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Self-healing biomaterials[(3)]

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Abstract

The goal of this review is to introduce the biomaterials community to the emerging field of self-healing materials, and also to suggest how one could utilize and modify self-healing approaches to develop new classes of biomaterials. A brief discussion of the *in vivo* mechanical loading and resultant failures experienced by biomedical implants is followed by presentation of the self-healing methods for combating mechanical failure. If conventional composite materials that retard failure may be considered zeroth generation self-healing materials, then taxonomically-speaking, first generation self-healing materials describe approaches that “halt” and “fill” damage, whereas second generation self-healing materials strive to “fully restore” the pre-failed material structure. In spite of limited commercial use to date, primarily because the technical details have not been suitably optimized, it is likely from a practical standpoint that first generation approaches will be the first to be employed commercially, whereas second generation approaches may take longer to implement. For self-healing biomaterials the optimization of technical considerations is further compounded by the additional constraints of toxicity and biocompatibility, necessitating inclusion of separate discussions of design criteria for self-healing biomaterials.

Keywords

self-healing; biomaterials; material failure; bone cement; mechanical failure

1. Introduction

Biological materials such as bone, skin, and muscle, when healthy, undergo *in situ* self-healing through a cycle of consumption and regeneration that prevents the accumulation of defects due to tissue ageing and fatigue. Healing and biomaterials are most commonly linked through the tissue response to the presence of an implant [1-3]. Ratner has coined the term “biomaterials that heal” to describe biomaterials that actively promote wound healing [4] as opposed to those aimed at passivity or inertness. While the biology and chemistry of healing have significant impacts on biomaterial performance, biological healing does not address the physical repair of biomaterials that experience mechanical and chemical

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breakdown as they are subjected to loading and degradation effects *in vivo*. Developing synthetic biomaterials with the intrinsic ability to autonomously repair mechanical and chemical damage would be particularly important for implants that replace tissues that are also capable of self-repair.

The *in situ* repair of synthetic materials for engineering applications first requires the ability to detect the damage — usually by visual inspection or by non-destructive testing techniques such as ultrasonics, x-ray tomography, computerized vibro thermography, and infrared thermography — followed by time-consuming and/or expensive steps to repair or replace the damaged section [5]. *In situ* detection and repair of biomaterials is particularly difficult due to the lack of adequate *in vivo* imaging techniques to detect failures and suitable minimally invasive methods to repair the damage. Overall, only substantially damaged or compromised biomaterials can be detected *in situ*, and if detected are generally retrieved and replaced [6-12].

The development of synthetic materials that autonomously repair *in situ* on the microscopic level before suffering macroscopic failures would significantly extend the lifetime of a given structure or device. This is precisely the motivation behind the newly emerging class of "self-healing materials" that are endowed with the intrinsic ability of self-repair in response to damage arising from physical and chemical stresses within its use environment [5,13-17]. Generally speaking, self-healing materials are designed to sense, halt, and even reverse damage, ideally without requiring the application of external physical or chemical stimuli. These materials hold the potential for significantly extending material lifetimes by avoiding failures initiated by accumulated microcracks. To date, the majority of the research conducted on self-healing bulk materials has employed composites, adhesives, and cements proposed for applications in traditional engineering applications [5,13-18].

Here the common mechanical failure modes of existing polymeric implants are reviewed followed by a description of traditional composite approaches employed to retard these failures. Next materials intended to halt and then ultimately repair microscopic damages before they coalesce into macroscopic failures are discussed. If traditional materials that retard failure may be considered zeroth generation self-healing materials, then taxonomically-speaking, first generation self-healing materials may be used to describe approaches that "halt" and "fill" damage, whereas second generation self-healing materials describe those that strive to "fully restore" the pre-failed material structure. Note that these designations are tied only to the material design and do not refer to the quality of performance of such materials. They do not imply that one approach is necessarily "better" or "more suitable" than another. Finally, these concepts of self-healing materials are placed in the context of building self-healing biomaterials that also must possess the vital characteristics of biocompatibility and non-toxicity.

2. Mechanical failure of polymeric biomaterials

2.1. Loads seen by biomedical implants

Physiological loads experienced by implants vary according to complex loading patterns as well as the activity levels of the recipient (Table 1). For example, the stresses on artificial

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heart valves and TJRs fluctuate throughout daily activities such as strenuous exercise or sleep and may reach maximums in individual instances of injury. Materials used to replace these tissues are generally selected to have mechanical tolerances that exceed these physiological stresses by several orders of magnitude [19,20]. However, a singular instance of normal loading rarely leads to the implant failure; rather it is the repeated normal loading of the implant that incrementally leads to failure. Therefore, mechanical failure in polymeric biomedical implants most often arises from cyclic loading that leads to microcracking, wear, fatigue, and material deformation and loss (Table 2). Furthermore, aqueous polyelectrolytic biological fluids, such as blood, interstitial fluid, and lymph that bathe polymer implants represent an aggressive use environment that exacerbates failures arising from plasticizing, crazing and crack propagation, wear, and corrosion [21]. Plasticizers interfere with the interchain interactions, thereby enabling the polymer chains to slide past each other, reducing the physical entanglements that maintain polymer cohesion. Plasticization yields a polymer with a lower glass transition temperature, T_g, that is more susceptible to mechanical deformation under loading, which can promote crack formation and material failure [19].

2.2. Crazing and crack formation

Microscopic examination of cyclically loaded polymeric implants often reveals the presence of crazed microcracks characterized by a network of fibrils that span the crack edges[19]. Crazes and microcracks form to relieve internal or external stresses in areas of high stress concentration, such as along a pre-existing crack, at the surface of the polymer, or at a void within the polymer. A crack will propagate if the stress on the system is reduced by its growth. As propagation occurs, the fibrils joining the bulk surfaces of the polymer can either behave in a ductile manner by recruiting fresh material from the edge of the bulk surface to maintain the fibril connections, or the fibrils can behave in a brittle manner and proceed to fracture.

2.3. Wear and wear particle formation

Wear is the loss of bulk material through adhesion, abrasion, erosion, fretting, and/or fatigue [22,23]. Wear damage in biomaterials is common to the articulating surfaces in TJRs and is regarded as the primary failure mode that influences the long-term performance of such implants [9,19,22-26]. Particles that break off from the bulk material during wear comprise both mass loss from the original implant as well as debris that can lead to added abrasion. Attempts by the immune system to consume and remove these wear particles often leads to a state of a chronic inflammation. It has also been observed that wear debris cleared from the joint space by lymph or blood flow collects in the lymph nodes and other organs of the immune system [23,27,28].

