Article Title: Self-Healing Biomaterials: The Next Generation is Nano

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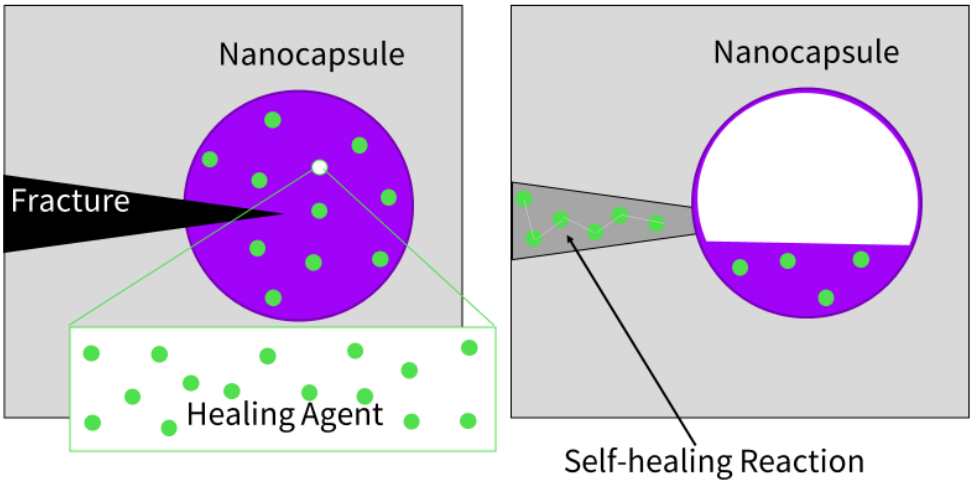
Abstract

The U.S. Agency for Healthcare Research and Quality estimates that there are over 1 million total hip and total knee replacements each year in the U.S. alone. Twenty five percent of those implants will experience aseptic loosening, and bone cement failure is an important part of this. Bone cements are based on poly(methyl methacrylate) (PMMA) systems that are strong but brittle polymers. PMMA-based materials are also essential to modern dental fillings, and likewise, the failure rates are high with lifetimes of 3-10 years. These brittle polymers are an obvious target for self-healing systems which could reduce revision surgeries and visits to dentist. Self-healing polymers have been described in the literature since 1996 and examples from Roman times are known, but their application in medicine has been challenging. This review looks at the development of self-healing biomaterials for these applications and the challenges that lie between development and the clinic. Many of the most promising formulations involve introducing nanoscale components which offer substantial potential benefits over their microscale counterparts especially in composite systems. There is substantial promise for translation, but issues with toxicity, robustness, and reproducibility of these materials in the complex environment of the body must be addressed.

Graphical/Visual Abstract and Caption



Graphical Abstract Caption: Self-healing biomaterials have the potential to be used clinically in a wide variety of medical applications; however, issues with toxicity, robustness, and reproducibility of these materials in the complex environments of the body must first be addressed.

1. INTRODUCTION

Self-healing materials for biomedical applications have received a great deal of attention over the last 15 years. Self-healing hydrogels have the potential to facilitate new kinds of printing approaches (Loebel, Rodell, Chen, & Burdick, 2017) and soft robotics (W. Wang, Narain, & Zeng, 2018). Most self-healing hydrogels consist of a double network structure, one that includes both reversible and irreversible bonds, to both recover any damaged structures and to hold the main network structure, respectively (S. Zhu et al., 2017). There are two categories used for the self-healing mechanisms in self-healing hydrogels: covalent bonding and non-covalent bonding.(F. Li et al., 2017) Key characteristics of self-healing hydrogels include biocompatibility, autonomous healing, repeatable and efficient healing, and morphological and mechanical healing.(F. Li et al., 2017) There have been a number of beautiful reviews for self-healing hydrogels over the last few years that have focused on the challenges associated with their development and application in a number of applications (Echeverria, Fernandes, Godinho, Borges, & Soares, 2018; Li, Yang, Pageni, & Tang, 2017; W. Wang et al., 2018; Y. Wang, Adokoh, & Narain, 2018).

While there have been extensive papers and reviews on self-healing hydrogels and soft materials systems, there has been more limited work looking at self-healing systems for hard materials such as bone cement and dental resins. These materials are often thought of as mature technologies with little room for innovation, but the impact of their failures is significant, and if we can find ways to safely innovate in these areas, there will be a major clinical impact. The U.S. Agency for Healthcare Research and Quality estimates that there are over 1 million total hip and total knee replacements each year in the U.S. alone. Twenty five percent of those implants will experience aseptic loosening, and bone cement failure is an important part of this. Bone cements are based on poly(methyl methacrylate) (PMMA) systems that are strong but brittle polymers. PMMA-based materials are also essential to modern dental fillings, and likewise, the failure rates are high with lifetimes of 3-10 years. Extending the lifetime of these materials through self-healing approaches would mean fewer revision surgeries and fewer dental restorations. Materials that can repair

themselves have the potential to extend the quality of people's lives substantially, but they have to be reliable, effective, and safe.

Self-healing materials exhibit the autonomic ability to repair themselves and recover functionality after degradation, damage, and/or failure, without intervention.(Aïssa, Therriault, Haddad, & Jamroz, 2012) Although unknown at the time, the first example of a synthetic self-healing effect in materials was utilized in ancient Roman constructions, which are still standing today.(Brinkman, 2011) The Romans used mortar as glue to bind together the bricks used to develop stone bridges and aqueducts. This mortar, which consisted of volcanic ash and calcium carbonate (lime), acted as a synthetic self-healing agent.(Jonkers, 2007) Ultimately, rain water dissolved the lime, which then seeped into other places, such as cracks in the construction. When the water vaporized, the lime was deposited in the cracks, hardened, and repaired the structures locally.(Van Tittelboom & Belie, 2009)

Largely inspired by biological systems, self-healing approaches to combat structural failures are currently being explored, and have become an increasingly popular area of study over the last two decades.(Y. Yang, Ding, & Urban, 2015) The development of self-healing materials allows for autonomous repair in situ on the microscopic level before macroscopic failures ensue.(Brochu, Craig, & Reichert, 2011) These materials can be of utmost value societally and economically, as they inspire sustainable manufacturing and construction. Self-curing properties can be integrated into many different materials including polymers and composites, asphalt and concrete, coatings, metals and ceramics, and micro-electronics.(Brinkman, 2011)

