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Threats to Adhesive/Dentin Interfacial Integrity and Next Generation Bio-enabled Multifunctional Adhesives

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Abstract

Nearly 100 million of the 170 million composite and amalgam restorations placed annually in the U.S. are replacements for failed restorations. The primary reason both composite and amalgam restorations fail is recurrent decay, for which composite restorations experience a 2.0 to 3.5-fold increase compared to amalgam. Recurrent decay is a pernicious problem—the standard treatment is replacement of defective composites with larger restorations that will also fail, initiating a cycle of ever-larger restorations that can lead to root canals, and eventually, to tooth loss. Unlike amalgam, composite lacks the inherent capability to seal discrepancies at the restorative material/tooth interface. The low-viscosity adhesive that bonds the composite to the tooth is intended to seal the interface, but the adhesive degrades, which can breach the composite/tooth margin. Bacteria and bacterial by-products such as acids and enzymes infiltrate the marginal gaps and the composite's inability to increase the interfacial pH facilitates cariogenic and aciduric bacterial outgrowth. Together, these characteristics encourage recurrent decay, pulpal damage, and composite failure. This review article examines key biological and physicochemical interactions involved in the failure of composite restorations and discusses innovative strategies to mitigate the negative effects of pathogens at the adhesive/dentin interface.

Keywords

dental restoration; adhesive/dentin interface; proton sponge; autonomous strengthening; peptide engineering

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Dental Amalgam and Composite Restorations

Clinical need:

Nearly 60% of the roughly 170 million composite and amalgam restorations placed annually in the U.S. [1] are replacements for failed restorations. [2] The number of replacement restorations is expected to grow with the increased use of dental composite. Dental composites have replaced amalgam as the most popular material for the repair and reconstruction of lost or damaged tooth structure.[2,3] This shift, which is fueled both by composite's aesthetic appeal and by environmental-mercury-driven global efforts to phase out dental amalgam, is not without consequences. Composite restorations fail at 2 to 3.5 times the rate of dental amalgam.[4,5–7] This shortened restoration lifespan is a pernicious problem that leads to frequent replacement. Each subsequent restoration risks pulpal injury, increased tooth weakness, and eventually, total tooth loss.[8,9] High-risk patients and patients with advanced carious lesions are particularly vulnerable to composite-restoration failure.[6,10] This increased failure rate will also significantly affect quality of life for a substantial fraction of the ~32% of the U.S. population with natural dentition who do not receive regular dental treatment.[11] Moreover, increased susceptibility of composite margins[12] to higher concentrations of the cariogenic bacterium *Streptococcus mutans* will increase the risk of untreated decay in the 4 million U.S. children who do not receive regular dental care.[13] Without substantial improvements in composite restoration durability, this shift away from amalgam will translate to productivity losses from patients' inability to concentrate and more time spent away from school and work.[14]

Composites and cariogenic plaque:

The primary reason for replacing composite restorations[15] is development of cariogenic plaque[16]-induced lesions (secondary decay) at the margins of existing restorations.[3,15,17] Cariogenic plaque forms when the population of aciduric bacteria increases following high-frequency exposure to sugars and fermentable carbohydrates.[18] Metabolic activity of these microbiota acidifies the plaque (pH < 5), which demineralizes the tooth and damages the composite surface, prompting further plaque attachment and restoration deterioration.[19] Composite's inability to neutralize these acids facilitates outgrowth of cariogenic and aciduric bacteria,[20,21] which causes composites to accumulate more plaque [20,21] and facilitates compositional shifts that are advantageous for cariogenic bacteria and detrimental for beneficial bacteria.[22]

Composite/Tooth Bond

Since composite is too viscous to establish a direct bond, a low-viscosity adhesive is required at the tooth/composite interface. While efforts to bond adhesive to enamel have been successful, efforts to bond dentin have been fraught with problems. The lack of effective dentin adhesives is particularly problematic for gingival-margin lesions, which typically have very little bondable enamel. Restorations at this margin are also particularly susceptible to recurrent decay. Indeed, 80–90% of recurrent decay is located at the gingival margin of Class II and V restorations.[23] For these restorations, the adhesive often serves as the barrier between the tooth and the oral environment,[24] and its degradation[25,26] leads to

gaps at the restoration's margin[21] that bacteria, oral fluids, and bacterial enzymes can infiltrate. Dentin margins are particularly susceptible, especially those under mechanical load.[27] Thus, failed adhesives drive increased susceptibility to recurrent decay and composite-restoration failure.[3]

Difficulties in establishing a durable dentin-adhesive bond:

Dentin surfaces are acid etched to prepare them for adhesive bonding. With the wet-bonding technique, acid-etching removes the dentin's mineral phase without altering the collagen matrix. The resulting voids in the water-laden collagen matrix are filled with adhesive that undergoes *in situ* polymerization to create the hybrid layer.[28] The ideal hybrid layer would be a completely polymerized 3D polymer/collagen network that provides a continuous and stable link between the adhesive and dentin. Studies indicate that this ideal is not achieved[29–40]—the hybrid layer retains water-rich pockets of resin-sparse collagen fibrils. (Figure 1) These pockets arise from a discrepancy between the depth of dentin demineralization and adhesive infiltration.[28,33,34,41–45] Acid-etching[46] initiates a cascade that can degrade this resin-sparse collagen by activating proteolytic enzymes that include collagen-degrading matrix metalloproteinases (MMPs).[47] MMPs are also abundant in caries-affected dentin,[48] which is often the clinical substrate that must be bonded. The predominant methods to address MMP attack entail the use of MMP inhibitors or MMP-inhibitor-conjugated resin monomers.[49] While these-inhibitors can reduce collagen degradation[49] and shift the major site of failure elsewhere,[28] the method can cause decreased monomer-to-polymer conversion.[50] Remineralization[51] also impedes MMP-attack, but this technique alone does not prevent degradation of the adhesive component in the hybrid layer.[49] As a result, the primary mechanisms of hybrid-layer failure are degradation of resin-sparse collagen fibrils and deterioration of the adhesive.[28,44,52]