The current gold standard for articulating surface applications is UHMWPE [25]. With a molecular weight between 2 and 6 million, UHMWPE imparts toughness through crystallinity between 39 and 75% and the extensive intertwining of the extremely long molecular chains that interlock the crystalline domains, restricting motion to the amorphous polymer regions [12]. The capacity of UHMWPE to resist cyclic fatigue can be augmented by direct compression molding and hot isostatic pressing to give better fatigue resistance and smooth surface finish than that afforded by extrusion techniques [6,12,29,30].

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The currently available alternatives to UHMWPE in TJRs are the limited use of alumina and zirconium as the articulating surfaces [31]. While these ceramics demonstrate excellent strength, stiffness, and lubricity, they have poor toughness and resistance to crack propagation. Attempts have been made to improve the surface properties of metals through the application of diamond-like, titanium nitride, and chromium nitride coatings, but poor adhesion of these coatings to the metal substrate also results in debris that compromises the implant[28].

3. Zeroth generation self-healing materials: Composites that retard but do not repair mechanical damage—Composite materials are attractive because they can be designed to improve material stiffness and strength by dispersing stiffer or stronger particulates or fibers into the softer polymer matrix [19,30]. By employing materials with different mechanical properties for the matrix and additive phases, the overall properties of the composite will reflect the most desirable traits of each material. Dispersed particulates and fibers of composite structures can also increase the toughness, impact strength, and wear resistance of the base matrix by absorbing a greater fraction of the load, by inhibiting pathways for crack propagation, and by resisting void formation.

Properly designed composite materials thus have the capacity to retard mechanical failure but do not have the ability to repair damage. As such, traditional composites behave like a “stuck zipper” that is hard to un-zip, but also one that cannot be re-zipped. This capacity gives traditional composite materials a “zeroth-order” self-healing status.

Huang and Ramakrishna provide an excellent and comprehensive review of biomedical composite materials [32]. Table 3 summarizes the use of polymer-based composite biomedical implants. In spite of a long history of development in load-bearing applications, only a few composite devices have progressed to widespread clinical use [32]. The lack of success with composite biomaterials may be attributed to the deleterious effects of placing the material in an environment that accelerates water absorption and compromises adhesion between the dispersed and matrix phases; i.e. a 37 degree, cyclically-loaded, aqueous, high-salt polyelectrolytic environment.

Selecting a chemically inert nonpolar matrix polymer has the advantage of resisting water absorption, but it also increases the difficulty of finding a dispersed phase that bonds well with the matrix material. Strong interface bonding is necessary for efficient transferring of loads between the two phases and the prevention of voids or crack formation at the interfaces, which can serve as stress concentrators that initiate crack propagation [19]. Finding suitable materials to disperse in nonpolar and chemically inert UHMWPE thus has proven to be problematic. For example, carbon fiber-reinforced UHMWPE has shown poor results clinically because the carbon fibers did not bond well with the UHMWPE matrix, serving as stress concentrators and sources of crazing [30]. Consequently, fatigue cracks propagate up to eight times faster in carbon-reinforced UHMWPE than in pure UHMWPE [30].

Self-reinforcing (SR) materials are a special class of composites consisting of a matrix and reinforcing additive made from the same material [33]. Ideally, the compatibility between dispersed and matrix phases made of the same material will allow for composite

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strengthening through improved interface bonding. SR-PGA and SR-PLLA have been shown to exhibit shear strengths of 2-3 fold higher than the <100MPa shear strengths of their injection-molded counterparts [34,35]. This approach is also attractive because cytotoxic adhesion promoters such as silanes are not required [24]. SR rods, plates, pins, screws, and tacks have all been produced from SR-PLA, PGA, and their copolymers and are most commonly used as osteofixation devices in craniomaxillofacial implants[24,32,33].

4. First generation self-healing materials: Composites that irreversibly repair but do not restore damaged matrix

An emerging area of composite research is the development of dispersed components that respond to the presence of damage by releasing a healing agent. This “first generation” of self-healing materials employs the process of matrix repolymerization to replace the damaged original material with a cured substitute. Here, matrix repolymerization is analogous to gluing together the two sides of an open zipper, which will close the zipper but is irreversible and does not restore its original zipped structure.

Kessler and Murphy both provide excellent reviews and in-depth discussions of matrix repolymerization self-healing systems that have been investigated in recent years [13,36]. Two common matrix repolymerization systems employed to date rely on a ruthenium-based Grubbs’ catalyst to induce ring-opening metathesis polymerization (ROMP) of a dicyclopentadiene (DCPD) monomer [5,13,14] or various reactive epoxy resins that induce curing of a bisphenol-A epoxy matrix [15]. Microencapsulated PDMS self-healing systems have also been investigated [37,38]. While many groups have successfully utilized these systems, the following is meant to discuss illustrative examples of the feasibility of the approach.

Figure 1 illustrates the matrix repolymerization method utilizing microencapsulated healing agent dispersed in a catalyst-embedded polymer matrix. When a propagating crack encounters a microcapsule, it causes the capsule shell to rupture, releasing the healing agent into the crack plane via capillary action or crack closure following unloading. Crack formation also exposes embedded catalyst that initiates curing of the healing agent released from the capsules into the crack area. The reaction binds the surfaces of the crack together, halting its progression through the material [5,13,14,37,39,40] . The reverse case of microencapsulated catalyst and phase-separated healing agent has also been explored [37,38].

Healing agent-filled hollow cylinders and branched network structures also have been employed to increase the efficiency of healing agent delivery to the defect area. Bleay et al. investigated a variety of small diameter hollow glass fibers that were capable of simultaneously storing healing agent and providing structural reinforcement to an epoxy matrix. However, this group encountered problems with release of healing agent from smaller diameter fibers [13]. Toohey et al. and Lee et al. have proposed three-dimensional networks capable of autonomously healing following repeated damage [16,17] but in both approaches the vascular network must be replenished with monomer healing agent between each damage event. Regardless of whether one employs microcapsules, hollow fibers, or network structures, the encapsulating vessel must be large enough to release a sufficient

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amount of healing agent to repair the defect but small enough to not negatively impact matrix material mechanical properties.

White et al. were able to successfully encapsulate DCPD within a polymer matrix containing Grubbs' catalyst. Following the formation of microcracks and subsequent ROMP reaction, this group demonstrated up to 75% recovery of the virgin fracture toughness following 48 hours of healing time [14]. Healing efficiency was assessed by comparing the critical loads at fracture of healed and virgin specimens following TDCB testing. A more detailed description of TDCB testing can be found in various references, including [5,36,41]. This group also found that the average critical load for virgin self-healing matrices containing DCPD and Grubbs' catalyst was 20% higher than the control group containing no microspheres or embedded catalyst, indicating improved matrix toughness through the inhibition of craze formation and subsequent crack propagation.