2. SELF-HEALING MATERIALS

First published in 1969, self-healing has drawn significant interest; however, since 2001, the rate of study and publications has significantly increased.(Malinskii, Prokopenko, Ivanova, & Kargin, 1970; Van Tittelboom & De Belie, 2013a) When "self-healing biomaterial" was used as the key words in a web of science search, only 1 article appeared to be published in 2001; however, 70 publications were present in 2018. Today, many types of design strategies exist to form self-healing materials. These include the release of healing agents, reversible cross-linking, electrohydrodynamics, shape-memory effects, conductivity, and co-deposition.(Ghosh, 2009) These various types of self-healing systems can be generally divided into three overarching categories: intrinsic, vascular, and capsule-based.(Blaiszik et al., 2010) Intrinsic self-healing involves healing through the inherent reversibility of bonds which act as the healing agent. In these systems, self-healing occurs at the molecular level, and bond forming reactions develop after a source of energy induces the mobility of the molecules.(Diesendruck, Sottos, Moore, & White, 2015) Vascular self-healing incorporates healing agents into the matrix through hollow micro-channels.(Diesendruck et al., 2015) When vascular systems are damaged, self-healing agents are released; however, these networks are able to be refilled by an external source or from an undamaged connecting vascular network.(Blaiszik et al., 2010) Capsule-based self-healing materials sequester the healing material in discrete capsules.(Blaiszik et al., 2010) These capsules are usually microcapsules or nanocapsules. Microcapsules and nanocapsules are vesicular, hollow spherical structures composed of a polymer matrix.(Alexander-Bryant, Vanden Berg-Foels, & Wen, 2013) When the capsules are physically damaged, for example, by the propagation of a crack in the resin, the initiator and the reactants encapsulated are released and allowed to react together. Ultimately, healing occurs when the self-healing agent is released from the capsules, fills the cracks, and polymerizes; this polymerization between the crack edges inhibits further crack

propagation.(Kessler, Sottos, & White, 2003) Diba et al. recently redefined the characterization of these self-healing systems and separated them into two categories: extrinsic and intrinsic. Materials with extrinsic self-healing capacity require external aid. This external aid includes capsules and/or vascular systems that contain self-healing agents to enable self-healing. Intrinsic materials can self-heal without any external aid.(Diba et al., 2018) The classic example of this are shear-thinning materials.

Self-healing systems have great aptitude and are needed in many biomedical applications that experience physiological stresses; however, self-healing materials have yet to be trialed clinically due to both technical optimization constraints as well as issues with toxicity and biocompatibility.(Brochu et al., 2011) Some applications in which self-healing biomaterials would provide a crucial impact are artificial heart valves, vascular grafts, bone cements, dental implants, and intraocular lenses. These materials often experience crazes and microcracks that form to relieve internal and external stresses in high pressure areas.(Brochu et al., 2011) The self-healing counterpart to these materials have the potential to be superior to the non-self-healing materials as the self-healing materials can repair small cracks in the materials autonomously thus eliminating the need for complete restorations; however, none have been tested clinically.

In particular, biomaterials in dentistry and orthopedics have become increasingly studied due to the elevated failure rate experienced in both dental resins and bone cements that often require complete restorations. Dental diseases are the most prevalent chronic diseases worldwide and are costly burdens to health care services.(P. Puska, 2003) Dental caries (tooth decay) is considered a major part of oral disease globally, affecting nearly 100% of the population in most countries.(Petersen, Bourgeois, Ogawa, Estupinan-Day, & Ndiaye, 2005) To treat dental caries, diseased tissue is removed, and teeth are restored with appropriate materials.(*Future Use of Materials for Dental Restoration*, 2010) However, durability is a major problem in posterior dental composites, as the typical life-span of posterior composites ranges from 3 to 10 years. Large fillings usually persist fewer than 5 years.(Manhart, Chen, Hamm, & Hickel, 2004) Failure in dental resins is extremely costly and can be dangerous. The treatment of dental diseases accounts for between 5% and 10% of total health care expenditures in industrialized countries.(P. Puska, 2003) Failure in dental resins only increases this cost. These failures must be restored or else the ensuing results could be life-threatening. When the composite filling breaks, food particles and decay-causing bacteria can fill the gap and lead to decay under the filling; this decay, when undiagnosed and untreated, can progress to infect the tooth's nerves and blood supply.(Association, 2005) This infection, when left untreated, can also result in a tooth abscess, which can become infected and trigger life-threatening complications, such as an infection in the bloodstream or sepsis.(Staff, 2017)

Similar to dental resins, the robustness of bone cement is of large concern. It is estimated that over 25% of all prosthetic implants will undergo aseptic loosening.(Wooley & Schwarz, 2004) Aseptic loosening is "a multifactorial phenomenon involving interfacial failure, bond failure, bone remodeling, and cement failure."(Spector, 1992) Bone cement failure can be caused by joint loosening, microcrack formation and accumulation through cyclic loading, and creep under compression.(Brochu et al., 2011) The wear debris that results during aseptic loosening provokes negative biological effects, including granuloma formation, inflammatory cell influx, bone resorption, and even the loss of the prothesis support.(Wooley & Schwarz, 2004) Aseptic loosening cannot be prevented or treated by existing nonsurgical methods; therefore, surgical

revision is needed to repair the prothesis.(Wooley & Schwarz, 2004) Revision surgeries are technically demanding, expensive, and result in a low satisfaction rate.(Apostu, Lucaciu, Berce, Lucaciu, & Cosma, 2018) For these reasons, the biomaterials that will be more thoroughly investigated in this review are dental composites and bone cements. Both types of biomaterials are classically comprised of a methacrylate resin. Methacrylate is a monocarboxylic acid anion that forms when a proton is removed from the carboxylic acid group of the methacrylic acid. Figure 1 depicts the two-dimensional structure of a methacrylate.

