New Resins for Dental Composites

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Abstract
Restorative composites have evolved significantly since they were first introduced in the early 1960s, with most of the development concentrating on the filler technology. This has led to improved mechanical properties, notably wear resistance, and has expanded the use of composites to larger posterior restorations. On the organic matrix side, concerns over the polymerization stress and the potential damage to the bonded interface have dominated research in the past 20 y, with many "low-shrinkage" composites being launched commercially. The lack of clinical correlation between the use of these materials and improved restoration outcomes has shifted the focus more recently to improving materials' resistance to degradation in the oral environment, caused by aqueous solvents and salivary enzymes, as well as biofilm development. Antimicrobial and ester-free monomers have been developed in the recent past, and evidence is mounting for their potential benefit. This article reviews literature on the newest materials currently on the market and provides an outlook for the future developments needed to improve restoration longevity past the average 10 y.

Keywords: permanent dental restorations, composite resins, polymerization, methacrylates, BisGMA, stress

Introduction

The significant evolution of composites for direct tooth restorations since their introduction on the market has allowed the expansion of their indications to larger posterior restorations, which were classically only restored with amalgams. Most of the developments have focused on the filler systems, leading to improvements mainly in mechanical properties and notably on wear resistance (Ferracane 2011). Irrespective of these improvements, the average life span of a composite restoration is still only around 10 y (Demarco et al. 2012). In the early 2000s, greater attention was focused on the further development of the organic matrix, which to date had been based exclusively on methacrylate chemistry, more specifically BisGMA (bisphenol A glycidyl dimethacrylate), TEGDMA (triethylene glycol dimethacrylate), BisEMA (ethoxylated bisphenol-A dimethacrylate), and UDMA (urethane dimethacrylate). Alternative monomers began to be developed with the common objective of reducing polymerization shrinkage and stress, as the possible association between stress development and gap formation at the bonded interface was being emphasized (Feng et al. 2010). The new monomers were either based on ring-opening polymerizable moieties (with the only commercial example being Filtek LS, based on silorane chemistry) or on higher molecular weight molecules (Fig. 1), with both strategies proving successful at reducing the molar shrinkage coefficient and ultimately the polymerization stress measured in vitro (Boaro et al. 2010). Clinical studies, however, have failed to show differences between the "low-shrinkage/low-stress" materials and their conventional counterparts in terms of restoration survival and incidence of secondary decay. This is likely due to the multifactorial nature of caries development and the overall technique sensitivity of the restorative procedure (Magno et al. 2016). More recently, the focus in resin development has shifted to improving the overall resistance of the restoration to degradation in the oral environment, including the actual hydrolysis of ester bonds present in methacrylates by salivary and bacterial enzymes, as well as by preventing biofilm formation on the surface and interface of composite restorations (Wu et al. 2015). In addition, much effort has been concentrated on developing materials that are simpler to use by virtue of requiring fewer application steps, such as bulk-fill and self-adhesive composites.

A 2011 review approached the inorganic phase of the resin composite (Ferracane 2011). Specifically on the organic matrix realm, another review has covered many aspects of the low-shrinkage/low-stress strategies, including multi-methacrylates, ultra-rapid methacrylates, thiol-ene polymerizations, and alternative polymerization routes, as well as aspects related to inclusion of nanoparticles and filler surface treatment (Cramer et al. 2011). The present review focuses solely on the organic phase of restorative composites, including novel monomer systems, polymeric additives, and other resin-related modifications. The text emphasizes literature published in the last 10 y, indexed in Scopus and/or in the patent literature. Developments in materials involving fewer application steps and self-adhesive, bioactive, and antibacterial materials with commercial examples are analyzed. Finally, we provide an outlook for the future

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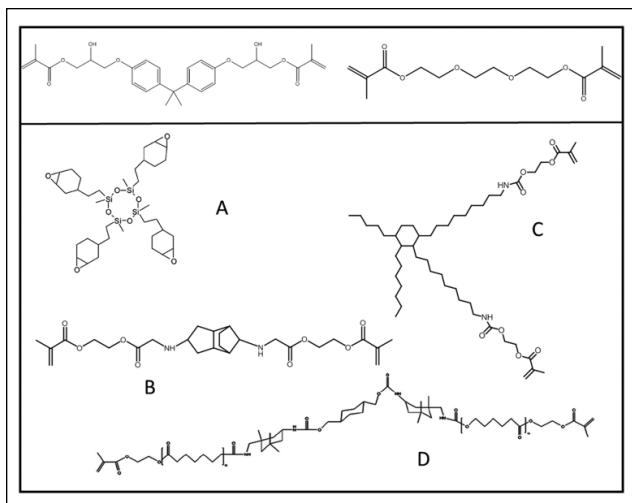Email: pfeiferc@ohsu.edu