Andersson et al. described the self-healing capabilities of PDMS with UF microcapsules following tear testing [37]. These investigators showed that the samples were able to consistently recover more than 70% of the original tear strength of the polymer. In research conducted by Blaiszik et al., UF microcapsules containing epoxy resins (Epon 828 and 862) and solvents for use in self-healing applications were successfully engineered [15]. These microcapsules were shown to satisfy the desirable requirements for self-healing materials, including processing survivability, thermal stability, and efficient *in situ* rupture for the delivery of the encapsulated healing agent. Table 4 summarizes the catalyst and matrix materials previously used with repolymerization self-healing techniques.

With any self-healing system, the healing process must occur on the same time scale as the event that initiates and propagates the damage. With current systems the incorporation of mechanically stable curing periods is essential to achieve adequate healing [37]. Clearly, incorporating long curing periods is not feasible with many biomedical applications of constant or semi-constant cyclic loading, such as in orthopedic, dental, and cardiovascular applications. As a result, the competition between crack propagation and self-repair represents a recurring and significant challenge for extension into biomaterials.

There are also a number of widely recognized, general technical challenges associated with implementing first generation self-healing materials in engineering applications. These include identifying catalyst and resin systems that maintain chemical reactivity while encapsulated, can be deployed in response to the presence of microcracks, will infuse adequately into these cracks upon release, will progress to a fully cured product, and will form stable chemical bonds within the matrix material. While promising results have been demonstrated with other materials, effective self-healing materials require careful optimization of the physio-chemical characteristics of the catalyst, the healing agent, the encapsulation/release vehicle materials, and the matrix. Clearly, full optimization is application-specific; however, this field is still very new and the published work to date has primarily focused on characterizing self-healing model systems rather than designing materials for specific applications.

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The only self-healing material of this design nearing commercial application is not polymer-based, but a self-healing concrete being developed at the University of Michigan [18,42]. This self-healing concrete is designed to bend under tensile strain via the formation of tiny microcracks while, alternatively, existing concrete forms large cracks under the same forces. The mixture contains dispersed depots of dry cement within the concrete matrix that are exposed to water and carbon dioxide as cracks form. The reaction of these components forms a calcium carbonate "scar" that fills the defect and halts crack propagation. It was demonstrated that self-healing concrete is capable of withstanding strains up to 5% (compared to 0.01% tensile strain that causes failure of standard concrete) and will recover most, if not all, of its mechanical strength after deformation [18].

While first generation systems are conceptually straightforward and have received the greatest attention for engineering applications to date, there still remain a number of concerns that have limited their more widespread usage. Clever solutions for many of these challenges have been demonstrated for non-biological, *ex vivo* materials, but the constraints are much more severe for *in vivo* applications. In the next section, we discuss the near-term prospects for self-healing biomaterials in the context of specific candidate systems.

Technical concerns associated with first generation approaches:

- Healing agent/catalyst consumption [13,17]
- Healing agent stability in microcapsules [5,14,15]
- Microcapsule shell process survivability [14,15]
- Release of healing agent from capsule [14,39]
- Capsule/matrix interface bonding [14,15,39]
- Healing agent viscosity and volatility [15,43,44]
- Healing agent must infiltrate crack plane readily but not diffuse away too quickly [44]
- Uneven healing agent/catalyst distribution or ratios in matrix [5,17,45-47]

Superimposed upon the above concerns are the following considerations specific to biomaterials:

- May require longer healing times not feasible with cyclically-loaded implants [5,37]
- Complex loading patterns limit healing opportunities
- Functional lifetime of encapsulated agent
- Toxicity of healing agent/catalyst system

5. Candidate systems for first generation self-healing biomaterials

Clotting and scar formation follow a first generation self-healing paradigm; i.e. both are intended to halt and repair damage but do not restore the tissue to its original undamaged state. For example, a defect (wound) initiates the catalytic system (thrombin formation) that causes the healing agent (fibrinogen) to cure and fill the wound site with healing matrix (crosslinked fibrin) [3,48]. As such, fibrin glue is a commercial topical adhesive that consists

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of fibrinogen and thrombin that form a fibrin coagulum within one minute of mixing. It is used to arrest bleeding and for sealing tears in delicate tissues where sutures or staples are not appropriate. Fibrin glue is non-toxic, tissue compatible, and promotes wound healing; however, fibrin coagulum is a soft material with poor mechanical properties [49]. This limits the use of fibrin glue to very soft tissues (e.g. lung, spleen, kidney, etc) that are typically not subject to mechanical loading. The more practical challenge in biomaterials is to identify non-toxic and mechanically robust self-healing systems that can lessen the wear and degradation of mechanically loaded implants, such as orthopedic, cardiovascular, and dental materials (Table 1). To our knowledge, no such self-healing biomaterials system has been reported.

Arguably, self-healing bone cement represents the simplest and most straightforward mechanically loaded first generation self-healing biomaterial to design and test. PMMA bone cement is a space-filling matrix that forms mechanical interlocks between the stem of the implant and the surrounding boney tissue [50]. Bone cement consists of two components: low molecular weight PMMA powder plus an initiator (e.g. benzoyl peroxide), and liquid MMA monomer. Mixing the two components forms a slurry that initiates polymerization yielding a workable dough that is applied to the implant, which next hardens into a solid mass after the implant is inserted into the boney tissue [50]. Cemented total joint replacements are commonly used to provide superior long-term survival of the implant through bone integration but lose effectiveness following wear and microcracking [7,8]. Minimizing the generation of wear particles associated with cemented joint replacements through development of a first generation self-healing bone cement would contribute significantly to the extension of the implant lifetime and improve patient quality of life.

Following the matrix repolymerization paradigm outlined previously (Figure 1), self-healing bone cement would consist of the PMMA matrix plus an embedded catalyst and a dispersed microencapsulated healing agent. Figure 2 illustrates how one might incorporate a self-healing capability into the two-component bone cement; e.g. incorporating encapsulated healing agent into the liquid monomer component, and the healing agent catalyst into the powder component. Mixing the two components polymerizes the PMMA and distributes the encapsulated healing agent and healing agent catalyst throughout the resultant PMMA matrix. Because the cement is mixed in the operating room and then applied directly to the implant there are also no manufacturing or machining processes that must be followed to produce implants of specific sizes and geometries, further simplifying material design.

