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Strategies to design extrinsic stimuli-responsive dental polymers capable of autorepairing

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Abstract

Objectives.—For many years, the requirements for dental polymers were limited to inertially filling the cavity and restoring form, function, and esthetics. Inorganic filler systems were widely enhanced to maximize the mechanical properties and optimize finishing and polishing procedures. The development of alternative photoinitiator systems also improved the carbon-carbon double bond conversion, increasing biocompatibility, wear, and stain resistance. However, despite laudable progress, the clinical life span of dental restorations is still limited, and their replacement is the most common procedure in dental offices worldwide. In the last few years, the development of materials with the potential to adapt to physiological stimuli has emerged as a key step to elevating dental polymers to a higher excellence level. In this context, using polymeric networks with self-healing properties that allow for the control of the propagation of microcracks is an appealing strategy to boost the lifetime of dental restorations. This review aims to report the current state-of-the-art of extrinsic self-healing dental polymers and provide insights to open new avenues for further developments. General classification of the self-healing polymeric systems focusing on the current extrinsic strategies used to inhibit microcracks propagation in dental polymers and recover their structural integrity and toughness are presented.

Search Strategy.—An electronic search was perfomed using PubMed, Google Scholar, and Scopus databases. Only studies published in English on extrinsic self-healing polymeric systems were included.

Overall Conclusions.—Self-healing materials are still in their infancy in dentistry, and the future possibilities are almost limitless. Although the mouth is a unique environment and the restorative materials have to survive chemical, physical, and mechanical challenges, which limits the use of some strategies that might compromise their physicochemical performance, there are countless untapped opportunities to overcome the challenges of the current systems and advance the field.

Keywords

Dental polymers; self-healing; bioresponsive; dental resin composites; polymers

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Introduction

Implementation of thermoset polymers as restorative materials was a crucial development in dentistry and allowed clinicians to seek a higher level of excellence in terms of mechanical and esthetic properties.[1] In fact, most procedures performed in clinical dentistry are based on the interaction of the dental tissues with thermoset polymers such as adhesive systems, direct and indirect resin composites, resin cement, and other adjunctive materials used in impressions. These polymers comprise a 3-dimensional (3D) network with varying levels of crosslinks between the macromolecular chains.[2] They have been widely used as raw materials in various automotive, pharmaceutical, biomedical, and industrial and infrastructure manufacturing applications.[3] These versatile polymers have excellent thermal stability, mechanical properties, wear resistance, dielectric strength, corrosion resistance, and optical properties, and, at least for commodity examples, they are relatively low cost.[2] However, the permanent nature of the crosslinked polymeric structure also makes traditional thermoset polymers intractable and unable to respond adaptively to external stimuli.[4]

The main issue with currently available materials for the dental application is that 50% of all restorations fail in less than 10 years after being placed.[5] The major contributors to the shortened clinical lifetime are caries underneath or surrounding the restoration and catastrophic fracture.[6] The presence of microdisruptions in the polymeric structure over time leads to the formation of macrogaps or microcracks, which makes the restoration surface susceptible to biofilm recolonization and subsequent demineralization of the adjacent tissues, and fractures that catastrophically compromise the bulk of the restoration.[7] In summary, internal defects jeopardize the polymer performance and serve as catalysts for further damage to the tooth structure.[7] Because the damage of polymer chains is the starting point for the structural break-up,[7] researchers have been developing a bioinspired generation of stimuli-responsive, self-healing polymers. The goal is to bridge the gaps between thermoplastic and thermoset polymers by the design of polymeric networks capable of repeatedly repairing micro-scaled damage and, ultimately, counter the polymer degradation and expand its lifetime and reliability.[4,8]

Our review presents an overview of the strategies used to impart thermoset polymers with the built-in capability to repair damages in their network structure automatically. Rather than being limited to the methods already used in dentistry, this broad scope review was designed to provide (1) an understanding of the existing research and debates involved in the development of extrinsic dental self-healing systems and (2) insights into the development of a new generation for potential use as dental polymers inspired by strategies that are already well-established in others fields. Potential alternatives are identified by leveraging the status of the literature in dental materials and other fields. It is mainly focused on the extrinsic approaches, which have been the most common strategies used to design self-healing dental polymers. Unlike other reviews published in the dental materials field, this review aims to cover the fundamentals of self-healing systems to encourage the readers to think about potential new strategies. The most common strategy used in self-healing dental polymers represents an incremental improvement of an approach developed 20 years ago,[9] which still presents significant drawbacks that need to be addressed to enhance translational potential, as discussed later in this article. Therefore, this review is presented

as a comprehensive discussion on the classification of self-healing systems, the different subcategories of microcapsule-based systems, and the synthetic methods used to encapsulate healing agents, which, as far as we know, have not been previously covered in any other literature review in dentistry. In addition, although it is recognized that the microvascular network-based strategy is underexplored in dentistry and only a minimum number of studies are available, it is believed that the 3D printing expansion may be a driving force for the use of this technology in a not so distant future.