Hybrid-layer deterioration involves hydrolysis and leaching of the adhesive.[34,36] The structure of methacrylate adhesives suggests a general mechanism for their chemical and enzymatic degradation.[23] Leaching is facilitated by water ingress into the adhesive's loosely cross-linked domains.[53] Water may also be trapped within the adhesive.[26,54,55] Water plasticizes the polymer and promotes chemical hydrolysis of ester bonds in methacrylate materials.[56] The carboxylate and alcohol degradation products of ester hydrolysis are more hydrophilic than the parent ester, further enhancing the local ingress of water. Over time, local domains of the methacrylate network become sufficiently degraded to permit access to salivary esterases[57–64] and esterases from *Streptococcus mutans*[64] that accelerate ester-bond hydrolysis.

Esterase-catalyzed degradation by-products may accumulate within the micro-environment of the adhesive/dentin interface—these degradation by-products have been shown to promote bacterial growth and up-regulate *S. mutans* virulence genes and proteins. [65–67] These by-products could promote deterioration of the interfacial seal and contribute to a micro-environment that promotes secondary decay and composite restoration failure. [68]

Strategies to Increase the Durability of Adhesives

Numerous strategies have been proposed to enhance the hydrolytic stability of dental adhesives and to promote the integrity and durability of the adhesive/dentin interface. One strategy is focused on changing the monomer structure to increase the hydrophobicity. The hydrophobicity of the monomers is increased by introducing either a urethane group, [69–71] branched methacrylate linkage, [72] or ethoxylated BisGMA (BisEMA) [73]. These strategies temporarily depress water sorption, i.e. the materials will generally become saturated within 7–60 days [74]. Other strategies involve enhancing the monomer conversion in the hybrid layer—these strategies focus on providing photoinitiators that are compatible with the hydrophobic- and hydrophilic-rich phases that make up the adhesive, [75,76] or increasing the time for light-curing [77,78].

Investigators have also proposed to increase the durability of the adhesive bond to dentin by using inhibitors (such as zinc or zinc-chelators) of dentin matrix metalloproteinnases (MMPs) or biomimetic remineralization [79–82]. While MMP-inhibition and biomimetic remineralization have shown promise, [83] these techniques can also lead to detrimental changes in the material, e.g. decreased monomer/polymer conversion [84]. Remineralization offers protection for the collagen, but this technique alone does not address the potential for hydrolysis of the adhesive [80].

Bisphenol A-glycerolate dimethacrylate (BisGMA) is the most popular crosslinking monomer in dental adhesives, but the susceptibility of this monomer to hydrolysis threatens the durability of the adhesive. To address this problem, we synthesized silyl-functionalized BisGMA (e.g. sily-BisGMA). Adhesive formulations based on a methoxysilyl-functionalized BisGMA derivative (silyl-BisGMA) showed autonomous strengthening, i.e. as opposed to property degradation during aqueous aging the mechanical properties increased and the amount of leached HEMA was reduced over 90%. The increase in mechanical properties following aqueous aging and the significant decrease in leached HEMA reflect a resistance to hydrolysis in the silyl-BisGMA adhesive formulations. The introduction of silyl-BisGMA in the adhesive formulation led to higher crosslinked networks as compared to BisGMA/HEMA formulations. [85] The higher crosslinked networks are envisioned as an important component of a multi-factorial approach to durable adhesives.

We have developed a strategy to enhance the hydrolytic-resistance of adhesives by introducing photoacid-catalyzed sol-gel reaction together with the free radical photo-polymerization of methacrylate. [86–88] The resin, which contains γ-methacryloxyproyl trimethoxysilane (MPS) as its Si-based compound, exhibits intrinsic reinforcement of the polymer network. The behavior of this novel resin is reminiscent of autonomous strengthening properties found in nature.

The proposed mechanism for the intrinsic self-strengthening processes found in these novel resin formulations is presented in Figure 2. When the liquid resin formulation is irradiated by visible-light, polymethacrylate-based matrix network is formed by simultaneous free radical cross-linking polymerization of methacrylate monomers (HEMA, BisGMA, and MPS) and the methoxysilyl groups shows limited hydrolysis and condensation. The

photoacid-induced sol-gel reaction continued while the sample was stored in the dark and after 48 h, about 65% of methoxysilyl groups have been hydrolyzed (Figure 2A). After soaking the specimens in water or lactic acid solution, the autonomous hydrolysis and condensation of methoxysilyl moieties continues and new crosslinked points are formed (Figure 2B). At the same time, the silanol groups react with the hydroxyl groups of HEMA or BisGMA to obtain covalent bonds (Si−O−C). In the MPS-containing formulations, the rate of hydrolysis of the trialkoxysilyl group is relatively slow as compared to the free radical polymerization of the C=C bonds in the methacrylate monomers. The autonomic sol-gel reaction provided a slow and continued reaction, which can gradually generate the Si–O–Si bond and resist hydrolytic degradation. [85]

Antimicrobial Composites and Adhesives

After nearly 6 decades of research, dental composites continue to show limited clinical service as a result of recurrent decay or fracture.[2,6,89] Recurrent decay remains the primary reason for replacing composite restorations [56] and is a key driver of the ongoing quest to develop restorative materials with antibacterial properties.[7] Chlorhexidine, fluoride, and silver ions are among the antimicrobial agents incorporated in dental materials.[56,90–92] These agents generally achieve their antimicrobial activity through gradual release, an approach that can lead to inconsistent dosage, short-term effectiveness, decreased mechanical properties, and toxicity to host tissues.[56,90]

