@126.com (Q. Zhang).

https://doi.org/10.1016/j.polymdegradstab.2019.02.024
0141-3910/

1. Introduction

Tooth decay occurs frequently causing a significant financial burden worldwide, especially with an aging population and increases in tooth retention rates in seniors [1,2]. Resin composites are often used to restore tooth cavities due to their tooth-color esthetics [3–5]. However, a major drawback is that nearly half of all restorations fail in less than 10 years, and fracture has been identified as one of the main reasons for failure, especially with large-sized restorations in load-bearing locations [6,7]. Indeed, more than 25% of all composite failures and replacements were due to reasons related to fractures [8]. For example, in large cavities, even after only 5 years of use, restoration fracture was identified as the primary reason for failure [9]. The mouth is a challenging environment, and the composite restoration experiences repeated mastication forces and thermal stresses, which can cause microcrack initiation and accumulation, leading to composite fracture [10,11]. Previous studies have contributed to the development of improved composites with enhanced resistance to crack formation. These studies made significant progress in improving the inorganic filler level, decreasing the filler particle size to the nanoscale [12,13], incorporating strengtheners such as whiskers and fibers [14,15], changing the polymer chemistry and enhancing the polymerization reactions [16,17] and fabricating low-shrinkage composites [18,19]. Nonetheless, fracture and failure are still frequent occurrences, warranting further research and improvements.

A novel approach is the development of self-healing dental resins with the potential of autonomically repair cracks and damage, thereby recovering the stress-bearing capability [20–23]. This self-healing method involves the embedding of microcapsules into the resin matrix, with each microcapsule having an external shell that encapsulates a healing liquid [24,25]. When damage or microcrack occurs in the resin matrix, the microcapsules would be ruptured by the crack to release the healing liquid. The healing liquid then flows into the crack planes, thus exposing itself to the catalyst in the resin. This in turn causes self-healing to occur, with the polymerization of the healing liquid filling the crack and bonding the cracked planes together to form a cohesive resin to regain the load-bearing ability [26–28].

This review article focuses on cutting-edge research on self-healing dental and biomedical materials. While much of the recent research on self-healing dental resins has been reported by our group, this article also covers publications by other groups. This includes the synthesis and properties of self-healing dental resin composites and adhesives, the combination of self-healing capability with calcium phosphate nanoparticles for remineralization of tooth lesions, and the incorporation of antibacterial agents into the self-healing dental resins to inhibit dental plaque growth, and reduce biofilm acid production and dental caries. These materials possess therapeutic properties, which in this article refer to the properties on the inhibition of bacteria and biofilm growth, the suppression of acid production, calcium phosphate remineralization, and healing of fractures. In addition, because the mouth is an aqueous environment exposed to saliva and beverage drinks, this article also reviews recent developments on the self-healing of dental resins while being immersed in an aqueous environment, and the effect of long-term water-aging time from 1 day to 6 months on the self-healing efficacy.

2. Self-healing polymeric materials and biomaterials

Pioneering research on self-healing polymers containing microcapsules was reported by White et al. [29,30]. The healing agent dicyclopentadiene (DCPD) was encapsulated in poly(urea-formaldehyde) (PUF) shell by *in situ* polymerization in an oil-in-water emulsion, as showed in Fig. 1A. The microcapsule diameters ranged from approximately 10 to 1000 μm. These microcapsules were added into an epoxy matrix. The Grubb's catalyst, a transition metal carbine complex, was used in the epoxy matrix to trigger the polymerization of the released DCPD. The microcapsules exhibited a good rupture manner to release the healing agent, as showed in Fig. 1B. Fractography of the healed and fractured surfaces revealed irregular polymer films of the released healing agent of DCPD supporting the self-healing mechanism, which was showed in Fig. 1C. This approach achieved a healing efficiency of 75%, defined as the fracture toughness K_{IC} of the healed polymer divided by the K_{IC} of the original virgin polymer. Several other studies reported microcapsules of various shell and healing liquid compositions. Yuan et al. [31] fabricated poly(melamine-formaldehyde) (PMF) capsules containing diglycidyl tetrahydro-o-phthalate (DTP, a low viscosity and high-activity epoxy monomer) and polythiol (a highly active low-temperature hardener for epoxy materials). The epoxy composites containing the microcapsules showed autonomous restoration capabilities even after exposure at 250 °C for 24 h [31] and proving that these microcapsules could be successfully employed for self-healing thermosetting polymers (cured epoxy) and thermoplastic polymers [32]. A further improvement was achieved when Blaiszik et al. [33] combined ultrasonication and *in situ* encapsulation techniques to generate nano-scale capsules with a mean diameter of 220 nm. The development of nanocapsules could allow for the incorporation of healing functionality in composites with smaller interstitial spaces, with potential applications in self-healing thin films, coatings, and adhesives which require smaller capsules. An epoxy matrix with well-dispersed nanocapsules showed a nearly 59% increase in fracture toughness for a capsule volume fraction of 1.5%, compared to that with 0% capsules. Fracture surface examination revealed that nearly all of the capsules were successfully ruptured during fracture. However, the self-healing efficacy was not reported. Further research is needed to solve the problem of low healing agent content arising from the capsule size reduction.

In addition to dental resins, the self-healing concept was also extending to biomaterials such as bone cements [34–38]. There are on average 200,000 total hip replacements and 400,000 knee

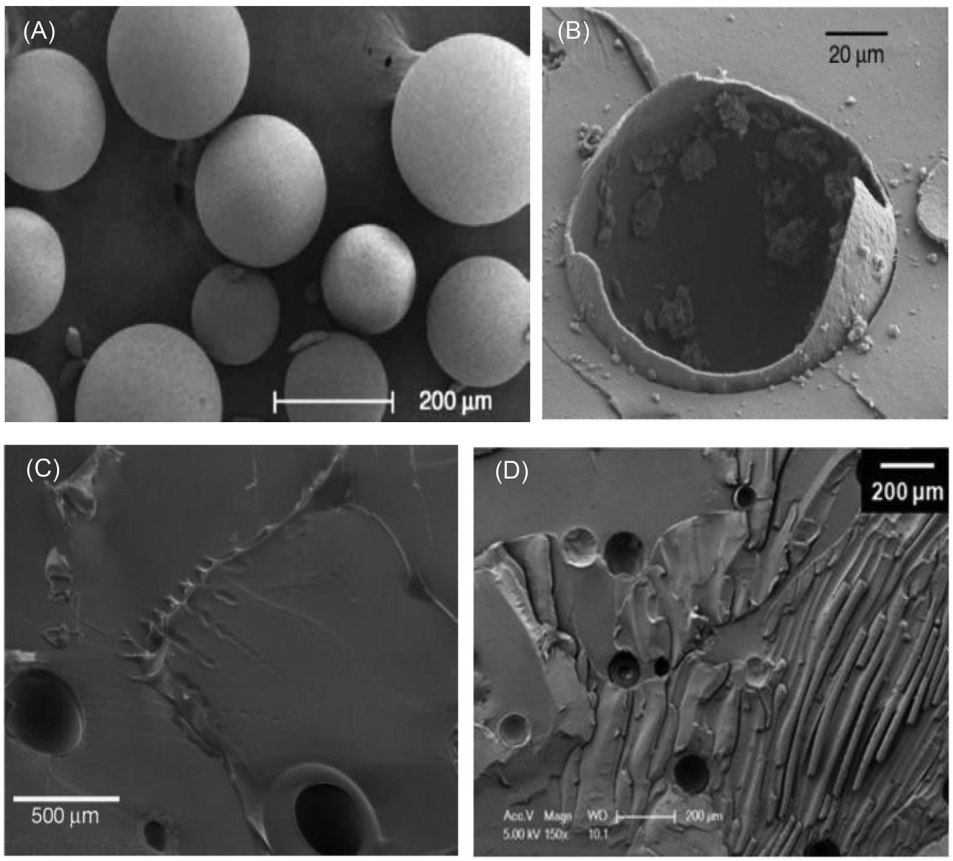

Fig. 1. SEM image of microcapsules and self-healing in an epoxy polymer. (A) Microcapsules were prepared via *in situ* polymerization. (B) SEM image showed the fracture plane of a self-healing material with a ruptured PUF microcapsule in a polymer matrix. (C) SEM image showed one area of the fracture plane of a healed specimen in which the poly (DCPD) film was still attached to the interface. (D) SEM image of healed fracture surface after healing at 37 °C in the environmental chamber at 40% relative humidity: immersion in the SBF (Reproduced with permission from Ref. [29], Elsevier, 2001, and Ref. [38], Wiley, 2014).

replacement surgeries performed each year in the U.S., and the patients typically undergo revision surgeries about every 10 years, mainly due to dislocation and loosening of the initial prosthesis from the bone [39,40]. As the fixation of total joint replacements, the acrylic bone cement is challenged by long-term stability due to the brittleness and poor wear resistance of the polymeric matrix in the complex environment of the human body [41,42]. Hence, developing biocompatible materials with self-healing ability to autonomously repair mechanical and chemical damage is particularly important. Biggs et al. [34] used the formulation of White (PUF- DCPD microcapsules + Grubb's catalyst) to create a self-healing bone cement. Adding microcapsules into the commercial poly (methyl methacrylate) (PMMA) bone cement increased the crack resistance by 4–8 folds, compared to the unmodified formulation. However, the toxicity and cost of the catalyst are still a concern, discouraging the use of this self-healing chemistry in a practical biomaterials application. Subsequently, a water-reactive tissue adhesive 2-octyl cyanoacrylate (OCA) was successfully microencapsulated in polyurethane (PUR) shells via interfacial polymerization and incorporated into commercial Palacos R bone cement by Brochu et al. [36,37]. Their results demonstrated that the addition of a lower wt% of OCA-containing microcapsules into commercial bone cement moderately increases the static mechanical properties without increasing the toxicity of the material. In addition, Dailey et al. [38] developed a two-capsule self-healing system based on free-radical polymerization for the biomaterials. One capsule contained a peroxide initiator, while the other capsule contained two acrylate monomers and a tertiary amine. The two capsule system design made it easy to optimize the reaction components. An epoxy matrix containing two-capsule self-healing system achieved a high healing efficiency of 75% in air and 64% in a simulated body fluid solution (SBF) environment. Fig. 1 D shows a SEM image of the healed fracture surface after healing in SBF. The irregular polymer films on the healed surface proved the healing ability of this novel biomaterial. These novel self-healing systems are promising for use in dental resins and acrylic-based orthopedic cement applications, which require further studies.

3. Self-healing dental restorative materials

Dental resins play an increasingly important role in modern dentistry, including restorative materials for direct restorations and indirect restorations including inlays, onlays, crowns and bridges, as well as adhesives and cements for single or multiple tooth prostheses and orthodontic devices [1,3,4,43–46]. Microcracking induced by thermal stress and fracture due to chewing forces in the harsh oral environment is a long-standing problem impairing the durability of resin composites [10,47]. Therefore, efforts have been made to develop self-healing composites with improved resistance to fracture failures.