Methods & Discussion

Classification of self-healing materials

Self-healing synthetic materials can be classified on the basis of 2 criteria: (1) the need for the intervention to trigger the healing process and (2) the nature of the material transport in the polymer.

According to the first criteria, self-healing materials can be classified as autonomous or nonautonomous in a simplistic view. Autonomous (or passive) self-healing systems can trigger and control the healing process alone, without outside intervention.[10–12] In contrast, nonautonomous (or active) systems have their self-healing kinetics triggered and controlled by outside intervention.[10–12] Although apparently straightforward, this classification can be highly challenging and paradoxical depending on what is considered an outside intervention.[10] Although some researchers understand outside intervention as an energy source (eg, light or temperature change), others rely on the need for human intervention to determine if a self-healing system is nonautonomous or autonomous. The complexity of this classification is mainly related to the attempt to differentiate between biological and synthetic healing.[10] In dentistry, the need for human intervention has been generally considered the decisive factor for autonomy, but because the development of bioinspired polymers in dental materials is still incipient, it is important to critically analyze the classes and the criteria they are based on.

In terms of the nature of the material transport, the self-healing systems can be classified as extrinsic or intrinsic. In extrinsic systems, the healing agent is sequestered into microscaled containers (such as capsules and vascular systems) or nanoparticles and embedded into the polymeric matrix.[11] Conversely, intrinsic systems comprise latent functional end groups with the ability to reorganize and reform (ie, the polymeric matrix is inherently selfhealable)[11,13] (Figure 1). Despite the common goal of inhibiting the crack propagation and rebuilding the damaged area, the strategies are significantly distinct, as are their challenges, advantages, and drawbacks. This review focuses on extrinsic strategies because they have been the most commonly used to design and synthesize self-healing dental polymers.

Overview of the extrinsic strategies

In extrinsic self-healing polymers, the healing agent is kept isolated from the organic matrix until the crack propagation leads to the rupture of the microcontainers in which it is contained.[11] Essentially, the healing agent is a low viscosity multifunctional monomer

capable of flowing to the crack area and forming covalent crosslinked bonds with the organic matrix.[14] The polymerization of the healing agent is triggered by exposure to catalysts, curing agents, or reaction initiators, which are maintained separated from the healing agent until release.[15] The Table lists the required characteristics of healing and curing agents for self-healing polymeric systems.

In dentistry, the most common healing agent compounds are dicyclopentadiene,[9,16–18] triethylene glycol dimethacrylate (TEGDMA),[19–22] and a mixture of urethane dimethacrylate, bisphenol A-glycidyl methacrylate, and ethoxylated trimethylpropane triacrylate.[23] The most traditional catalysts, curing agents, and reaction initiators are Grubbs[9,16–18] and the amines N-N-bis(2-hydroxyethyl)-P-toluidine,[19–21] and 4,40-methylene-bis (N, N-dimethylaniline) combined with benzoyl peroxide (BPO) or phenyl acetate solvent.[23] In addition to that, glass ionomer cement-based systems were developed.[24,25] In this system, the healing powder is composed of strontium fluoroaluminosilicate, and the healing liquid is a solution of polyacrylic acid.[24,25]

As mentioned above, in extrinsic autonomous self-healing systems, the healing agent and the catalyst, curing agent, or reaction initiator must be sequestered until the healing kinetics is triggered by crack propagation. There are essentially 2 model systems used to this end—microcapsules and microvascular networks.

Microcapsule-based systems

Strategic Approach—The healing agent compound and the amine are encapsulated in microcapsules in these systems. If required, the catalyst, curing agent, or reaction initiator can be dispersed into the organic matrix, encapsulated in a separated or a different layer of a double-shell microcapsule.[10,11,26] As described previously,[26] there are 5 models of microcapsule-based systems (Figure 2):

Single capsule.: The healing agent compound is encapsulated and, once released, it reacts with latent functional groups in the organic matrix, and then the polymerization reaction is triggered by external factors (such as the surrounding moisture of the environment or light), or can be initiated by intrinsic mechanisms such as conductive bridging or chain entanglement across the fractured surface. No additional catalyst, curing agent, or reaction initiator is required (Figure 2A).

Capsule or dispersed catalyst.: The healing compound and an amine are loaded into capsules, and the catalyst is dispersed or dissolved into the organic matrix. In a redox chemical reaction, the healing agent polymerization is triggered once the capsules are broken (Figure 2B). This is the most common microcapsule-based system reported in dental research, although no commercial examples exist to date, despite promising in vitro results.