The promise and pitfalls of quaternary ammonium methacrylate (QAM):

QAM-based composites, adhesives, and primers offer promise in terms of antimicrobial activity[93–97] but suffer from important deficiencies. [7] QAMs may alter the polymer's network structure, decrease monomer-to-polymer conversion, decrease mechanical properties, [98] and increase sorption of ethanol, water, and other solvents.[7,56,99,100] Furthermore, the cationic monomer's high affinity for cell membranes is not limited to bacteria—since adhesive and composite polymerization is incomplete, unreacted monomer could also leach into tissues, where its high affinity for cell membranes raises cytotoxicity concerns.[7,101] In addition, quaternary ammonium compounds (QACs) have been associated with the growing problem of antimicrobial resistance.[102–107] For example, the quaternary amines dimethylaminododecyl methacrylate (DMADDM) and benzalkonium chloride (BZK) induced development of drug resistance in a biofilm model of *S. gordonii*.[108] Likewise, exposure to the QAC dimethaylaminohexadecyl methacrylate (DMAHDM) induced drug tolerance in an *S. mutans* biofilm model.[109]

Minimally Invasive Restorations

The high failure rate of composites and the loss of tooth structure associated with each replacement are driving demand for minimally invasive cavity preparations.[9,110]. Indeed, selective removal of carious tissue is encouraged with composite restorations.[21] Such cavity preparations are routinely infected with residual *S. mutans.*[111] If, like amalgam, the material has bacteriostatic effects [7] or if there is an impervious seal between the material and the tooth, these residual bacteria might not be major concern. However, current adhesives do not provide an impervious seal, and enzymes, oral fluids and bacteria permeate the failed

adhesive's gaps. These agents, together with increased levels of *S. mutans* localized at the composite material's perimeter,[20,112] contribute to recurrent decay and failure of composite restorations.[21,22] The inability of dentin adhesives to provide a durable bond with the clinical substrate is one of the major problems with the use of composites in direct restorative dentistry.[24]

Strategies for Adhesive/Dentin Interfacial Integrity

Supramolecular approaches and rational design

The demand for adhesives that provide a durable barrier to recurrent decay will not be met by strategies focused solely on traditional approaches. Based on recent evidence, successful approaches will require novel, rationally designed materials that leverage the multifaceted attributes of biomolecules, exploit non-covalent interactions, and provide structural and functional properties that mimic native tissues.[113] Such supramolecular approaches are being explored—for example, bioactive peptide scaffolds have been used to induce stem-cell-based regeneration of dental pulp[114] and to promote *de novo* production of enamel.[115] To date however, the majority of these biomaterials have been soft, rapidly eroding hydrogel-based materials that degrade or clear after a few weeks *in vivo*.[113] Such biomaterials are not suitable for use as dental adhesives—successful adhesives will require both bioactivity *and* durability.

While investigators would agree that supramolecular approaches offer promise as next generation dental adhesives, the design and production of these materials poses significant challenges. The properties of adhesives depend on a large parameter space associated with features such as composition, polymerization rate, geometry, and processing parameters. Optimization of these properties is typically a laborious, iterative process where features are systematically changed and the effects determined by measuring the properties of the new adhesive—this process will only become more intractable as additional biological parameters are included.

With their ability to enable *in silico* parameter optimization, computational models to correlate system parameters with material properties are indispensable for providing guidance for targeted design optimization. [24,116–123] Modeling coupled with multi-scale characterization provides insights beyond what could be accomplished if either of the approaches were applied independently. For example, the modeling effort aims to reveal how the micro-scale properties affect the behavior of materials under a range of conditions, from quasi-static to dynamic. The desired properties of materials exist on multiple time and length scales—the modeling can be performed at each of these scales to capture behavior such as mechanical response, transport properties, degradation and failure. Insights from these efforts can inform the material design process by narrowing the parameter space to focus experimental efforts on the formulations most likely to provide the desired properties and outcomes.

In our group, we treat polymer systems as though they possess a pseudo-granular structure in which the grain-interactions represent: the average behavior of the covalent bonds within a chain, the covalent cross-links between segments in two different polymer chains, non-

covalent hydrogen bonds, van der Waals interactions, entanglements, and other physical interactions. We have used granular micromechanics theory and finite-element modeling for describing rate-dependent visco-damage and chemo-poro-viscoelastic behavior of a variety material systems,[124–127] including for water-hydrophilic-hydrophobic phases in adhesives.[128] The knowledge gained through these efforts has suggested the required monomer characteristics for robust polymers with improved durability in harsh, *in vivo* environments.

Strategically linking biology and engineering

Successful approaches to next generation dental adhesives will require knowledge and expertise from diverse disciplines. The remainder of this review will examine approaches that strategically link biology and materials engineering to develop durable adhesives—materials that will offer adhesive/dentin interfacial integrity with inherent biological functionality.

Proton Sponge Adhesives:

The increased incidence of caries at the margins of composite restorations implies that the restoration itself may foster conditions that promote decay.[3,17,20–22,27] Cariogenic plaque is the direct cause of decay at the margins of composite restorations[16] and the extended acidification of cariogenic plaque (pH < 5) provokes events that undermine the composite restoration, e.g. the acid demineralizes the tooth and causes severe damage to the composite surface prompting further plaque attachment and deterioration of the restoration.[19] The chemical and enzymatic degradation of the methacrylate-based matrix in composites and adhesives could augment the low pH environment, e.g. degradation of methacrylate ester groups produces carboxylic acids, which contain the same functional group that is the culprit in lactic acid-induced decay.