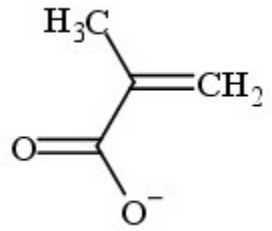


Figure 1. Methacrylate is a key component of both dental resins and bone cements.

3. DENTAL COMPOSITES

Arguably some of the first self-healing biomaterials to reach clinical trials, dental resins are consistently on the leading edge of novel materials in biomedical applications. Resins have been replacing traditional mercury-comprised amalgams for dental restorations, whose toxicity, both biologically and environmentally, has been debated for many years.(Chin et al., 2000) Dental resins are composite materials containing organic fillers and additives bound together with a polymer matrix used for dental reconstruction.(Habib, Wang, Wang, Zhu, & Zhu, 2016) Dental resins have been conventionally formed via methacrylate chemistry, as previously mentioned, such as BisGMA (bisphenol A glycidyl dimethacrylate), TEGDMA (triethylene glycol dimethacrylate), BisEMA (ethoxylated bisphenol-A dimethacrylate), and UDMA (urethane dimethacrylate). However, the longevity of dental resins is limited.(Spencer, Ye, Misra, Goncalves, & Laurence, 2014)

Although there are over one hundred published, peer reviewed studies pertaining to dental composites clinically, clear reasons for the failure of these composites have not been established; therefore, the capability to predict the clinical performance of dental composites has not been significantly advanced in nearly twenty years.(Ferracane, 2013) Mechanically speaking, the structural integrity of resins is compromised by one or a combination of the following types of wear: fatigue, cracking and chipping, dislocation from the base, and the formation of wear particles.(Brochu et al., 2011; Lee et al., 2009; Taylor & Agar, 2002) Apart from the mechanical problems of the dental resin, issues can also arise from polymerization shrinkage, polymerization-induced stress, a thermal expansion mismatch, abrasion and resistance, marginal leakage, and toxicity.(Cramer, Stansbury, & Bowman, 2011) In one study performed by Opdam et al., the main reasons for composite failures were restoration fracture, caries (particularly secondary caries), root canal therapy, defective margin, and lack of proximal contact.(Opdam, Loomans, Roeters, & Bronkhorst, 2004) Out of the 290-million cavities restored each year in the United States, 200 million are replaced due to failed restorations.(Murray, Windsor, Smyth, Hafez, & Cox, 2002) This is problematic not only because failed restorations are expensive, but also because their failure can lead to life-threatening conditions. If a crack forms in the composite, one must obtain an

entirely new composite; if the crack is left untreated, infection under the filling can develop.(Staff, 2017) To combat the frequent failures in dental composites and reduce the risk of infection, a variety of cutting edge biomaterial innovations are being trialed, one being self-healing biomaterials.(Fugolin & Pfeifer, 2017)

Current research thrusts related to the development of sustainable dental resins include stress-reducing materials, degradation resistant materials, and as previously stated, self-healing materials.(Ferracane, 2013) These improvements would limit the formation of gaps in resins resulting from stress generation at the bond interface.(Bacchi, Nelson, & Pfeifer, 2016) The intent behind developing stress-reducing materials is to modify the polymer network so that it simultaneously reduces stress and enhances mechanical properties and monomer conversion in the resin.(Bacchi et al., 2016) To design degradation resistant materials, alternative resin chemistries have been proposed altogether. One study performed by Bacchi et al. formulated composite materials modified with thio-urethane additives to assess the degree of conversion, reaction kinetics, bulk mechanical properties, and polymerization shrinkage and stress.(Bacchi et al., 2016) Modified chemistries have also been trialed. Methacrylamide monomers have demonstrated more stability in aqueous environments, unlike the traditionally used vinyl bonds and methacrylate monomers. Several bisacrylamides have been evaluated as potential crosslinkers for dental resins.(Moszner, Fischer, Angermann, & Rheinberger, 2006) Additionally, other chemistries, such as thiol vinyl sulfone polymerization, vinyl ether homopolymerization, and azide-alkyne click polymerization, have been evaluated as alternatives for the conventional methacrylate chemistry in dental resins.(Gonzalez-Bonet et al., 2015; Podgorski, Becka, Chatani, Claudino, & Bowman, 2015; Song et al., 2016) Self-healing biomaterials are some of the more promising developments as they are easier to implement, do not change the overall structural composition of resins, and are able to mitigate any damage at the onset of the impairment thus eliminating the risk of infection and restoration costs.

The Role of Nanotechnology in Dental Composites

There have been a number of reviews in recent years looking at implementation of nanotechnology in dental resins. (Ahmadian, Shahi, Yazdani, Maleki Dizaj, & Sharifi, 2018; Kavoosi, Modaresi, Sanaei, & Rezaei, 2018; Padovani et al., 2015; Tomsia, Lee, Wegst, & Saiz, 2013) Much of this work has focused on the use of nanomaterials as drug delivery systems to reduce infections and nanomaterials as ceramic fillers. Both of these are extremely important areas of research and are complements to work looking at nanomaterials for self-healing systems. On the self-healing front, nanocapsules have been developed to improve bonding with native tissue (Xiaobai Ouyang et al., 2011). This approach is a variant of the capsule-based systems described in depth below, but this system focuses on increasing the bond strength between the implant and surrounding tissue rather than focusing on self-healing within the implant materials itself. Both are critical issues for long-term success of fillings.

4. BONE CEMENTS

Similar to dental composites, bone cements, specifically polymethyl methacrylate (PMMA), are attractive biomaterials in which to implement self-healing properties. First used about 60 years ago, PMMA is a matrix used to bind the stem of an implant to the surrounding boney tissue.(Hoey & Taylor, 2009; Stryker, 2006) Bone cement is not a glue but instead more of a space-filler that holds the implant solidly in place.(Cluett, 2018) It relies on close mechanical interlock between

the bone surface and the prothesis.(Vaishya, Chauhan, & Vaish, 2013) In terms of orthopedics, the main roles of bone cements are to increase the load carrying capacity in the prothesis-bone cement-bone system (also known as the construct).(Lewis, 1997) Ultimately, the bone cement transfers stress from the prothesis to the bone cement and to the bone.(Deb, 1999) More specifically, PMMA bone cement is a two component thermoset that does not require post-polymerization modifications.(Brochu et al., 2011) Methyl methacrylate is a methyl ester of methacrylic acid; it is a reactive resin whose polymerized form is used as a cement in areas such as dentistry, orthopedic surgery, and ophthalmology.("National Center for Biotechnology Information,") Figure 1 depicts the two-dimensional structure of a methacrylate.