Figure 1. Top: Molecular structures of BisGMA (bisphenol A glycidyl dimethacrylate) (left) and TEGDMA (triethylene glycol dimethacrylate) (right). Bottom: Molecular structure of alternative monomers currently used in commercial products. (**A**) Oxirane (Filtek LS; 3M-ESPE), (**B**) TCD-urethane (Venus Diamond; Heraeus Kulzer), (**C**) dimeracid dimethacrylate (N'Durance; ConfiDental-Septodont), and (**D**) DuPont DX-511 (Kalore; GC America).

of composites based on ongoing research efforts in the areas of network modification (i.e., through the use of covalent adaptable networks and the use of prepolymerized and tailorable nanoparticles) and the production of more degradation-resistant materials. It is evident from the amount of activity in the past 5 to 10 y that the topic of improvement of dental composites, specifically the organic matrix, remains relevant. The goal of researchers in this area is to produce a composite material with all the esthetic advantages of current materials but one that will last at least twice as long as current formulations, thus more capably preserving the patient's natural tooth structure and avoiding costly retreatments.

Commercially Available Materials

One of the main drawbacks of resin composites compared with other direct placement materials, such as amalgam, is the technique sensitivity of the restorative procedure. This means the clinical outcomes of different types of restorations are strongly dependent on the operator (Scotti et al. 2016). For example, the adhesive application involves many steps, and there is ample opportunity for operator error. Also, the incremental layering technique is time-consuming and introduces additional variables to the treatment. With the aim of simplifying the procedure, bulk-fill and self-adhesive materials were developed, with the first few clinical trials being published.

Bulk-Fill Composites

Bulk-fill resin composites have been introduced to the market in both flowable and conventional/sculptable viscosities, with the premise of simplified application, while still ensuring

adequate depth of cure. This has been achieved for different commercial materials via different routes, which include optimization of the initiator system (novel photoinitiators or greater concentration of conventional photoinitiators), modifications of the filler system (larger fillers or more translucent fillers), or inclusion of different chemistries in the composition (Miletic et al. 2017; Son et al. 2017). Flowable bulk-fill materials generally have lower filler loading than nonflowable, sculptable materials and require that the occlusal layer be filled with a "cap" of a more highly filled composite that is expected to be stronger and more wear resistant under occlusal loading. One example is SureFil SDR flow (Dentsply). According to the manufacturer, this product features, in addition to the lower filler content, a novel UDMA-based monomer with high molecular weight (849 g/mol), which helps to reduce shrinkage. The novel part of the monomer, to which the manufacturer refers as "polymerization modulator," consists of photoactive groups embedded in the backbone of an oligomeric species (Xiaoming et al. 2015). The rationale is that as the material is exposed to light, the photoactive groups undergo photo-cleavage, at the same time breaking the oligomer chain to accommodate stress and generating radicals, which can further contribute to the overall conversion and crosslinking of the material. Indeed, these materials have been shown to reduce polymerization stress without reducing the polymerization rate or degree of conversion (Kim et al. 2015). In theory, this would eliminate the need for incremental filling on the basis of stress reduction.

Other nonflowable bulk-fill materials include Tetric EvoCeram Bulk-Fill (Ivoclar Vivadent) and Filtek Bulk-Fill (3M-ESPE). Tetric EvoCeram uses a photoinitiator system containing Ivocerin—a germanium-based light initiator, whose greater quantum yield conversion makes it more efficient in promoting polymerization in depth despite the shorter wavelengths needed for its optimal activation (λ_{max}) (Moszner et al. 2009). For this material, shrinkage is reduced and stress is further relieved through the inclusion of prepolymerized resin filler particles. Studies have confirmed low shrinkage stress and efficient depth of cure (Jang et al. 2015). In the case of Filtek Bulk-Fill (3M-ESPE), among other compositional features, at least 1 monomer capable of undergoing addition fragmentation chain transfer is included in the formulation (3M technical profile). This mechanism has been widely described in the literature for applications where strain accommodation and stress reduction are desirable features, such as in the polymer coatings industry (Kloxin et al. 2010; Park et al. 2010). The main effect of this chemistry is that it renders the covalent network capable of adapting to stress generation via bond breakage and re-formation, without net loss of crosslinking via an allyl disulfide bond (Park et al. 2012). Results with experimental materials have demonstrated at least maintenance of mechanical properties and up to 30% reduction in polymerization stress with model molecules (Park et al. 2012).