Then et al. [48] produced melamine modified UF microcapsules to enhance the properties of the microcapsules. Urea-melamine-formaldehyde (UMF) polymers had a higher bond strength due to its cross-linking ability [49]. Thus, UMF microcapsules had a tougher shell and better adhesion to the host resin. These DCPD-containing microcapsules were embedded in a dental composite

matrix consisting of bisphenol-A-glycidyl dimethacrylate (BisGMA) and triethylene-glycol dimethacrylate (TEGDMA). The incorporation of small amounts of the microcapsules did not affect the mechanical performance of the matrix as indicated by a flexural strength test. Scanning electron microscopy (SEM) analysis indicated excellent bonding of the microcapsules to the host material which was important for maintaining strong mechanical properties of the dental composite with self-healing ability [48]. Highly-filled dental composites with automatic crack repair ability were formulated by Wertzberger et al. [50]. The resin matrix contained TEGDMA, urethane dimethacrylate (UDMA) and BisGMA, which was filled with 55 wt% silanated barium borosilicate glass particles. The self-healing system consisted of encapsulated DCPD and Grubbs' catalyst. Self-healing specimens were loaded to failure and left to sit for 7 days to determine the healing effect. Self-healing test showed that this material had a 57% recovery of the original K_{IC}. The results demonstrated that despite the highly-filled nature, the dental resin composites could recover mechanical properties by the incorporation of embedded self-healing monomers.

Kafagy et al. [51,52] also synthesized UF microcapsules containing monomer mixture of Tri-methyl Propane Ethoxylate Triacrylate (TMPET), UDMA, Polyethylene glycol extended UDMA (UDMA PEG), and BisGMA. These microcapsules were incorporated into dental resin composites. The addition of 5 wt% microcapsules to the dental composite served to increase the virgin toughness by 40%, resulting in extending the fatigue life of dental composites.

Next, the use of a self-repair bonding resin to improve the durability of dental adhesives was described by Ouyang et al. [53]. TEGDMA nanocapsules were synthesized via interfacial polycondensation in a mini-emulsion. The bond strength and biocompatibility of the dental adhesive were not negatively affected with the incorporation of nanocapsules. However, these nanocapsules contained no catalyst for polymerization, and the self-healing effect on cracking in the adhesive was not reported [53].

More recently, a self-healing dental composite model was developed and evaluated by Huyang et al. [54]. Glass ionomer cement (GIC) powder of strontium fluoroaluminum inosilicate particles and aqueous solution of polyacrylic acids were used as the healing powder and healing liquid, respectively. The healing liquid was encapsulated in silica microcapsules. Healing powder and the microcapsules containing healing liquid were incorporated into a resin to form the self-healing dental composite. As cracking, the released healing liquid from the broken microcapsules reacted with the healing powder exposed by the crack. This formed a reaction product that filled and sealed the cracks. Their research showed that the average healing efficiency reached 25% when 5 wt% or 10 wt% microcapsules were added into the composite. The morphological and chemical changes after healing were confirmed by SEM equipped with Energy dispersive X-ray spectroscopy (EDS). They showed that a new material was formed on the cross-sections of the specimens after the healing process was completed. This material had a different appearance from the non-healed fracture surface (Fig. 2A and B). The new material was expected to be GIC, which was the reaction product of the healing powder and the healing liquid. The EDS examination confirmed the chemical transition from healing powder to GIC on the healed fracture surface. As the key elements in the formation of GIC, the elements Al, Si and Sr were identified. In the sections before healing (Fig. 2C and E), the Si content was higher than Al, while in the healed regions (Fig. 2D and F), the contents of Al and Sr were increased. All the images indicated that the liquid reacted with the powder exposed by the crack formation, thus forming an insoluble reaction product of GIC that healed the crack. In addition, these microcapsules were functionalized by silane coupling agent and bonded to the resin matrix to improve the mechanical properties [55]. Regarding the fatigue crack growth behavior, there was a significant increase in the resistance to fatigue crack growth and an increase of 580% in the fatigue life for this new material [55]. Importantly, this self-healing dental composite contained only clinically-tested, biocompatible materials (the GIC powder and liquid were already being used in dental clinics), making this new self-healing material readily applicable for clinical use. However, the self-healing efficacy of the composite needs to be further increased. In addition, since oral biofilm acids and demineralization are key causes of failures for dental composite restorations, it would be highly desirable for the smart resin to not only have self-healing ability, but also possess therapeutic properties including antibacterial and remineralization capabilities.

4. Effects of microcapsule mass fraction in resin on self-healing efficacy

To improve the self-healing efficacy, the microcapsule mass fraction in dental resin on self-healing was investigated [56]. Even though efforts were made to incorporate DCPD-containing microcapsules and Grubb's catalyst into a composite [48,50], literature search revealed no further report on the use of DCPD and Grubb's catalyst in dental materials, likely due to toxicity concerns. The DCPD toxicity [57], Grubb's catalyst toxicity, and their high cost [58] remain challenges in using them in dental composites. Recently, Wu et al. [56] developed novel microcapsules containing polymerizable TEGDMA and *N,N*-dihydroxyethyl -*p*-toluidine (DHEPT) for the first time. TEGDMA monomer is flowable and has been used in dentistry for decades 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 DHEPT has good solubility and stability in TEGDMA. Therefore, a self-healing liquid of DHEPT-TEGDMA was used inside PUF microcapsules [56]. The microcapsules were prepared by *in situ* polymerization of formaldehyde and urea, following previous studies [30,59]. The characterization of these microcapsules was showed in Fig. 3. Fig. 3A showed a representative example of a microcapsule. The microcapsules had an average diameter of $70 \pm 24\,\mu m$ ($n = 200$). Fig. 3B showed that the microcapsules had a black ring outside and a relatively bright area inside, indicating that the TEGDMA was successfully encapsulated by the PUF shell. The SEM image in Fig. 3C showed the external surface of the microcapsules. Higher magnification in Fig. 3D revealed details of the shell, showing numerous nanoparticles attaching to a smooth shell surface to form a rough shell. Fig. 3E displayed the shell wall of a microcapsule at a high magnification. The thickness of the shell was estimated to be 230 ± 43 nm (mean $\pm$ sd; $n = 6$). Fig. 3F shows the crushed microcapsules with shell fragments and the released healing agent between two glass slides, further demonstrating the liquid filled-structure of the microcapsules. These microcapsules were added into the dental resin of BisGMA and TEGDMA at microcapsule mass fractions of 0%, 5%, 10%, 15% and 20%. Mechanical test showed that the flexural strength and elastic modulus of resins containing 0%–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. Hence, the optimal microcapsule mass fraction in this system appeared to be 15% [56].

Previous studies assessed the healing ability of materials by comparing the fracture toughness K_{IC} of the material before and after self-healing [60]. In several studies, a single edge V-notched beam (SEVNB) method [61,62] was used to measure the K_{IC}. In Fig. 4A, the virgin K_{IC} (before healing) and the healed K_{IC} (after healing) of the resin were plotted vs. microcapsule mass fraction. Adding microcapsules into the resin increased the virgin K_{IC}, which

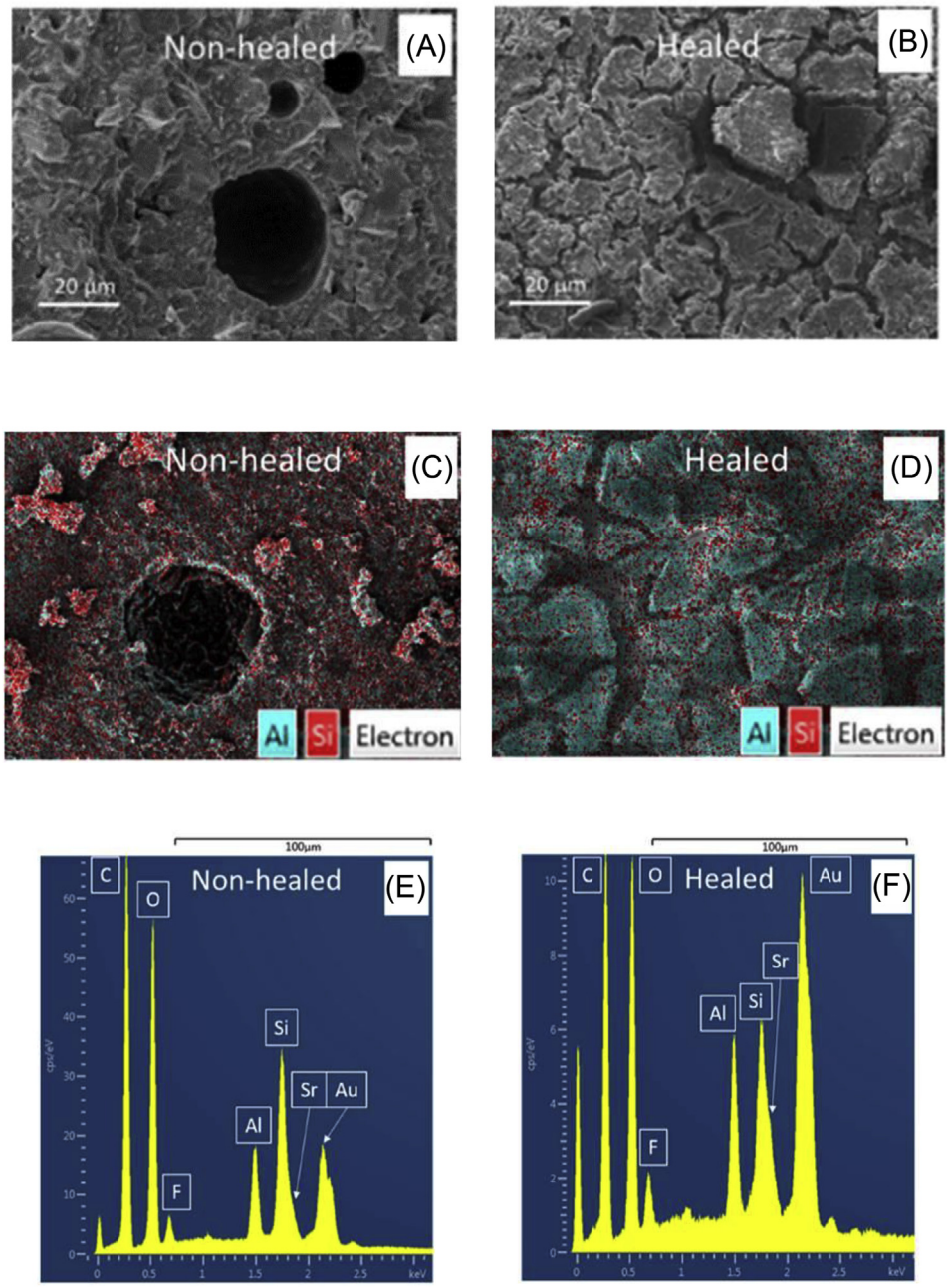

Fig. 2. Characteristics of self-healing dental composites surfaces. SEM images of the (A) non-healed self-healing dental composites surface, and (B) the healed surface. SEM-EDS images of (C) non-healed self-healing dental composites surface, and (D) the healed surface, artificially colored to match the signal count of Al and Sr. Elemental analysis by EDS on sections of the (E) non-healed, and (F) healed regions of the self-healing dental composites. All the images proved that the healing liquid reacted with the healing powder exposed by the crack, thereby forming an insoluble reaction product of GIC that healed the crack. (Reproduced with permission from Ref. [54], Elsevier, 2016).

was about 40% higher at 15% microcapsules than that at 0% microcapsules ($p < 0.05$). The toughening mechanism appeared to be crack-pinning and deflection caused by the microcapsules in the resin [63]. To measure 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. Then the K_{IC} of the healed specimens was measured. The healed K_{IC} significantly increased, from no healing at 0% microcapsules to maximum healing at 10% and 15% microcapsules ($p < 0.05$). As shown in Fig. 4B, a self-healing efficacy of 64%–68% in K_{IC} recovery was obtained when the microcapsule concentration in the resin was ≥10%. The high healing efficacy came from the good rupture manner of the embedded microcapsules and polymerization of the released healing liquid of TEGDMA-DHEPT and BPO in the resin matrix. Most importantly, this study employed common dental monomers (TEGDMA, DHEPT, and BPO) for the healing liquid polymerization, making this method readily applicable to a wide range of dental resinous systems. 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. Further study is needed to test its self-healing ability in vivo.