The only report to date of developing a self-healing biomaterial of any sort came from Biggs et al.[51] who incorporated the matrix repolymerization formulation of White et al.[14] directly into a commercial two-component PMMA bone cement. The Biggs study consisted of encapsulating DCPD monomer in UF microcapsules[52], and blending the microcapsules and organo-metallic Grubbs' catalyst with the PMMA powder component. Mechanical testing of the cured cement was used to demonstrate that the self-healing material formulation increased fracture crack resistance by a substantial 4-8 fold compared to the unmodified formulation. Clearly, Grubbs' catalyst was efficient in catalyzing ROMP of DCPD, and thus effective in sealing microcracks in PMMA matrix; however, DCPD and Grubbs' catalyst are mildly and acutely toxic, respectively[53,54]. UF may also be a problem due to the potential

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for formaldehyde leaching. These toxicity considerations would render the formulation of White et al. undesirable for biomaterials applications. That said, the prospect of self-healing bone cements remains a straightforward and attractive biomaterial prospect, but only if an appropriately non-toxic formulation can be identified.

Table 5 lists some less toxic healing agent systems that could be incorporated into PMMA bone cement. Depending on the system chosen, it may make more sense to separate the placement of the healing agent and catalyst, or possibly to put both healing agent and catalyst in the same component of the bone cement system (Figure 2). Each of these systems requires an embedded catalyst except for the cyanoacrylates, for which the catalyst would be moisture that infuses into the matrix upon microcrack formation.

6. Second generation self-healing materials: Materials that reversibly restore damaged matrix

A “second generation” self-healing material, as defined here, reversibly restores a damaged material to its original, undamaged state. This is analogous to the act of opening (introducing damage) and then closing (initiating repair) a zipper. Except in the melt, reversible repair of most polymers is kinetically inaccessible because the energy barrier to molecular rearrangement is high and the molecular dynamics are slow. Consequently, all second generation self-healing polymer systems currently under investigation concern either the chemistry of weak bonds that are reversible at low temperature or techniques that input the energy necessary for molecular rearrangement. Regardless of temperature and absolute time scale, however, the two approaches are united in that local reversibility (i.e. bond reforming reactions) must be significantly faster than global processes (e.g. polymer flow and macroscopic deformation).

Table 6 provides a summary of a variety of different second generation systems that have been explored. The examples discussed here are again meant to provide a brief introduction to the breadth of the field.

6.1. Second generation self-healing materials based on shape restoration

Second generation strategies for self-healing materials might involve hybrid architectures that possess both reversible and irreversible interactions. Upon application of a force, the ensemble of weak reversible interactions preferentially yields (providing deformability), while the stronger irreversible interactions remain intact (providing scaffolding). Ideally, when the force is removed, the scaffold of irreversible interactions guides the reassembly of the reversible interactions, restoring the material to its original undeformed state (Figure 3). Shape restoration materials therefore differ from “shape memory materials” because they are driven by end group associations rather than by an energy-consuming transition between two states. The successful implementation of the shape restoration strategy might allow for energy dissipation and structural recovery occur on length and time scales such that damage (and the subsequent repair) is never observed. In many situations, the distinction between self-repair, as described here, and highly efficient energy dissipation eventually becomes rather fine to the point of being moot.

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The molecular basis for this strategy finds its roots in dynamic covalent chemistry, which comprises the reversible making and breaking of covalent bonds, and supramolecular chemistry, which imparts the capability of self-assembly or self-organization using highly directional and reversible non-covalent interactions that dictate the overall mechanical properties of a material [55]. The dynamic dissociation and reassociation of stress-bearing bonds allow for rapid conformational changes that affect the properties of shape restoration materials[56,57]. These properties depend on the characteristics of the association, the overall flexibility of the molecule, and the environment of the system[57]. Current dynamic covalent methods comprise a wide range of well-known reaction types[58], and retro Diels-Alder reactions[40], disulfide exchange reactions[59,60], and hydrazone linkages[61] are all potentially compatible with biological environments. Reversible supramolecular interactions in polymers are generally achieved through numerous mechanisms[56,62,63], including: hydrogen bonding, exemplified by the ureidopyrimidinone unit of Sijbesma and Meijer[62]; metal coordination chemistry, for example silver complexation by tridentate heterocyclic peptides[64] or calcium-bridged carboxylates[65]; or π-stacking, such as that seen with triphenylene motifs[66]. Other synthetic supramolecular motifs are known to function in biological environments, but an even greater repository of useful structures is likely found in biology itself; for example, peptide-peptide, ligand-receptor, and nucleic acid-based interactions [67-72].

6.2. Second generation self-healing materials based on application of heat or light

A somewhat exotic but interesting example of heat-induced defect repair is polymer flow caused by projectile puncture. Research conducted at the NASA Langley Research Center described self-healing characteristics of EMAA (Surlyn), ethylene-octene (Affinity EG 8200), and PB-g-PMA-co-PAN that utilize the heat produced by a penetrating projectile (e.g. a bullet) to induce localized melting and rapid reassociation of polymer chains, inducing repair [13,73,74]. While such materials may have military and space exploration applications, this approach does not seem well-suited for biomaterials applications [75]. Interested readers are encouraged to view a short NASA Real World Mathematics eClip, accessed online on May 19, 2010, at: http://www.nasa.gov/audience/foreducators/nasaeclips/realworld/aeronautics.html.

In contrast to repair by localized polymer flow are self-healing systems that repair defects by reforming bonds upon the application of heat, radiation, or electric fields (Figure 4). As with the shape restoration strategies in the preceding section, a primary challenge is to identify chemistries in which localized bond forming takes place on time scales that are much shorter than both material flow/deformation and crack propagation. One demonstrated example of such chemistry is the Diels-Alder reaction, in which a diene and a dienophile undergo cycloaddition to form the Diels-Alder adduct that can dissociate at high temperatures via the retro-Diels-Alder reaction [76]. As such, polymers containing Diels-Alder chemistries have reversible covalent bonds that can be formed and broken by thermal cycling. These polymers are particularly useful because they minimize free radical formation that could lead to undesirable chain reactions resulting in improper structural recovery [77]. Chen et al. were able to design a matrix able to repeatedly heal under mild conditions (i.e. 75°C for 3 hours) without requiring a catalyst, additional monomer, or special surface treatments of the

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fracture plane [78,79]. This group found that the energy needed to break the Diels-Alder adducts was much lower than the energy required to break other covalent bonds, demonstrating the preferential failure of these interactions. Recovery of about 57% of the original fracture load was reported. The group proposed using this material for electronic packaging applications where cracking occurs due to differences in the thermal index of expansion [78].

