Composite restorations have higher failure rates, more recurrent caries and increased frequency of replacement as compared to dental amalgam. Penetration of bacterial enzymes, oral fluids, and bacteria into the crevices between the tooth and composite undermines the restoration and leads to recurrent decay and failure. The gingival margin of composite restorations is particularly vulnerable to decay and at this margin, the adhesive and its seal to dentin provides the primary barrier between the prepared tooth and the environment. The intent of this article is to examine physico-chemical factors that affect the integrity and durability of the adhesive/dentin interfacial bond; and to explore how these factors act synergistically with mechanical forces to undermine the composite restoration. The article will examine the various avenues that have been pursued to address these problems and it will explore how alterations in material chemistry could address the detrimental impact of physico-chemical stresses on the bond formed at the adhesive/dentin interface.
**INTRODUCTION**

**I. CLINICAL PERFORMANCE: COMPOSITE VERSUS DENTAL AMALGAM RESTORATIONS**

In 2005, 166 million dental restorations were placed in the United States [1] and clinical studies suggest that more than half were replacements for failed restorations. [2] Replacement of failed restorations accounts for nearly 70% of all restorative dentistry [2] and the emphasis on replacement therapy is expected to increase as concern about mercury release from dental amalgam forces dentists to select alternative materials. The use of dental amalgam is being discontinued in response to global concerns about mercury in the environment. Dental amalgam is identified as one of the top five mercury-added products; it is rated #5 behind batteries, measuring devices, electric switches and relays, and mercury-containing light bulbs. [3] The most common alternative to dental amalgam is resin composite [4] but composite restorations have higher failure rates, more recurrent caries and increased frequency of replacement [2, 4-10].

In 2009, based on the review of dental records from 3,071 patients, Simecek and colleagues reported a significantly higher risk of replacement for posterior composite restorations as compared to amalgam [4]. In a study of amalgam and composite restorations placed by 243 Norwegian dentists, the mean age of failed amalgam was ~11 years while the mean age for failed composite was statistically significantly lower at 6 years. [8] The need for additional treatment was 50% greater in children receiving composite restorations as compared to children treated with dental amalgam [11]. After nearly 4 decades of research the clinical lifetime of large to moderate posterior composite restorations continues to be approximately one-half that of dental amalgam [12].

The reduced clinical lifetime of moderate to large class II composite restorations can be particularly detrimental for our patients because removal of these restorations can lead to extensive loss of sound tooth structure. For example, the removal of composite restorations produced significantly greater increases in cavity volume in comparison to the removal of amalgam [13]. The increase in cavity volume and increased frequency of replacement means that significantly greater amounts of sound tooth structure will be lost with treatment and re-treatment of class II composite restorations [13]. Over the lifetime of the patient, the additional loss of tooth structure will translate to more complex restorations and eventually total tooth loss. The reduced longevity, increased frequency of replacement and the need for a more complex restoration means increased costs to the patient in terms of both time and money [14].

**II. COMPOSITE RESTORATION FAILURE**

The primary factor in the clinical failure of moderate to large composite restorations is secondary decay at the margins of the restorations [8]. As an example, in a study of radiographs from 459 adults, age 18-19 years, the investigators reported that among 650 interproximal restorations the failure rate as a result of secondary or recurrent decay was 43% for composite as compared to 8% for amalgam [7]. In a separate study of amalgam and composite restorations placed in 8-12 year old children, the primary reason for failure of both materials was secondary decay, but secondary decay was 3.5 times higher in composite restorations [5].