Phase-separated droplet or capsules.: One of the healing components is added to the matrix and undergoes phase separation, whereas the other component is encapsulated (Figure 2C).

Dual or multicapsules.: A dual system in which part of the capsules contains the healing agent compound and another contains the catalyst, curing agent, or reaction initiator (Figure 2D).

Double-shell microcapsule.: The healing monomer and catalyst, curing agent, or reaction initiator are confined into single multicompartmentalized capsules, separated by a membrane (Figure 2E). Certain characteristics are important for the constituent polymers of the shell wall. These include (1) absence of reactivity with the core material (healing agent) and the surrounding organic matrix, (2) mechanical properties that are lower than the organic matrix but high enough to survive mixing and handling procedures, (3) allow for proper dispersion of the capsules into the matrix, and (4) thermal stability.[12] In the dental literature, (poly)urea-formaldehyde (PUF),[19–21] urea-melamine-formaldehyde (UFM),[18] and silica[24,25] have been used for capsule shell wall synthesis.

Synthesis: Microencapsulation Techniques—The encapsulation process is performed by chemical reactions involving in situ, interfacial, or a combination of in situ and interfacial polymerizations.[10] In in situ polymerization, the healing agent monomer (oil phase) is encapsulated via oil in water double emulsion stabilized by ethylene-maleic anhydride (surfactant) in an acid-catalyzed reaction between urea, resorcinol, and formaldehyde (water phase).[12] This reaction relies on the water solubility of the shell wall compounds and, after a certain oligomerization level, the change in polarity, which causes the oligomer to migrate to the oil phase (healing agent). The addition of formaldehyde promotes the crosslinking of the oligomer, leading to the formation of a membrane around the healing agent.[10] This is the method used to synthesize PUF and UFM capsules. In interfacial polymerization, 2 phases are also required, but both compounds come from each of the phases and react at the oil-water interface, which leads to the formation of a polymeric membrane around the smaller phase.[10] The synthesis of silica microcapsules is based on this mechanism.[24,25] Water, polyacrylic acid, nonionic surfactant, and decahydronaphthalene are mixed to create an emulsion. Silica is mixed with tetraethoxysilane (hydrophobic) and hydrochloric acid and added dropwise into the emulsion. This leads to the hydrolysis at the water continuous phase (healing agent) and the formation of the silica interface around the droplets (shell compounds) via a condensation reaction.[27] Finally, if the goal is to synthesize double-shell microcapsules, in situ and interfacial polymerization techniques may be combined.[28] In addition, Pickering emulsion templating, miniemulsion polymerization, solvent evaporation and solvent extraction, and sol-gel reaction are alternative encapsulation routes used in other fields.[26]

Advantages—The advantages of the microcapsule-based strategy lie mainly in the compatibility of the capsules with the most diverse polymeric systems[13] and the versatility in terms of healing chemistries and encapsulation routes, which makes the technique highly tunable.[11] In addition, the encapsulation routes do not require specialized and expensive armamentarium, and considering how the restorative dental materials are manufactured, this is the strategy with the highest translational potential.

Challenges—Despite the appealing healing efficiency presented by microcapsule-based systems, several critical drawbacks must be considered and overcome to make this strategy commercially and clinically feasible. The size of capsules and their morphologic characteristics are highly sensitive and dependent on the type of emulsifier, core to shell monomers mass ratio, reaction temperature, solution pH, and agitation rate used in the in situ or interfacial polymerization synthesis routes.[9,26] The dispersity in microcapsule dimensions are not negligible, with variations in diameter ranging from 15 through 300 μm and in shell thickness from 0.1 through 30 μm.[9,26] In addition, the high susceptibility to coalescing and merging of the innermost drops with the continuous phase before the consolidation is fully completed and the difficulty of scaling up the process are additional challenges related to these synthesis techniques.

The crack response to the presence of the microcapsules is also a key aspect of the healing efficiency. As discussed above, the healing process starts when the crack reaches the capsules and breaks them. Therefore, it is crucial to ensure that the crack does not deflect away from the microcapsule,[29] which is, at least in part, related to the stiffness ratio between the capsule and the organic matrix. If the capsule stiffness is higher than the organic matrix, there is a strong undesirable tendency for the crack to be deflected away from the capsules, which would impair the triggering of the healing process[29] (Figure 3). This points to the importance of standardizing the encapsulation routes to produce capsules with shell wall thickness within the proper range (160 μm-220 nm[9]). Other important aspects to consider are the spatial distribution of the capsules into the organic matrix, reaction initiator concentration dispersed into the matrix, and microcapsule size, which are mainly related to the healing capacity and performance of the systems.[26,30]