In general, the utilization of bulk-fill resin composites in posterior restorations has been shown to reduce cusp deformation (Rosatto et al. 2015; Van Ende et al. 2017) and polymerization stress (Fronza et al. 2015), as well as increase the fracture resistance (Leprince et al. 2014; Rosatto et al. 2015)

when tested in vitro. However, flowable bulk-fill materials produce lower mechanical properties in comparison with highly filled nano-hybrid composites and regular consistency bulk-fill materials, which can restrict their utilization under high occlusal load (Tomaszewska et al. 2015). Recent clinical studies indicate that flowable and regular-consistency bulk-fill materials present similar clinical performance compared with conventional materials (van Dijken et al. 2016).

Self-Adhesive Composites and Resin Cements

Self-adhesive resin composites, such as Vertise Flow and Dyad Flow (Kerr Corporation), have been developed with the goal of simplifying the composite restorative procedure by eliminating its most technique-sensitive step: the adhesive application. The resins in these composites contain glycerol phosphate dimethacrylate, a self-etching, dimethacrylate monomer capable of crosslinking and copolymerization with other methacrylates (Yuan et al. 2015), as well as the potential for chemical bonding with the tooth's mineral content. There is also some evidence for micromechanical interlocking between polymerized monomers and partially demineralized collagen fibrils (Shafiei et al. 2016). All commercial self-adhesive resin-based materials commercialized to date are flowable (i.e., materials designed to enhance adaptation to the substrate by virtue of their low viscosity). Several studies published fairly recently have demonstrated, however, that the bond strength values of resin-based self-adhesive cements and restorative flowable composites are not as high as those achieved with separate adhesives and composite restoratives to tooth structure (Poitevin et al. 2013). This has been attributed to the fact that the acidity of the monomers in the self-adhesive materials is not low enough to promote extensive resin penetration through smear-covered surfaces or into aprismatic enamel, and to the fact that the viscosity presented by flowable materials is not low enough to ensure good adaptation to the cavity walls (Yuan et al. 2015). Their bond strength is improved only after traditional etch-and-rinse procedures with concentrated phosphoric acid are performed (Schuldt et al. 2015). In the case of bonding of fiber posts to root canals, which involves dentin in different depths and, therefore, with different structures, self-adhesive cements presented similar bond strengths compared with conventional controls (Vieira-Filho et al. 2017). In that case, the dentin structure seems to play a more important role than the cement composition. In addition, there is evidence for high water sorption and solubility, as well as increased microleakage for self-adhesive cements (Yuan et al. 2015), although hardness and elastic modulus appear to be comparable to other materials (Salerno et al. 2011).

Finally, even though this is not the focus of this review, it is important to note that soluble inorganic compounds, such as sodium silicates and biomimetic polyanions, can also be used to mediate adhesion (Sauro et al. 2016). Flowable resins containing these types of compounds have been demonstrated to stabilize the hybrid layer through apatite crystallite deposition in collagen (Sauro et al. 2013).

Bioactive Materials

In the past decade, in addition to lower stress generating/high-strength materials, researchers in academics and industry have also focused on developing materials with bioactive characteristics. The ideal restorative material of the future will not only be able to withstand occlusal loads and develop low polymerization stress but also be antifouling, antibacterial, and remineralizing, in addition to being biocompatible. Many efforts have been focused on each of these areas, as will be explored in the following sections as they relate to developments in resin-based systems.