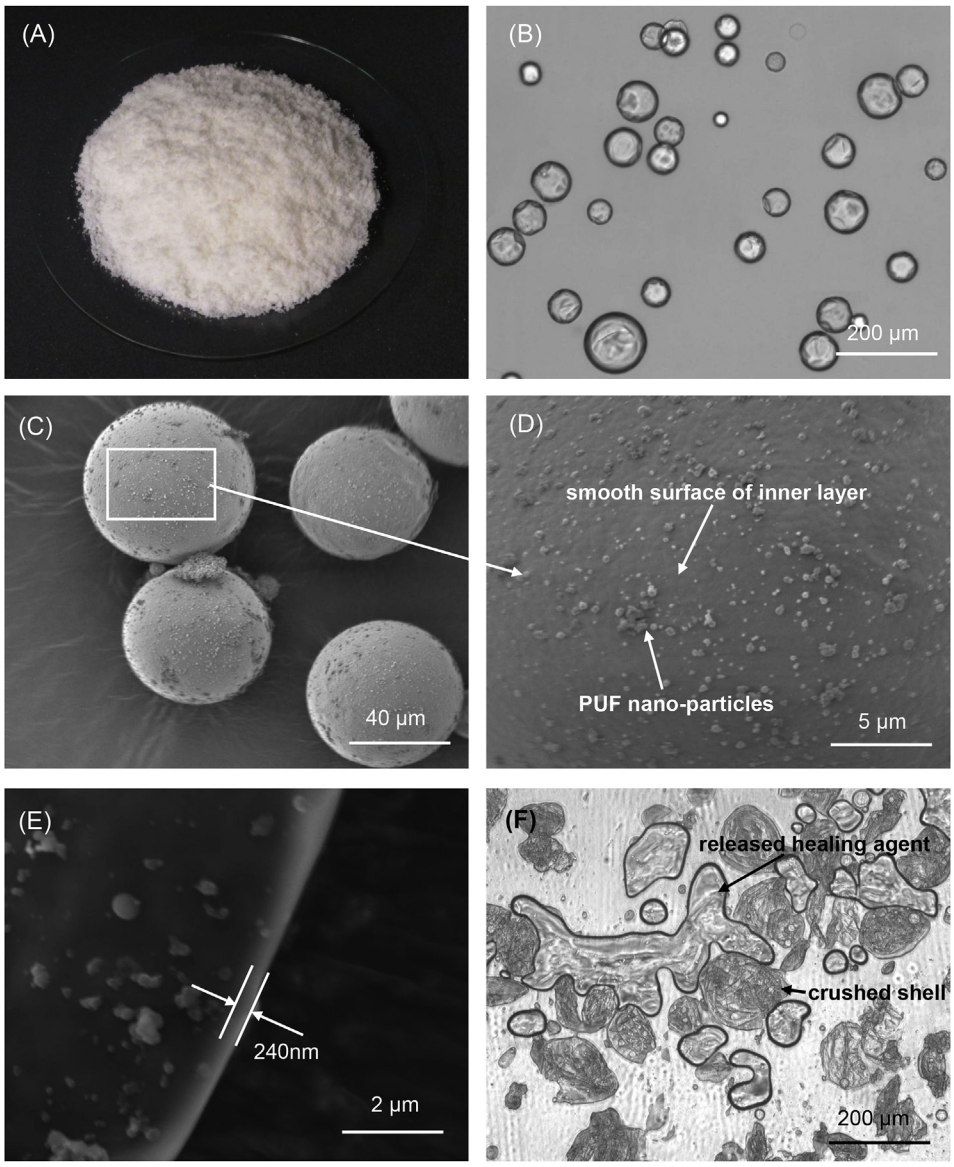

Fig. 3. Microcapsules were prepared with polymerizable TEGDMA-DHEPT healing liquid inside PUF shells. (A) Photo showing a pile of microcapsules. (B) Transmitting optical image showing the shell structure as a dark ring. (C) SEM image showing typical microcapsules. (D) High magnification SEM image of 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. (Reproduced with permission from Ref. [56], Elsevier, 2016).

5. Dental composite with triple benefits of self-healing, antibacterial and remineralization capabilities

Studies suggest that fracture was a frequent reason for composite failure, while secondary caries was a common reason for failure after five years of clinical service [9]. Indeed, bulk fracture and secondary caries are the two main problems [64]. Replacing the failed restorations accounts for 50–70% of all restorations performed [65],and replacement dentistry represents a significant financial burden [66]. Therefore, it would be highly desirable to develop a new composite with self-healing capability to heal cracks *in situ* while also possessing a caries-inhibiting capability. Unfortunately, the currently-available resin composites were shown to accumulate more biofilms and plaque than other restorative materials [67,68]. Biofilms could produce acids, leading to dental caries [69]. Therefore, it would be beneficial to incorporate antibacterial agents into composites to inhibit bacteria and acid production. Indeed, research efforts were devoted to develop quaternary ammonium methacrylates (QAMs) to inhibit oral biofilms [70]. Imazato et al. invented 12-methacryloyloxydodecylpyridinium bromide (MDPB), which was copolymerized in dental polymers to achieve strong antibacterial activities [71,72]. In addition, methacryloxylethylcetyl dimethyl ammonium chloride (DMAE-CB), polyethylenimine nanoparticles, and several other novel compositions were synthesized [73–76]. Recently, a new antibacterial monomer dimethylaminododecyl methacrylate (DMAHDM) with an alkyl chain length of 16 was synthesized and incorporated into resins, showing a strong antibacterial effect [77]. Furthermore, nanoparticles of amorphous calcium phosphate (NACP) were incorporated into composites for remineralization of tooth lesions [78].

Recently, a novel composite was developed with triple benefits of self-healing, antibacterial and remineralization properties [79]. The composite contained PUF microcapsules with TEGDMA,

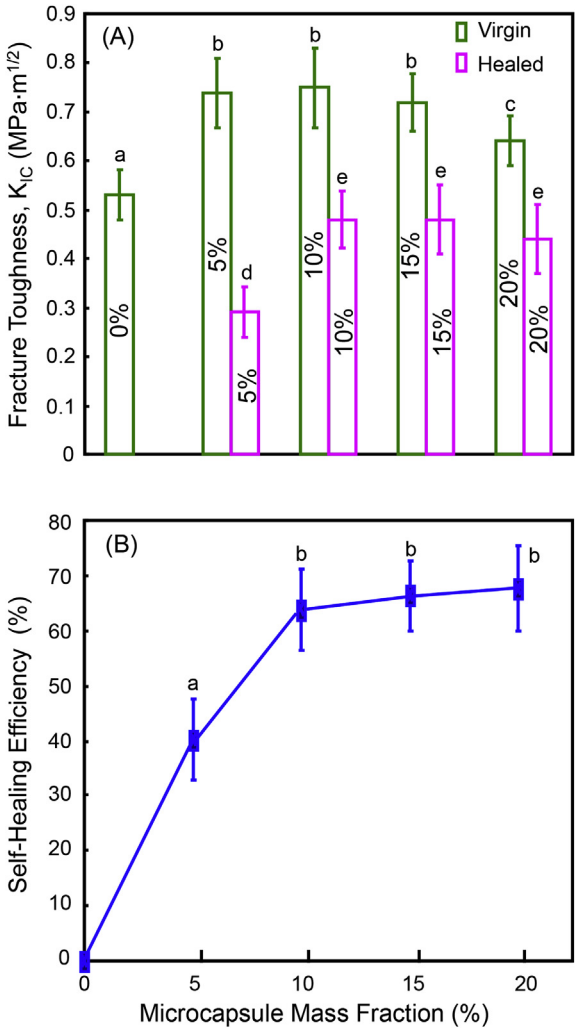

Fig. 4. Self-healing of resin containing microcapsules: (A) fracture toughness, and (B) self-healing efficiency (mean ± sd; $n = 6$). 0% refers to resin containing 0% microcapsules, 5% refers to resin containing 5% microcapsules, and so on. In each plot, values with dissimilar letters are significantly different from each other ($p < 0.05$). (Reproduced with permission from Ref. [56], Elsevier, 2016).

antibacterial monomer of DMAHDM and remineralizing agent NACP. DMAHDM was added into the BisGMA-TEGDMA resin at 10% by mass, following a previous study [80]. The resin matrix was filled with 20% NACP for Ca and P ion release and remineralization [78], and 35% glass fillers for mechanical reinforcement. This resin composite was then mixed with microcapsules at microcapsule mass fractions of 0%, 2.5%, 5%, 7.5% and 10%. The flexural test showed that there was no significant difference in strength and elastic modulus among the groups with microcapsule mass fraction from 0% to 7.5%. However, the mechanical properties at 10% microcapsules were significantly lower than the other groups. For $K_{IC\text{-}virgin}$, there was also no significant difference from 0% to 7.5% microcapsules, and further increasing the microcapsule mass fraction to 10% reduced the $K_{IC\text{-}virgin}$, from 1.16 MPa m$^{1/2}$ at 0% to 0.91 MPa m$^{1/2}$ at 10% microcapsules. The $K_{IC\text{-}healed}$ significantly increased from no healing at 0% microcapsules to maximum healing at 7.5% and 10% microcapsules, due to the increasing microcapsule mass fraction. A K_{IC} recovery of 65%–81% was achieved for composites with microcapsule mass fractions at 7.5% and 10% microcapsules. The outstanding self-healing efficacy and recovery of load-bearing capability benefited from the substantial *in situ* curing of the reactive TEGDMA as triggered by free-radical initiation. The released and polymerized healing liquids halted the crack propagation, bonded the cracked planes together and healed the specimen [79]. Therefore, remineralization agent (NACP) and antibacterial agent (DMAHDM) could be incorporated into a self-healing composite, while still achieving self-healing efficacy similar to the reported values where remineralization fillers and antibacterial monomers were not used.

