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Bio-inspired multifunctional adhesive system for next generation bio-addivitely designed dental restorations

Rizacan Sarikaya[a,b], **Linyong Song**[a], **Esra Yuca**[a,c], **Sheng-Xue Xie**[a], **Kyle Boone**[a,d], **Anil Misra**[a,e], **Paulette Spencer**[a,b,d], **Candan Tamerler**[a,b,d,*]

[a]Institute for Bioengineering Research (IBER), University of Kansas (KU), 1530 W. 15th St, Lawrence, KS 66045, USA

[b]Department of Mechanical Engineering, University of Kansas (KU), 1530 W. 15th St, Lawrence, KS 66045, USA

[c]Department of Molecular Biology and Genetics, Yildiz Technical University, Istanbul, 34210, Turkey

[d]Bioengineering Program, University of Kansas, 1530 W. 15th St, University of Kansas (KU), Lawrence, KS 66045, USA

[e]Civil, Environmental and Architectural Engineering Department, University of Kansas (KU), 1530 W. 15th St, Lawrence, KS 66045, USA

Abstract

Resin-based composite has overtaken dental amalgam as the most popular material for the repair of lost or damaged tooth structure. In spite of the popularity, the average composite lifetime is about half that of amalgam restorations. The leading cause of composite-restoration failure is decay at the margin where the adhesive is applied. The adhesive is intended to seal the composite/tooth interface, but the adhesive seal to dentin is fragile and readily degraded by acids, enzymes and other oral fluids. The inherent weakness of this material system is attributable to several factors including the lack of antimicrobial properties, remineralization capabilities and durable mechanical performance — elements that are central to the integrity of the adhesive/dentin (a/d) interfacial seal. Our approach to this problem offers a transition from a hybrid to a biohybrid structure. Discrete peptides are tethered to polymers to provide multi-bio-functional adhesive formulations that simultaneously achieve antimicrobial and remineralization properties. The bio-additive materials design combines several functional properties with the goal of providing an adhesive that will serve as a durable barrier to recurrent decay at the composite/tooth interface.

[*]**Corresponding author:** Candan Tamerler, PhD, Associate Dean for Research, School of Engineering, Wesley G. Cramer Professor, Mechanical Engineering Department, Bioengineering Program, Director, Bioenabled and Biomimetic Materials, Institute for Bioengineering Research, Core Director, Biomaterials and Tissue Engineering, Bioengineering Program, University of Kansas Office: (785) 8642984 ctamerler@ku.edu.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

This article provides an overview of our multi-faceted approach which uses peptides tethered to polymers and new polymer chemistries to achieve the next generation adhesive system — an adhesive that provides antimicrobial properties, repair of defective dentin and enhanced mechanical performance.

Keywords

Bio-additives; Adhesive Design; Peptide Engineering; Antimicrobial Peptide; Mineralization; Polymer Chemistry

1. Introduction

According to a global burden disease study, dental caries which affected 3.5 billion people globally with untreated caries in 2017 is one of the most prevalent health problem [1–7]. Resin-based composites are among the most commonly used materials to restore form and function to teeth damaged by decay[8–9] however, the clinical lifetime of composite-restorations can be as low as 5 to 7 years[10]. The problem of repeated composite restoration replacement is pervasive—nearly 70% of all composite restorations are replacements for failed resin restorations[10]. Repeated dental-restoration replacement risks pulpal injury, increased tooth weakness, and eventually, total tooth loss[11].

The leading cause of composite-restoration failure is recurrent marginal decay. In brief, restoration of the tooth surface involves removal of decay, acid-etching of enamel and dentin, application of dental adhesive, and finally, restoring of form and function using composite restorative material. The composite is too viscous to bond directly to the tooth—a lower viscosity adhesive is used to bond the composite to the tooth structure. The infiltration of the adhesive into the acid-etched dentin, i.e. the demineralized dentin collagen, is termed hybridization, and the resulting structure has been named the “hybrid layer”[12–14]. The ideal hybrid layer is described as the demineralized dentin collagen completely encased in adhesive, but this ideal structure has not been achieved in vivo[4, 8, 15–16]. This failure is attributed, in part, to a discrepancy between the depth of adhesive infiltration and the depth of demineralized dentin collagen[3, 8, 15, 17–20]. In addition to the hybrid layer, other factors that affect the overall quality of the a/d interfacial seal include the clinical substrate (variation in composition, heterogeneous structure, caries-affected dentin, sclerotic dentin, etc.), adhesive composition, operator technique, moisture contamination, and patient characteristics[21].

The oral cavity is a caustic environment that challenges the durability and integrity of the most dental resins. To improve the compatibility between the dental adhesive and the wet, demineralized dentin matrix, hydrophilic and ionic monomers have been incorporated in contemporary dental adhesives [22]. The increase in hydrophilic components facilitates adhesive infiltration, however there are several disadvantages including increased water sorption which weakens the polymer. Water plasticizes the polymer and promotes chemical hydrolysis of the adhesive [19]. Salivary esterases[23–30] and esterases from *Streptococcus mutans*[30] may accelerate this hydrolysis process leading to long-term release of degradation

by-products. The by-products accumulate at the a/d interface and increase the virulence of cariogenic bacteria, e.g. S. mutans, provoking a degradative positive-feedback loop.

Adhesion of the cariogenic bacteria, *S. mutans,* to the tooth/adhesive/composite interface creates a microenvironment that promotes the subsequent attachment and growth of bacteria and biofilms. Lactic acid produced by *S. mutans* demineralizes the tooth surface, acid as well as enzymes produced by *S. mutans* erode the dental adhesive, and together these activities lead to wider and deeper gaps at the margin between the tooth and composite. The gaps provide an ideal environment for bacteria to proliferate which leads ultimately to recurrent decay and failure of the composite restoration[20, 31–33].

1. Bio-additive hybrid dental adhesives

Dental adhesives possess broad and versatile properties, but they lack the bioactivity that is associated with native structures including biomolecules. Incorporating peptides with specific biological functionalities, e.g. antimicrobial and remineralization properties, as part of the material system could enhance the durability and integrity of the adhesive and the seal formed at the a/d interface. Polymer-peptide conjugates are generally hybrid soft materials, which are designed to achieve synergistic behavior of both components while overcoming the disadvantages inherent to the individual components[34–35]. Over the past two decades, studies of the polymer-peptide conjugates have ranged from fundamental science to biomedical and nonbiological applications[35–43]. To date, the majority of these polymer-peptide conjugates have been soft, rapidly eroding hydrogel-based materials that degrade or clear after a few weeks in vivo.[44] The relatively low mechanical properties and rapid erosion of these conjugates inhibit their application as dental restorative materials. Designing the conjugates to achieve their full potential is still a major challenge for biomedical applications.

Our recent investigations have led to a synergistic approach to the design and development of a bio-additively designed hybrid dental adhesive. As Fig. 1 illustrates, this biohybrid design is promising for achieving superior performance while regaining the integrity of the tooth structure within the a/d interface. The antimicrobial and remineralization activities are enabled by the peptides conjugated to the polymer while new polymer chemistries lead to enhanced mechanical properties via an autonomous strengthening reaction. The polymer-peptide conjugation provides relatively high antimicrobial activity and promising remineralization of dentin at the a/d surface. The polymer alone does not inherently possess antimicrobial properties or remineralization capabilities. The novel polymer chemistries enhance the mechanical behavior through a mechanism that provides intrinsic reinforcement of the polymer network in both neutral and acidic conditions[45].