The inability of the composite to neutralize the acids facilitates the outgrowth of more cariogenic and aciduric bacteria.[20,21] The lack of buffering capabilities can facilitate compositional shifts in plaque that are advantageous for cariogenic bacteria and detrimental for beneficial bacteria.[22] The impact of cariogenic plaque at the margin of the composite restoration could be reduced by engineering novel dentin adhesives that neutralize the acidic microenvironment[129].

Integrating basic moieties with an appropriate pKa into methacrylate derivatives provides the opportunity to act as an acid-neutralizing proton sponge. We explored this strategy by determining the neutralization capacity of amine-containing monomers and the effects of solvent environment on pKa[130]. The neutralization capacity of polymers was studied by adjusting the crosslinking density and employing different amine-containing monomers (pKa 6.2 to 9.7), e.g. 2-(dimethylamino) ethyl methacrylate (DMAEMA), 2-(diisopropylamino) ethyl methacrylate (DIPAEMA), 2-(tert-butylamino) ethyl methacrylate (TBAEMA) and 2-N-morpholinoethyl methacrylate (MEMA).[131] (Figure 3) While amine monomers with higher pKa values provided increased neutralization capacity, those with physiologically relevant pKa values provided the most-effective buffering and yielded a less-alkaline end point.[131] Further investigations with MEMA indicated that the crosslink density of the polymer network was associated with neutralization rate, i.e. the lower the crosslink

density the faster the neutralization rate. [132] Based on these results, the introduction of amine-containing co-monomers offered a promising approach for mitigating acid-provoked damage at the composite/tooth interface however the potential for leaching amine-containing cytotoxic species is problematic. An alternative strategy involves the use of biomolecules, e.g. lysine.

Modulating pH with biomolecules:

Lysine, an essential amino acid, can act as a weak base with a pKa value of 10.5 for the side amine group [133–135]. (Figure 4) Lysine has been widely used in biomaterials [136–138] and studies have revealed its antibacterial properties [139140] and biofilm-disrupting activity [141]. When incorporated in the adhesive formulation, this essential amino acid could buffer the interfacial micro-environment without leaching amine-containing cytotoxic species. Results from a recent investigation indicated that lysine-containing adhesives can provide acute neutralization of the acidic micro-environment. [135] The incorporation of lysine in dental adhesives offers promise as one component of a multi-faceted approach to reduce the negative impact of bacteria at the margins of composite restorations. Interestingly, investigations with arginine-based dental adhesives have provided evidence that arginine-release increases the pH of local oral biofilms. [135,142–144] Similar to lysine-release, this activity could retard the outgrowth of acid-producing cariogenic bacteria.

Peptide Engineering and Dentin Adhesives

Matrix metalloproteinases (MMPs) are proteinases that degrade both extracellular matrix (ECM) proteins and non-ECM proteins. [145] While MMPs are crucial for normal biological function, changes in the levels and activity of these proteinases have been implicated in a variety of diseases, e.g. cancer metastasis, periodontal inflammation, and tuberculosis. [117,146–153] MMPs have also been implicated in the degradation of the bond at the composite/tooth interface [47]. Specifically, MMP-8, a collagenase, has been shown to degrade type I collagen in dentin. Regulating the activity of MMP-8 as well as other metalloproteinases that contribute to the failure of the bond formed at the composite/tooth interface has been the subject of numerous investigations. [49,153]

Strong inhibition of MMP-8 was achieved using a small metal binding peptide (metal abstraction peptide, MAP). [154] MAP is a small peptide (functional unit is three amino acids long) that is capable of robbing transition metal ions, e.g. Zn^{2+} from chelators. [155] As shown in Figure 5, the MAP was incorporated into a longer peptide (tether-MAP) and tether-MAP was grafted to the surface of amine-containing polymers. The results from this investigation showed that the peptide achieved excellent inhibition of MMP-8. The mechanism of MMP-8 inhibition by the tether-MAP peptide was investigated in a subsequent study using ellipsometry. Based on the MAP chemistry, it was postulated that MMP-8 inhibition could involve: 1) shared binding of the zinc ion at the active site of MMP-8 by the MAP sequence or 2) abstracting the zinc ion from the catalytic portion of the MMP-8 by the MAP tag [156]. Tether-MAP was attached to hydroxyl- and amine-terminated self-assembled monolayers. The peptide coupled surfaces were exposed to MMP-8 and an increase in thickness was recorded, suggesting binding between the two species. The binding interaction was reduced

by blocking the metal-binding site in the tether-MAP. The results suggest that the mechanism for MMP-8 inhibition by the tether-MAP peptide occurred through the interaction between the MAP tag and the Zn^{2+} active site in MMP-8. [156]