This novel self-healing composite possessed a strong antibacterial function, as shown in Fig. 5. Representative live/dead staining images were shown in (A) control composite without DMAHDM, and (B) composite containing 7.5% microcapsules and 3% DMAHDM in the resin composite. Live bacteria were stained green, while dead bacteria were stained red. The control composite had continuous green coverage of live biofilm. The composite with DMAHDM showed mostly red staining, indicating a strong antibacterial activity. The MTT (3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay results were plotted in (C), and the lactic acid production by biofilms is plotted in (D). Biofilms on the control composite had relatively high metabolic activity and acid production. In contrast, biofilms on composites containing DMAHDM had much lower metabolic activity and acid production. The metabolic activity was about 1/25 that of the control, and the lactic acid production was nearly 1/100 that of the control. The composites containing DMAHDM, regardless of microcapsule mass fractions, reduced the CFU of biofilms by 3–4 orders of magnitude, compared to control composite without DMAHDM. This was achieved with microcapsule mass fraction varying from 0 to 10%, indicating that microcapsule incorporation did not significantly interfere with the antibacterial effect. Regarding the antibacterial mechanism, the strong antibacterial property of DMAHDM came from the positively-charged quaternary amine N^+, which could attract the negatively-charged cell membrane of the bacteria, disrupt the membrane and cause cytoplasmic leakage [81,82]. It was suggested that long-chained quaternary ammonium compounds could insert into bacterial membranes like a needle, leading to disruption of the bacteria [83].

Besides the self-healing ability and antibacterial activity, the composite had the third benefit of Ca and P ion release for remineralization. The fact that Ca and P ion release could cause remineralization of tooth lesions was demonstrated in previous studies [78,84–86]. In addition, previous studies showed that the NACP composite was “smart” and could increase the release of Ca and P ions at a cariogenic low pH, when such ions would be most needed to combat caries [78]. Furthermore, NACP was shown to be able to neutralize acid challenges by increasing the pH from a cariogenic low pH to neutral pH to avoid tooth demineralization [84]. Indeed, a NACP composite remineralized enamel lesions in vitro [85]and inhibited caries formation in a human *in situ* study [86]. NACP composites were shown to successfully remineralize enamel and dentin lesions, regenerate the lost minerals and increase the hardness back to normal, and inhibit secondary caries in vivo in human participants [85–89]. Further study is still needed to investigate the effects of the composite with triple benefits of self-healing, antibacterial and remineralization properties under clinically-relevant in vivo conditions.

6. Effects of water-aging on self-healing dental composite

Previous studies showed that self-healing composite containing microcapsules exhibited good self-healing performance [56,79]. However, in these studies, the cured specimens were immersed in water for only 1 day or not immersed at all before self-healing testing [56,79]. Dental composites in the oral environment are required to survive being wet for long periods of time to be successful clinically. Previous studies on non-self-healing dental

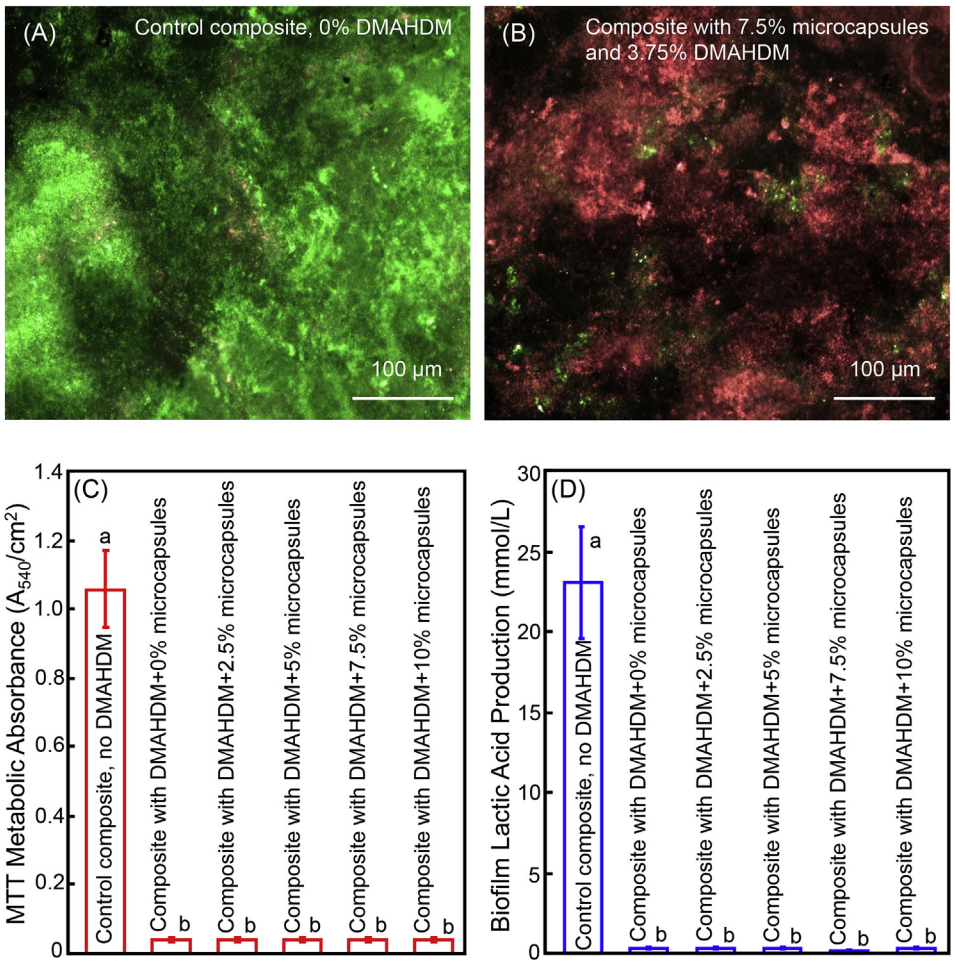

Fig. 5. Dental plaque microcosm biofilm growth on composites. (A) and (B) Representative live/dead images of dental plaque microcosm biofilms on control composite and that with DMAHDM, respectively. Live bacteria were stained green, and dead bacteria were stained red. Live and dead bacteria that were close to each other yielded yellow/orange colors. (C) MTT metabolic activity, and (D) lactic acid production of biofilms (mean ± sd; n = 6). In each plot, values with dissimilar letters are significantly different from each other ($p < 0.05$). (Reproduced with permission from Ref. [79], Elsevier, 2015)

composites showed that the composites were weakened by long-term water-aging, which could degrade the fillers [90], soften the resin matrix due to the plasticizing action of water [91], and cause hydrolytic breakdown of the interfaces between the fillers and the resin matrix [91,92]. It is not clear how water-aging would affect the self-healing resin, the microcapsules and the encapsulated healing liquid, thereby affecting the healing liquid polymerization with the initiator in the matrix.

Recently, a novel self-healing dental composite containing PUF microcapsules with TEGDMA and DHEPT healing liquid was developed, and the effect of water-aging on the self-healing properties was investigated [93]. The basic formulation of resin composite was 30% dental resin monomer and 70% glass fillers by mass. The composite containing 7.5% microcapsules was immersed in distilled water at 37 °C for 1 day, and 1, 2, 3 and 6 months for the water-aging test [93]. Water-aging significantly decreased the $K_{IC\text{-}virgin}$ from 1 day to 30 days. Further immersion from 30 days to 6 months showed little further decrease in $K_{IC\text{-}virgin}$ [91,92]. The $K_{IC\text{-}virgin}$ of the composite after 6 months of water-aging was 0.72 MPa $m^{1/2}$, within the reported K_{IC} range for commercial dental composite which were not water-aged and contained no microcapsules for self-healing [94]. $K_{IC\text{-}healed}$ showed a similar trend to $K_{IC\text{-}virgin}$. The healing efficiency varied between 60% and 70%, and there was no significant loss in self-healing efficiency from 1 day to 6 months of water-aging.

In another study, Caruso et al. [95]tested solvent-based healing systems aged in the air, showing that the healing efficiency decreased quickly after one month of aging, and decreased to zero after eight months due to the lack of residual functionality groups. In contrast, in another study, long-term stability was achieved for self-healing epoxy by Jin et al. [96],showing 68% healing efficiency after aging for six months in ambient air. This was because the initiator was maintained to be stable over that period of time [96]. Self-healing efficiency of 64% was achieved after water-aging for 6 months in Wu's study [93], indicating a good self-healing durability of this novel resin composite. This may be because that the embedded microcapsules maintained an effective rupture during cracking to release the healing liquid, and the initiator BPO in the resin matrix did not leach out and was still able to trigger the polymerization of the released healing agent. However, further study is needed to investigate the self-healing of this promising dental composite after longer periods of aging, such as several years.

Next, Wu et al. [93] investigated the novel resin composite self-healing behavior in water. Specimens containing 7.5 wt% microcapsules were fractured and self-healed while being immersed in water for 24 h. In addition, specimens healed in humidor without immersion in water served as control. Fig. 6 plots the self-healing results. In (A), healing in water achieved the same $K_{IC\text{-}healed}$ and the same self-healing efficiency compared to specimens without immersion. In (B), a 60% recovery in fracture toughness was

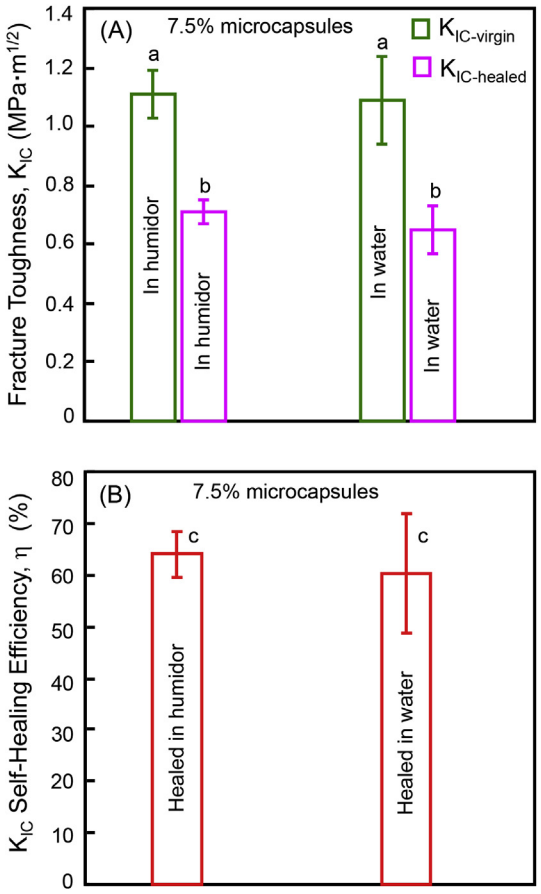

Fig. 6. Self-healing while being immersed in water for composite containing 7.5% microcapsules. (A) Virgin and healed fracture toughness, and (B) self-healing efficacy (mean ± sd; n = 6). Healed in humidor: specimens were water-aged for 1 day and then fractured to measure $K_{IC\text{-}virgin}$. They were then healed in a humidor in air for 1 day and then re-fractured to measure $K_{IC\text{-}healed}$. Healed in water: specimens were water-aged for 1 day and then fractured to measure $K_{IC\text{-}virgin}$. They were then healed while being immersed in water for 1 day and then re-fractured to measure $K_{IC\text{-}healed}$. Values with the same letter are similar ($p > 0.1$). (Reproduced with permission from Ref. [93], Elsevier, 2016).

achieved, indicating that immersion in water did not significantly compromise the healing process. Regarding the mechanism, two factors may have contributed to this result. First, the cured BisGMA-TEGDMA matrix of the composite was relatively hydrophobic and not very wettable [97], hence it would act to repel water. This would likely make it difficult for water to infiltrate the crack in the composite. Second, water did not block the self-healing polymerization [97], and the initiator-catalyst reaction occurred in the resin because water was not penetrating into the chemical structure. Even if there was water, it would not affect the polymerization. Indeed, previous studies showed the presence of water to have little appreciable effect on photo-polymerization rate or the degree of double bond conversion [97,98], and the free-radical polymerization could occur completely in water [99]. Hence it was anticipated that this novel composite would be effective in self-healing in the wet oral environment and retain its self-healing ability after water-aging treatments. Further studies are needed to test long-term immersion in saliva on the self-healing properties [93].