2. Adhesive/dentin interface as the weak link

In spite of improvements in dental adhesive technology, the integrity of the a/d interface is vulnerable to degradation under the caustic conditions present in the mouth. The integrity of the a/d interface and the durability of the bonds formed at this interface have been linked directly to the quality of the hybrid layer. The characteristics of the etched dentin surface,

structural and compositional heterogeneity of the hybrid layer and the physicochemical properties of adhesives have been summarized to clarify their effects on the integrity of the a/d interface [46–47].

The demineralized dentin collagen matrix acts as the scaffold for the resin infiltration. Due to the varied amphiphilicity of the components in the dental adhesives and the fluid filled demineralized dentin matrix, adhesive infiltration into the collagen matrix results in an imperfect hybrid layer[15, 48–49] as shown in Fig. 2. The imperfect hybrid layer leads to exposed collagen fibrils. The inferior properties of the exposed collagen as compared to resin-infiltrated or mineralized collagen[50] lead to collagen that is not protected against challenges that can provoke denaturation and early failure[51]. The limited durability of the imperfect hybrid layer shortens the lifetime of tooth-colored resin-based restorations.

3. Tuning the antimicrobial property of dental adhesive with peptide conjugation

Antimicrobial peptides (AMPs) have been widely recognized as existing in all life forms as part of the immune systems to fight infections. Large databases, such as the Antimicrobial Peptide Database[52] and LAMP database,[53] identify thousands of naturally occurring AMPs. All known taxa produce AMPs[54–58] which often serve as part of the innate immune response. In addition to naturally occurring peptides, synthetically-designed peptides are needed to address drug resistance in pathogens without leading to reduction of the efficacy of naturally produced AMPs. Recently, AMPs have been engineered to have superior bactericidal characteristics and broad-spectrum activity[59–61].

AMPs have been studied in various dental applications such as coating agents for implants[62–63] and additives for adhesive materials[64–65] to combat pathogenic microorganisms[66]. Despite these advances, successful commercial applications that realize the vast potential of AMPs are quite limited in dentistry. Using high concentrations of AMPs through systemic delivery raises toxicity concerns, showing the need for an alternative delivery strategy. Another issue is non-specific interactions between AMPs and polymers—these non-specific interactions may limit the peptides' availability, causing reduced antibacterial efficacy. [65, 67–68]

Strategies to conjugate peptides to polymers, which are referred as the hybrid constructs, involve different coupling chemistries combining defined monomer and amino acids sequences. Our approach involves tethering peptides with distinctive bioactivities site specifically to monomers using an oligomeric spacer group to form peptide-monomer pairs. Next, these peptide-monomer pairs were copolymerized and the resulting polymers exhibited antimicrobial and remineralization properties simultaneously. Different strategies that have been pursued by other groups include an exploration of the interdependence of linked components. The interdependence has been studied by tuning the component's physical properties to optimize the biologic functionalities [43, 69–70].

In tissue engineering[71–72] and in surgical wound dressings,[73–75] AMPs have been successfully incorporated into hydrogels via conjugation. Robust antimicrobial activity has

been demonstrated with AMP-hydrogels developed from either natural or synthetic materials[39, 71, 76–77]. Despite successful antimicrobial efficacy, currently developed natural or synthetic hydrogels with antibiotic functionality showed limited application in dentistry due to poor mechanical strength. The typical compression moduli of studied AMP-hydrogel conjugates varies from about 0.1 to ~40 kPa[71, 76, 78–83], which are not suitable for use in dental restorations. The reported Young's modulus of hydrated commercial dental adhesives ranges from 0.5 to 4 GPa at 37°C[84–85]. Until recently, no polymer material has been developed to combine the mechanical strength necessary to serve as a dental adhesive and provide antimicrobial activity from AMPs[80].

Peptide diffusion in the resin could be a challenging as peptide may have restricted conformation limiting its activity due to non-specific adsorptions[55, 67]. To prevent this, we incorporated an AMP sequence specifically conjugated to a commonly used monomer for dental adhesive formulation (Fig. 3). The antimicrobial peptides GH12 and AMP2 were selected with their well-known activities against and reduction of cariogenic virulence factors of *S. mutans* [62, 86–8889]. We designed engineered derivatives from GH12 and AMP2 with an addition of a spacer sequence. The α-NH_2 of lysine (K) in both GH12 and AMP2 peptide derivatives was used to react with –COOH of methacrylic acid (MA) or mono-2-(methacryloyloxy) ethyl succinate (MMES) for the synthesis of peptide-monomers (Table 1). Both MA and MMES have one carboxylic acid group for peptide conjugation and one C=C bond for copolymerization with the polymer matrix. The difference between MMES and MA is the chain length and the flexibility. ε-NH_2 of lysine (K) was blocked before cleavage and ε-NH_2 of lysine (K) can be used for conjugation of other functional groups. To provide the conformational flexibility between the peptide and the polymer matrix, a spacer domain is introduced. Several tailored AMP-monomers have been synthesized using GH12 and AMP2 derivative sequences to enable subsequent methacrylate conjugation. The spacer-integrated antimicrobial peptides were linked to MA or MMES and the resulting MA-AMP or MMES-AMP monomers were then copolymerized into dental adhesives. Among the two different spacer sequences investigated for the AMP-adhesive polymer sets, the ones with GGG spacer demonstrated significantly more activity compared to the ones with SSSGGG spacer (Table 1 and Fig. 4(a))[62, 90–91,92–93].

Computationally generated secondary-structure ensembles were used to estimate the changes in secondary structure of the active antimicrobial peptide domain with the selected spacer sequences. As a description of the patterns of hydrogen bonds in the peptide backbone, the secondary-structure ensembles have been shown to model conformations of the peptide that are associated with increasing concentrations of the kosmotropic agent tetrafluoroethanol (TFE). These structures may be more informative of folding behavior when the peptide acts in more ordered environments, such as in the bacterial membrane. Hydrogen bond patterns can be used as an indication on the effect of the spacer sequence if the twisting motion of the spacer is significantly different than the motion occurring in the free peptide. This twisting motion propensity is estimated by computationally folding the peptide with the spacer and comparing the hydrogen bonding patterns seen in the models with varying spacers and without a spacer. Based on these analyses, the GGG spacer has produced less secondary structural feature shifts than the SSSGGG spacer. Minimizing conformational shift may be one way to display improved functionality of the active domain.

Our current models incorporate the secondary structure predicted in solution as an indirect method for estimated antimicrobial activity in solution as well as an integral part of the adhesive system.

In solution activity of a modified peptide can be different than its conjugated activity within a polymer network. Interestingly, the MIC values of MA-AMPM7 and MMES-AMPM7 in the monomeric state were the same (Table 1). When the antimicrobial activity of AMP-polymer conjugates against *S. mutans* was investigated, MA-AMPM7 did not display significant inhibition against *S. mutans* (Fig. 4). However, MMES-AMPM7 significantly improved antimicrobial activity as compared to MA-AMPM7 in the same crosslinked conjugates (Fig. 4b). The improved antimicrobial activity following polymerization associated with the monomer MMES may be attributed to the conformational differences of the secondary structure of the active antimicrobial peptide domain based upon the length of monomer MA and MMES.