Antimicrobial Materials

One of the main reasons for composite restoration failure is secondary caries development, presumably related to biofilm formation on and within gaps at the restoration margins (Lempel et al. 2015). Antimicrobial materials, therefore, have long been sought to either kill the bacteria on contact (bactericidal effect) or prevent bacterial adhesion (antifouling effect), and many strategies have been pursued. Quaternary ammonium methacrylates (QAMs) are being extensively studied and have been introduced in resin composites since they show bactericidal effects and are able to reduce bacterial adhesion (Cheng et al. 2015; K. Zhang et al. 2016). Dimethylaminododecyl methacrylate (DMAHDM), bis(2-methacryloyloxyethyl) dimethylammonium bromide (QADM), 12-methacryloyloxydodecylpyridinium bromide (MDPB), methacryloxylethylcetylammonium chloride (DMAE-CB), and quaternary ammonium polyethylenimine (QPEI) are some examples of the compounds that have been studied. Their demonstrated antibacterial effects come without compromise to the mechanical properties and short-term biocompatibility in highly filled composites (Ge et al. 2015). DMAHDM in particular seems to be able to inhibit the metabolic activity and lactic acid production of biofilm bacteria and to drastically reduce biofilm growth, since its positive charge interacts with the negatively charged bacterial wall, and the long side chain functions as a lancet to disrupt wall structure (Wu et al. 2015). Some examples of commercial materials relying on charged monomer technology include one adhesive system (Clearfil SE Protect, Kuraray Dental) that contains MDPB (12-methacryloyloxydodecyl pyridinium bromide) and Activa BioActive-Restorative resin composite (Pulpdent), which is formulated with an ionic-resin consisting of di-tri multifunctional monomers in an network crosslinked by polyacids (Activa technical profile). One aspect that cannot be ignored, despite the clear and encouraging evidence to support the use of antimicrobial materials, is the fact that for any agent to be effective in the long term, there needs to be substantial and prolonged activity at the surface, as well as in the bulk of the biofilm layer (Takenaka et al. 2008). Since the mechanism of action of QAMs necessarily involves contact with the bacterial cell surface, the reported effects in the bulk of the biofilm can be speculated to be due either to unreacted or degraded monomer leaching into the biofilm. If that is the case, toxicity concerns are raised.

One major point that relates to biofilm formation is that once the acquired pellicle is formed on the tooth or material surface, the contact kill mechanisms described so far are hampered, and bacterial adhesion is facilitated (S. Zhang et al. 2016). Oral microbes interact with surfaces coated with a glycoprotein-rich pellicle, to which early colonizers bind and then coadhere with other species (Paula et al. 2016). The growth and development of biofilms are regulated by the characteristics of oral surfaces, including energy, charge, chemical composition, mechanical properties, and hydrophilic character (Paula and Koo 2016). Negatively charged surfaces, highly hydrophobic or hydrophilic surfaces, and nanoscale surface roughness have all been investigated as a means to reduce bacterial attachment (Song et al. 2015). Since the bacterial cells are negatively charged, a normally negatively charged surface would repel bacterial and limit adhesion. However, some bacteria are remarkably resourceful and can adapt to better attach to negatively charged surfaces as well (Song et al. 2015). For this reason, it is advantageous to combine antibacterial and antifouling materials, with one example being 2-methacryloyloxyethyl phosphorylcholine, MPC (Zhang et al. 2015). Antifouling polymers are surface active and prevent bacterial attachment by disrupting the adsorption of proteins from the acquired pellicle (L. Zhang et al. 2016). The combination of MPCs with QAMs has shown a synergistic effect in inhibiting biofilm formation, without affecting materials' mechanical properties (L. Zhang et al. 2016).

Remineralizing Materials

The rationale for the development of remineralizing dental materials is to replenish the lost mineral content from early disease to prevent cavitation of the lesion (L. Zhang et al. 2016). Calcium fluoride ($nCaF_2$), amorphous calcium phosphate (nACP), and nanohydroxyapatite (nHA) and nanofluorohydroxyapatite (nFHA) nanoparticles have been widely studied as remineralizing agents, with studies predominantly focusing on repairing relatively small defects (Li et al. 2014). Nanoparticle characteristics such as surface charge, degree of hydrophobicity, ratio of surface area to biofilm mass, and the ability to adsorb or be collected on the surface of the biofilm can all be tailored (Melo et al. 2014). Importantly, it has been shown that the incorporation of acidic monomers, such as PMGDM (pyromellitic glycerol dimethacrylate), in a BisEMA resin positively affects the potential for calcium and phosphate ion recharge/release from the restoration to inhibit caries (L. Zhang et al. 2016). In addition, an enhancement in the remineralization effect provided by calcium phosphate (nACP) has been shown when it is used in combination with poly(amide amine) (PAMAM). PAMAM has been shown to be an excellent mineral nucleation template, and when combined with nACP, not only is remineralization favored, but demineralization is also hampered via the neutralization of biofilm acids by nACP (Liang et al. 2016).