The development of secondary decay indicates that the seal at the composite/tooth interface is not resistant to the physical, chemical, and mechanical stresses that are present in the mouth (Figure 1). Indeed, the clinical failure of moderate to large composite restorations has been linked to a breakdown of the bond at the tooth surface/composite material interface [12,15-20] and increased levels of the cariogenic bacteria, Streptococcus mutans, at the perimeter of these materials [21-25]. The breakdown of the composite/tooth bond has been attributed to the failure of our current adhesives to consistently seal and adhere to the dentin [2,20-29]. Results from both in vitro and in vivo studies indicate that failure of the adhesive/dentin (a/d) bond allows bacterial enzymes, oral fluids, and even bacteria to infiltrate the spaces between the tooth and composite [30] (Figure 2). The penetration of these agents into the spaces between the tooth and composite undermines the restoration and leads to recurrent caries, hypersensitivity, and pulpal inflammation [2,20,26,31,32].

Clinical studies report poor marginal adaptation, marginal discoloration, and loss of retention of the composite restoration when the a/d interface is exposed to the oral cavity 33. Acid-etching provides effective mechanical bonding between the composite restoration and treated enamel, but breakdown at the dentin surface continues to threaten the long-term viability of moderate to large posterior composite restorations [18,20,22,31,34,35].
Under clinical conditions, one can frequently detect a separation between the composite material and the tooth surface at the gingival margin [34]. Clinicians frequently find very little enamel available for bonding at the gingival margin of class II composite restorations and thus, the bond at this margin depends on the integrity of the seal formed with dentin. The gaps at the gingival margin of class II composite restorations (Figure 3) have been related to very technique sensitive and unreliable dentin bonding [34,36].
The gingival margin in class II composite restorations is the most common location of bonding failures [37]. Purk and colleagues [38] compared the microtensile dentin bond strength of gingival and proximal cavity walls of class II restorations. Their results showed that the dentin adhesive bond of composites to gingival walls was significantly weaker, and thus, at increased risk of failure compared to the bond to proximal walls.

Spectroscopic results from a separate study indicated a twofold difference in the depth of dentin demineralization at the gingival and proximal margins [29]. The differences in demineralization depth may be due to less mineralized dentin at the gingival margin. For example, the mineral/matrix ratio in dentin at the gingival margin was less than half the ratio at the proximal wall. Less mineral and increased density and size of the tubules [39] translate to faster and deeper etching at the gingival margin as compared to the proximal wall.

Although dentin etching was deeper, there was considerably less adhesive penetration at the gingival margin as compared to the proximal wall [29]. This discrepancy between etching depth and adhesive penetration led to a large area of exposed collagen at the gingival margin. It was suggested previously that adhesives could infiltrate dentin at the gingival margin more efficiently because of the increased number of tubules per unit area [40]. However, water content is higher in dentin at the gingival margin. This is not only because of the water already present within the demineralized dentin matrix, but also because patent tubules contribute to the contamination of the prepared surface with a great amount of dentinal fluid [41]. The cumulative effect of the increased water leads to reduced adhesive infiltration and lower monomer/polymer conversion of the adhesive at the gingival margin as compared to the proximal wall [29]. Under in vitro conditions, adhesive monomers or oligomers and unprotected collagen at the gingival margin of Class II composite restorations undergo hydrolytic degradation after 90-days aqueous storage [28].

III. DENTIN BONDING & THE HYBRID LAYER

Based on numerous morphologic investigations and bond strength studies [42-46] it is generally accepted that the primary factors critical in determining an adequate a/d bond are: wetting of the dentin substrate by components of the adhesive system [42,47] and micromechanical interlocking via resin penetration and entanglement of exposed collagen fibrils in the demineralized dentin [48-50]. Morphologic evidence of resin penetration of the exposed collagen fibrils was first reported by Nakabayashi [51] and he called the distinct zone between the bulk adhesive and the non-demineralized dentin the ‘hybrid layer’. Current adhesive systems that acid etch the dentin characteristically bond via hybridization [52].