We tested the mechanical properties of engineered AMP-polymer conjugates using compression testing. With the same crosslinker (TEGDMA) concentration, the Young's moduli of the control and experimental (w/o peptide) specimens are found to be comparable at the level of 0.05 (Fig. 5). As the TEGDMA increased from 5, 10, 15, to 20 wt%, the Young's moduli of the control samples were recorded as 1.81±0.13, 5.23±0.38, 9.36±0.20, and 16.17±0.35 MPa, respectively. Meanwhile, the corresponding AMP-polymer conjugates resulted in Young's moduli of 2.43±0.26, 5.10±0.18, 9.12±0.49, and 16.63±0.45 MPa, respectively, which are comparable to the modulus of the formulations along the water-adhesive phase boundary[94–95]. The addition of AMP monomers in the formulation does not indicate a loss of stiffness of the tested adhesive materials. AMP-hydrogels have been reported to achieve superior antimicrobial efficacy, however their mechanical strength was reported to be compromised limiting their potential application in dental restorative materials[70–71, 76, 78–79, 81–83]. Engineered AMP-polymer conjugates offers promising path to further explore as alternative restorative constructs maintaining the mechanical strength while providing antimicrobial properties.

4. Hybrid to biohybrid design: the strategy to achieve superior mechanical performance

During acid etching, the mineral phase of dentin is removed to expose the collagen and with the wet bonding technique, the collagen matrix remains moist to avoid collapse. Adhesive infiltrates the wet collagen matrix, the adhesive undergoes in situ polymerization and the collagen-polymerized adhesive construct, i.e. the hybrid layer, is formed. As noted above (sections 1 and 2), the mechanical properties of the hybrid layer deteriorate under aging conditions relevant to in vivo function.

Demineralization of dentin is one of the major reason for the deterioration of mechanical properties. There have been different top-down and bottom-up approaches proposed to address this problem[15, 96–97]. The lack of seed crystallites in the hybrid layer will significantly limit the remineralization, epitaxial growth over the seed crystallites as a classical top down approach was used to address this problem. Whereas bottom up approach

involves protein, peptides, or biomimetic analogs to mediate or template the nucleation and growth within the collagen matrix [97]. Peptide mediated remineralization of the dentin can be one approach to mitigate the negative impact of the deteriorating mechanical properties. Nevertheless, controlling the orientation of crystallites and achieving complete remineralization still present a challenge[15, 98]. Indeed, atomic computations suggest complex binding interactions between peptides and mineral surfaces that prefer specific conformations and compatible crystallite habit[99].

Along with the remineralization approach, our polymer chemistry investigations have led us to new strategies for addressing deteriorating mechanical properties that are generally noted in dental adhesives under in vivo conditions. We reported the self-strengthening strategy to reinforce the polymethacrylate-based dental adhesive by introducing photoacid-induced sol-gel reaction[45, 100–102] for the first time. The results indicated that in both neutral and acidic conditions, the self-strengthening significantly improve the mechanical properties. By tuning the alkoxysilane monomer's structure and functionalities, we have engineered dental adhesives that provide the requisite hydrophilic-hydrophobic balance, a more homogenous structure and self-strengthening properties [100, 102].

4.1. Peptide Mediated Remineralization

Endogenous enzymes such as matrix metalloproteinases that degrade the exposed demineralized dentin; bacteria and saliva enzymes and factors such as chemical and enzymatic hydrolysis cause deterioration of the bond between dentin and low viscosity adhesive used to connect the composite to the tooth[103]. In the process following this degradation, the bacteria penetrate the interface, the cariogenic plaque accumulates in the exposed, demineralized dentin leading ultimately to decay and failure of the composite restoration. Failure to maintain the integrity of the a/d bond reduces the clinical lifetime of composite restorations [104–105]. Remineralization of deficient/damaged dentin matrices at the a/d interface, mediated by peptides, [106–107] provides a viable solution to this problem.

To mimic biomolecular interactions at the material-tissue interface, we as well as many other groups selected peptides for metals, minerals and semiconductors using combinatorial biology protocols, e.g., phage and cell surface displays[108–122]. We utilized these peptides in several bioactive and antimicrobial surface design, inorganic material synthesis and directed nanoparticle or biomolecule assembly[121, 123–134,135]. Our prior art includes a hydroxyapatite binding peptide (HABP: CMLPHHGAC) selected using phage display method demonstrating a control over the hydroxyapatite mineralization kinetics and resulting in a specific morphology[136]. In a different study this peptide was also shown to bind to the mineralized tissues after incorporating into a fluorescent probe [137]. We further explored this peptide for achieving remineralization at the biohybrid layer (Fig. 6)

Remineralization is one clear component of a multi-faceted strategy to achieve a durable, integrated a/d interface that will provide a critical barrier between the repaired tooth and the oral environment. The HABP peptide that is genetically inserted into a green fluorescent protein was explored to mineralize deficient dentin matrices at the a/d interface. Our analyses on the collagen, adhesive and mineral demonstrated the homogenous distribution of mineral achieved throughout the dentin interface. [138]. We next designed an engineered

peptide-based copolymer system using a spacer integrated HABP derivative to conjugate it to methacrylate. When resulting methacrylate-HABP monomers were copolymerized into dental adhesive formulation, we observed a mineral forming effect using an alizarin red staining assay (Fig. 7). Moreover, the spherical particle formed was confirmed by the SEM images (Fig. 7). The overall porosity of the dental adhesive structure decreases in peptide-polymer conjugates and mineralization favors high porosity. Our results demonstrates that significant mineralization is achieved in the polymer-peptide conjugate structure as compared to the polymer only structure (Fig. 8).

Building on these promising results, we studied the potential of using peptide-protein conjugates to achieve peptide-mediated mineralization at the a/d interface. Fig. 9 reveals that significant remineralization is achieved at the a/d interface, which was exposed to mineralization solution after being demineralized and then infiltrated with adhesive that contains peptide. Further investigation is required to optimize the peptide-tethered-adhesive to provide peptide-mediated mineralization under conditions relevant to the in vivo settings.

4.2. New polymer chemistries: self-strengthening property

In our previous investigations,[45, 100–102] the self-strengthening adhesives showed: 1) formulation with lower viscosity and higher C=C bond conversion; 2) significantly improved crosslinking density and mechanical performance in wet conditions; 3) dramatically reduced leachates, especially HEMA. These results support the use of self-strengthening adhesives as one component of a multi-faceted strategy to promote the durability and integrity of the a/d interface.

The novel alkoxysilane-containing adhesives capitalize on free-radical polymerization and sol-gel reactions to provide self-strengthening polymers. The relatively slow rate of the photoacid-induced sol-gel reaction compared to the free-radical polymerization provides a novel way to tune the network structure after light irradiation. Fig. 10 shows the proposed mechanism for the self-strengthening reactions after light irradiation. When the liquid resin is irradiated by visible-light, the polymethacrylate-based matrix is formed by free radical polymerization of the co-monomers, e.g., HEMA and BisGMA. Simultaneously, the alkoxysilane groups are hydrolyzed in a reaction catalyzed by the photoacid produced during the visible-light irradiation. Soaking the resin in water or lactic acid furthers the autonomous hydrolysis and condensation of the alkoxysilyl moieties, creating new crosslink points. The resulting silanol groups react with the hydroxyl groups of HEMA or BisGMA to form covalent bonds. The autonomic sol-gel reaction continues in the wet environment, leading to intrinsic reinforcement of the network. As Fig. 11 indicates, the simulation based on Prony series-fitting[139] showed that the mechanical properties of polymers were significantly improved by the self-strengthening reaction in the first few days whereas the formulation without self-strengthening property fails after the first testing day (Sarikaya *et al.*, unpublished observations). With the increase in soaking time, the effect of self-strengthening reaction on the stress relaxation behavior of bulk polymer decreases due to the gradual increase in the crosslinking density of the polymer. In comparison, the DMA test results indicated that the self-strengthening contributed to the further crosslinking reaction even after 8 weeks soaking in water[45, 102]. Within the polymethacrylate-based matrix, the self-

strengthening adhesive provided a slow, persistent crosslinking reaction, which can promote the formation of Si-O-Si bonds and improve the hydrolytic resistance.