Bone cement is in high demand, as the number of hip and knee arthroplasties in 2017 were over 1.6 million, of which 966,000 were knee replacements.("Total Knee Replacement Statistics 2017: Younger Patients Driving Growth," 2018) Kim et al. analyzed data in the Nationwide Inpatient Survey from 1997 to 2004 and described the recent trend of hip and knee replacements in the United States. This finding can be seen in Figure 2.(Kim, 2008) Although the predictions are a bit higher than the statistics reported in 2017 for primary total knee replacements, the trends in this graph do portray the rapid increase in the amount of hip and knee arthroplasties in the past 20 years.

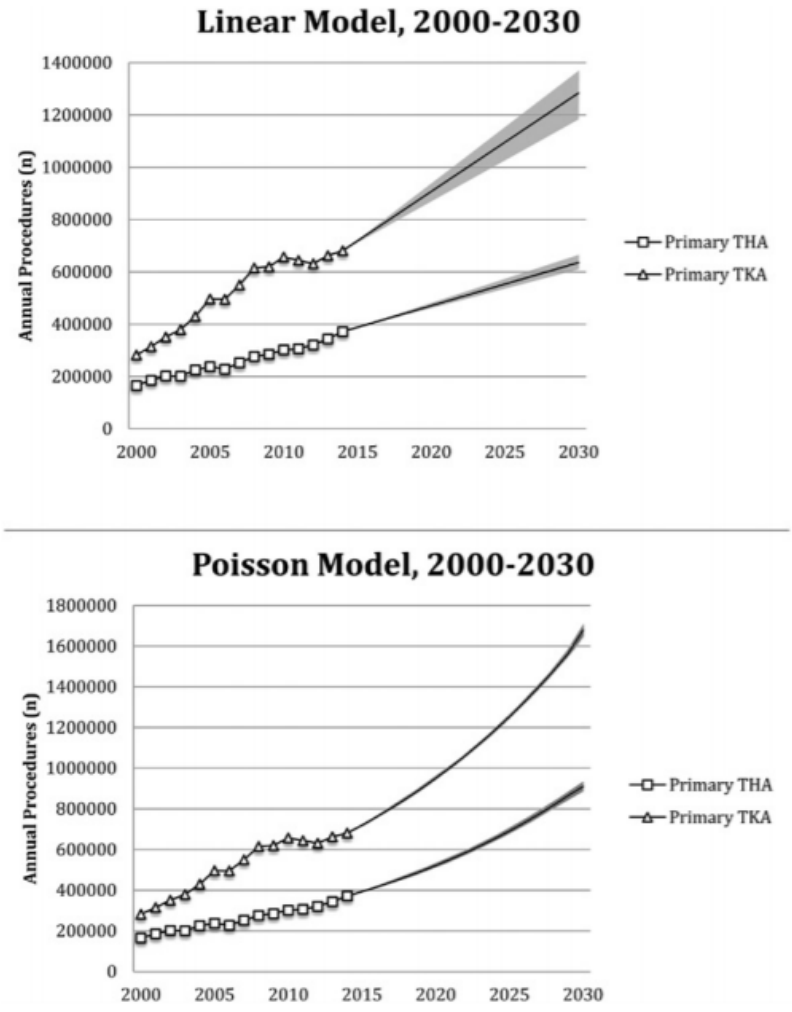


Figure 2. Linear and Poisson regression model projections of primary total joint arthroplasty (TJA) procedures volume in the U.S. from 2000 to 2030.Reprinted with permission from (Sloan, Premkumar, & Sheth, 2018) Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are broken out in the graphs.

Though bone cement continues to be largely coveted, bone cement has a plethora of drawbacks including but not limited to chemical and thermal necrosis of the bone, shrinkage of the cement during polymerization, a large stiffness mismatch between the cement and the adjoining bone, weak zones which consist of the interfaces between the bone cement and the prothesis and the bone cement and the bone, and cement particle interaction with the surrounding tissues.(Harrigan & Harris, 1991; Kindt-Larsen, Smith, & Jensen, 1995; Lewis, 1997; Spector, 1992; Wilson et al., 2010) Mechanical failure in bone cement is postulated to be one of the main causes of mechanical failure in protheses, especially hip arthroplasties.(Deb, Abdulghani, & Behiri, 2002) Hill et al. stated that a successful total hip replacement has a lifetime of 10 to 20 years with over 75% of failures caused by aseptic loosening, which is directly related to cement mantle failure.(Hill, Orr, & Dunne, 2008) It is important to note that PMMA, as an acrylic cement, is reasonably strong in compression but since it is a brittle material, it is prone to fracture resulting from tensile stresses.(Dunne, Orr, Mushipe, & Eveleigh, 2003) Mechanical failure in the bone cement can result in an increase in cement particles which interact with the surrounding tissues and can contribute to an inflammatory response, increased bone destruction, and accelerated prothesis loosening (which frequently requires correction via revision surgery which is costly and places patients at higher risks of infections).(Topoleski, Ducheyne, & Cukler, 1990)

Improvements to bone cement have been made; these improvements can be separated into three distinct categories: changing the cement mixing methodologies, reinforcing the existing cements, and developing new formulations.(Deb, 1999) Modern mixing techniques have been utilized to reduce porosity, a suspected cause of fatigue failure in the bone cement. These techniques include mixing the cement in a vacuum and centrifuging the mixture during curing.(James, Jasty, Davies, Piehler, & Harris, 1992) A review by Arora et al. concluded that there are many bone cement additives including but not limited to steel fibers, glass fibers, carbon fibers, and titanium fibers; however, none of these additives perfectly enhance strength without inducing adverse effects. The authors suggest that mechanical strength and interface integrity should be improved through the use of rubber-toughened cements, amphiphilic bonders, and increased trabecular bone concentrations.