In addition to the work to inhibit MMP using the MAP tag, we have explored the potential of using peptides to provide an integrated interface at the boundary between the adhesive and dentin. [157,158] The foundation for this work was the pioneering research conducted by Tamerler and colleagues. Tamerler's research team investigated biocombinatorially selected peptides that have specific binding affinities to solid materials including minerals. [159–163] By subjecting their peptide selection to cross material screens, they identified peptide sequences that exhibit a high degree of specificity compared to other closely related compounds. [164,165] They demonstrated that peptides, specific to hydroxyapatite mineral, mediated amorphous calcium phosphate mineralization. [165] The group further developed bi-functional peptides and demonstrated that hydroxyapatite specific peptides when coupled with another peptide having gel-forming properties provided biological-like apatite formation in the peptide-hydrogel matrix. [159,166] By using a knowledge based design using a combination of experimental and computational approaches, Tamerler and colleagues also designed amelogenin protein-derived peptides that promoted rapid nucleation of calcium/phosphate to remineralize artificial root caries *in vitro*. [164,167]. Based on this prior art, we explored peptide-mediated mineralization of resin-sparse collagen exposed at the interfacial boundary between adhesive and dentin. As shown in Figure 6 an engineered hydroxyapatite specific peptide (HABP) was used to remineralize deficient dentin matrices by self-anchoring the peptide to the adhesive/dentin interface. We used a fluorescence protein (GFP) which is genetically conjugated to the mineralization peptides as a biomarker (GFP-HABP). [168] The distribution of adhesive, collagen and mineral along the depth and breadth of the interface was determined using micro-Raman spectroscopy and fluoresence microscopy. The results indicated peptide-based remineralization of the deficient dentin matrices with homogeneous distribution of mineral at the adhesive/dentin interface. [157] We recently further expanded our peptide engineering efforts to further improve the interface properties at the boundary between the adhesive and dentin. We developed a dental adhesive formulation to incorporate an antimicrobial peptide to target S. mutants. With the emergence of bacterial resistance, antimicrobial peptides, which are naturally integrated in the oral fluids, [169,170] are getting high attention as a promising solution to prevent bacterial infections at the a/d interface. [171] Building upon the strength of our research team in antimicrobial peptide design and application at biomaterial interfaces, [172–175] we modified an antimicrobial peptide sequence to integrate into a dental adhesive system. The antimicrobial peptide coupled adhesive formulations demonstrated significant antimicrobial activity with the resin, when applied to the discs. [176] Integrating antibacterial or mineralization activity using engineered peptides within an adhesive provides a path for providing diverse biofunctions to the interface between the adhesive and dentin.

Summary

The high susceptibility of composite restorations to recurrent decay is a multifactorial problem involving patient characteristics, such as risk factors for decay, gaps at the material/tissue interface, residual *S. mutans* in the cavity preparation, and increased levels of *S.*

mutans at the restoration perimeter. Addressing this multifactorial problem requires a paradigm shift—as opposed to strategies that focus singularly on structural requirements and mechanical properties, integrated approaches that start with the fundamental biology of the tissue are sorely needed. [177,178] More comprehensive, biologically informed strategies are required to provide dental adhesives that are capable of exploiting native tissue repair processes to provide self-healing at the composite/tooth interface.

While biologically informed strategies offer significant promise, they also increase the complexity of adhesive development. Large chemical- and process-parameter spaces must be probed to optimize adhesives and this process will only become more intractable as additional biological parameters are included. Exploring and exploiting such large parameter spaces through experimentation alone is both time and resource intensive. Computational models to correlate system parameters with material properties have the potential to support *in silico* parameter optimization for next generation bio-enabled multifunctional dental adhesives.

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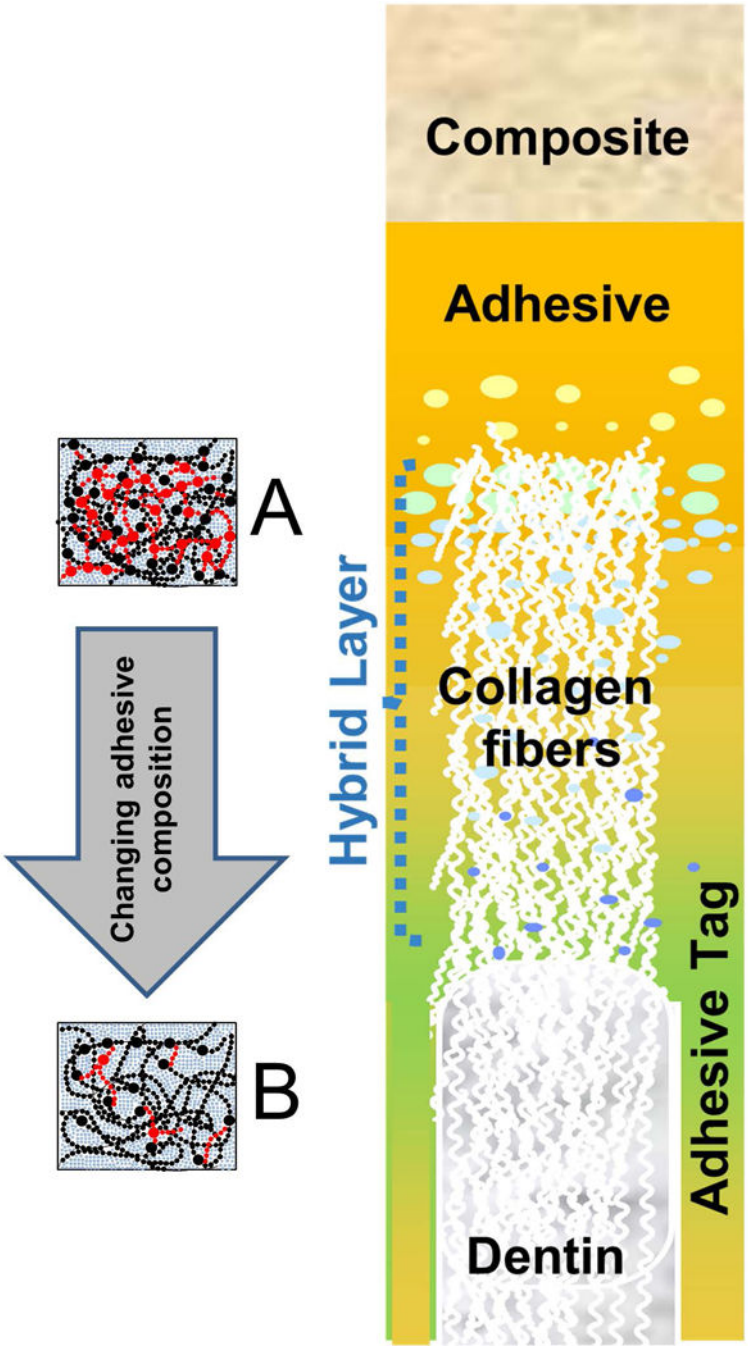

Figure 1:
Schematic of the adhesive/dentin interface. Within the hybrid layer, the hydrophilic component increases and the crosslink density decreases as one traverses from composite to dentin. The hybrid layer is characterized by water-rich pockets of resin-sparse collagen fibrils.