6. Conclusions

The bioinspired materials design approach offers significant promise for promoting the integrity of the a/d interface and providing a concomitant increase in the lifetime of composite restorations. Here we summarize synergistically working bio-hybrid constructs that are designed by engineering peptides combined with new polymer chemistries. Discrete peptides are tethered to polymers to provide multi-bio-functional adhesive formulations that simultaneously achieve antimicrobial and remineralization properties. Spacer sequences are used to provide reactive groups for simultaneously tethering functionally distinctive peptides to the monomer as well as providing the length and flexibility required to maintain the peptide's original bioactivities when applied as an adhesive at the tooth surface. Examples on peptide-polymer conjugates are provided to remineralize the deficient/mineral-depleted dentin matrices as well as to promote antimicrobial activity at the a/d interface without compromising the polymer`s mechanical properties. This hybrid approach includes new polymer chemistries resulting dental adhesives with self-strengthening properties, enhanced hydrolytic stability and decreased degradant release.

The inherent specificity of peptides makes them ideal molecules for conjugation with synthetic polymers to create new functional biomaterials. The physical limitations of peptides, such as their sensitivity to pH, temperature, and degradation, could be mitigated through conjugation with polymers[34–35]. However, conjugation often leads to a significant reduction in the peptide's bioactivity. Typically, the polymer-peptide conjugates are soft materials that are used in solution, hydrogels, or loosely crosslinking gels to maintain the peptide's bioactivity[35, 43]. Therefore, one important consideration for the peptide-polymer conjugate used in a dental adhesive application is the balance between bioactivity, durability and mechanical properties. To address this challenge, optimization of the peptide bioactivity and control of chemical conditions such as the ratio of peptide-to-polymer, as well as the resin components, should be thoroughly investigated. With the fundamental knowledge of structural and biological properties of polymer-peptide conjugates, the investigations can lead to an ability to tailor the conjugates to meet the needs of specific applications. The efforts to develop polymer-peptide conjugates have the potential of providing new roadmaps for material design and this work offers promise for advancing the development of materials for a variety of biomedical applications [42, 140–141]. The resulting biofunctional materials may be exploited in a wide variety of applications including, but not limited to, the treatment of secondary caries, enhanced durability of dental composite restorations, antimicrobial gels, and tissue engineering applications. In tissue engineering, free-radical crosslinked polymers are desirable because they can be polymerized in direct contact with tissues, either in solution, or in thin layer on the surface[141–143]. Polymer-peptide conjugates hold great promise as a new class of hybrid biomaterials with diverse attributes, such as antimicrobial properties,[144–145] cell-penetration scaffolds,[146] mineralized tissue repair and bioadhesive properties[147]. With the introduction of self-strengthening characteristic, the conjugates can be tailored to achieve target properties required for specific biomedical applications. This strategy could be introduced into the biomaterials to tune the mechanical properties, e.g.

viscoelasticity, which is desirable for tissue engineering, and numerous other applications, such as 3D printing, wound dressing, scaffold materials, as well as bone regeneration.

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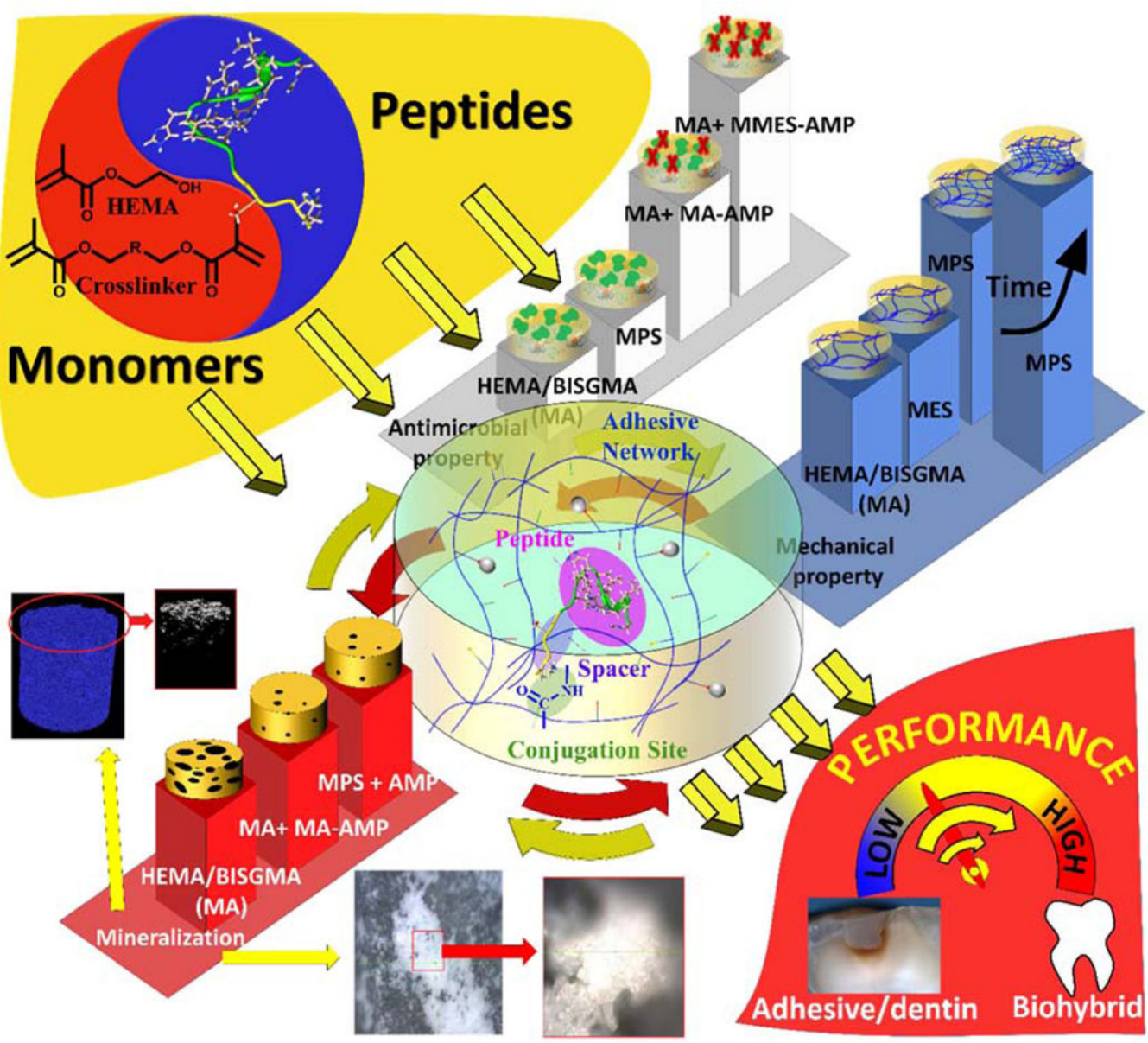

Fig. 1.
Bio-additive hybrid material design strategy leading to high performance a/d interface.