The Role of Nanotechnology in Bone Cements

Like their counterparts in the dental resin area, nanotechnology is bone cements has focused a great deal of attention on combating infections and nanoscale fillers that augment the mechanical properties of the cements.(Al Thaher, Perni, & Prokopovich, 2017; Hesaraki, 2016; Sanz-Ruiz et al., 2018; Shadjou & Hasanzadeh, 2016; T. Wu et al., 2018)Arora, 2013 #146]. In terms of new formulations for bone cement, there are other types of commercially available bone cement such as calcium phosphate cements (CPCs) and glass polyalkenoate cements (GPCs); however, their formulations have low mechanical strength.(Vaishya et al., 2013) Introducing self-healing biomaterials to bone cements holds potential to alleviate microcracks and crazes that form in the cement before calamitous failure occurs.

5. CAPSULE BASED SELF-HEALING SYSTEMS

Because failures are so critical for both dental resins and bone cementers, self-healing approaches offer great potential to improve the use of these materials and reduce revision procedures. It is hypothesized that if the microcracks are healed when the crack first forms, then catastrophic failure in the resin can be avoided, ultimately reducing the need for revisions.(Awaja, Zhang, Tripathi, Nikiforov, & Pugno, 2016) Self-healing resins have proven to be able to self-repair when degraded or damaged to avoid complete failure in the composite and are thus highly sustainable. One self-healing material that has been frequently trialed to improve the longevity of dental resins and bone cements is the capsule-based self-healing system. These systems are easy to implement in both dental resins and bone cement because these systems often contain other filler particles to enhance the mechanical properties of the materials.(Fugolin & Pfeifer, 2017; Kenny & Buggy, 2003) Initially, the self-healing capsules simply act as an additional filler. The capsules in these self-healing systems are particles that contain core materials encapsulated by coatings or shells.(L. Yuan, Liang, Xie, & He, 2007) Ultimately, the approaching crack bursts the embedded capsules, which then release healing agents into the crack via capillary action.(White et al., 2001) This results in polymer crosslinking and repair in the damaged resin.(Fugolin & Pfeifer, 2017) The same type of capsule-based self-healing system can be used in both dental resins and bone cements theoretically because both of these resins experience similar types of failure. This type of healing is classified as extrinsic self-healing because it relies on the release of healing liquids from embedded capsules.(Diba et al., 2018)

Tremendous strides have been made in the generation of self-healing materials, particularly for capsule-based self-healing systems; however, much is still to be learned to better optimize this technology for all self-healing systems. It is important to note that all the materials involved in the system must be carefully engineered to ensure proper bursting of the capsules when needed. It is important for the capsules to not prematurely rupture before the propagation of a crack but to rupture in a timely matter in the presence of a crack. To warrant this, the encapsulation procedure must be chemically compatible with the healing agent. Furthermore, the capsule walls need to be resistant enough to withstand the physical stresses they must endure when implanted into a material but also adhere to the composite material to burst during the onset of composite fracture.(Aïssa et al., 2012) Capsule characteristics can vary depending on the intended system. These capsule characteristics include resultant morphology, average size, size distribution, shell thickness, mechanical properties, content and reactivity of encapsulated agent, and shelf-life.(Aïssa et al., 2012; Brown, Kessler, Sottos, & White, 2003; Jin et al., 2012) These characteristics are reliant on solvent types and amount, surfactant type and amount, temperature, pH, agitation rate, reaction time, and mode of addition of the oil phase to the aqueous phase.(Jin et al., 2012)

Nanoscale Capsule Technologies for Improved Performance

Controlling the size of the self-healing capsules has proven to be extremely important. The size of the capsules strongly depends upon the application of the self-healing system. Larger capsules contain a bigger volume of healing chemicals and allow bigger cracks to be healed. Conversely, large capsules negatively influence the propagation of cracks as well as the roughness of the material's surface; therefore, it has proven more beneficial to use smaller, nano-sized capsules. Although the nano-sized capsules are limited in their healing ability due to the reduction in the volume of the healing agents that can be delivered from one capsule, the smaller capsules are

thought to more efficiently heal nano-sized cracks in the material in which they are implanted before the cracks can propagate into more sizeable cracks.(Diesendruck et al., 2015)

The choice of capsule shell material is also an important aspect of the self-healing system. Perhaps the most familiar material is urea-formaldehyde (UF). This material displays good thermal stability; however, it has its drawbacks. Aggregated nanoparticles debris have reportedly formed when synthesizing UF microcapsules; these nanocapsule aggregates could potentially act as crack initiation sites. Furthermore, the rough agglomerated nanocapsules on the surfaces of the microcapsules could decrease the adhesion of the capsules to the composite in which it is added. Lastly, the rubbery and thin capsule walls threaten the containment of the self-healing material before the onset of a crack in the composite.(Aïssa et al., 2012; Brown et al., 2003)

Other capsule shell materials that have been successfully synthesized include melamine-formaldehyde (MF), melamine-urea-formaldehyde (MUF), and polyurethane (PU).(Aïssa et al., 2012; Liu, Sheng, Lee, & Kessler, 2009; J. Yang, Keller, Moore, White, & Sottos, 2008; L. Yuan et al., 2007; Y. C. Yuan et al., 2008) MF is thermally stable up to 69°C and has reportedly had a shell thickness up to 30.0 μm. Due to the high thermal stability of the crosslinked MF and the formation of a smooth surface, MF capsules with dicyclopentadiene has proven to have better thermal stability when compared to UF capsules encapsulating dicyclopentadiene.(L. Yuan et al., 2007) Liu et al. observed that MUF microcapsules showed narrow size distribution with shell thickness ranging from 700 to 900 nm. The capsules appeared to have neat outer surfaces with minor roughness and were thermally stable up to 300°C. Overall, Lui et al. reported that capsules composed of MUF had superior properties compared to those made of UF used for self-healing systems to date. Additionally, the synthesis of MUF microcapsules was noted to be significantly easier than that of UF.(Liu et al., 2009) PU is another type of polymer used. The shell thickness has been found to be roughly uniform and in the micrometer range (1-15 μm); this acts as an appropriate barrier to premature leakage and to prevent premature rupture.(Huang & Yang, 2011) It has been used in the health field for nearly half a century and is one of the most popular groups of biomaterials applied to medical devices.(Santerre, Woodhouse, Laroche, & Labow, 2005) Specifically, PU are block copolymers, made of two or more polymeric blocks attached by covalent bonds. Due to their block-copolymer character, polyurethanes have a wide range of versatility in terms of their physical properties and ability to biodegrade. Proven to be biocompatible, PU is formed by the chemical reaction between isocyanates, that have more than one reactive isocyanate group (-NCO), and alcohols, with two or more reactive hydroxyl (-OH) groups per molecule; this reaction forms repeating urethane groups.(Santerre et al., 2005) The polyurethanes are also thermally stable in the body, as the thermal decomposition temperature for urethane linkages ranges from 150 to 250°C.(Simon, Barla, Kelemen-Haller, Farkas, & Kraxner, 1988)