The hybrid layer is formed when an adhesive resin penetrates a demineralized or acid-etched dentin surface and infiltrates the exposed collagen fibrils. During acid etching, the mineral phase is extracted from a zone that measures between 1 and ~10 µm of the dentin surface [53-55]. The composition of the exposed substrate differs radically from mineralized dentin. For example, mineralized dentin is 50% mineral, 30% collagen, and 20% water by volume [56], whereas demineralized dentin is 30% collagen and 70% water [53-57]. With removal of the mineral phase, the collagen fibers are suspended in water. If there is a substantial zone of demineralization and the water supporting the collagen network is removed either by air drying or the action of an air syringe the collagen will collapse [57-59]. A collapsed collagen network reduces the porosity and inhibits resin penetration through the demineralized layer [57]. It forms a barrier between the demineralized layer and the underlying intact or unreacted dentin surface [46,59,60]. A collapsed collagen network compromises the a/d bond [46,53,58,59] as well as the marginal integrity of the composite restoration.

III.A. Wet bonding

In the early 1990s, wet bonding was introduced to counteract the problems of collagen collapse [48,61-64]. Wet bonding means that the dentin is kept fully hydrated throughout the bonding procedure; the surface morphology of the demineralized dentin does not change because the water supporting the collagen matrix is not removed [65]. Bond strength results [48,61-64] with “wet” bonding support these findings, that is, the higher bond strengths with this technique reflect the minimal collapse of “wet” versus air-dried dentin collagen [57]. It is speculated that moist dentin provides a more porous collagen network and that increased porosity means more space for adhesive infiltration [43,46,57,61-63].

With wet bonding techniques, the channels between the demineralized dentin collagen fibrils are filled with water, solvent, conditioner, and/or oral fluids [57,66]. The only mechanism available for adhesive resin infiltration is diffusion of the resin
into whatever fluid is in the spaces of the substrate and along the collagen fibrils. Ideally, the solvent in combination with hydrophilic monomers, (e.g. hydroxyethyl methacrylate (HEMA)) conditions the collagen to remain expanded during adhesive infiltration. However, HEMA, a primary component in many single bottle commercial dentin adhesives, can dramatically reduce the evaporation of water[67]. The addition of HEMA reduces the mole fraction of water and therefore reduces the partial pressure of water (Dalton’s law of partial pressures). As the partial pressure of water drops it becomes more and more difficult to remove residual water from the demineralized dentin matrix. Hydrophobic monomers, such as 2,2-bis[4(2-hydroxy-3-methacryloyloxy-propoxy)-phenyl] propane (BisGMA), would resist diffusing into these sites where there is residual water[50,68,69].

Under in vivo conditions, there is little control over the amount of water left on the tooth. As a result, it is possible to leave the dentin surface so wet that the adhesive actually undergoes physical separation into hydrophobic and hydrophilic-rich phases [68]. Results from our laboratory indicated that excess moisture prohibited the formation of an impervious, structurally integrated a/d bond at the gingival margin of Class II composite restorations[28,29]. Clinicians must routinely attempt to bond to naturally wet substrates such as caries-affected dentin [70] or deep dentin[71-74]. The water content of caries-affected dentin has been reported to be 2.7 times greater than that of normal dentin[70]. In deep dentin, 22% of the surface area is exposed tubules while exposed tubules account for 1% of the surface area of dentin close to the DEJ[75]. The large increase in surface area attributable to tubules means that in deep dentin, pulpal fluid will contribute additional moisture to that already present within the demineralized dentin matrix. Since our current adhesives are very sensitive to excess moisture, bonding to these clinically relevant substrates is a formidable challenge[74,76-78].

III.B. Sensitivity of adhesive to wet bonding conditions

The sensitivity of our current adhesives to excess moisture is reflected in the water-blisters that form in adhesives placed on over-wet surfaces [79-81] and adhesive phase separation that leads to very limited infiltration of the critical dimethacrylate component [50,68,82]. The optimum amount of wetness varies as a function of the adhesive system [83]. Additionally, it is impossible to simultaneously achieve uniform wetness on all of the walls of the cavity preparation [84]. Wet bonding is, in short, a very technique-sensitive procedure and optimum bonding with our current commercial adhesives occurs over a very narrow range of conditions, e.g. water content [73].