Although the probability of crack-capsule collision is enhanced as the microcapsule volume fraction ratio increases, the bulk properties of the polymer may be undesirably affected by adding more than 7.5 wt% of microcapsules into the resin composite.[19] In addition, most studies tested capsules without surface functionalization, which then behave as voids, with a detrimental effect on the mechanical properties. The impact of the presence of broken (activated) capsules in the polymeric network on mechanical strength is also a potential concern related to this approach. Although the polymer film formed by the polymerization of the healing agent seems to be capable of filling the area in which the original capsule was entrapped, it is not clear if the presence of a great fraction of broken microcapsules might act as voids or defects and compromise the mechanical strength of the material over time.

The limiting healing cycles are also an inherent characteristic of the microcapsule-based approach because once a capsule is broken and the healing agent is released, the life span of that capsule is over.[11,31] Moreover, the biocompatibility of these systems is also a matter of concern because the remaining unreacted monomers may leach out and lead to toxic or inflammatory responses. Finally, the long-term stability of the extrinsic self-healing systems must be comprehensively assessed. The literature shows that 6 months was the longest period used to analyze dental self-healing polymers.[19] Although the maintenance of self-healing performance found in this study is encouraging, longer storage times are required because the thermal stability of the healing agents may be a drawback, along with potential oxidation of the amides.

Current State and Future Perspectives in Dentistry—The first successful microcapsule-based autonomic self-healing approach used for thermoset polymers was developed almost 2 decades ago and was based on PUF microcapsules containing dicyclopentadiene monomer, which in contact with ruthenium-based Grubbs catalyst dispersed into the epoxy matrix, initiated a ring-opening metathesis polymerization, leading to up to 75% recovery in toughness (capsule and dispersed catalyst type).[29] However, the system had to be modified over time because of biocompatibility and cost concerns regarding dicyclopentadiene and Grubbs catalyst.[32,33] Therefore, encapsulating low viscosity difunctional methacrylate TEGDMA in PUF shells emerged as an alternative. To trigger the redox chemical polymerization reaction, N-N-bis(2-hydroxyethyl)-P-toluidine was dissolved at 1 wt% into the TEGDMA, and BPO was dispersed at 0.5 wt% into the organic matrix.[19–21] The results showed healing efficiency of around 65% in polymeric systems containing 10 through 20 wt% of capsules. A mixture of ethoxylated trimethylpropane triacrylate, urethane dimethacrylate, and bisphenol A-glycidyl methacrylate containing 4,40-methylene-bis (N, N-dimethylaniline) was also tested. In this strategy, BPO and phenylacetate were encapsulated as the initiation system in a double capsule system[23] (Figure 2D model). The healing efficiency averaged 40% in simulated physiological conditions.[23,34]

Modifications on the shell walls have also been suggested with the development of UFM capsules. The replacement of up to 5 wt% of urea in the PUF shell wall for melamine is suggested as an alternative to chemically bond the wall to the organic matrix and to increase the mechanical properties of the microcapsules.[18,34,35] The addition of melamine creates stronger crosslinking and increased branched methylene bonds, reinforcing the shell wall.[35] In addition, the loss of formaldehyde seems to be decreased in systems of UFM capsules.[35]

An alternative model of self-healing composites based on adding silica microcapsules loaded with polyacrylic acid into the organic matrix containing fluoroaluminasilicate glass powder was designed.[24,25] This approach also tested the effect of the functionalization of the capsule surface on the efficiency of system healing.[24] The results showed healing efficiency up to 25% in systems containing 5 wt% of microcapsules. The functionalization of the shell wall seemed capable of promoting strong surface binding with the organic matrix, which ensured that the microcapsules were successfully broken as the cracks propagated.[24] Finally, antimicrobial (dimethylaminohexadecyl methacrylate) and remineralizing agents (amorphous calcium phosphate) have been incorporated in multipurpose self-healing capsules and added into dental adhesive formulations.[36] The preliminary results were encouraging, with a healing efficiency of 67%, associated with 4-fold biofilm reduction.[36]

However, there are innumerable unexplored options regarding capsule design and healing agent compositions. The use of high toughness healing polymers may lead to the sealing of the damaged area and reinforcement of the polymeric network. Self-healing agents capable of autorepair by rearrangement of chemical bonds also represent a compelling alternative, which would overcome the drawback of the single self-healing cycle of the current systems. In addition, the encapsulation techniques need to be redesigned to allow for scalability; as of now, the existing synthesis routes require excess amounts of reagents and result in large polydispersity. Moving forward, the potential scope of applications can also be

significantly broadened by designing stimulus-responsive shell walls, which could adapt to pH, temperature, light, or free radicals variations. That way, environmental factors other than the mechanical stimulus given by crack propagation may be harnessed to break the capsules and trigger the healing process.