There are two overarching categories used to organize self-healing capsule-based systems: dual and mono capsule self-healing systems.(Van Tittelboom & De Belie, 2013b) A comparison of these capsule systems is shown in Figure 3. Dual capsule self-healing systems contain two sets of capsules, one set containing the monomer and the other set comprising the hardener/polymerizer/catalyst.(Jin et al., 2012; Van Tittelboom & De Belie, 2013b) Mono capsule self-healing systems include only one set of capsules. These capsules can incorporate a range of healing agents, such as reactive chemicals, suspension solvents, low melting point metals, and monomers (with catalysts suspended freely in the matrix). These mono capsule systems also

include all-in-one capsules where both the monomer and required catalyst are either held in the core of the capsule, separated by layers, or are encapsulated in separated smaller spheres that are stored within a larger sphere. These capsules are also susceptible to rupture during crack formation. When the capsule cracks, the healing agent is released and the self-healing is achieved, as shown in Figure 4.(Van Tittelboom & De Belie, 2013b; White et al., 2001; D. Y. Zhu, Rong, & Zhang, 2015)

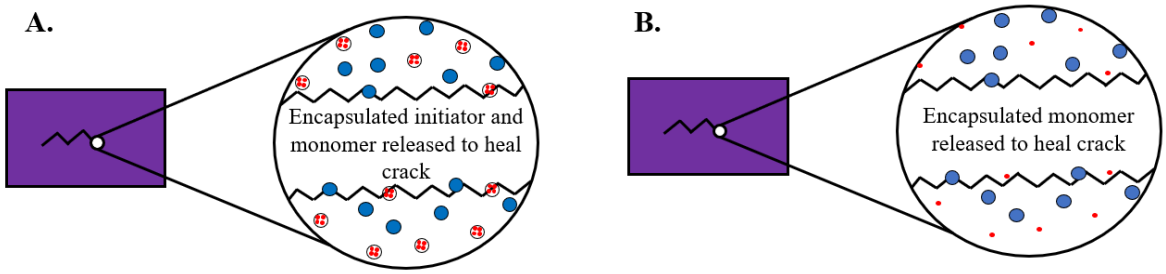


Figure 3. (A) The dual capsule based self-healing system contains two sets of capsules, one with the monomer and one with the initiator. (B) The mono capsule based self-healing system only contains one set of capsules.

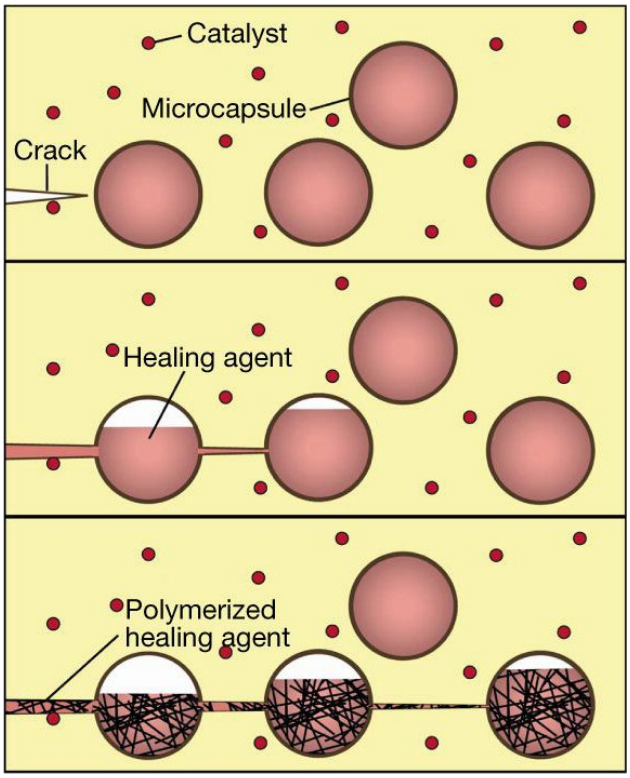


Figure 4. This image depicts microcapsules with healing agents added to a composite matrix containing catalyst throughout the composite as in a mono capsule self-healing system. From top to bottom of this image, one can see a crack forming in the matrix. In the second box, the crack ruptures the capsule and releases the self-healing agent. Then, in the bottom box, the healing agent comes into contact with the catalyst and polymerization occurs. Reprinted with permission from (White et al., 2001)

Biocompatibility is essential for self-healing systems used in biomedical applications; if the system is effective in healing a crack but toxic, it is futile in these applications. Self-healing materials formulations proposed for a biomedical application must pass both ASTM and ISO standards for mechanical and biocompatibility characterization of the materials.(Brochu, Matthys, Craig, & Reichert, 2015) Standard protocols are yet to be established for the quantification of the self-healing capacity of biomaterials.(Diba et al., 2018) Currently, for self-healing systems in hard biomaterials, such as dental resins and bone cements, static mechanical properties (flexural strength, flexural modulus, etc.) are often measured.(Diba et al., 2018) Nevertheless, there is a push toward measuring dynamic testing conditions as these conditions mimic the cyclic loading settings to which the systems are exposed in the body.(Ruben, Roeters, Montagner, & Huysmans, 2014)