One suggested approach to these problems is “ethanol-wet bonding” [33,85]. A concern with this method is that in the clinical setting this solvent may be diluted because of repeated exposure of the material to the atmosphere or concentrated because of separation of the bonding liquids into layers within the bottle. Results from our lab have shown an inverse relationship between mechanical and thermal properties and the concentration of ethanol that is present during photo-polymerization of model BisGMA-based adhesives [86]. In addition, the hybridization process is very sensitive to the ethanol content in the adhesive system [78]. Although the effect of “ethanol-wet bonding” on durability is not known, results from our lab suggest that this approach will not overcome the clinical challenges associated with a/d bonding.

Current strategies to promote bonding of the resinous materials to intrinsically wet substrates also include the incorporation of ionic and hydrophilic monomers into the adhesive [87]. These adhesives etch and prime simultaneously, thus addressing the problems of collagen collapse and simplifying the bonding protocol. Unfortunately, the hydrophilic nature of these components enhances water sorption and hydrolytic breakdown in the mouth [84,87-90]. With these systems, the bonded interface lacks a nonsolvated hydrophobic resin coating and thus, the resultant hybrid layers behave as semi-permeable membranes permitting water movement throughout the bonded interface even after adhesive polymerization [33]. The higher concentration of hydrophilic monomers in these systems is associated with decreased structural integrity at the a/d interface [33,91]. In vivo aging studies have reported degradation of the a/d bond at 1-year even when the bonded dentin was protected by enamel from direct exposure to the oral environment [92]. These results suggest that hydrophilicity and hydrolytic stability of resin monomers are generally antagonistic [84].

IV. Ideal Hybrid Layer

It is generally accepted that the fundamental processes involved in bonding an etch-and-rinse adhesive to dentin are: removal of the mineral phase.
from the dentin without altering the collagen matrix and filling the voids left by the mineral with adhesive that undergoes complete in situ polymerization. Ideally, the resultant resin-reinforced or hybrid layer would be a 3-dimensional polymer/collagen network that would provide both a continuous and stable link between the bulk adhesive and dentin substrate. There is substantial evidence to suggest that this ideal objective is not achieved. [28,49,50,69,77,82,93-97] Instead of serving as a stable connection between the bulk adhesive and subjacent intact dentin, the hybrid layer has been called the weakest link in the adhesive/dentin (a/d) bond [98].

IV.A. Degradation of the hybrid layer

Degradation of the hybrid layer could be broadly divided into 2 major categories: hydrolytic degradation of the collagen matrix and hydrolytic degradation of the adhesive within the hybrid layer. [99] It has been hypothesized that the in vivo degradation of the hybrid layer follows a cascade of events that begins when the dentin is acid-etched. [100,101] Disruption of the tooth structure by acid-etching exposes and activates proteolytic enzymes, e.g. matrix metalloproteinases (MMPs) which can degrade the exposed collagen component of the hybrid layer. [102,103] Degradation of the hybrid layer by MMPs is expected to be most important acutely in the period following adhesive application.

Investigators have sought to address the impact of MMPs using techniques that would remineralize the collagen that is not infiltrated by adhesive. [104] While remineralizing the exposed collagen within the hybrid layer is interesting, other investigators have reported that an adhesive that replaces the spaces occupied by free and loosely bound water within the exposed collagen (demineralized dentin matrix) inhibits MMP activity. [105,106] Cationic quaternary ammonium methacrylates also inhibit MMP activity. [107]

Chronic deterioration of the hybrid layer involves hydrolysis and leaching of the adhesive that has infiltrated the collagen (demineralized dentin matrix). [50,69,99,108,109] Leaching is facilitated by water ingress into the loosely cross-linked or hydrophilic domains of the adhesive. The hydrophilic domain exhibits limited monomer/polymer conversion because of adhesive phase separation [68] and lack of compatibility between the hydrophobic photoinitiator and hydrophilic phase. [110,112] The poorly polymerized hydrophilic phase degrades rapidly in the aqueous environment. Resin elution continues to occur through the nanoleakage channels; water movement along the length and breadth of the hybrid layer becomes more rapid as transport pathways form relatively large water-filled channels. [33,83,113] The previously resin-infiltrated collagen matrix is exposed and vulnerable to attack by proteolytic enzymes [114,115].