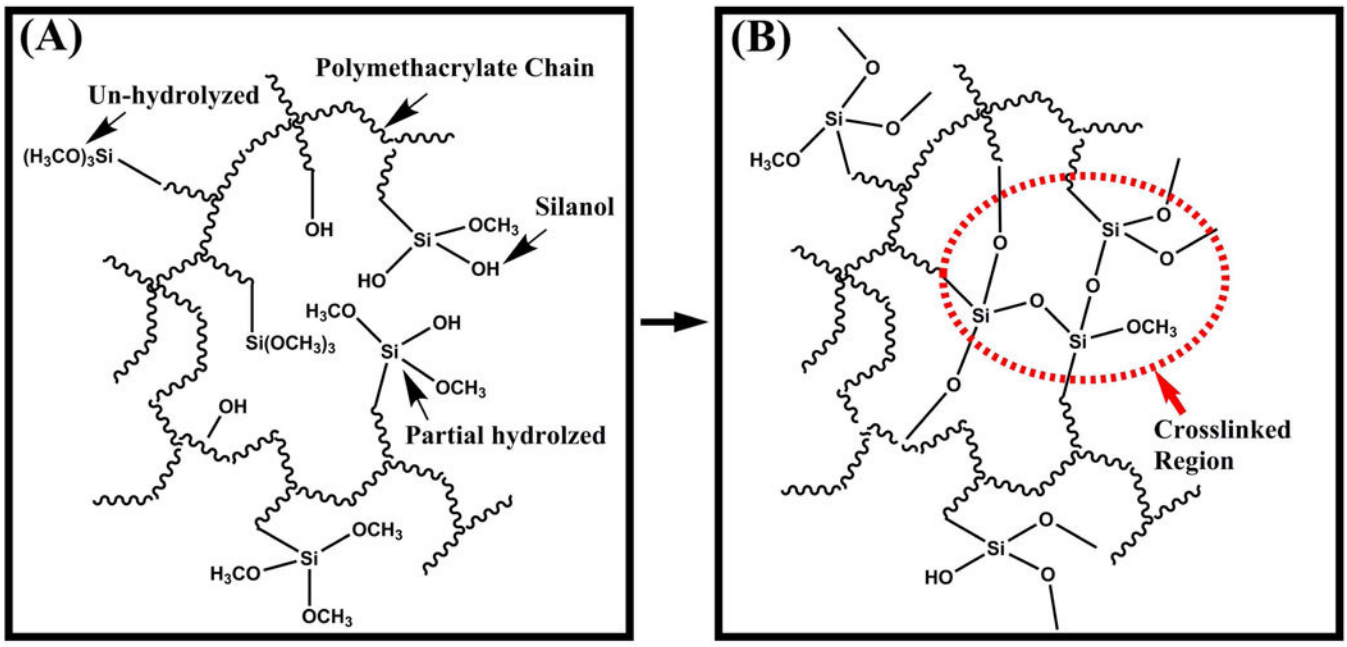

Figure 2:

Proposed polymethacrylate-based network structure and intrinsic self-strengthening processes: (A) polymethacrylate-based network formed by free-radical initiated polymerization and limited photoacid-induced sol-gel reaction after 40 s irradiation; (B) in wet environment, self-strengthening via sol-gel reaction.