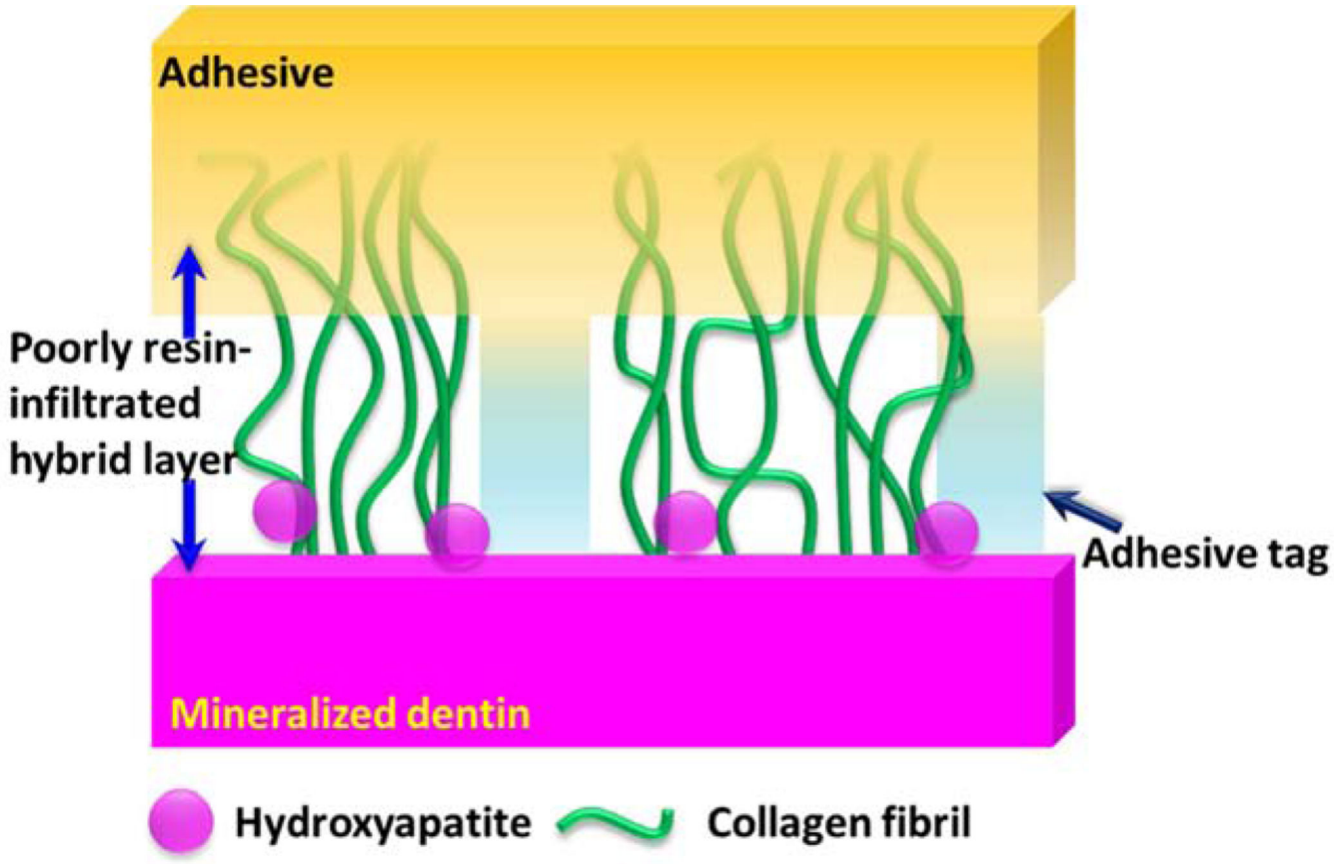

Fig. 2.

Non-ideal a/d interface exhibiting heterogeneity in terms of composition of the hybrid layer and adhesive throughout the depth of the demineralized dentin collagen.

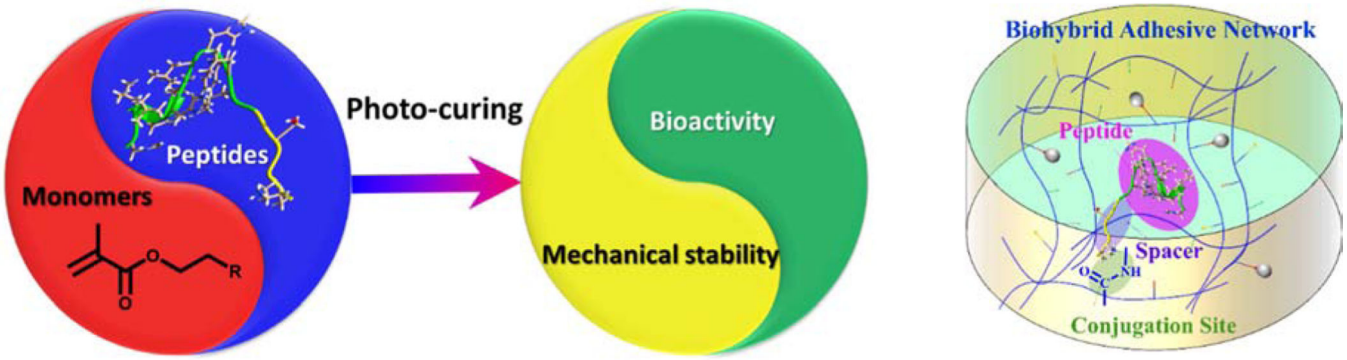

Fig. 3.

Tethering peptides to polymers leading to superior antimicrobial property and mechanical performance.

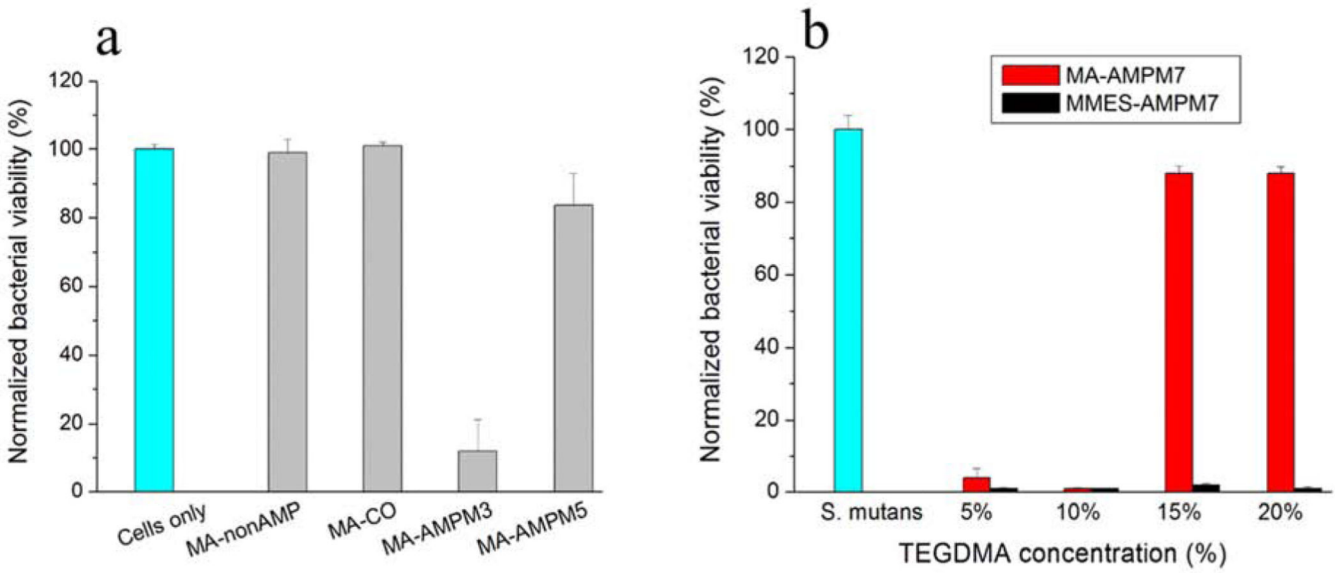

Fig. 4.