The structure of methacrylate adhesives suggests a general mechanism for their chemical and enzymatic degradation in the mouth. On prolonged exposure of the restoration to oral fluids water begins to penetrate the resin. Water initially enters the matrix by diffusion into loosely cross-linked or hydrophilic domains or may be trapped within the matrix during photopolymerization. [70,116] Portions of the matrix may be directly exposed to oral fluids, particularly at the gingival margin of Class II and V composite restorations. Mechanical wear of the exposed adhesive may further accelerate matrix degradation by abrading the surface, increasing the surface area and allowing greater ingress of both water and enzymes. The presence of water promotes the chemical hydrolysis of ester bonds in methacrylate materials. This reaction is expected to be relatively slow at the neutral pH typical of saliva, but excursions in pH caused by foods or cariogenic bacteria may lead to transient acid or base catalysis. The carboxylate and alcohol degradation products of ester hydrolysis are more hydrophilic than the parent ester, further enhancing the local ingress of water. Over years of exposure to salivary fluids, local domains of the methacrylate network may become sufficiently degraded and/or hydrophilic to permit access by esterases, which greatly accelerate ester bond hydrolysis.

Human saliva contains a variety of enzymes which may participate in the degradation of the adhesive as well as the composite [89,92,117-121]. The susceptibility of acrylate dental materials to degradation by esterases is well established [119,122-126]. The esterase-catalyzed degradation of monomethacrylates, dimethacrylates and commercial dental resins has been documented in solution [122-124,126], in saliva samples [124,125,127], and in vivo [92]. In vitro studies have typically used one or more of the following esterases: cholesterol esterase (CE; EC 3.1.1.13) [122,124,126] acetylcholinesterase (ACHE; EC 3.1.1.7) [122,126] and pseudocholinesterase (PCE, aka butyrylcholinesterase; EC 3.1.1.8) [122,124,126]. Human saliva samples have been shown to contain CE and PCE activity in sufficient quantity to degrade composite resins [124,128]. In vitro degradation of dimethacrylates (BisGMA, TEGDMA) in the presence of PCE and CE was reduced by a specific esterase inhibitor, phenylmethylsulfonyl fluoride [124], supporting an...
esterase-catalyzed mechanism of degradation. Esterases in solution and in saliva catalyze the hydrolysis of both soluble methacrylate monomers and polymer particulates [125,126], suggesting that solid dental restorations are directly susceptible to esterase attack. Monomers and polymers of the monomethacrylates (e.g., HEMA) have been shown to be more resistant to esterase digestion (by ACHE, CHE) than the dimethacrylates [126]. CE and PCE have been shown to act synergistically in degrading dimethacrylates (BisGMA, TEGDMA) in vitro [122]. A modified dimethacrylate containing urethane segments (urethane-modified BisGMA) showed up to an 86-fold reduction in CE-catalyzed degradation relative to the unmodified control (BisGMA) [123]. This enhanced esterase resistance was attributed to the chemistry of the modified dimethacrylate, particularly the greater hydrophobicity and hydrogen-bonding capability of the urethane segments [123]. Dimethacrylates containing aromatic functional groups or branched methacrylate linkages have also shown greater esterase resistance [126].

Although many factors may contribute to the breakdown of methacrylate adhesives, their chemical “Achilles heel” may be the ester linkages. Indeed, the breaking of covalent bonds within the polymer by addition of water to ester bonds is considered one of the main reasons for resin degradation within the hybrid layer [83,84]. When exposed to oral fluids, the ester bonds within the methacrylate matrix are vulnerable to two forms of hydrolytic attack: (i) chemical hydrolysis catalyzed by acids or bases, and (ii) enzymatic hydrolysis catalyzed by salivary enzymes, particularly esterases. Both require the presence of water in close association with the bond that will be hydrolyzed. Resin degradation is also directly related to water sorption and high water sorption has been reported for hydrophilic resin systems [70,129]. These relationships highlight the challenges associated with the development of an adhesive that is resistant to hydrolytic attack, but also miscible with wet demineralized dentin matrices and compatible with our current dental composites.