Repair by the application of light is also of considerable interest. The Urban research group has developed a self-healing material consisting of oxetane-substituted chitosan precursors incorporated into polyurethane networks [80]. These systems use ultraviolet light to recombine free radicals to form crosslinks and have been found to repair surface scratch damage in less than one hour. These materials have been proposed for use in automotive coatings that are both damaged and exposed to ultraviolet light during common usage. This system also may be employed regardless of ambient temperature or humidity, further enabling its widespread use. Unfortunately, development of self-healing biomaterials based on energy-dependent mechanisms will be limited to surface-accessible environments such as cutaneous repair unless it can be tied to a deeply-penetrating heat or radiation source.

In comparison to first generation self-healing materials, the second generation approach is more compatible with “soft”, low-modulus material applications. In addition, there exists the possibility of pseudo-infinite cycling and potential advantages that come with a single-component (as opposed to composite) system. Nevertheless, the utility of second generation materials currently lags that of first generation materials, and a number of significant challenges exist.

Technical concerns associated with second generation approaches:

- Without energy input
  - Lack structural properties to sustain significant loads[77,81]
  - Inadvertent triggering of reversibility mechanism
  - Formation of free radicals[78,79]
  - Potential for improper structural recovery
  - Design complexity
- With energy input
  - Requires external application of forces[13]
  - Polymer remains in failed state indefinitely
  - No autonomous method to recognize damage[13]
  - Slow time scale of healing[78]

As with first generation systems, there are also unique concerns with second generation approaches that are associated with biocompatibility constraints:

- Toxicity of materials

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- Diffusion of reversible crosslink materials out of scaffold

7. Candidate systems for second-generation self-healing biomaterials

Shape restoration exists in a number of biological systems. For example, the native double helical structure of DNA is reversibly restored during DNA synthesis and repair by the breaking and reforming of paired, hydrogen-bonding purines and pyrimidines [82]. Similarly, many denatured proteins can “renature” to their native conformation, given proper conditions of ionic strength and temperature, by reforming hydrogen, ionic, and hydrophobic bonds between specific amino acid residues [82]. A third example of reversible shape restoration behavior is the protein elastin where the deformed (i.e. extended) state strains the kinked peptide chains that generate the entropy-driven shape restoration force of elastic tissues [83]. In each case the native structure is deformed and then restored (if the damage is not too extensive) by disassociation and then reassociation of an ensemble of individually weak interactions. The key to biological shape restoration is that the native state is both thermodynamically favorable and kinetically accessible. Following the concept of weak reversible interactions incorporated within stronger irreversible networks, Thompson et al. have reported that bone contains certain “sacrificial bonds” that protect the biopolymer backbone and dissipate energy. These sacrificial bonds are found within or between the collagen molecules and contribute to the toughness of the bone by acting as reversible crosslinks that undergo predictable and sequential failure [84]. Synthetic materials with similar properties are also known[85].

Work by Leibler's group has utilized supramolecular assembly to create a self-healing and thermoreversible rubber that demonstrates remarkable recoverable extensibility and minimal creep under applied load [86]. The material network was generated from fatty dimer acids from vegetable oils and urea. The group found that the strain at break exceeded 500%, confirming the rubber-like properties of the material. Samples were also able to completely recover their dimensions following the application of a stress of 5kPa for more than 22 hours. These mechanical properties illustrate that the material behaves like a rubber although it is made of oligomers. Furthermore, when the sample was cut into pieces, the individual pieces could self-heal when brought into contact at room temperature. The material is capable of undergoing many cycles of stretching, breaking, and healing; contact times as short as 15 minutes were found sufficient to achieve healing.

This supramolecular material contains three types of functional groups, amidoethyl imidazolidone, di(amido ethyl) urea, and diamido tetraethyl triurea, that associate via multiple hydrogen bonds. Self-healing is therefore efficient because there are a large number of groups available to restore linkages at the fracture plane. Although the Leibler work is conducted by looking at macroscopic failure that requires the broken interfaces to be held together to achieve healing, similar processes could happen internally to repair microcrack damage. An approach similar to this one could produce a material capable of “healing” damage before it is even detectable.

Many groups have also investigated polymers that incorporate oligonucleotide sequences that hybridize to form reversible crosslinks (Figure 5)[68,69,87-98]. Changing the specificity, affinity, density, and accessibility of the reversible crosslinks allows them to tailor the

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mechanical and shape restoration properties of these materials. However, when DNA crosslinks are disrupted, additional crosslinking DNA must be provided, but no catalyst is required to restore lost linkages [87]. These approaches demonstrate that there is a robust toolkit of interactions both from nature and through synthesis that could be utilized in future work to develop self-healing biomaterials. “Softer” biological materials, such as synovial fluid or cartilage, may provide the ideal introductory pathway for second generation approaches to biomaterials.

8. Design criteria: Requirements for self-repair

All biomaterials experience a wide variety of degrading conditions throughout the lifetime of the implant, often losing viability as time progresses. Titanium and titanium alloys are the only clinically used biomaterials that demonstrate any capacity to self-repair *in situ* [21]. These materials have the ability to spontaneously form a tightly adherent and corrosion-resistant titanium oxide under physiological conditions. This property enables titanium-based biomaterials to re-passivate areas where the protective oxide layer is damaged through wear or impact, thus intrinsically resisting corrosion-induced failures. That said, these metals are not capable of repairing mechanical damage, nor are any other ceramic, polymeric, or composite biomaterials currently in use.

Currently, all materials used in implants are incapable of effectively preventing or delaying the advance of mechanical damage, much less managing or even reversing damage. The following list summarizes the basic design requirements for all generations of self-healing materials as well as the considerations for biocompatible self-healing materials. Most importantly, these materials must address the issues associated with the formation and coalescence of microcracks within the bulk material using non-toxic approaches.

General requirements for self-healing materials:

- Suitable mechanical and structural properties for intended application
- Processed using existing or inexpensive techniques without losing healing capabilities
- Must not be prohibitively expensive
- Capable of healing repeatedly, autonomously, and rapidly
- Capable of sensing damage without external intervention
- Able to repair defects of various sizes

Additional constraints for biocompatible self-healing materials:

- Sterilized using existing or inexpensive techniques
- Low cytotoxicity to minimize immune responses and potential tissue damage
- Produce benign byproducts during the healing reaction to reduce potential of leaching of toxic materials
- Implanted with the same level of ease as existing biomaterials and implant

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- Shelf-lives similar to or better than those of existing biomaterials
- Capable of withstanding the body's harsh environment

It has been well-documented that microcracks propagating through a polymer matrix will cause the release of healing agent capable of polymerizing to restore the material strength [13-15,37,38]. Self-healing implants designed using the first generation approach will eventually deplete the supply of healing agent or embedded catalyst, but a reasonable goal for a first generation self-healing biomaterial is to extend implant lifetime rather than providing sustainable healing capabilities.