The first recognized self-healing capsule-based system in polymer composites, a mono capsule-based system, consisted of dicyclopentadiene encapsulated in a poly (urea-formaldehyde) shell that formed a microcapsule (50 to 200 um). Grubb's catalyst was used to initiate the polymerization of the dicyclopentadiene. This first-generation self-healing system relied on ring opening metathesis polymerization and proved to self-heal efficiently in an epoxy matrix, yielding up to 75% recovery in toughness in the matrix. Until 2001, the only successful crack healing methods reported required some form of manual intervention.(White et al., 2001) For dental use, Wertzberger et al. characterized the self-healing system consisting of encapsulated dicyclopentadiene and Grubb's catalyst and achieved a recovery of 57% of the virgin fracture toughness of the composite.(Wertzberger et al., 2010) Biggs et al. further studied the dicyclopentadiene/Grubb's catalyst system and demonstrated significantly lower crack propagation rates in Surgical Simplex P, a commercially available PMMA bone cement, specimens with the self-healing system compared to the specimens without the self-healing system.(Biggs, Jones, Wellborn, & Lewis, 2009) However, high cost and toxicity concerns curbed the use of both dicyclopentadiene and the Grubb's catalyst in dental composites.(Caruso et al., 2007; J. Wu et al., 2016)

Another, more recent, study developed nanocapsules with TEGDMA liquid encapsulated in polyurethane. In this study, no self-healing effect was reported since no catalyst for polymerization was present.(X. Ouyang et al., 2011) When microcapsules with polymerizable TEGDMA with N,N-dihydroxyethyl-p-toluidine (DHEPT) healing liquid in poly (urea-formaldehyde) shells were prepared by Wu et al. in a mono capsule self-healing system with benzoyl peroxide (BPO), the catalyst, freely added to the resin, self-healing efficiency showed that about 65% of the virgin fracture toughness could be achieved when using 15% microcapsules. The microcapsules also proved to have low cellular cytotoxicity.(J. Wu et al., 2016) Figure 5 shows an optical image of the microcapsules synthesized by Wu et al.

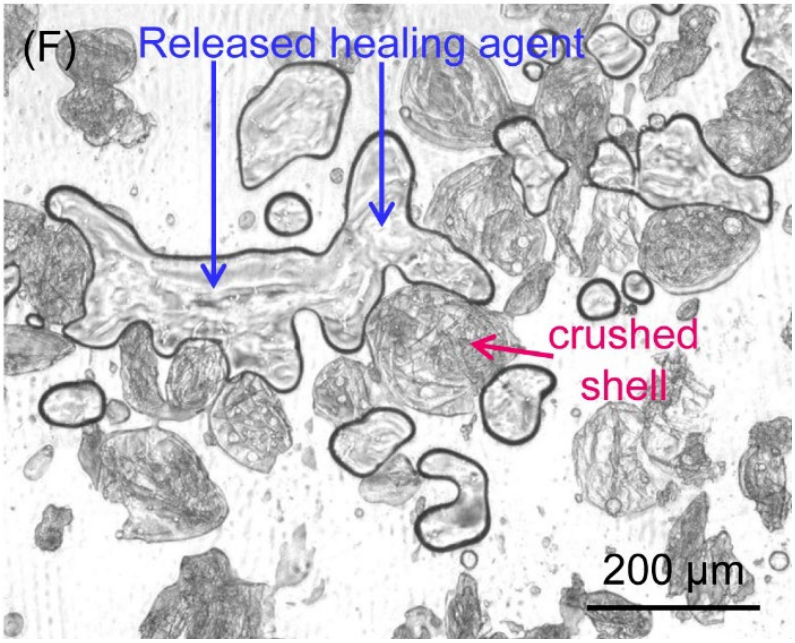


Figure 5. This figure displays an optical image of crushed microcapsules and the healing liquid films being released from the capsules. Reprinted with permission from (J. Wu et al., 2016)

Wilson et al. developed an example of a dual capsule self-healing system to be used in bone cement. UF microcapsules containing BPO were embedded in epoxy vinyl ester resin samples. When a mixture of acrylic monomers and tertiary amine activators were injected into a cracked plane of the sample after initial fracture, an estimated 80% healing efficiency was recorded in preliminary tests. This study focused on the free-radical-initiated polymerization of acrylates because after investigation, this chemistry stands out as "the most attractive chemistry for designing a self-healing system for bone cements." Unfortunately, a dual capsule self-healing system was not fully developed in this study since the main objective was to determine the peroxide initiator best suited to the diverse demands of various self-healing systems.(Wilson et al., 2010) However, in 2013, using the findings from Wilson et al., Dailey et al. created a dual UF microcapsule self-healing system, shown in Figure 6. The initiator capsules contained BPO, and the monomer/activator capsules contained 4'-methylenebis(N,N-dimethylaniline) (MBDMA) (the tertiary amine), trimethylol-propane ethoxylate triacrylate (TMPET) (an acrylate monomer), and bisphenol A ethoxy-late diacrylate (Bis-EMA) (an acrylate monomer). When tested, this system restored approximately 75% of the original fracture toughness at room temperature in an EVE matrix. Although initially intended for use in bone cement, the possible applications for this system have not been fully explored.(Dailey et al., 2014)

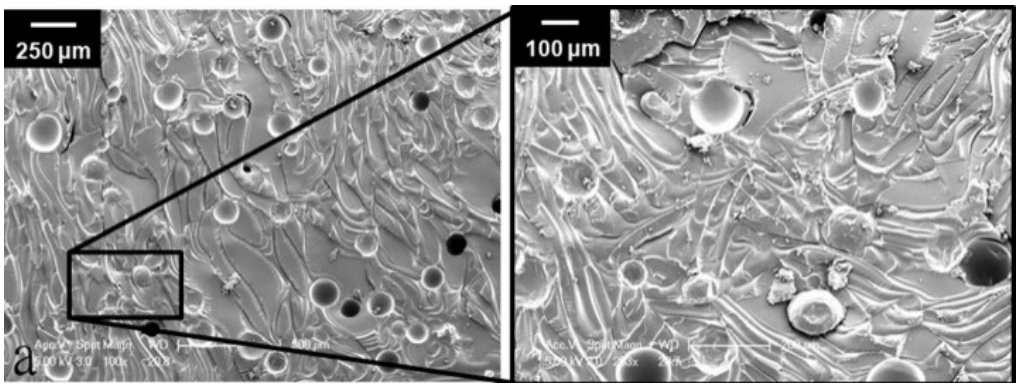


Figure 6. This SEM image portrays the healed fracture plane for the dual UF microcapsule self-healing system (10 wt % capsules loadings). Reprinted with permission from (Dailey et al., 2014)