The last important point is assessment of the healing efficiency in dentistry. Typically, the healing efficiency has been tested for fracture toughness by the single-edge notched method. After the bars are completely broken, the halves are maintained in contact at 37 °C for 24 hours and retested. The healing efficiency is calculated on the basis of the fracture toughness ratio between the healed and the virgin bar. Although serving as helpful proof of concept and screening tools, this method does not represent the clinical situation in which the healing systems would be more useful in repairing subcritical cracks before they have a chance to propagate and lead to catastrophic failure. The field lacks systems that (1) simulate dynamic and cyclic assays in which the materials are subjected to more clinically-relevant forces,[37] (2) allow for the repair to be measured on the microscale, and (3) mimic physiologically relevant conditions in the oral cavity, including biofilm formation.

Microvascular-based systems

Strategic Approach—The principle of this system lies in sequestering the healing agent and the reaction catalyst, curing agent, or reaction initiator in a vascular network comprising interconnected capillaries or hollow channels.[13] Healing is triggered by rupture of the vascular network by crack propagation, releasing the healing compounds into the damaged area.[13] One, 2-, or 3-dimensional microvascular channel networks (Figures 4A-C, respectively) can be created with this approach.[38]

Synthesis: Microvascularization Techniques—The success of this bioinspired approach is highly dependent on the design and fabrication of a complex and interconnected network.[12] Five different techniques can be used for this purpose.

Hollow fibers.: In this approach, hollow glass fiber capillaries or tubes (diameter range, 5–500 μm) filled with healing and curing agents in separate fiber units are mounted, forming a lattice, and embedded into the organic matrix.[39,40] This technique is restricted to connection in a single dimension and cannot be used to build multidimensional complex channel networks.[38]

Sacrificial fibers.: This technique integrates a 3D microstructure of sacrificial fibers into the host polymer to serve as a preformed mold. After polymerization of the material, the sacrificial fibers are removed (manually or by means of an increase in temperature or change in pH), and a hollow microchannel network is left behind in the host polymer, which is later filled up by injection of the healing agents. Similar to the hollow fibers, this manufacturing method is useful for 1-dimensional microvascular network structure.[41] These sacrificial fibers can be premanufactured or fabricated by melt spinning and electrospinning techniques, which allow for tuning fiber dimensions and selecting the most appropriate membrane material.[41]

Sacrificial 3D-printed scaffolds.: In this technique, 3D-printed scaffolds are created in lieu of the sacrificial fibers to mimic a hollow biomimetic framework. The 3D microvascular structure is commonly assembled by direct-write of a fugitive ink.[41,42] The fugitive ink is robotically deposited on a moving x-y platform initially, which yields the formation of a 2-dimensional framework. In the next step, a deposition nozzle mounted on the z-stage is activated, and another layer is deposited. Successive alternating cycles are performed until a 3D scaffold is built, and then, the structure is infiltrated by the host polymer. The last step is the fugitive ink removal, which leaves behind a highly customizable, 3D interconnected hollow structure.[42] A variation of this technique is the soft lithography method in which the biomimetic microvascular network is designed and a mold is printed using a biomaterial (eg, polydimethylsiloxane). This negative impression is filled up by gelatin and, after its solidification, is embedded into the host organic matrix. After gelatin removal, a microvessel network pattern is left inside the polymer.[41,43]

Electrostatic discharge.: This method irradiates the host polymer with an electron beam, and a negative charge is accumulated inside the material. In the next step, the material is subjected to a discharge with a grounded electrode, creating a 3D random leaf venation pattern of microchannels of 10 through 500 μm in diameter.[41,44]

Except for the hollow fiber strategy, in which the healing agents are preloaded into the fibers before they are embedded into the host polymer, the healing components must be pumped into the microchannel network. The efficiency of this process is highly dependent on the rheological properties of the healing agents, network architecture, and level of hierarchical branching.[45]

Advantages—The advantages of this strategy include releasing a larger volume of healing agents to the damaged area,[40] multiple healing cycles because of the multiconnected vascular network,[46] possibilities of refilling the network,[38] and homogenous dispersity of the channels beneath the surface.[11]

Challenges—Most of the challenges with microvascular self-healing systems are similar to the microcapsule-based approach.[10] The proper rupture of the fibers by the crack in propagation is a key factor in ensuring the release of the healing and curing agents.[40] The hydraulic pressure and the laminar nature of the flow into the channels and microcracks are also concerns because they may lead to poor mixing of healing and curing agents and hamper polymerization kinetics. In general, the success of this method is related to the complex balance between the capillary forces and the viscosity of the loaded healing agents, as well as the secondary molecular interaction forces required to make the system heal as the crack propagates.[41,47] Although the multiconnected vascular networks are theoretically capable of being refilled, the practical techniques for filling the hollow fibers with the liquid healing agents are not straightforward, as mentioned above.