IV.B. Strategies

Our strategy for reducing the hydrolytic degradation of methacrylate adhesives while also, promoting bonding to wet dentin has involved a three-pronged scheme. Molecular and mechanical modeling were used in conjunction with synthesis of new methacrylate monomers and multi-scale a/d interfacial characterization. [130,135] Methacrylate side chains have been selectively modified so that they were both water compatible and esterase resistant. [136-140] This was accomplished by using bulky and/ or branched functional groups that were poor esterase substrates but sufficiently hydrophilic to be water compatible. Water-compatible photoinitiators were developed as a means of promoting monomer/polymer conversion and thus, reducing the susceptibility to esterase hydrolysis by reducing the number of unreacted pendant groups [11,112,141-143].

Complementary techniques were used to provide in situ detection of the interfacial molecular structure and micro-mechanical features of the a/d interface. The experimental program did not, however, provide complete constitutive behavior. Instead, it provided fragmented information that had to be interpreted and unified.

In general, material constitutive behavior critically depends upon the mechanisms that occur at scales smaller than the material-scale. Thus, our research team developed modeling methodologies to account for these underlying mechanisms. The modeling in conjunction with our multi-scalar structure/property characterization has allowed us to project the long-term mechanical durability of the novel water-compatible, esterase-resistant adhesives under conditions that simulate function in the mouth [28,29,49,50,54,68,69,74,76,82,111,131,133-140,143-160].

In summary, factors that prohibit the formation of an ideal hybrid layer and a durable a/d bond include inadequate monomer/polymer conversion, adhesive phase separation, water sorption and hydrolysis of the adhesive. These factors may be addressed by using an iterative combinatorial optimization (molecular design/synthesis approach in conjunction with a/d interfacial multi-scale characterization and modeling to design, synthesize and develop water-compatible, esterase-resistant methacrylate-based dentin adhesives [28, 29, 49, 50, 54, 55, 68, 69, 74, 76, 78, 82, 86, 96, 97, 110, 112, 131, 137, 138, 140, 144, 145, 147, 150, 154, 155, 158-169]. Finite element (FE) modeling is used to project the long-term mechanical durability of the new adhesives under conditions that simulate function in the mouth [149,150].

V. Biofilms, Dental Plaque and S. mutans

The failure of the a/d bond in concert with reports of increased levels of cariogenic bacteria at the perimeter of composite materials points to an interesting interplay between microbiology and adhesive degradation as
key elements in the premature failure of moderate-to-
large composite restorations. Adhesion of S. mutans
to surfaces in the mouth creates an environment that
supports the subsequent attachment and growth of
other bacterial species, ultimately forming a micro-
ecosystem known as a biofilm.

In the oral cavity, microorganisms mainly
exist as biofilms on saliva-coated surfaces, e.g.
teeth, restorative materials, and so forth. The key
interaction in the initiation of biofilm development is
the adhesion of primary microorganisms to a surface.
The pioneer bacteria then recruit other bacteria by
providing a new surface and metabolic products that
facilitate the succeeding attachments. Streptococci
constitute >60% of the bacteria found in the early
communities in salivacoated tooth enamel. [170] The
initial colonization involves interaction of bacterial
cell surface proteins with saliva components (dental
pellicle) adsorbed to the tooth surface. Salivary
agglutinin, a ~400 kDa oligomeric complex of the
cysteine-rich glycoprotein gp340, is the key
component of the saliva that mediates the attachment
with the bacterial cell surface proteins. [171] For
cariogenic S. mutans, antigen I/II (AgI/II), also known
as SpaP or P1, is the cell surface protein that interacts
with gp340 to attach them to dental pellicle.