Thus far, more mono capsule self-healing systems have been developed. In 2015, Gladman et al. developed a thermoplastic solvent-healing method for bone cement. In this single, biofriendly capsule approach, microencapsulated solvent was embedded in Simplex P bone cement. In this approach, the self-healing polymerization does not rely on chemical reactions or external stimuli, and the capsules can be added as an independent component of the bone cement formulation.(Gladman, Celestine, Sottos, & White, 2015) Brochu et al. also fabricated a capsule-based self-healing system using only materials that are currently in clinical use. This system encapsulated the water reactive healing agent, 2-octul-cyanoacrylate (OCA) tissue adhesive, in PU microcapsules. The capsules were then dispersed in a matrix of Palacos R PMMA bone cement.(Brochu et al., 2015) Like Gladman's system, this is a catalyst free self-healing bone cement system. The most recent mono capsule self-healing system intended for use in either dental composites or bone cements was the model published by Huyang et al. in 2016. The self-healing dental composite contained a healing powder, strontium fluoroaluminosilicate particles, and a healing liquid, aqueous solutions of polyacrylic acids. The powder was freely present throughout the composite; however, the healing liquid was encapsulated in silica microcapsules. When the microcapsule cracks, the healing liquid is released, interacts with the healing powder, and reacts to form glass ionomer cements (GIC) within the crack. Figure 7 depicts the self-healing steps in this model.(Huyang, Debertin, & Sun, 2016)

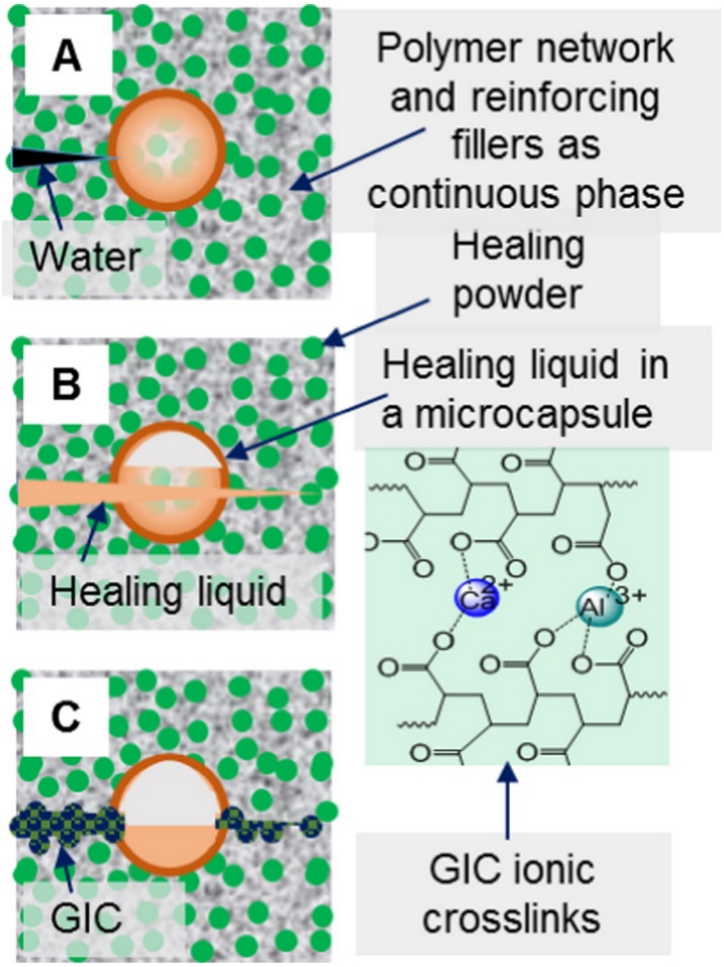


Figure 7. This image portrays the self-healing dental composite developed by Huyang et al. (A) A crack forms, and water enters the composite. (B) A microcapsule is broken due to the propagation of the crack, and the healing liquid is released. (C) The healing liquid and healing powder react to form GIC. Reprinted with permission from (Huyang et al., 2016)

What Are the Challenges that Remain for Deploying Self-Healing Systems in Dental Resins and Bone Cements?

Self-healing systems could address some of the most substantial challenges in dental resins and bone cements, but there are issues that need to be addressed from both a materials perspective and biological perspective before moving towards clinical trials with self-healing systems. The systems must be based on non-toxic materials and be biocompatible. The addition of capsules to dental resins and bone cements can alter the mechanical properties of the bulk material.(Sanz-Ruiz et al., 2018) One of the greatest motivations for having nanocapsules in these systems over their microcapsule counterparts is to avoid disrupting the resin matrix.(Neubauer, Poehlmann, & Fery, 2014; Shi et al., 2014) Ultimately, though, to fully characterize these materials, standard protocols need to be developed and validated that can correlate critical mechanical properties with biomedical performance as well as determine the degree and efficacy of the self-healing components.(Diba et al., 2018) Since these systems are designed for in vivo applications, these

properties need to be considered within the complex environments they will be used. The oral environment, for example, can vary from person to person. These disparities result from not only bacteria cultures present but even the alignment of the teeth in the mouth.("The Anthropology of Modern Human Teeth," 2018; Dewhirst et al., 2010) The variability in the environment means that testing needs to be done over a broad range of conditions to be able to assess the potential of novel materials for dental resins and bone cements. It takes a thoughtful, careful approach and strong experimental design, but doing so has the potential to greatly benefit patients.

CONCLUSION

Self-healing systems have the potential to address the high failure rates and poor patient outcomes for dental resins and bone cements. There have been a number of systems pursued, but to date, the majority of these systems either use components with potential issues of biocompatibility or suffer from reduced mechanical properties following the incorporation of capsules to deliver the self-healing components. Nanomaterials have the potential to maintain the required mechanical properties as well as provide self-healing behaviors, but these materials need to be thoroughly characterized and compared against current materials in a broad range of environments to assess their safety and function before translation to the clinic.

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