In summary, the fiber design (diameter, wall thickness, hollowness) and the rheological properties and reaction kinetics of the healing agents impose a challenging environment for the refilling process.[40,41] In addition, the spatial distribution of the fibers plays a crucial role in the host polymer mechanical behavior and may lead to undesirable inhibition of plastic

deformation and, consequently, delamination.[48,49] Furthermore, to maximize the possibility of the self-healing triggering, the microvascular network has to reach all the areas of the polymeric structure uniformly.[41] However, the mechanical properties of the host polymer can be negatively affected by the presence of an extensive hollow microvascular network, which makes it crucial that a critical balance exists between the channel network distribution and the preservation of the mechanical properties of the host polymer.

Current State and Future Perspectives in Dentistry—The microvascular extrinsic approach is the most complex to be translated to dental materials applications. The nature of the technique itself precludes its use in direct restorative materials, which significantly limits the clinical scope. Manufacturing these networks remains an unmet challenge given the time-intensive processes, incompatibility with existing manufacturing methods, complexity, and lack of scalability.[50] In dentistry, this technique has been limited to engineering microfluidic devices to study on-site cellular behavior.[51] However, given the substantial growth and progressive expansion of digital dentistry, printing prostheses and indirect restorations in dental offices is now feasible. This may represent a driving force for the expansion of the microvascular approach in a scenario in which ceramic or composite restorations are designed and printed with the microchannel network.

Conclusions

Preembedding healing agents into the polymeric matrix has been the most popular strategy employed in dentistry to enable the polymer to self-repair autonomously. However, optimized manufacturing processes are needed to potentiate bench-to-bedside translation. In this context, 3D printing technology may be an important tool for expanding the microcapsule- and microvascular-based strategies. In addition, the nanoparticle-based approach has been revisited and emerged as an option. The idea is that nanoparticles dispersed into the organic matrix migrate to the cracked area to repair it.[52] Despite being tested with the use of polymethylmethacrylate[53] and poly(bisphenol-A-co-epichlorohydrin)[54] thermoplastic particles, new systems were successfully validated to be used in self-healing hydrogels under physiological or room temperatures. These were based on dynamic ionic interaction between carboxylic acid and silver ions from silver chloride nanoparticles,[55] poly(vinyl alcohol) combined with cucurbit[8]uril and cellulose nanocrystals,[56] and poly(vinyl alcohol) and borax associated with nanostructured cellulose nanofibers and polypyrrole[57] systems. Although the polymer network environment of hydrogels is fundamentally different from most dental polymers because it is designed to absorb large amounts of water, and there is no requirement for high mechanical strength to support masticatory forces or internal stress, some similar strategies might be translatable to the development of dental adhesives with autonomic reparability, which acts as a semipermeable membrane in situ.[58] In fact, incorporating thermoplastic elements and functional filler particles into the dental resins has been tested and validated as a promising strategy.[59,60,61]

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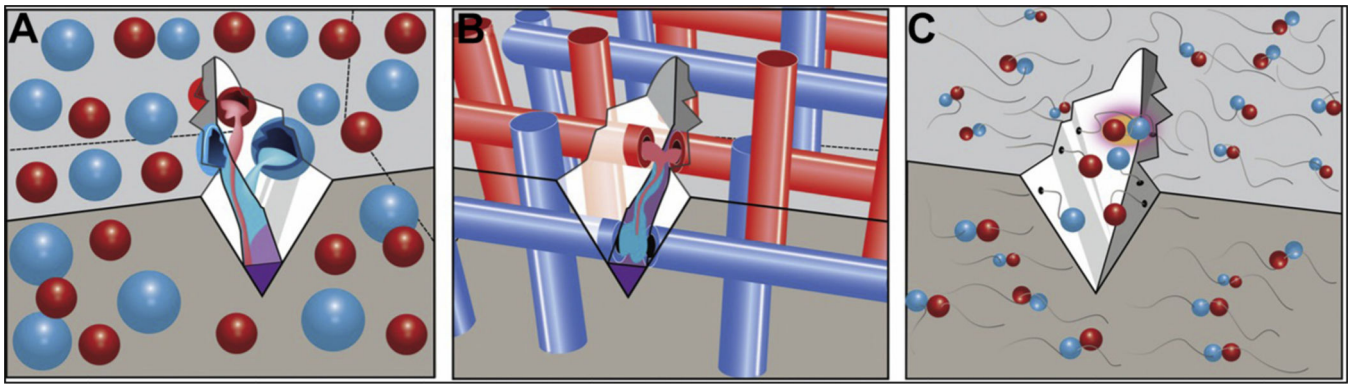

Figure 1.