7. Self-healing adhesive with antimicrobial and remineralization properties

Polymeric composites are filled into tooth cavities and bonded to tooth structures via bonding agents. The polymer-tooth bonded margin is the "weak link" of the restoration [100]. Secondary caries at the bonded tooth-composite margins is one of the primary reasons for restoration failures [100–102]. Therefore, rendering the adhesive polymer antibacterial would be beneficial to inhibit bacteria and combat caries at the margins [103]. Antimicrobial bonding agents were developed by incorporating QAMs including DMAE-CB and MDPB [74,104], quaternary ammonium polyethylenimine (PEI) nanoparticles [105], and nano-silver [106]. In addition, DMAHDM showed a potent anti-biofilm activity in dental adhesive [107,108]. Furthermore, adhesives containing NACP could remineralize tooth lesions and neutralize acids [109,110].

At the restoration-tooth bonded interface, the bond longevity is mainly affected by the microcracks at the margins induced by polymerization shrinkage, cyclic loading, and thermal and mechanical fatigue [111]. Since the microcracks could result in microleakage and bacteria invasion [112], it would be highly desirable to develop an adhesive having autonomous crack-healing ability to self-heal these microcracks, as well as antibacterial functions. Recently, an adhesive resin with triple benefits of autonomous crack-healing, antimicrobial and remineralizing capabilities was demonstrated by Yue et al. [113]. The experimental primer contained pyromellitic glycerol dimethacrylate (PMGDM) and 2-hydroxyethyl methacrylate (HEMA). The experimental adhesive consisted of BisGMA and TEGDMA, with 7.5% microcapsule, 10% DMAHDM and 20% NACP. Scotchbond Multi-Purpose primer and adhesive (SBMP) served as a commercial control. The dentin shear bond test results were shown in Fig. 7 [113], showing that incorporation of self-healing microcapsule, DMAHDM and NACP at the designated percentages did not negatively affect the dentin bond strength.

A SEVNB method was used to calculate the K_{IC} and self-healing efficiency. The $K_{IC\text{-}virgin}$ of adhesive slightly decreased from 0.68 MPa m$^{1/2}$ to 0.57 MPa m$^{1/2}$ after incorporation of microcapsule, DMAHDM and NACP. However, the values were still within the reported range of 0.37–0.94 MPam$^{1/2}$ for dentin bonding resins [114], and 0.30 to 1.4 MPam$^{1/2}$ for resin-based luting cements [115]. The crack-healing efficiency for Resin + Microcapsule + DMAHDM + NACP was 67%, and that for Resin + Microcapsule was 69%. All other groups without microcapsules had no self-healing. The healing efficacy of 67% was

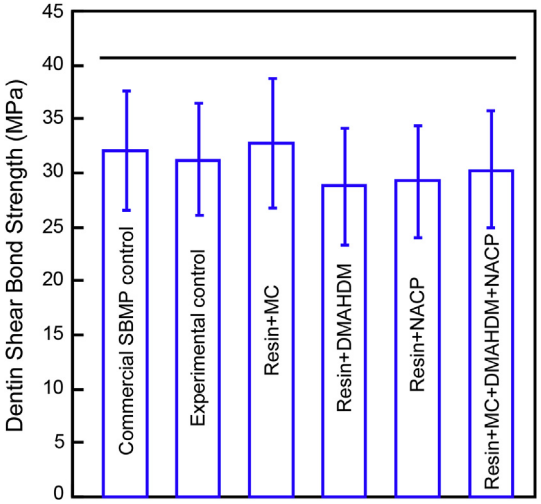

Fig. 7. Human dentin shear bond strength using extracted teeth (mean ± sd; n = 10). Horizontal line indicates values that are not significantly different from each other ($p > 0.1$). (Reproduced with permission from Ref. [113], Elsevier, 2018).

consistent with previous reports on other self-healing materials without antibacterial and remineralization properties [50,56]. An oral plaque microcosm biofilm model was used to determine the antibacterial properties of the self-healing bonding agent. Resin + Microcapsule + DMAHDM + NACP and Resin + DMAHDM reduced the biofilm CFU by 4 orders of magnitude, compared to that without DMAHDM. The biofilm lactic acid production was reduced to 1% that without DMAHDM. These results demonstrated the potent antimicrobial activity of the self-healing bonding agent, which would be highly beneficial in reducing secondary caries at the margins. Further studies are needed to evaluate the effects of this new adhesive in protecting the interfacial bond and autonomous-healing of cracks, as well as in reducing biofilm acids and recurrent caries at the margins in vivo.

8. Self-healing dental luting cement for indirect restorations

Besides composites and bonding agents, dental luting cements also play an important role in modern dentistry to attach indirect restorations including inlays, crowns and bridges to the prepared teeth [116]. Success of indirect restorative procedures depends partly on the cementation technique. Although clinical performance has been improved, dental cements still have relatively poor physical properties compared to bulk restorative filling materials, and cements are relatively prone to fractures [117,118]. At the restoration-tooth cemented interfaces or margins, the bond longevity is mainly affected by microcracks induced by polymerization shrinkage, repetitive dynamic mechanical loading, water sorption and thermal fatigue [119–121]. These microcracks could coalesce under cyclic stresses and eventually cause cement fracture, which is a main reason for the failure of cemented restorations [115,122]. Therefore, extensive efforts have been undertaken to improve the properties of dental luting agents to increase the clinical service life. These efforts included modifying the chemical compositions [123–125] and optimizing the physical and handling properties [126,127]. However, there have been few reports on inhibiting microcrack propagation to protect the integrity of the cements.

Recently, the first self-healing dental luting cement was developed by Wu et al. [128]. A cement film thickness of approximately 50 μm is typically advised by clinicians to maintain the properties of the cement and the support for the restorations [129]. In previous studies, microcapsules of a diameter of 70 μm were developed for use in self-healing resins for direct restorations and adhesives [56,79,113]. However, the 70 μm microcapsule size is too large use in cements with film layer thickness of about 50 μm for indirect restorations. Therefore, in Wu's recent study [128], smaller microcapsules of a mean diameter of 24 μm were generated by increasing the agitation rate via an emulsion polymerization technique. Different mass fractions of 0%, 2.5%, 5%, 7.5% and 10% microcapsules were added into an experimental luting cement containing an acidic functional adhesive monomer 4-methacryloyloxyethyl trimellitic anhydride (4-META). A commercial cement of Clearfil™ SA containing 10-Methacryloyloxydecyl dihydrogen phosphate (MDP) was used as control. Dentin shear bond test was conducted and there was no significant difference in bond strength with microcapsule mass fractions from 0% to 7.5%. However, the incorporation of 10% microcapsules negatively affected the dentin bond strength. Adding 10% microcapsules also significantly decreased the flexural strength and elastic modulus of the cement. The results of K_{IC} test by the SEVNB method showed that there was no significant difference in $K_{IC\text{-}virgin}$ from 0% to 7.5% microcapsules. However, further increasing the microcapsule mass fraction to 10% reduced the $K_{IC\text{-}virgin}$ from 1.1 MPa $m^{1/2}$ at 0% to 0.79 MPa $m^{1/2}$ at 10% microcapsules. $K_{IC\text{-}healed}$ was significantly increased from 0% to 10% microcapsules. The higher $K_{IC\text{-}healed}$ deriving from higher microcapsule concentrations may be explained by more healing agent release, resulting in re-bonding of the cracked planes. A K_{IC} recovery of 68% and 77% was obtained for cements with 7.5% and 10% microcapsules, respectively, similar to previous studies using 70 μm microcapsules at the same mass fractions [56,79,113]. These results indicate that using smaller microcapsules could still achieve the same self-healing efficacy as larger microcapsules, while enabling a finer microstructure and thinner cement films.

Water sorption has a negative effect on the mechanical properties of cements [130]. The absorbed water works as a plasticizer to cause the plasticization and hydrolytic degradation within the cement matrix [131,132]. Furthermore, studies of long-term durability of dental cements showed that water-aging decreased the cement mechanical properties and bond strength [133–135]. Wu et al. [128] selected the self-healing cement containing 7.5% microcapsules for water-aging test for 6 months. The cured specimens were immersed in distilled water at 37 °C for 1 day and 1, 2, 3 and 6 months. The results were plotted in Fig. 8. In (A), water-aging significantly decreased the $K_{IC\text{-}virgin}$ from 1 day to 30 days. The $K_{IC\text{-}virgin}$ of the cement after 30 days of water-aging was 0.71 MPa $m^{1/2}$, representing a decrease of nearly 30% compared to 1 day. These results are similar to previous studies on water-aging effects on mechanical properties of composite [90–92]. There was no further decrease in $K_{IC\text{-}virgin}$ from 1 to 6 months. This was likely because once the polymer network was saturated with water and became slightly softened, the composite structure stabilized and there was no further reduction in mechanical properties within the tested time frame [91]. In (B), there was no significant loss in self-healing efficiency in water-aging from 1 day to 6 months. The self-healing efficiency of 65% after 6 months of water-aging was maintained, indicating that the self-healing system was not significantly degraded by water-aging. The healing agent of TEGDMA and the initiator of BPO in the surrounding matrix were not leached out and lost over time, and the embedded microcapsules were stable and maintained a good rupture manner by cracks after water-aging, thereby exerting a long-lasting self-healing effect. Therefore, it is anticipated that this new self-healing dental luting cement could be effective for applications in cemented restorations to inhibit fracture, even after long-term immersion in an aqueous environment. Self-healing smart materials represent a new class of dental materials that show exciting potential for load-bearing applications to heal cracks, resist fracture, and prolong service life. Further studies are needed to investigate this new class of self-healing materials for long-term crack healing and under conditions simulating the oral environment.

9. Conclusions

This article reviewed recent research on the synthesis and characterization of novel self-healing and bioactive dental resins. The new class of self-healing dental materials have established excellent self-healing efficacy in various material systems including resins, bonding agents, composites and cements. These new materials possess capabilities to heal crack, regain load-bearing ability, inhibit oral bacterial pathogens, reduce or eliminate biofilm acids, raise biofilm pH, and regenerate lost tooth minerals. Furthermore, their effects were indicated to be durable and long-lasting. This novel class of dental materials with triple benefits of self-healing, antibacterial and remineralization capabilities offer the much-needed properties to address the two main reasons for restoration failures: fracture and secondary caries. Therefore, these self-healing and therapeutic materials and their synthesis methods are promising for a wide range of dental and biomedical applications to overcome the primary failure problems and prolong the restoration life.