Second generation approaches to self-healing are theoretically capable of fully restoring a damaged matrix. Using reversible chemical linkages to achieve self-healing in materials is particularly intriguing because this could allow for sustained healing capabilities not possible with first generation approaches (i.e. there are is no longer the issue of healing agent or catalyst depletion) [68,81]. Modifications of stimuli-responsive polymers could also yield healing systems that respond to specific triggers seen with particular biomedical applications (i.e. pH, temperature, specific forces or loading patterns). Whereas the first generation approach is somewhat limited in its uses and primarily combats microcrack propagation, reversible chemistries could be used to treat various types of damage, both mechanical and chemical in nature. Interestingly, such an approach might ultimately manifest itself as a more highly efficient zeroth generation material, in that damage might be so localized and repaired so quickly that it is never observed. Sustained self-repair has the potential for unprecedented implant success through tailored specificity, but also may make suitable chemistries extremely complicated to develop.

One of the most significant problems associated with any self-healing approach is developing a material with the necessary properties required for load-bearing applications. Self-healing polymer gels currently under development clearly lack the necessary mechanical durability [77]. Increasing the molecular weight of the self-healing gel would enhance material durability at the expense of reversibility.

9. Conclusions

Self-healing materials are an exciting new area that may broadly benefit materials science in applications ranging from aerospace engineering to construction materials. While several approaches are currently in development, none specifically address the need for biocompatible self-healing materials that could be employed for implants damaged via cyclic loading patterns.

A number of first generation and shape restoration techniques already exist that are feasible, realistic, and reasonably effective. With certain innovations it should be possible to adapt an existing mechanism to design biocompatible self-healing materials that irreversibly extend implant lifetimes. It is also possible to envision a genuinely self-healing biomaterial that employs a reversible self-healing chemistry designed to yield and reassociate under the precise loading patterns seen with specific implants. The requirement for sufficient molecular mobility also may limit second generation systems to mechanically weak

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hydrogels. Similar to the self-healing materials field in general, the first self-healing, load-bearing biomaterials to arise will likely employ an irreversible healing agent system rather than a more complex reversible system.

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Glossary of Terms

BIS-GMA	Bis-phenol A glycidyl methacrylate
CF	Carbon fibers
CS	Calcium silicate
DBTL	Di-*n*-butyltin dilaurate
DCPD	Dicyclopentadiene
DETA	Diethylenetriamine
EGDMA	Ethylene glycol dimethacrylate
EMAA	Ethylene-co-methacrylic acid
ENB	5-ethylidene-2-norbornene
Epon 682	Diglycidyl ether of bisphenol-F
Epon 828	Diglycidyl ether of bisphenol-A
HA	Hydroxyapatite
HEMA	Hydroxyethylmethacrylate
HOPDMS	Hydroxyl end-functionalized polydimethylsiloxane
KH-816	Cycloalipathic amine
MMA-MEA	Poly(methyl methacrylate-co-methyl ethylacrylate)
OMs	Oligonucleotide-based monomers
PB-g-PMA-co-PAN	Poly(butadiene)-graft-poly(methyl acrylate-co-acrylonitrile)
PBT	Polybutylene terephthalate
PC	Polycarbonate
PDES	Polydiethoxysiloxane
PDMS	Polydimethylsiloxane
PE	Polyethylene
PEEK	Polyetheretherketone
PEG	Polyethylene glycol

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PELA	Block copolymer of lactic acid and polyethylene glycol
PET	Polyethylene terephthalate
PHB	Polyhydroxybutyrate
PLA	Polylactic acid
PMMA	Poly(methyl methacrylate)
PP	Polypropylene
PPE	Poly(phenylene ether)
PS	Polysulfone
PTFE	Polytetrafluoroethylene
PU	Polyurethane
ROMP	Ring-opening metathesis polymerization
RP	Reversible polymer
SR	Self-reinforced
TDCB	Tapered-double cantilever beam
TJR	Total joint replacement
UF	Urea-formaldehyde
UHMWPE	Ultra high molecular weight polyethylene
YD-115	Butyl diglycidyl ether of bisphenol-A

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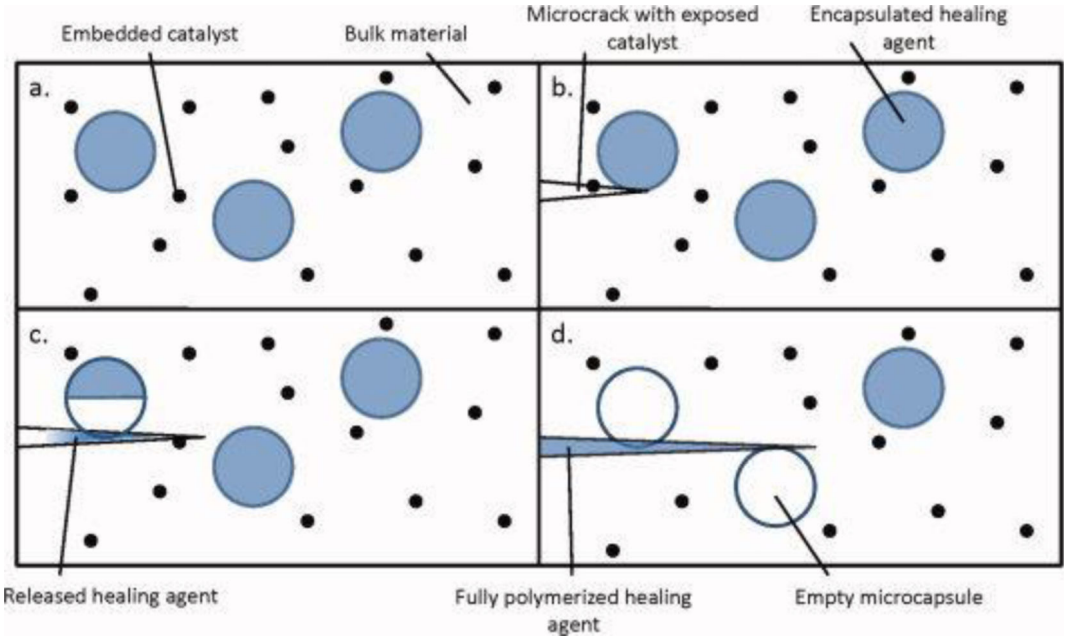

Figure 1.