Extrinsic (**A, B**) and intrinsic (**C**) approaches to develop bioinspired self-healing synthetic systems applicable for thermoset polymers. In the extrinsic strategy, the self-healing agent is sequestered in microcapsules (**A**) or a vascular network (**B**) until the crack propagation leads to their rupture and triggers the healing. Intrinsic systems (**C**) are characterized by the presence of latent functional end groups in the organic matrix that can reorganize and reform. Adapted with permission of Annual Reviews from Blaiszik et al.[13]

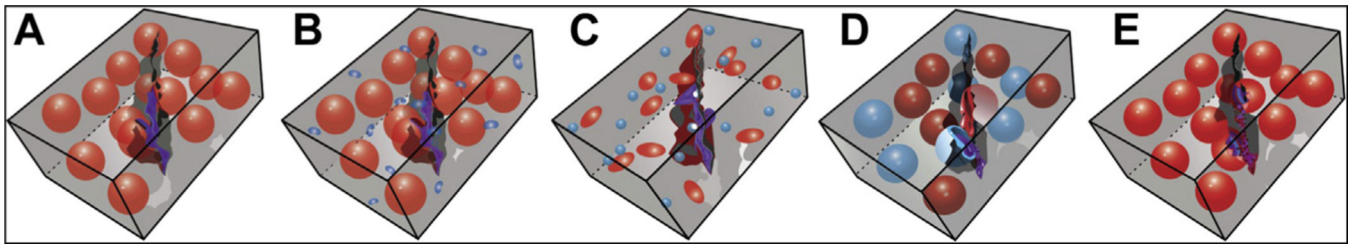

Figure 2.

Five microcapsule-based healing agent systems: **A.** Single capsules. **B.** Capsules and dispersed catalyst. **C.** Phase-separated droplet and capsules. **D.** Dual capsules. **E.** Double-shell microcapsules. Adapted with permission of Elsevier Science & Technology Journals from Zhu et al.[26]

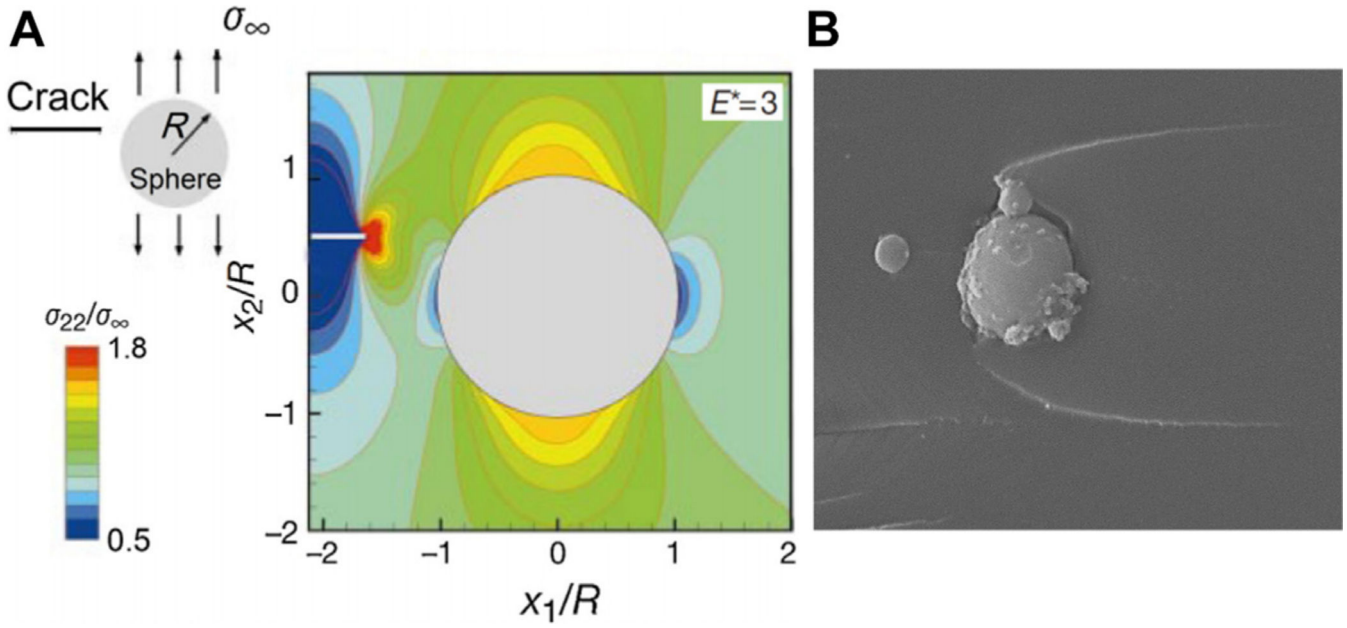

Figure 3.