(a) The viability of S. mutans cultures after overnight incubation with polymerized discs containing non-AMP-monomer or AMP-monomers. S. mutans: a positive control without a disc. Peptide control: MA-nonAMP with GGG as a spacer. MA-C0 is the methacrylate control polymer replacing methacrylate peptide conjugates with methacrylate monomer, and (b) the viability of S. mutans cultures after overnight incubation with polymerized discs containing MA-AMPM7 or MMES-AMPM7 monomers. S. mutans: a positive control without a disc.

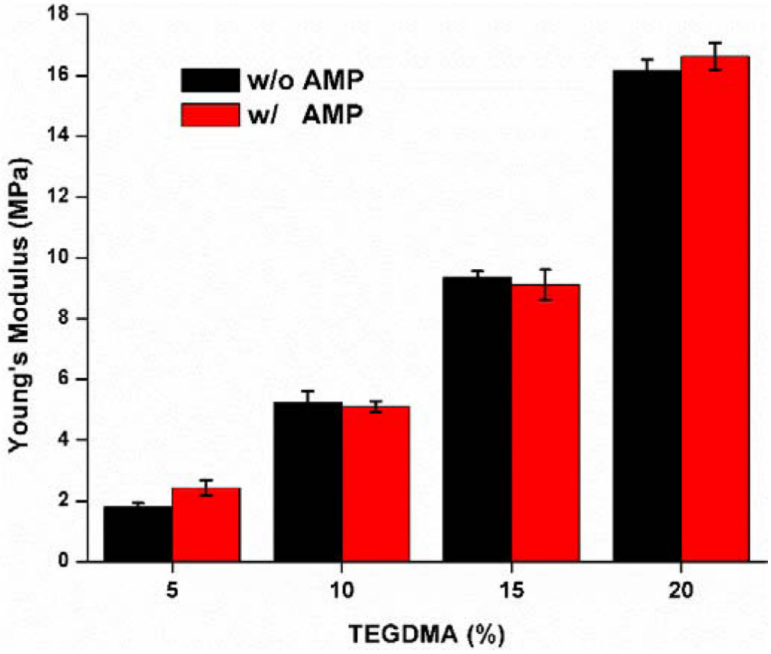

Fig. 5.
Young's moduli of the controls and AMP-polymer conjugates cylindrical samples.

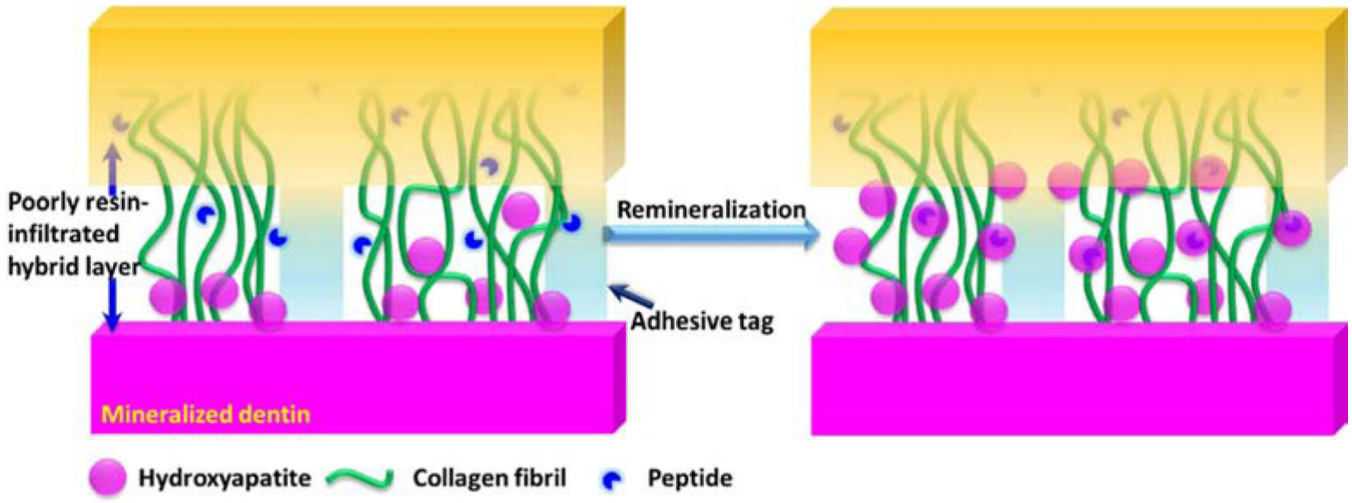

Fig. 6.
Biohybrid layer achieved through peptide mediated remineralization.

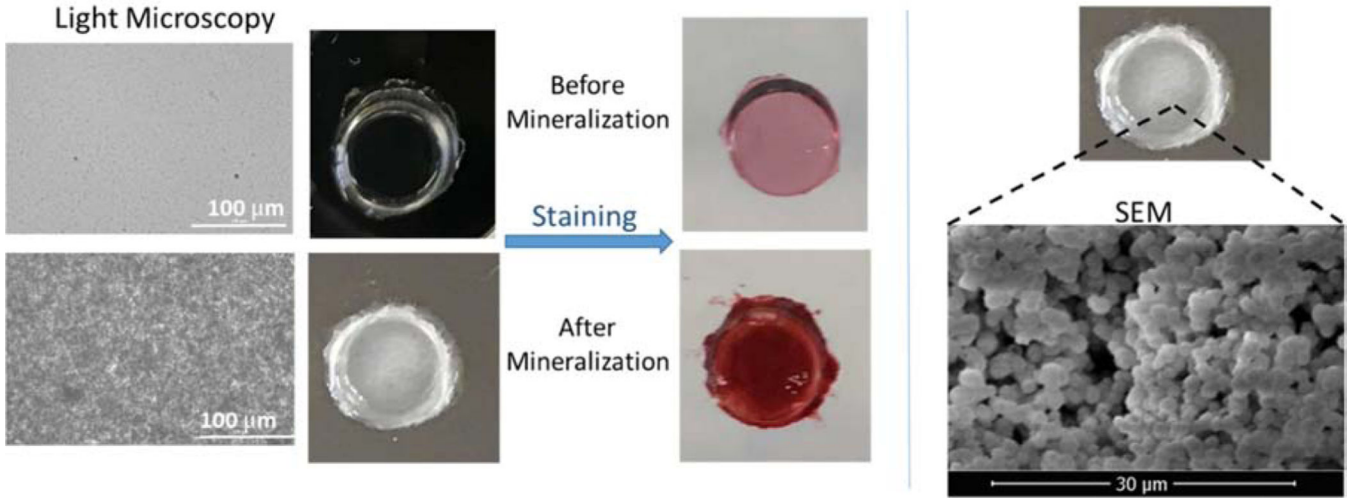

Fig. 7.