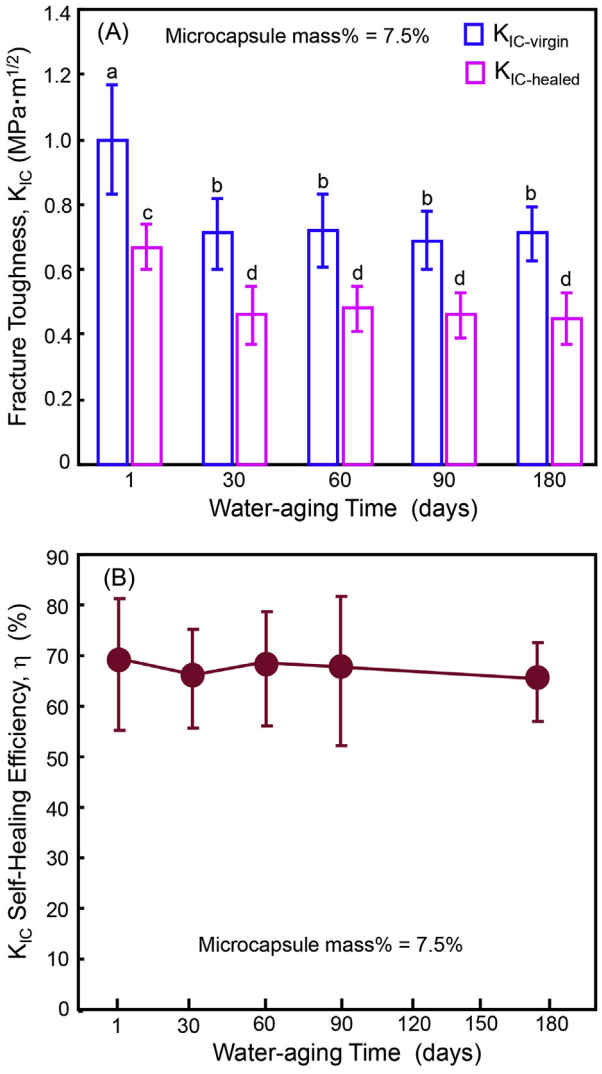

Fig. 8. Effect of water-aging time on self-healing cement containing 7.5% microcapsules.(A) Virgin and healed fracture toughness, and (B) self-healing efficiency (mean ± sd; n = 6). Specimens were water-aged for 1 day to 6 months, and then fractured to measure $K_{IC\text{-}virgin}$. They were then healed in a humidor in air for 1 d and then re-fractured to measure $K_{IC\text{-}healed}$. In (A), values with dissimilar letters are significantly different from each other ($p < 0.05$). In (B), all values are statistically similar ($p > 0.1$). (Reproduced with permission from Ref. [128], Elsevier, 2017).

Author contributions

Junling Wu, Xianju Xie, Han Zhou, Franklin R. Tay, Michael D. Weir, Mary Anne S. Melo, Thomas W. Oates, Ning Zhang and Qiang Zhang wrote the manuscript together. Hockin H. K. Xu edited the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by National Natural Science Foundation (NSF) of China 81671032 (JLW), National Natural Science Foundation (NSF) of China 81500879 (NZ), University of Maryland Baltimore seed grant (HX), and University of Maryland School of Dentistry bridge fund (HX).

References

[1] R.W. Nash, Direct composite resin restorations for today's practice, Dent. Today 32 (7) (2013), 114,116,118.
[2] R. López, P.C. Smith, G. Göstemeyer, F. Schwendicke, Ageing, dental caries and periodontal diseases, J. Clin. Periodontol. 44 (18) (2017) S145.
[3] N. Ilie, R. Hickel, Resin composite restorative materials, Aust. Dent. J. 56 (1) (2011) 59–66.
[4] J.L. Ferracane, Resin composite-state of the art, Dent. Mater. 27 (1) (2011) 29–38.
[5] A. Van Ende, J. De Munck, D.P. Lise, B. Van Meerbeek, Bulk-Fill composites: a review of the current literature, J. Adhesive Dent. 19 (2) (2017) 95–109.
[6] I.A. Mjor, J.E. Moorhead, J.E. Dahl, Reasons for replacement of restorations in permanent teeth in general dental practice, Int. Dent. J. 50 (6) (2000) 361–366.
[7] R.L. Sakaguchi, Review of the current status and challenges for dental posterior restorative composites: clinical, chemistry, and physical behavior considerations, Dent. Mater. 21 (1) (2005) 3–6.
[8] J.P. Van Nieuwenhuysen, W. D'Hoore, J. Carvalho, V. Qvist, Long-term evaluation of extensive restorations in permanent teeth, J. Dent. 31 (6) (2003) 395–405.
[9] A. Brunthaler, F. Konig, T. Lucas, W. Sperr, A. Schedle, Longevity of direct resin composite restorations in posterior teeth, Clin. Oral Investig. 7 (2) (2003) 63–70.
[10] G.R. Baran, K.G. Boberick, J.I. McCool, Fatigue of restorative materials, Crit. Rev. Oral Biol. Med. 12 (4) (2001) 350–360.
[11] M. Naebe, M.M. Abolhasani, H. Khayyam, A. Amini, B. Fox, Crack damage in polymers and composites: a review, Polym. Rev. 56 (1) (2016) 31–69.
[12] P.S. Reddy, K.L. Tejaswi, S. Shetty, B.M. Annapoorna, S.C. Pujari, H.M. Thippeswamy, Effects of commonly consumed beverages on surface roughness and color stability of the nano, microhybrid and hybrid composite resins: an in vitro study, J. Contemp. Dent. Pract. 14 (4) (2013) 718–723.
[13] L.L. Valente, S.L. Peralta, F.A. Ogliari, L.M. Cavalcante, R.R. Moraes, Comparative evaluation of dental resin composites based on micron- and submicron-sized monomodal glass filler particles, Dent. Mater. 29 (11) (2013) 1182–1187.
[14] H. Zhang, B.W. Darvell, Mechanical properties of hydroxyapatite whisker-reinforced bis-GMA-based resin composites, Dent. Mater. 28 (8) (2012) 824–830.
[15] Q. Huang, S. Garoushi, Z. Lin, J. He, W. Qin, F. Liu, P.K. Vallittu, L.V.J. Lassila, Properties of discontinuous S2-glass fiber-particulate-reinforced resin composites with two different fiber length distributions, J. Prosthodont. Restor. 61 (4) (2017) 471–479.
[16] J. Zorzin, E. Maier, S. Harre, T. Fey, R. Belli, U. Lohbauer, A. Petschelt, M. Taschner, Bull-fill resin composites: polymerization properties and extended light curing, Dent. Mater. 31 (3) (2015) 293–301.
[17] S.M. Mousavinasab, M. Atai, L. Salehi, A. Salehi, Effect of shade and light curing mode on the degree of conversion of silorane-based and methacrylate-based resin composites, J. Dent. Biomater. 3 (4) (2016) 299–305.
[18] K. Nitta, R. Nomoto, Y. Tsubota, M. Tsuchikawa, T. Hayakawa, Characteristics of low polymerization shrinkage flowable resin composites in newly-developed cavity base materials for bulk filling technique, Dent. Mater. J. 36 (6) (2017) 740–746.
[19] C.T.W. Meereis, E.A. Münchow, W.L. de Oliveira da Rosa, A.F. da Silva, E. Piva, Polymerization shrinkage stress of resin-based dental materials: a systematic review and meta-analyses of composition strategies, J. Mech. Behav. Biomed. Mater. 82 (2018) 268–281.
[20] D.Y. Wu, S. Meure, D. Solomon, Self-healing polymeric materials: a review of recent developments, Prog. Polym. Sci. 33 (5) (2008) 479–522.
[21] A.B. Brochu, S.L. Craig, W.M. Reichert, Self-healing biomaterials, J. Biomed. Mater. Res. 96 (2) (2011) 492–506.
[22] C.E. Diesendruck, N.R. Sottos, J.S. Moore, S.R. White, Biomimetic self-healing, Angew. Chem. Int. Ed. 54 (36) (2015) 10428–10447.
[23] P. Zhang, G. Li, Advances in healing-on-demand polymers and polymer composites, Prog. Polym. Sci. 57 (2016) 32–63.
[24] M. Samadzadeh, S.H. Boura, M. Peikari, S.M. Kasiriha, A. Ashrafi, A review on self-healing coatings based on micro/nanocapsules, Prog. Org. Coating 68 (3) (2010) 159–164.
[25] D.Y. Zhu, M.Z. Rong, M.Q. Zhang, Self-healing polymeric materials based on microencapsulated healing agents: from design to preparation, Prog. Polym. Sci. 49–50 (2015) 175–220.
[26] M.R. Kessler, N.R. Sottos, S.R. White, Self-healing structural composite materials, ComposPart A. Appl. Sci. Manuf. 34 (8) (2003) 743–753.
[27] W.H. Binder, Self-healing polymers: from principles to applications, Macromol. Rapid Commun. 34 (2013) 290–309.
[28] D.G. Bekas, K. Tsirka, D. Baltzis, A.S. Paipetis, Self-healing materials: a review of advances in materials, evaluation, characterization and monitoring techniques, Compos.Part B. 87 (2016) 92–119.
[29] S.R. White, N.R. Sottos, P.H. Geubelle, J.S. Moore, M.R. Kessler, S.R. Sriram, E.N. Brown, S. Viswanathan, Autonomic healing of polymer composites, Nature 409 (6822) (2001) 794–797.
[30] E.N. Brown, M.R. Kessler, N.R. Sottos, S.R. White, In situ poly(urea-formaldehyde) microencapsulation of dicyclopentadiene, J. Microencapsul.