A. Micromechanical modeling based on Eshelby-Mura equivalent inclusion method. This modeling studied the stress distribution in the equatorial plane of the capsule promoted by a crack in propagation as a function of the stiffness of the organic matrix and the capsule. The modeling simulated a condition in which the capsule to organic matrix stiffness ratio is 3, and the crack is deflected away from the capsule surface. E^*: Ratio between stiffness of the microcapsule and stiffness of the organic matrix. R: Radius of the microcapsule. σ: Applied stress perpendicular to the crack plane (σ_∞) and in the equatorial plane of the microcapsule (σ_{22}). x_1 and x_2: Stress state in the vicinity of a planar crack in relation to the radius (R) of the microcapsules. Reproduced with permission of Springer Nature from White et al.[29] **B.** Scanning electron micrograph of a crack being deflected away from a (poly)urea-formaldehyde microcapsule incorporated into bisphenol A-glycidyl methacrylate-triethylene glycol dimethacrylate organic matrix in a fractured flexural strength specimen (scanning electron microscope micrograph, ×500 magnification).

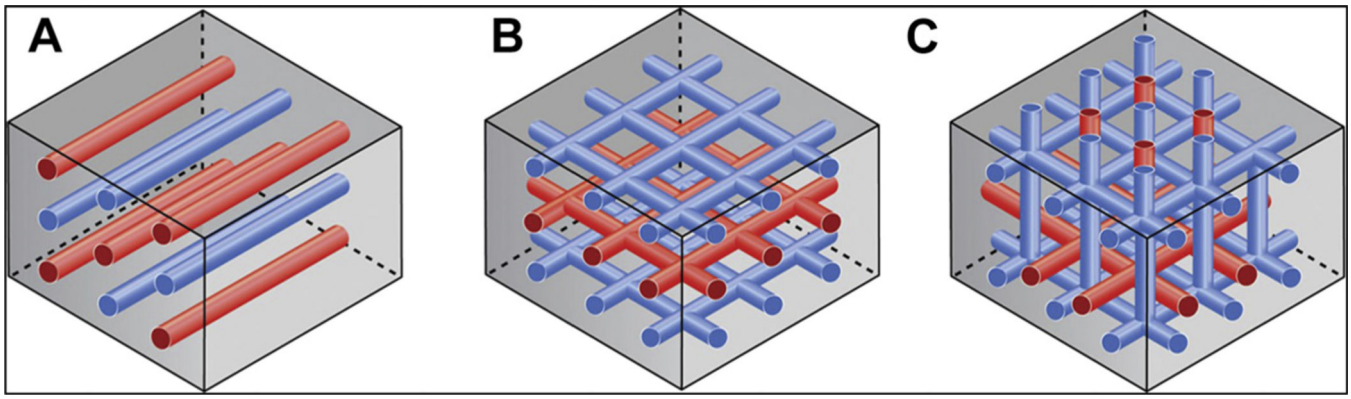

Figure 4.

Models of microvascular networks for self-healing polymers. Although the 1-dimensional systems are simpler to be designed and manufactured (**A**), the additional connectivity achieved in the 2- (**B**) and 3-dimensional (**C**) microchannel structures boosts the healing performance because each point of the system has multiple connections. Adapted with permission of *American Scientist*, magazine of Sigma Xi, The Scientific Research Society, from White et al.[38]

Table

Summary of the desirable properties for the self-healing system components.[11–13,26,62]

System Component	Desired Characteristic	Description
Healing agent	Chemical stability	Resist the encapsulation or vascular injection processes and stable containment once into the microcontainers
	Physical and mechanical properties	Equal or superior mechanical properties to the organic matrix
	Deliverability	Adequate flow and containment into the damaged site by capillary action
	Reactivity	Trigger quick polymerization reaction once in contact with the catalyst, curing agents, or reaction initiators
	Volumetric stability	Low shrinkage to prevent debonding
	Thermal stability	High boiling point and low freezing point
	Stoichiometry	Polymerization and crosslink need to take place under undefined mass or molar ratios
Curing agents	Chemical compatibility	Lack of premature reactivity with the organic matrix during storage and active curing
	Solubility	Rapid dissolution in the healing agent
	Dispersion	Homogeneously dispersed
	Reactivity	Fast polymerization kinetics but slow enough to allow the healing agent to flow
	Thermal stability	Stable over a wide range of temperatures