Light microscopy and SEM images of peptide mediated mineralization on polymer discs. Peptide integrated polymer discs were stained with Alizarin Red.

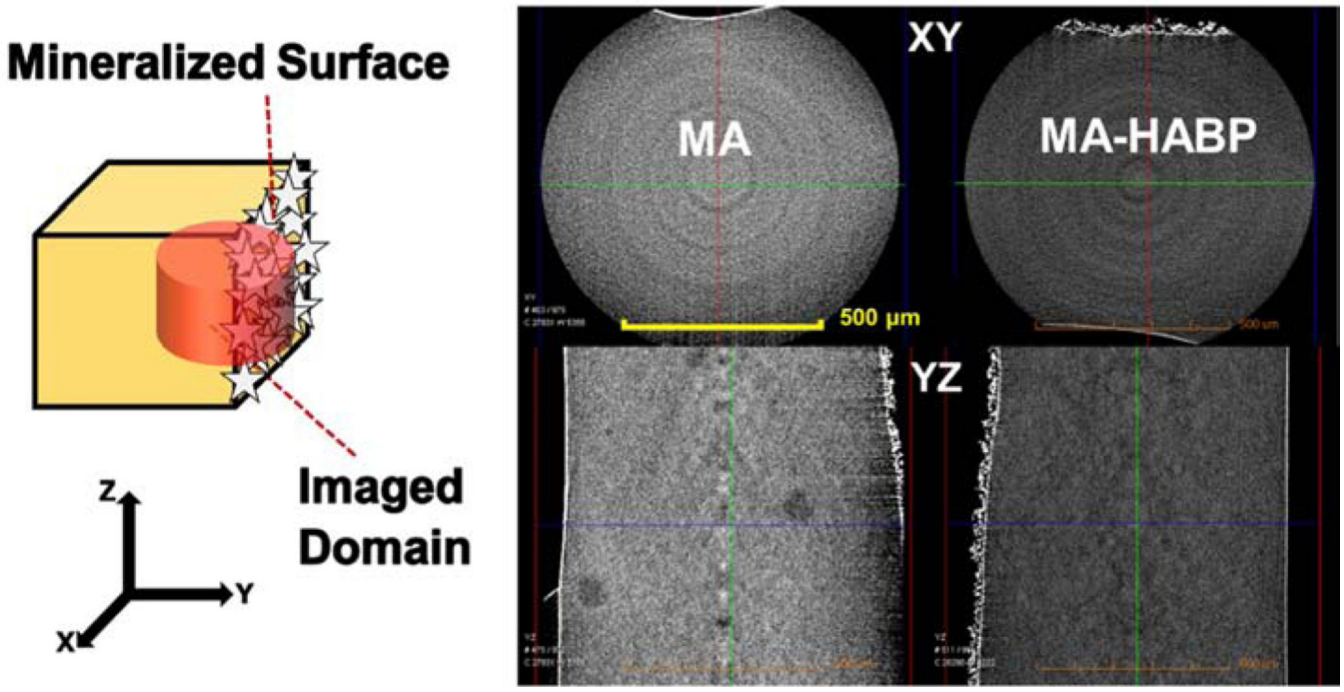

Fig. 8.
Micro-CT images of mineralization with and without peptide mediation on polymer disks.

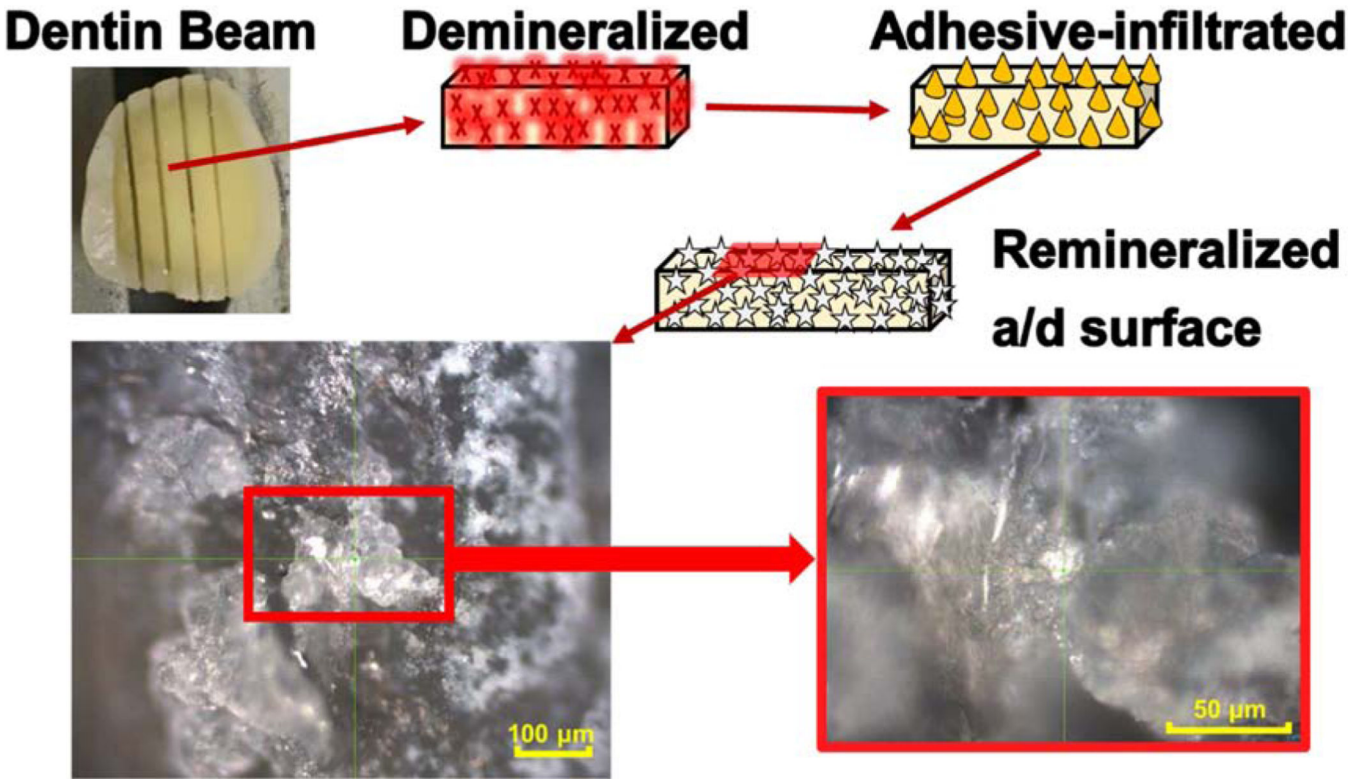

Fig. 9.
Light microscopy images showing peptide-mediated mineralization at a/d interface.