First generation self-healing mechanism. The undamaged matrix is shown in (a). Embedded catalyst is exposed as microcracks are generated (b). Microcapsules containing a healing agent are fractured by the microcracks, causing the release of healing agent and its subsequent reaction with the exposed catalyst (c). Following this polymerization, propagation of the microcrack is inhibited (d). Adapted from various works by M. Kessler, S. White, N. Sottos, et al.5, 13, 14, 77, 79 [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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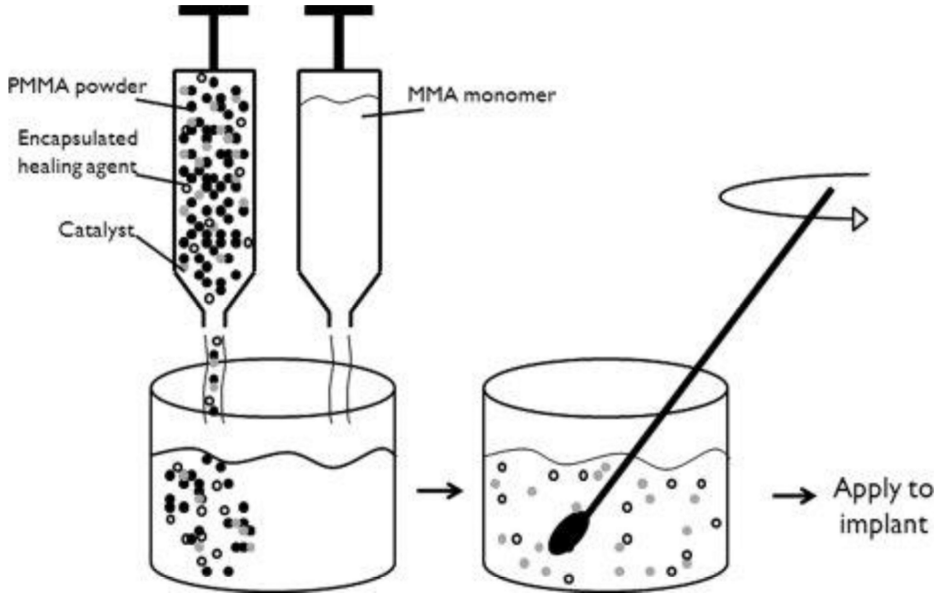

Figure 2.

Potential design for a self-healing bone cement utilizing the first generation self-healing approach. The catalyst and encapsulated healing agent to be embedded are packaged with the PMMA powder component of the bone cement. Mixture of the two bone cement components. Mixture of the two bone cement components will disperse the solid catalyst and encapsulated healing agent within the bone cement. The cement can then be applied to the implant following current protocols.

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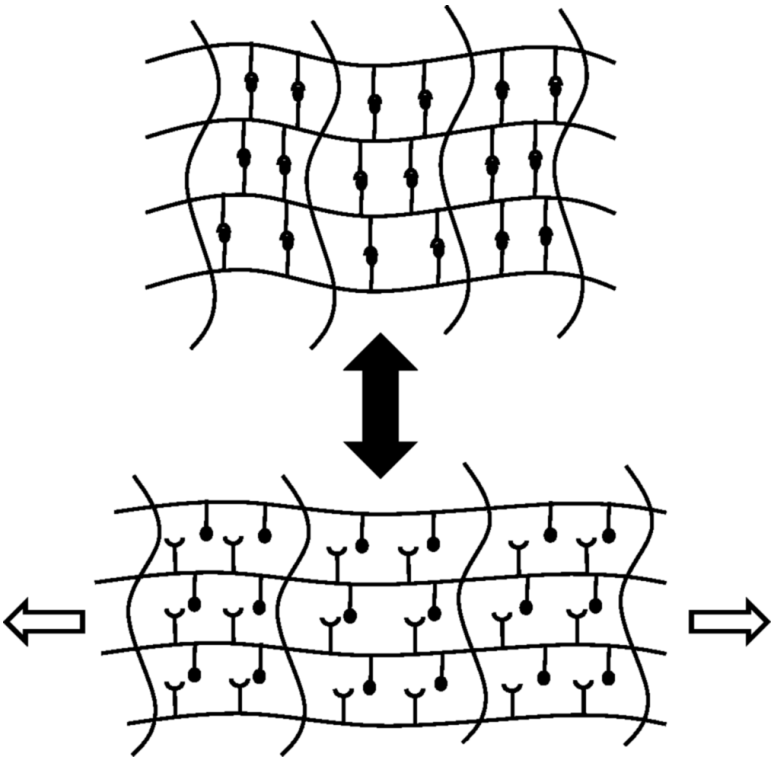

Figure 3.

Autonomous second generation materials. Following the application of a force, the reversible crosslinks dissociate while the covalent crosslinks remain intact. When the force is removed, the material returns to its original structure.

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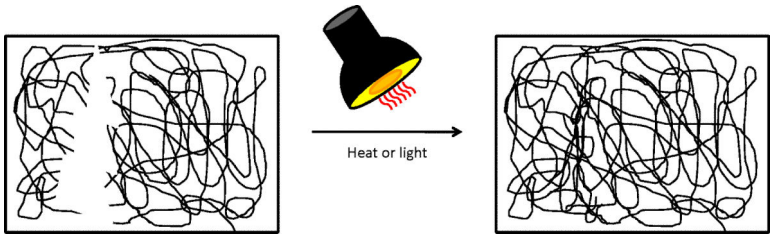

Figure 4.

Second generation materials requiring energy input to achieve healing. These materials are capable of restoring the original material structure following the application of an external force such as heat or light. As depicted, a polymer matrix is damaged and following the application of heat, the polymer chains are able to flow and restore matrix integrity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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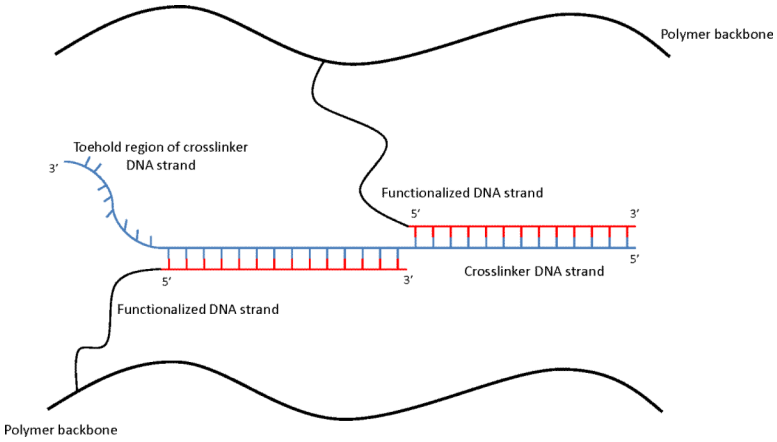

Figure 5.