20 (6) (2003) 719–730.
[31] Y.C. Yuan, X.J. Ye, M.Z. Rong, M.Q. Zhang, G.C. Yang, J.Q. Zhao, Self-healing epoxy composite with heat-resistant healant, ACS Appl. Mater. Interfaces 3 (11) (2011) 4487–4495.
[32] D.Y. Zhu, M.Z. Rong, M.Q. Zhang, Preparation and characterization of multilayered microcapsule-like microreactor for self-healing polymers, Polymer 54 (16) (2013) 4227–4236.
[33] B.J. Blaiszik, N.R. Sottos, S.R. White, Nanocapsules for self-healing materials, Compos. Sci. Technol. 68 (3–4) (2008) 978–986.
[34] P. Biggs, L. Jones, G. Lewis, An autonomically-healed PMMA bone cement: influence of the crystal size of Grubbs' catalyst on fracture toughness and polymerisation rate, Int. J. Nano Biomaterials (IJNBM) 2 (6) (2009) 494–504.
[35] A.B. Brochu, S.L. Craig, W.M. Reichert, Self-healing biomaterials, J. Biomed. Mater. Res.A. 96 (2) (2011) 492–506.
[36] A.B.W. Brochu, W.J. Chyan, W.M. Reichert, Microencapsulation of 2-octylcyanoacrylate tissue adhesive for self-healing acrylic bone cement, J. Biomed. Mater. Res. B. 100 (7) (2012) 1764–1772.
[37] A.B.W. Brochu, G.A. Evans, W.M. Reichert, Mechanical and cytotoxicity testing of acrylic bone cement embedded with microencapsulated 2-octyl cyanoacrylate, J. Biomed. Mater. Res. B. 102 (1) (2013) 181–189.
[38] M.M. Dailey, A.W. Silvia, P.J. McIntire, G.O. Wilson, J.S. Moore, S.R. White, A self-healing biomaterial based on free-radical polymerization, J. Biomed. Mater. Res. A. 102 (9) (2014) 3024–3032.
[39] Total Hip Replacements, 2010. Available at: www.aaos.org: American Academy of Orthopaedic Surgeons.
[40] Hip Joint Replacement, 2010. Available at: www.nlm.nih.gov:United States National Library of Medicine.
[41] S. Kurtz, K. Ong, E. Lau, F. Mowat, M. Halpern, Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030, J. Bone. Joint. Surg. Am. 89A (4) (2007) 780–785.
[42] S.M. Kurtz, E. Lau, K. Ong, K. Zhao, M. Kelly, K.J. Bozic, Future young patient demand for primary and revision joint replacement:national projections from 2010 to 2030, Clin. Orthop. Relat. Res. 467 (10) (2009) 2606–2612.
[43] J.R. Pereira, S. Pamato, M. Vargas, N.F. Junior, State of the art of dental adhesive systems, Curr. Drug Deliv. 15 (5) (2018) 610–619.
[44] D.H. Pashley, F.R. Tay, L. Breschi, L. Tjäderhane, R.M. Carvalho, M. Carrilho, Tezvergil-Mutluay, A. State of the art etch-and-rinse adhesives, Dent. Mater. 27 (1) (2011) 1–16.
[45] B. Van Meerbeek, K. Yoshihara, Y. Yoshida, A. Mine, J. De Munck, K.L. Van Landuyt, State of the art of self-etch adhesives, Dent. Mater. 27 (1) (2011) 17–28.
[46] J.R. Pereira, S. Pamato, M. Vargas, N. Fahl, State of the art of dental adhesive systems, Curr. Drug Deliv. 15 (5) (2018) 610–619.
[47] K.D. Jandt, B.W. Sigusch, Future perspectives of resin-based dental materials, Dent. Mater. 25 (8) (2009) 1001–1006.
[48] S. Then, G.S. Neon, N.H. kasim, Performance of melamine modified urea-formaldehyde microcapsules in a dental host material, J. Appl. Polym. Sci. 122 (2011) 2557–2562.
[49] S. Tohmura, A. Inoue, S.H. Sahari, Influence of the melamine content in melamine-urea-formaldehyde resins on formaldehyde emission and cured resin structure, J. Wood Sci. 47 (6) (2001) 451–457.
[50] B.E. Wertzberger, J.T. Steere, R.M. Pfeifer, M.A. Nensel, M.A. Latta, S.M. Gross, Physical characterization of a self-healing dental restorative material, J. Appl. Polym. Sci. 118 (1) (2010) 428–434.
[51] D.H. Kafagy, K. Adams, S. Khajotia, M. Keller, Quasi-Static characterization of self-Healing dental composites, in: W. Ralph, R. Singh, G. Tandon, et al. (Eds.), Mechanics of Composite and Multi-Functional Materials, vol. 7, Springer, Cham, 2017, pp. 203–208.
[52] D.H. Kafagy, S.S. Khajotia, M.W. Keller, Fatigue characterization of in-situ self-healing dental composites, in: P. Thakre, R. Singh, G. Slipher (Eds.), Mechanics of Composite and Multi-Functional Materials, vol. 6, Springer, Cham, 2018, pp. 151–155.
[53] X. Ouyang, X. Huang, Q. Pan, C. Zuo, C. Huang, X. Yang, Y. Zhao, Synthesis and characterization of triethylene glycol dimethacrylate nanocapsules used in a self-healing bonding resin, J. Dent. 39 (12) (2011) 825–833.
[54] G. Huyang, A.E. Debertin, J. Sun, Design and development of self-healing dental composites, Mater. Des. 94 (4) (2016) 295–302.
[55] M. Yahyazadehfar, G. Huyang, X. Wang, Y. Fan, D. Arola, J. Sun, Durability of self-healing dental composites:a comparison of performance under monotonic and cyclic loading, Mater. Sci. Eng. C 93 (1) (2018) 1020–1026.
[56] J. Wu, M.D. Weir, Q. Zhang, C. Zhou, M.A. Melo, H.H. Xu, Novel self-healing dental resin with microcapsules of polymerizable triethylene glycol dimethacrylate and N,N- dihydroxyethyl-p-toluidine, Dent. Mater. 32 (2) (2016) 294–304.
[57] C. Bevan, W.M. Snellings, D.E. Dodd, G.F. Egan, Subchronic toxicity study of dicyclopentadiene vapor in rats, Toxicol. Ind. Health 8 (6) (1992) 353–367.
[58] M.M. Caruso, D.A. Delafuente, V. Ho, N.R. Sottos, J.S. Moore, S.R. White, Solvent-promoted self-healing epoxy materials, Macromolecules 40 (25) (2007) 8830–8832.
[59] B.J. Blaiszik, M.M. Caruso, D.A. McIlroy, J.S. Moore, S.R. White, N.R. Sottos, Microcapsules filled with reactive solutions for self-healing materials, Polymer 50 (4) (2009) 990–997.
[60] R.P. Wool, K.M. O'Connor, A theory of crack healing in polymers, J. Appl. Phys. 52 (10) (1981) 5953–5963.
[61] J. Kuebler, Fracture Toughness of Ceramics Using the SEVNB method:Round Robin. VAMAS Report No.37, TWA3, ESIS Report D2-99, EMPA, CH-8600 Duebendorf, Switzerland, 1999.
[62] H.H. Xu, J.B. Quinn, A.A. Giuseppetti, Wear and mechanical properties of nano-silica-fused whisker composites, J. Dent. Res. 83 (12) (2004) 930–935.
[63] E.N. Brown, S.R. White, N.R. Sottos, Microcapsule induced toughening in a self-healing polymer composite, J. Mater. Sci. 39 (5) (2004) 1703–1710.
[64] F.F. Demarco, M.B. Correa, M.S. Cenci, R.R. Moraes, N.J.M. Opdam, Longevity of posterior composite restorations: not only a matter of material, Dent. Mater. 28 (1) (2012) 87–101.
[65] V. Deligeorgi, I.A. Mjor, N.H. Wilson, An overview of reasons for the placement and replacement of restorations, Prim. Dent. Care 8 (1) (2001) 5–11.
[66] R.A. Bagramian, F. Garcia-Godoy, A.R. Volpe, The global increase in dental caries. A pending public health crisis, Am. J. Dent. 22 (1) (2009) 3–8.
[67] M. Svanberg, I.A. Mjör, D. Orstavik, Mutans streptococci in plaque from margins of amalgam,composite, and glass-ionomer restorations, J. Dent. Res. 69 (3) (1990) 861–864.
[68] N. Beyth, A.J. Domb, E. Weiss, An in vitro quantitative antibacterial analysis of amalgam and composite resins, J. Dent. 35 (3) (2007) 201–206.
[69] J.D. Featherstone, The continuum of dental caries-evidence for a dynamic disease process, J. Dent. Res. 83 (2004) C39–C42, spec iss.
[70] S. Imazato, Review: antibacterial properties of resin composites and dentin bonding systems, Dent. Mater. 19 (6) (2003) 449–457.
[71] S. Imazato, M. Torii, Y. Tsuchitani, J.F. McCabe, R.R. Russell, Incorporation of bacterial inhibitor into resin composite, J. Dent. Res. 73 (8) (1994) 1437–1443.
[72] N. Hirose, R. Kitagawa, H. Kitagawa, H. Maezono, A. Mine, M. Hayashi, M. Haapasalo, S. Imazato, Development of a cavity disinfectant containing antibacterial monomer MDPB, J. Dent. Res. 95 (13) (2016) 1487–1493.
[73] N. Beyth, I. Yudovin-Farber, R. Bahir, A.J. Domb, E.I. Weiss, Antibacterial activity of dental composites containing quaternary ammonium polyethylenimine nanoparticles against Streptococcus mutans, Biomaterials 27 (21) (2006) 3995–4002.
[74] F. Li, J. Chen, Z. Chai, L. Zhang, Y. Xiao, M. Fang, S. Ma, Effects of a dental adhesive incorporating antibacterial monomer on the growth, adherence and membrane integrity of Streptococcus mutans, J. Dent. 37 (4) (2009) 289–296.
[75] X. Xu, Y. Wang, S. Liao, Z.T. Wen, Y. Fan, Synthesis and characterization of antibacterial dental monomers and composites, J. Biomed. Mater. Res.B. 100 (4) (2012) 1151–1162.
[76] Y. Weng, L. Howard, X. Guo, V.J. Chong, R.L. Gregory, D. Xie, A novel antibacterial resin composite for improved dental restoratives, J. Mater. Sci. Mater. Med. 23 (6) (2012) 1553–1561.
[77] F. Li, M.D. Weir, J. Chen, H.H. Xu, Effect of charge density of bonding agent containing a new quaternary ammonium methacrylate on antibacterial and bonding properties, Dent. Mater. 30 (4) (2014) 433–441.
[78] H.H. Xu, J.L. Moreau, L. Sun, L.C. Chow, Nanocomposite containing amorphous calcium phosphate nanoparticles for caries inhibition, Dent. Mater. 27 (8) (2011) 762–769.
[79] J. Wu, M.D. Weir, M.A. Melo, H.H. Xu, Development of novel self-healing and antibacterial dental composite containing calcium phosphate nanoparticles, J. Dent. 43 (3) (2015) 317–326.
[80] C. Zhou, M.D. Weir, K. Zhang, D. Deng, L. Cheng, H.H. Xu, Synthesis of new antibacterial quaternary ammonium monomer for incorporation into CaP nanocomposite, Dent. Mater. 29 (8) (2013) 859–870.
[81] S. Imazato, A. Kuramoto, Y. Takahashi, S. Ebisu, M.C. Peters, In vitro antibacterial effects of the dentin primer of clearfil protect bond, Dent. Mater. 22 (6) (2006) 527–532.
[82] W. Zhang, X.J. Luo, L.N. Niu, S.Y. Liu, W.C. Zhu, J. Epasinghe, L. Chen, G.H. Li, C. Huang, J. Mao, D.H. Pashley, F.R. Tay, One-pot synthesis of antibacterial monomers with dual biocidal modes, J. Dent. 42 (9) (2014) 1078–1095.
[83] H. Murata, R.R. Koepsel, K. Matyjaszewski, A.J. Russell, Permanent, non-leaching antibacterial surface-2:How high density cationic surfaces kill bacterial cell, Biomaterials 28 (32) (2007) 4870–4879.
[84] J.L. Moreau, L. Sun, L.C. Chow, H.H. Xu, Mechanical and acid neutralizing properties and inhibition of bacterial growth of amorphous calcium phosphate dental nanocomposites, J. Biomed. Mater. Res. B. 98 (1) (2011) 80–88.
[85] M.D. Weir, L.C. Chow, H.H. Xu, Remineralization of demineralized enamel via calcium phosphate nanocomposite, J. Dent. Res. 91 (10) (2012) 979–984.
[86] M.A. Melo, M.D. Weir, L.K. Rodrigues, H.H. Xu, Novel calcium phosphate nanocomposite with caries-inhibition in a human in situ model, Dent. Mater. 29 (2) (2013) 231–340.
[87] M.D. Weir, J.P. Ruan, N. Zhang, L.C. Chow, K. Zhang, X.F. Chang, Y.X. Bai, H.H. Xu, Effect of calcium phosphate nanocomposite on in vitro remineralization of human dentin Lesions, Dent. Mater. 33 (9) (2017) 1033–1044.
[88] K.N. Liang, S.M. Xiao, M.D. Weir, C.Y. Bao, H.B. Liu, L. Cheng, X.D. Zhou, J.Y. Li, H.H. Xu, Poly (amido amine) dendrimer and dental adhesive with calcium phosphate nanoparticles remineralized dentin in lactic acid, J. Biomed. Mater. Res. B. 106B (2018) 2414–2424.
[89] K.N. Liang, S.M. Xiao, J.L. Wu, J.Y. Li, M.D. Weir, L. Cheng, M.A. Reynolds, X.D. Zhou, H.H. Xu, Long-term dentin remineralization by poly(amido amine) and rechargeable calcium phosphate nanocomposite after fluid challenges, Dent. Mater. 34 (4) (2018) 607–618.
[90] H.H. Xu, Long-term water aging of whisker-reinforced polymer-matrix composites, J. Dent. Res. 82 (1) (2003) 48–52.
[91] J.L. Ferracane, H.X. Berge, J.R. Condon, In vitro aging of dental composites in