Finally, attempts to combine QAMs with ACP mineral particles have also shown great promise in vitro and in vivo, as there seems to be a synergistic effect between the antibacterial and remineralizing agents in preventing caries initiation and progression (Cheng et al. 2015).

Future Developments

Stress-Reducing Materials

Stress-reducing materials continue to be the focus of investigations due to their utility in preventing gap formation at the tooth-restorative material interface. However, rather than concentrating on shrinkage reduction, most current strategies propose some type of modification to the polymer network that can simultaneously decrease stress and either maintain or enhance mechanical properties and monomer conversion. One example is the development of thiourethane oligomers (Bacchi and Pfeifer 2016). These molecules are synthesized under mild conditions through a click reaction and feature pendant thiol functionalities that are available to participate in chain transfer reactions with the secondary vinyl monomer matrix. In this sense, thiourethanes rely on the same stress reduction mechanism leading to delayed gelation/vitrification as seen in classic thiol-ene reactions (Boulden et al. 2011). At the same time, they provide network reinforcement stemming from the incorporation of tough thio-carbamate bonds into the network (Lowe et al. 2010). When used in highly filled composites, thiourethanes have been shown to reduce polymerization stress by up to 50%, while leading to a 2-fold increase in fracture toughness (Bacchi et al. 2016). Other nano-sized prepolymerized particles have also shown significant shrinkage/stress reduction and represent a highly tailorable platform for material modification (Moraes et al. 2011). Another example of a stress-reducing strategy is the use of monomers with addition-fragmentation chain-transfer capabilities, such as that used in the commercial bulk-fill material, Filtek Bulk Fill (3M ESPE). The multifunctional monomers in this product contain an allyl disulfide moiety (among other possible examples), which then becomes incorporated into the network as a crosslink (Fig. 2). That allyl bond can be broken and reformed as the radical propagates, while keeping the net crosslinking density essentially unchanged. As a result, polymerization stress can be accommodated and ultimately reduced, while maintaining mechanical properties comparable to traditional glassy networks (Park et al. 2012).

Degradation-Resistant Materials

Despite the many changes to the organic matrix composition, dental composites are still polymerized via the vinyl bond of methacrylate monomers. This is due to many advantages associated with methacrylates, such as the ability to achieve degree of conversion values >60% to 70% in <1 min at room temperature using on-command photo-activated mechanisms, production of high Tg networks at room temperature, adequate mechanical properties, and highly esthetic restorations. One main disadvantage is that methacrylates are inherently hydrolyzable via their ester bonds, a process that can be accelerated at higher temperatures and low pH (Delaviz et al. 2014), which in turn are conditions consistent with those in the oral environment. In addition, incomplete conversion and water sorption/solubility decrease the stability of the polymer matrix and may, as some suggest, contribute to the less than optimal clinical