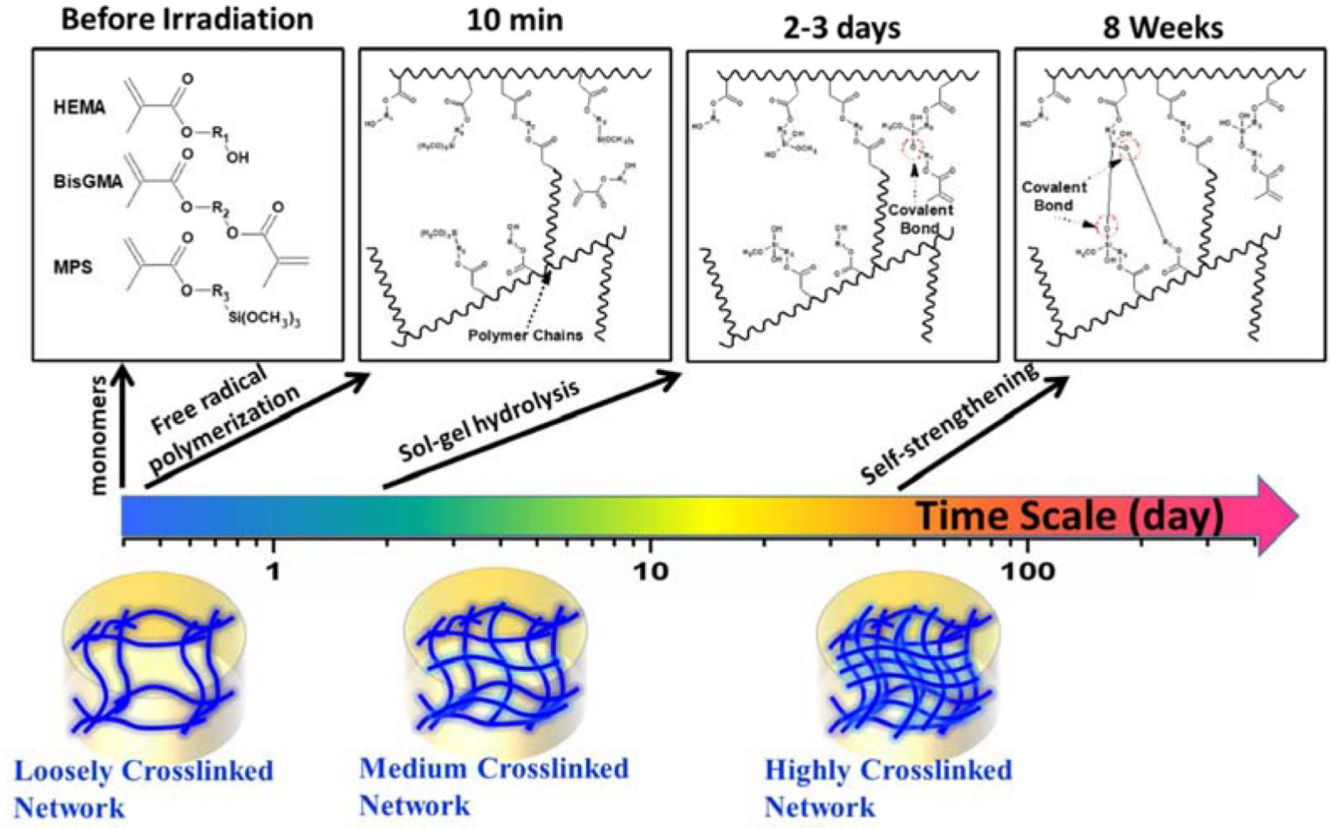

Fig. 10.
The evolution of network structure in adhesive through self-strengthening reaction.

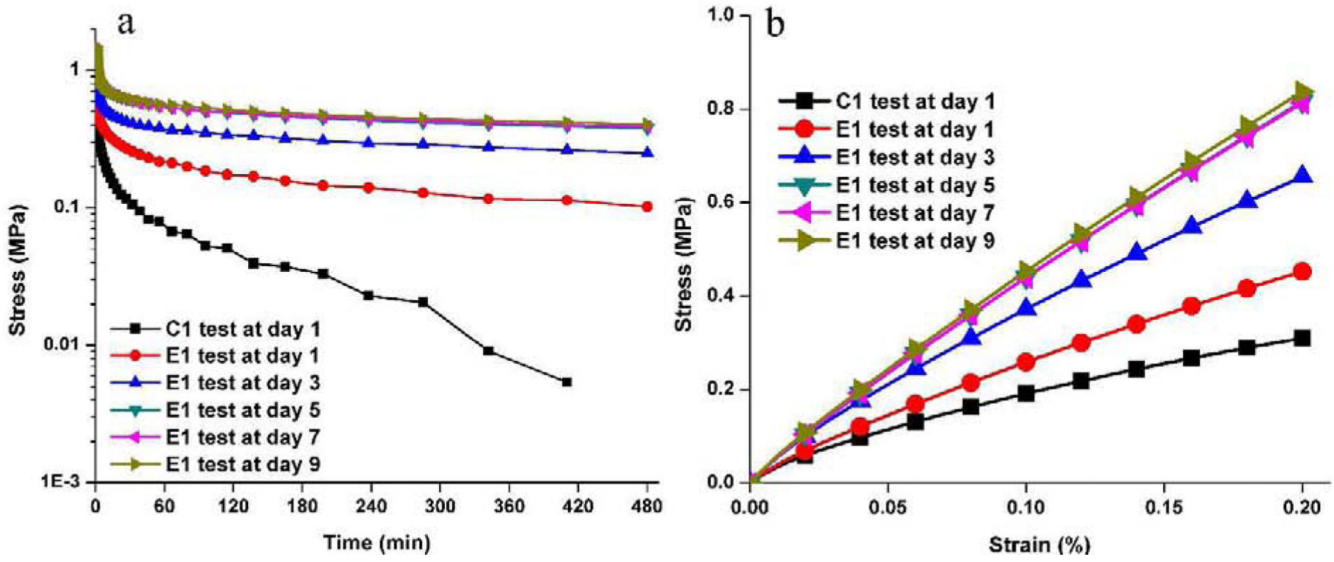

Fig. 11.

Improved mechanical performance of the self-strengthening polymer adhesive over time: (a) Stress-relaxation test results and (b) Stress-strain behavior prediction based on Prony-series-fitted stress-relaxation-test data. Stress relaxation test informs that HEMA/BISGMA/MPS formulation (E1) is superior to HEMA/BISGMA/MES formulation (C1) in terms of stiffening behavior in wet conditions.

Table 1.

The sequence information of the AMPs and AMP-monomers with their antimicrobial properties

AMP and AMP-monomer	Sequence	MIC (μg/mL)
GH12 (COOH)	GLLWHLLHHLLH (COOH)	15.6
AMPM1	K_GGGSG_GLLWHLLHHLLH (COOH)	31.3
AMPM3	K_GGG_GLLWHLLHHLLH-NH_2	7.8
AMPM5	K_SSSGGG_GLLWHLLHHLLH-NH_2	15.6
MA-AMPM1	MA-K_GGGSG_GLLWHLLHHLLH (COOH)	125
MA-AMPM3	MA-K_GGG_GLLWHLLHHLLH-NH_2	7.8
MA-AMPM5	MA_K_SSSGGG_GLLWHLLHHLLH-NH_2	15.6
AMP2-NH_2	KWKRWWWWR-NH_2	3.9
AMPM7	K_GGG_KWKRWWWWR-NH_2	7.8
AMPM8	K_SSSGGG_KWKRWWWWR-NH_2	31.3
MA-AMPM7	MA-K_GGG_KWKRWWWWR-NH_2	7.8
MA-AMPM8	MA-K_SSSGGG_KWKRWWWWR-NH_2	62.5
MMES-AMPM7	MMES-K_GGG_KWKRWWWWR-NH_2	7.8