Second generation materials based on DNA crosslinks. The toehold region of the crosslinker DNA strand can be used to eliminate the crosslinks. Addition of a DNA strand complementary to this toehold region results in competitive binding between the removal strand and the crosslinker DNA strand without requiring the application of further external forces. Adapted from Lin et al.103[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

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Table 1

Typical physiological stresses experienced by implants

Implant	Physiological stresses	References
Artificial heart valve	1.13-16kPa	[1], [99], [100], [101]
Vascular graft	10-15kPa	[1]
Artificial hip	360-960kPa	[6], [102]
Artificial knee	56-88kPa	[103]
Dental implant	11.6-76.8kPa	[104], [105], [106], [107], [108]
Intraocular lens	1.3-2.6kPa	[1]

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Table 2

Common implant materials and their modes of failure

Implant	Material	Failure Mode	References
Joint replacement load-bearing surfaces (hip, knee)	UHMWPE	Wear	[9, 25]
	HDPE	Wear and abrasion, strain softening after yield	[25]
	PTFE	Wear, creep under compression	[25, 26]
	Polyacetal	Wear, strain softening after yield	[25]
Heart valves	PU, silicone polyether urethanes, polycarbonate urethanes	Biodegradation, mineralization, fatigue, wear, crack formation	[10, 11]
Bone cement	Acrylics (ex: PMMA)	Joint loosening, microcrack formation and accumulation through cyclic loading, creep under compression, cause third body wear in joint replacement	[9, 109, 110]
Dental implants	HA, ceramics, UHMWPE, PTFE, PS, PET	Fatigue, cracking and chipping, dislocation from base, wear and the formation of wear particles	[106, 111, 112, 113, 114]
Dental cements and sealants	Zinc phosphate, zinc polycarboxylate, resin cement, glass ionmer	Degradation due to harshness of mouth environment, cracking, renewed tooth decay	[49]

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Table 3

Biomedical composites

Implant	Dispersed phase/matrix phase	Used clinically?	References
Acetabular cups	CF/UHMWPE, UHMWPE/UHMWPE	No	[32], [115], [116]
Articular surfaces in joint applications	CF/UHMWPE, CF/PMMA, CF/PS, CF/epoxy	No	[32], [117]
Bone plates	CF/epoxy, CF/PMMA, CF/PP, CF/PS, CF/PE, CF/nylon, CF/PBT, CF/PEEK, *CF/PLA*[*], glass fibers/epoxy	Yes, in part	[32], [118], [119], [120], [121], [122], [123], [124]
Bone grafts	Bioglass/PS, *HA/PE*, HA/PEG, HA/PBT, HA/PLLA, HA/PHB, CS/PEEK	Yes, in part	[32], [124], [125], [126]
Dental composites	Quartz, barium glass, or colloidal silica as fillers in BIS-GMA or urethane dimethacrylate matrices	Yes	[32]
Dental posts	Glass fibers/polyester, unidirectional carbon fiber/epoxy, braided CF/epoxy	No	[32], [127]
Hip stems	CF/PS, CF/carbon, CF/epoxy, *CF/PEEK*	Yes, in part	[32], [128], [117]
Intramedullary nails and screws	Glass fibers/PEEK, CF/Vectra A950, CF/PEEK, CF/PS, *PLA/PLA*, *PGA/PGA*, *PLGA/PLGA*	Yes, in part	[24], [32], [33], [129]
Lumbar interbody fusion	CF/PEEK, CF/PS	No	[32], [130], [131], [132]
Vascular grafts	Lycra-type PU fibers in a Pellathane-type PU/PELA mixture matrix	No	[32], [133]
Vertebral body replacement	Bioglass/PU	No	[32], [134], [135]
Vertebral disc replacement	PET/silicone rubber, PET/hydrogel	No	[32], [136], [137]

[*] Italicized materials denote those used clinically or currently undergoing clinical testing

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Table 4

Healing agents, matrix materials, and their composites studied for application with first generation self-healing techniques

Matrix Material	Healing Agent	Catalyst	References
Vinyl ester	HOPDMS and PDES (phase separated in matrix)	DBTL in PU microcapsules	37,38
Epon 828 cured with DETA	DCPD in UF capsules	Grubbs' catalyst in paraffin wax microspheres	45,138
PMMA	DCPD in UF capsules	Grubbs' catalyst	51
Epon 828 cured with DETA	Epon 862 or Epon 828 diluted with cholorobenzene, phenylacetate, ethyl phenylacetate in UF capsules	None	15
Epon 828 cured with DETA	DCPD in UF capsules	Grubbs' catalyst	5,13,14,43,44
YD-115 cured with KH-816	DCPD in UF capsules	Grubbs' catalyst	43,44
YD-115 cured with KH-816	ENB in UF capsules	Grubbs' catalyst	43,44

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Table 5

Possible healing agent systems for self-healing bone cement

Healing agent	Catalyst	Advantages	Disadvantages
Fibrin glue	Thrombin	Non-toxic, tissue compatible	Biodegradable, mechanically weak with lower adhesion strengths
MMA monomer	Benzoyl peroxide	Same base as PMMA bone cement, mechanically strong	Both components are toxic, MMA immiscible with water
Medical grade epoxy resin	Polyamine monomers	Good mechanical strength, bonds well with PMMA, proven system	Unreacted components are toxic, resin immiscible with water
Medical grade cyanoacrylate tissue adhesive	Moisture	Tissue compatible, bonds quickly to PMMA, good mechanical strength	Unreacted monomer may be toxic, cyanoacrylate subject to moisture intrusion

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Table 6

Second generation self-healing systems

Trigger mechanism	Autonomous healing?	Healing mechanism	References
Hydrogen bonding	Yes	Quadruple hydrogen bonds dimerized with 2-ureido-4-pyrimidone derivatives	62
Hydrogen bonding	Yes	Multiple hydrogen bonds formed between amidoethyl imidazolidone, di(amido ethyl) urea, and diamido tetraethyl triurea	86
Metal-ligand coordination	Yes	Bifunctional palladium or platinum coordinating with pyridine in hydrogel matrix	77
Heating	No	PPE repair achieved through oxygen and a copper catalyst resulting in polymerization	16
Steam	No	Polymerization of the PC backbone catalyzed by weak alkali	16,139
UV light	No	Recombination of free radicals to form PU crosslinks	80
Heat	Yes	Heat from projectile puncture repairs thin films of EMAA, ethylene-octene, and PB-g-PMA-co-PAN	74
Heat	No	Thermally reversible Diels-Alder cycloaddition of multi-furan and multi-maleimide	78,79
Heat	No	Thermoreversibility via denaturing double-stranded DNA crosslinks	69,87
Competitive binding	No	Competitive binding of a removal strand with DNA crosslink results in dissolution of DNA crosslinks	69,87
Electric field	No	Enhanced hydrogen bonding under positive electric field	140