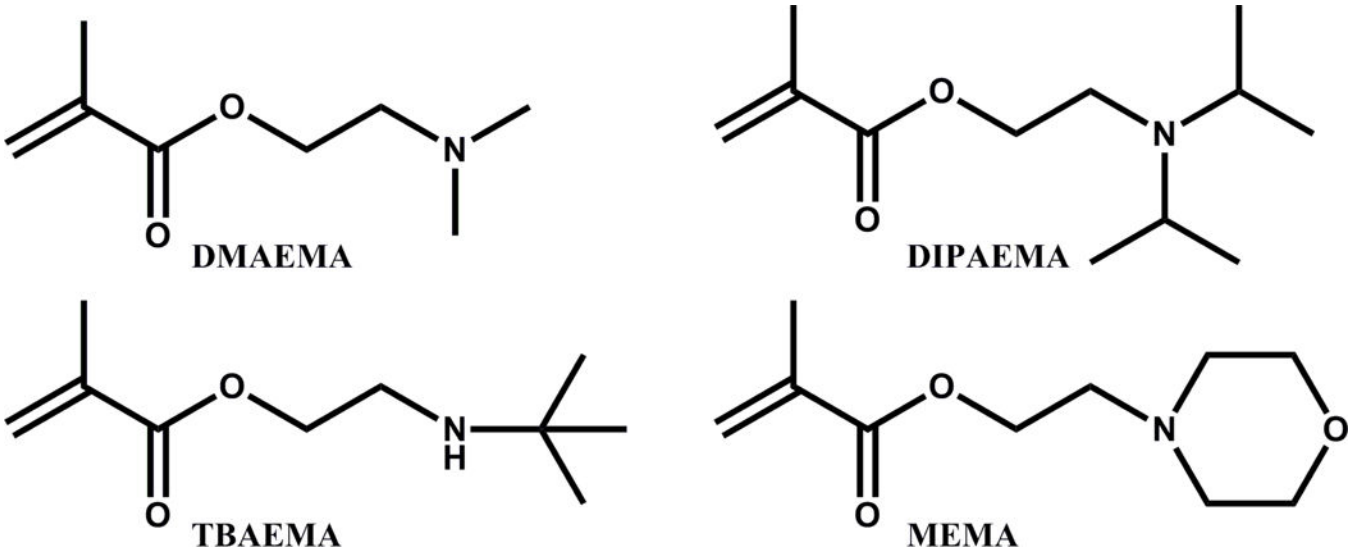

Figure 3:
Chemical structure of amine-containing monomers

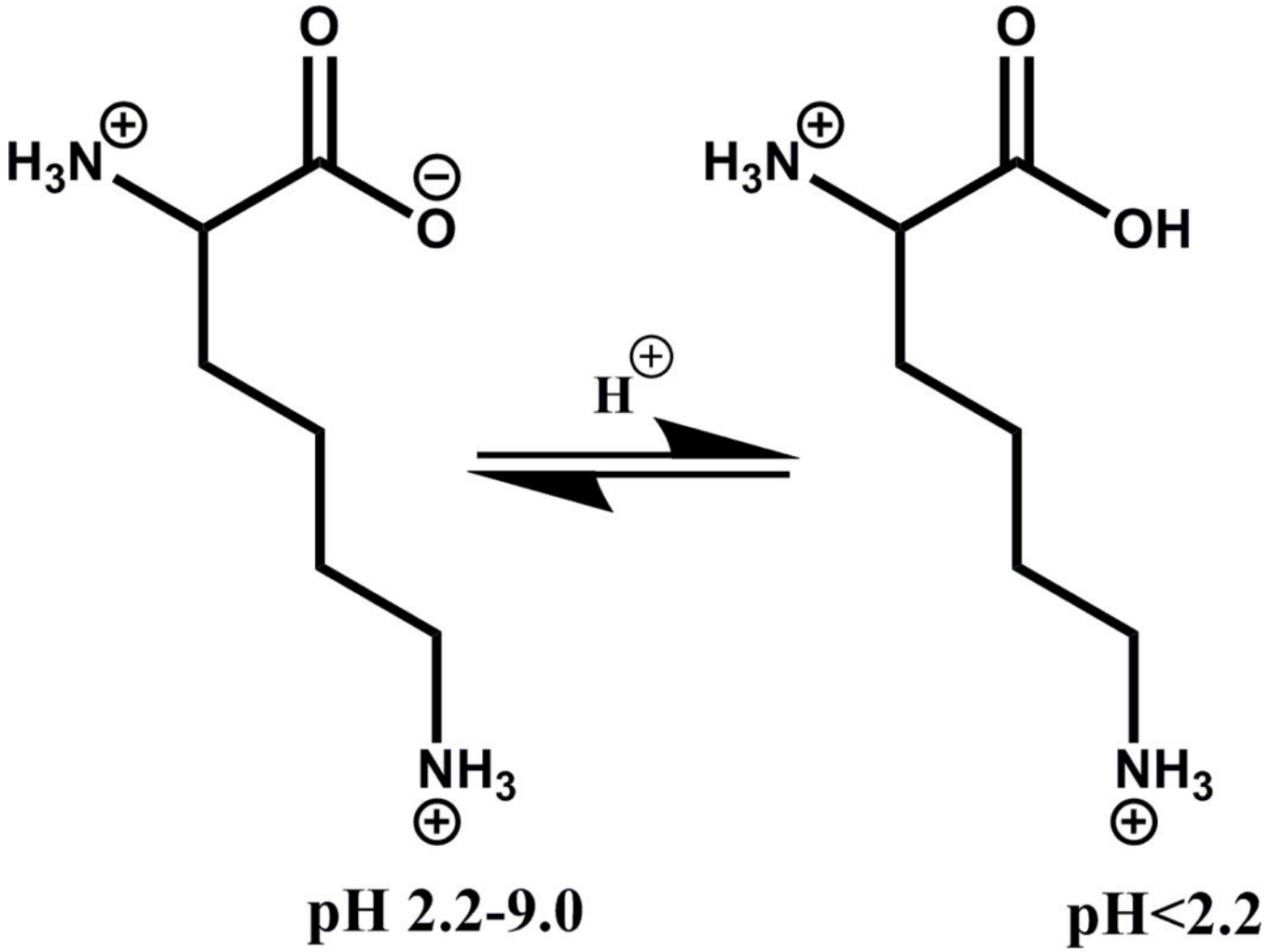

Figure 4:
L-lysine structures

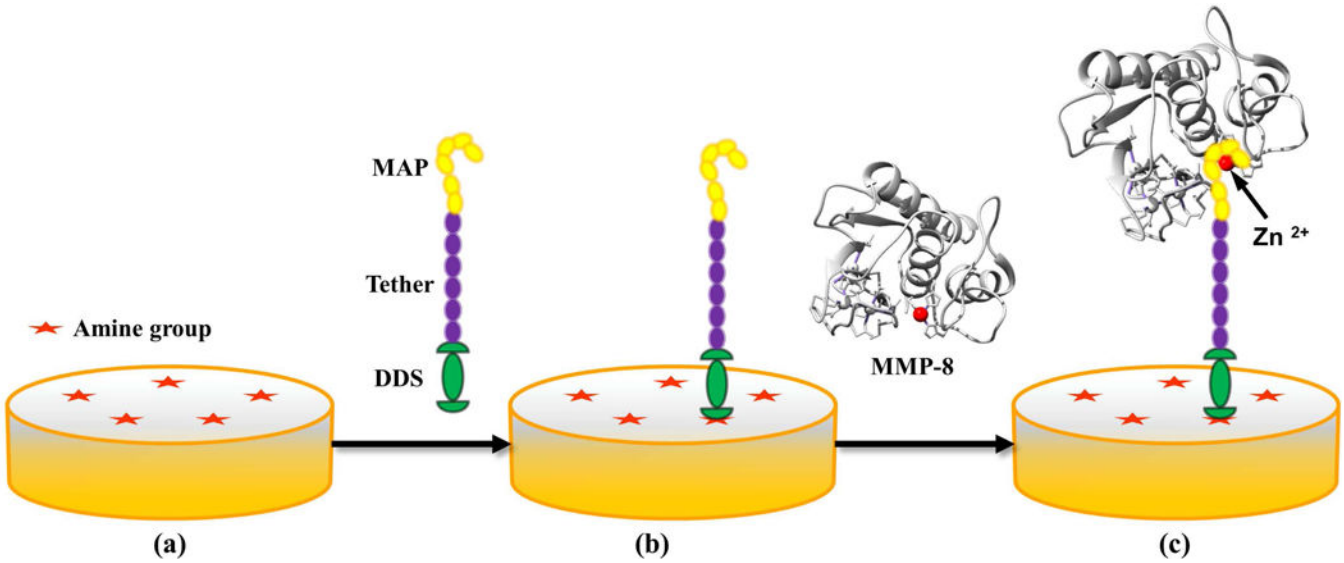

Figure 5:
Schematic of grafted polymer surface to inhibit MMP-8: (A) Amine-terminated polymer surfaces; (B) tether-MAP peptide grafted to amines via DSS linker chemistry; (C) MMP-8 inhibition by MAP. Figure adapted from Dixit et al. 2015 [138]

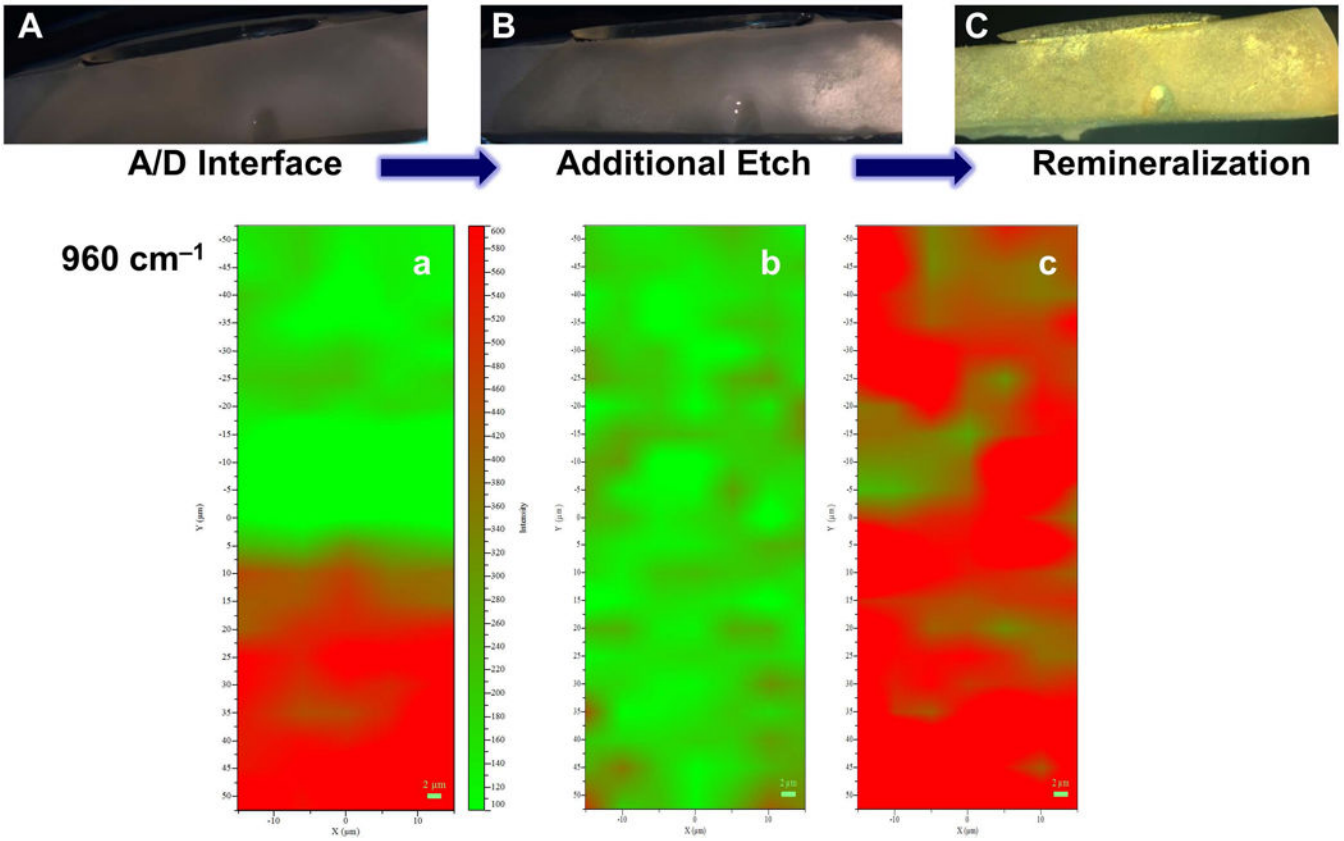

Figure 6:

Visible images and corresponding Raman spectroscopic images of adhesive/dentin (A/D) interface specimen. Visible images: (A) A/D interface specimen; (B) A/D interface specimen following additional etching; (C) peptide-mediated remineralization of deficient dentin within the A/D interface. Corresponding Raman spectroscopic images of A/D interface specimen: (a) Raman XY image of A/D interface, adhesive colored as green and mineral colored as red; (b) Raman XY image of A/D interface following additional etching; (c) Raman XY image of A/D interface following peptide-mediated remineralization, the spectral features associated with the mineral (PO_4^{2-} at 960 cm^{-1}) are colored red.