lifetime (Delaviz et al. 2014). To address these shortcomings, materials departing from methacrylate chemistry have been proposed for use as restorative composites. These include methacrylamides, vinyl ethers, azide-alkyne, thiol-vinyl sulfone, and improved thiol-ene chemistry (Fig. 3). Methacrylamide monomers have been demonstrated to be more stable in aqueous environments, including acidic conditions (Moszner et al. 2001; Salz et al. 2010). Specifically for dental uses, they have been proposed as monofunctional monomers for adhesives (with 1 commercial example, Adhese One F [Ivoclar-Vivadent]) (Salz and Bock 2010) and as multifunctional monomers for composites. Several bisacrylamides have been evaluated as crosslinkers for dental composites with physical properties comparable to methacrylates and greater stability in an aqueous environment (Moszner et al. 2006). Vinyl ethers have also been shown to be very stable, even after enzymatic challenge, and novel multifunctional monomers have shown mechanical properties comparable to methacrylate controls (Gonzalez-Bonet et al. 2015). However, the homopolymerization of such monomers does not progress at room temperature, so they either require a post-photoactivation heat treatment or must be copolymerized with a methacrylate (Gonzalez-Bonet et al. 2015). Azide-alkyne click polymerizations are very efficient, copper-catalyzed reactions that produce polymer networks with high Tg and toughness at room temperature. These materials also present lower polymerization stress and can be photoactivated, albeit with reduced mechanical properties compared with methacrylate controls (Song et al. 2016). Potential pitfalls related to the copper catalyst (present in minute concentrations) include toxicity and discoloration. However, these materials are ester free and have the potential for very high stability in the oral environment. Finally, thiol vinyl sulfone polymerizations have been proposed. These additional materials can produce networks with degree of conversion approaching 80%, in part owing to the development of efficient photobase generator initiators and, despite containing thiols, Tg as high as 100°C (Podgórski et al. 2015). In addition, monomer structure can be tailored in these materials to eliminate degradable esters and produce networks that are highly solvent resistant (Podgórski et al. 2015).
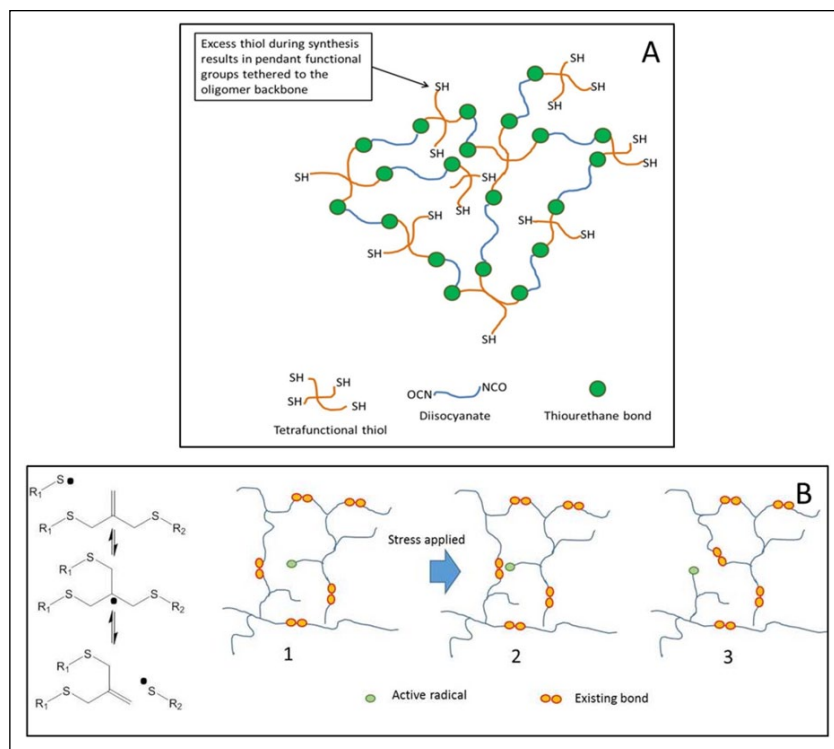

Figure 2. Diagram for network modifications leading to stress reduction with the use of thiourethane oligomers (**A**) and covalent adaptable networks formed via addition-fragmentation chain transfer (**B**).
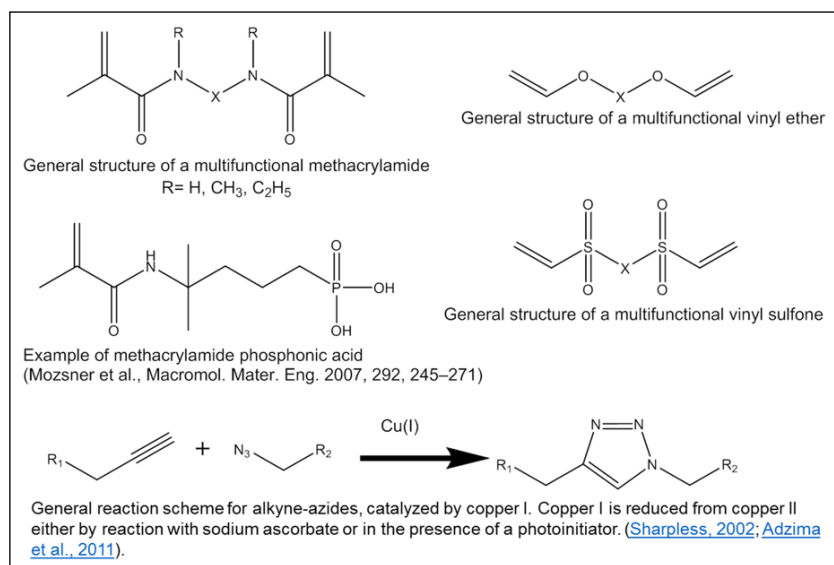

Figure 3. General molecular structure of materials being proposed as alternatives to methacrylates for dental applications.