water-effect of degree of conversion,filler volume,and filler/matrix coupling, J. Biomed. Mater. Res. B. 42 (3) (1998) 465–472.
[92] J.L. Drummond, Degradation, fatigue and failure of resin dental composite materials, J. Dent. Res. 87 (8) (2008) 710–719.
[93] J. Wu, M.D. Weir, M.A. Melo, H. Strassler, H.H. Xu, Effects of water-aging on self- healing dental composite containing microcapsules, J. Dent. 47 (4) (2016) 86–93.
[94] N. Ilie, R. Hickel, A.S. Valceanu, K.C. Huth, Fracture toughness of dental restorative materials, Clin. Oral Investig. 16 (2) (2012) 489–498.
[95] M.M. Caruso, B.J. Blaiszik, S.R. White, N.R. Sottos, J.S. Moore, Full recovery of fracture toughness using a nontoxic solvent-based self-healing system, Adv. Funct. Mater. 18 (13) (2008) 1898–1904.
[96] H. Jin, C.L. Mangun, D.S. Stradley, J.S. Moore, N.R. Sottos, S.R. White, Self-healing thermoset using encapsulated epoxy-amine healing chemistry, Polymer 53 (2) (2012) 581–587.
[97] H. Fong, Effects of water contents and postcuring conditions on Bis-GMA/TEGDMA dental restorative composite resins, J. Appl. Polym. Sci. 94 (2) (2004) 492–502.
[98] J. Park, Q. Ye, E.M. Topp, A. Misra, S.L. Kieweg, P. Spencer, Effect of photo-initiator system and water content on dynamic mechanical properties of a light-cured bisGMA/HEMA dental resin, J. Biomed. Mater. Res. A. 93 (4) (2010) 1245–1251.
[99] K.T. Nguyen, J.L. West, Photopolymerizable hydrogels for tissue engineering applications, Biomaterials 23 (22) (2002) 4307–4314.
[100] P. Spencer, Q. Ye, J.G. Park, E.M. Topp, A. Misra, O. Marangos, Y. Wang, B.S. Bohaty, V. Singh, F. Sene, Adhesive/dentin interface: the weak link in the composite restoration, Ann. Biomed. Eng. 38 (6) (2010) 1989–2003.
[101] N. Manuja, R. Nagpal, K. Pandit, Dental adhesion: mechanism, techniques and durability, J. Clin. Pediatr. Dent 36 (3) (2012) 223–234.
[102] A. Mazzoni, V. Angeloni, A. Comba, T. Maravic, M. Cadenaro, A. Tezvergil-Mutluay, D.H. Pashley, F.R. Tay, L. Breschi, Cross-linking effect on dentin bond strength and MMPs activity, Dent. Mater. 34 (2) (2018) 288–295.
[103] S. Imazato, Bio-active restorative materials with antibacterial effects: new dimension of innovation in restorative dentistry, Dent. Mater. J. 28 (1) (2009) 11–19.
[104] S. Imazato, Y. Kinomoto, H. Tarumi, S. Ebisu, F.R. Tay, Antibacterial activity and bonding characteristics ofan adhesive resin containing anti-bacterialmonomer MDPB, Dent. Mater. 19 (4) (2003) 313–319.
[105] N. Beyth, I. Yudovin-Farber, M. Perez-Davidi, A.J. Domb, E.I. Weiss, Poly-ethyleneimine nanoparticles incorporated into resin composite cause cell death and trigger biofilm stress in vivo, Proc. Natl. Acad. Sci. U.S.A. 107 (51) (2010) 22038–22043.
[106] L. Cheng, K. Zhang, M.D. Weir, M.A. Melo, X.D. Zhou, H.H. Xu, Nanotechnology strategies for antibacterial and remineralizing composites and adhesives to tackle dental caries, Nanomedicine 10 (4) (2015) 627–641.
[107] H. Zhou, F. Li, M.D. Weir, H.H. Xu, Dental plaque microcosm response to bonding agents containing quaternary ammonium methacrylates with different chain lengths and charge densities, J. Dent. 41 (11) (2013) 1122–1131.
[108] N. Zhang, K. Zhang, M.D. Weir, D.J. Xu, M.A. Reynolds, Y. Bai, H.H. Xu, Effects of water-aging for 6 months on the durability of a novel antimicrobial and protein-repellent dental bonding agent, Int. J. Oral Sci. 10 (2) (2018) 18–26.
[109] M.A. Melo, L. Cheng, K. Zhang, M.D. Weir, L.K. Rodrigues, H.H. Xu, Novel dental adhesives containing nanoparticles of silver and amorphous calcium phosphate, Dent. Mater. 29 (2) (2013) 199–210.
[110] M.A. Melo, L. Cheng, M.D. Weir, R.C. Hsia, L.K. Rodrigues, H.H. Xu, Novel dental adhesive containing antibacterial agents and calcium phosphate nanoparticles, J. Biomed. Mater. Res. B Appl. Biomater. 101 (4) (2013) 620–629.
[111] A.D. Loguercio, A. Reis, G. Bortoli, R. Patzlaft, S. Kenshima, L.E. Rodrigues Filho, M.L.R. Accorinte, J.W.V. van Dijken, Influence of adhesive systems on interfacial dentin gap formation in vitro, Operat. Dent. 31 (4) (2006) 431–441.
[112] Z.C. Li, S.N. White, Mechanical properties of dental luting cements, J. Prosthet. Dent 81 (5) (1999) 597–609.
[113] S. Yue, J. Wu, Q. Zhang, K. Zhang, M.D. Weir, S. Imazato, Y. Bai, H.H. Xu, Novel dental adhesive resin with crack self-healing, antimicrobial and remineralization properties, J. Dent. 75 (8) (2018) 48–57.
[114] S.S. Khajotia, V.B. Dhuru, R.A. Fournelle, M.A. McKinney, Fracture toughness and load relaxation of dentin bonding resin systems, Dent. Mater. 13 (3) (1997) 151–156.
[115] L.A. Knobloch, R.E. Kerby, R. Seghi, J.S. Berlin, J.S. Lee, Fracture toughness of resin-based luting cements, J. Prosthet. Dent 83 (2) (2000) 204–209.
[116] S.F. Rosenstiel, M.F. Land, B.J. Crispin, Dental luting agents: a review of the current literature, J. Prosthet. Dent 80 (3) (1998) 280–301.
[117] N. Attar, L.E. Tam, D. McComb, Mechanical and physical properties of contemporary dental luting agents, J. Prosthet. Dent 89 (2) (2003) 127–134.
[118] F.J. Burke, Trends in indirect dentistry: 3. luting materials, Dent. Update 32 (5) (2005) 251–254, 257-258, 260.
[119] N.E. Hersek, S. Canay, In vivo solubility of three types of luting cement, Quintessence Int. 27 (3) (1996) 211–216.
[120] N. Manuja, N.R. Agpal, I.K. Pandit, Dental adhesion: mechanism, techniques and durability, J. Clin. Pediatr. Dent 36 (3) (2012) 223–234.
[121] M. Sadeghi, A. Davari, C.D. Lynch, The effect of re-bonding using surface sealant or adhesive system on microleakage of class V resin composite restorations, Dent. Res. J.(Isfahan). 10 (5) (2013) 596–601.
[122] A.P. Manso, R.M. Carvalho, Dental cements for luting and bonding restorations:self- adhesive resin cements, Dent. Clin. N. Am. 61 (4) (2017) 821–834.
[123] J. Li, S. Forberg, R. Soremark, Influence of phytic acid on zinc phosphate cement, Acta Odontol. Scand. 52 (4) (1994) 209–213.
[124] N.H. Felemban, M.I. Ebrahim, Effects of adding silica particles on certain properties of resin-modified glass-ionomer cement, Eur. J. Dermatol. 10 (2) (2016) 225–229.
[125] S. Garoushi, P. Vallittu, L. Lassila, Hollow glass fibers in reinforcing glass ionomer cements, Dent. Mater. 33 (2) (2017) e86–e93.
[126] R.K. Bansal, U.S. Tewari, P. Singh, D.V. Murthy, Modified polyalkenoate (glass -ionomer) cement-a study, J. Oral Rehabil. 22 (7) (1995) 533–537.
[127] E.S. Duke, New technology directions in resin cements, Compend. Contin. Educ. Dent. 24 (8) (2003) 606–608, 610.
[128] J. Wu, Q. Zhang, M.D. Weir, T.M. Oates, C. Zhou, X. Chang, H.H. Xu, Novel self-healing dental luting cements with microcapsules for indirect restorations, J. Dent. 66 (2017) 76–82.
[129] A.P. Manso, N.R. Silva, E.A. Bonfante, T.A. Pegoraro, R.A. Dias, R.M. Carvalho, Cements and adhesives for all-ceramic restorations, Dent. Clin. North. Am. 55 (2) (2011) 311–332.
[130] J.A. Müller, N. Rohr, J. Fischer, Evaluation of ISO4049: water sorption and water solubility of resin cements, Eur. J. Oral Sci. 125 (2) (2017) 141–150.
[131] L.A. Knobloch, R.E. Kerby, K. McMillen, N. Clelland, Solubility and sorption of resin-based luting cements, Operat. Dent. 25 (5) (2000) 434–440.
[132] A. Petropoulou, A.D. Vrochari, E. Hellwig, S. Stampf, O. Polydorou, Water sorption and water solubility of self-etching and self-adhesive resin cements, J. Prosthet. Dent 114 (5) (2015) 674–679.
[133] U. Ortengren, U. Elgh, V. Spasenoska, P. Milleding, J. Haasum, S. Karlsson, Water sorption and flexural properties of a composite resin cement, Int. J. of Prosthodont. 13 (2) (2000) 141–147.
[134] J. Ellakuria, R. Triana, N. Mínguez, I. Soler, G. Ibaseta, J. Maza, F. Garcia-Godoy, Effect of one-year water storage on the surface microhardness of resin-modified versus conventional glass-ionomer cements, Dent. Mater. 19 (4) (2003) 286–290.
[135] L. Zhao, Y.T. Jian, X.D. Wang, K. Zhao, Bond strength of primer/cement systems to zirconia subjected to artificial aging, J. Prosthet. Dent 116 (5) (2016) 790–796.