Reinforcing and Self-Healing Materials

Self-healing materials are capable of restoring mechanical integrity after damage has occurred. The recovery is not always complete but allows for extension of the materials' survival
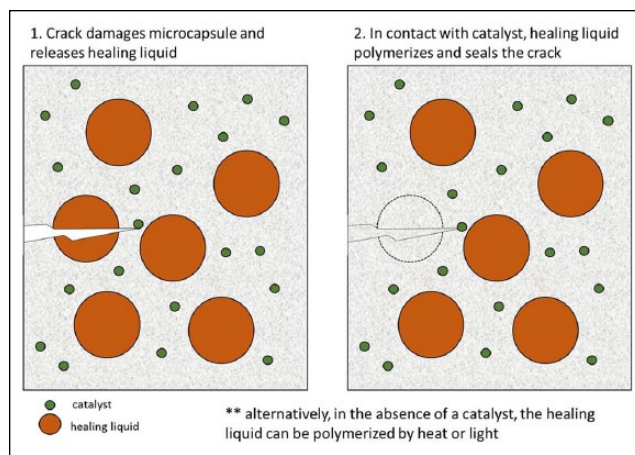
Figure 4. General scheme for the crack-healing mechanism using liquid-bearing microcapsules.

(Diesendruck et al. 2015). Self-healing materials are classified as either intrinsic or extrinsic, according to whether the reparative, highly reactive molecules are produced only when the damage occurs (intrinsic) or if they are somehow stored within the material (extrinsic) (Diesendruck et al. 2015). In the intrinsic self-healing materials, the healing occurs at the molecular level, and the bond-forming reactions begin when the reagents come within nanometer distances of each other, which makes it difficult for the healing of large gaps to occur. In addition, an external source of energy (light or heat) is required to impart the mobility needed to bring the reactants to within close proximity. Extrinsic self-healing materials usually rely on polymeric capsules loaded with the healing agent. In this situation, a polymerizable solution is encapsulated and the reactants are released when the capsules are physically damaged, for example, by the propagation of a crack within the matrix. An active catalyst, kept out of contact with the monomer, is also released by rupturing of a capsule and is responsible for crosslinking the polymer (Diesendruck et al. 2015) (Fig. 4). The first attempts to develop self-healing dental composites using the microcapsule approach resulted in materials showing significant fracture toughness recovery but equally significant biocompatibility concerns (Then et al. 2011). Several recent studies using microcapsules loaded with different healing agents have demonstrated at least 65% recovery of the virgin fracture toughness with minimal cytotoxicity. In at least 1 study, the self-healing efficacy was kept even after 6 mo of water storage, leading to the conclusion that the specific composition tested was promising for healing cracks, resisting fracture, and increasing the durability and longevity of dental restorations (Wu et al. 2016).

Conclusion

Ideally, directly placed esthetic dental restorations should 1) withstand occlusal loading, 2) be stable in the harsh oral environment, 3) minimize or prevent stress development and avoid gap formation, 4) prevent biofilm attachment/growth, 5) present remineralizing capabilities, 6) be able to self-repair, and 7)

be easy to use. By any engineering measure, this is a very challenging list of prerequisites. To date, no material commercially available or under development is able to fulfill all of them. Resistance to wear and strength of composites in general have significantly increased over the years, and materials with low stress generation have been developed and commercialized. However, no currently available material has substantial antibacterial, remineralizing, or general bioactive/biomimetic capabilities. When all of these factors are considered in conjunction with the intrinsic susceptibility of methacrylate-based networks to undergo hydrolytically and enzymatically driven degradation, the relatively short life span of composite restorations is widely justified. Until regenerative therapies are not a reality for larger tooth defects, restorative materials will need to be improved. Most of the research in this field has shifted the focus to concentrate on biofilm and host interactions. The ultimate goal is to produce materials that are better able to integrate with the environment where they are applied and withstand the challenges imposed in the oral cavity. It is evident from the amount of research activity in the field of dental polymer chemistry that the organic phase of composite materials is likely to drastically change in the relatively near-term. Along with novel developments in filler systems and self-healing materials, this has the potential to shift the status quo of current materials used to directly restore diseased and damaged teeth.

Author Contributions

Acknowledgments

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