[172] After the initial attachment, S. mutans
synthesizes glucans (extracellular polysaccharides)
from sucrose when it is present, by glucosyltransferases
(GTFs). The glucans then interact with glucan-binding
proteins (GBP) and with the glucan-binding domain
of GTFs, both of which are present at the surface of
S mutans. The primary aggregation of these bacteria
on the tooth surface serves as a platform for the
attachment of other bacteria for the accumulation of
biofilms, known as dental plaques. Thus, the key
step in the accumulation of dental plaque is the initial
interaction of bacterial P1 protein with the salivary
agglutinin gp340.

**V.A. SALIVARY AGGLUTININ GP340**

Investigators have reported a positive correlation
of the protein, gp340, with caries experience and
saliva adhesion of S. mutans. [173] Specific amino
acid sequences involved in P1 interaction with gp340
have been identified, [174] and peptide vaccines
based on these sequences have been shown to be
effective in preventing S. mutans attachment both in
vitro and in clinical trials. [175] We are intrigued by
the role of the solid surface in S. mutans attachment,
particularly with regard to its influence on the critical
protein-protein interactions. These effects are not
well understood at the molecular level. While there
have been studies documenting surface effects on S.
mutans attachment [176-178] most have employed
whole-cell assays of attachment. These studies have
helped to demonstrate that the surface does, in fact,
influence bacterial attachment, but provide little
information on the particular chemical interactions
involved. Lack of information at the chemical level
precludes the rational design of materials that limit
bacterial adhesion, since the relevant structure-
property relationships are not known.

Studies by Ligtenberg and others [179] have
suggested that the interaction of S. mutans with
the surface is influenced by the extent of gp340
binding. It is not known how gp340 interacts with the
methacrylate adhesive, but this information is vital
for understanding how the biofilm is anchored to the
adhesive surface. A common approach used to identify
specific regions of a protein involved in interaction
with another macromolecule is to cleave the protein
into smaller peptide fragments and determine which
pieces bind to the partner. The salivary agglutinin
gp340 was cleaved in this manner, and the fragment
primarily responsible for interaction with P1 from
S. mutans was identified. [174] Once an interacting
fragment is identified, higher-resolution analyses
can be performed to map the chemical moieties in
the peptide that directly participate in binding, e.g. a
methyl group from an Ala. Solution nuclear magnetic
resonance (NMR) spectroscopy is a suitable tool for
assessing such site-specific interactions, even when
they are weak (μM-mM KD) as is often the case with
peptides. Several NMR experiments reveal binding
sites between peptide fragments and large molecules.
The bound conformation of the peptide can be
determined and this information used to understand
how binding occurs. [180] Cross-validation of
the involvement of specific moieties is performed
by modifying the peptide slightly by blocking or
removing specific interactions.

**V.B. Novel interventions**

Adhesion of S. mutans to surfaces in the mouth
creates an environment that supports the subsequent
attachment and growth of other bacterial species,
ultimately forming a micro-ecosystem known as a
biofilm. Dental plaque biofilm cannot be eliminated,
[181] but the pathogenic impact of the biofilm at
the margin of the composite restoration could be
reduced by engineering novel dentin adhesives that
limit gp340/S. mutans attachment and neutralize the micro-environment to prevent damage (by lactic acid) to the adjacent tooth structure. Clearly, any change in the chemical structure will likely alter other mechanical and physicochemical properties. The optimal adhesive will be produced by balancing the desired physical, chemical and mechanical properties with the need for limited gp340/S. mutans attachment and neutralization capabilities. The combinatorial optimization approach allows the relative importance of each property to be varied and predicts novel methacrylate structures for further evaluation [131].

Lactic acid (LA) is the primary compound produced during acidification of the oral cavity by microbes. As such, we have developed an NMR-based assay for detecting the solution pH and changes in pH of samples containing lactic acid. Because LA is acidic, the addition of basic monomeric units or hydrated polymers that contain buffering moieties alters the pH of the sample. The degree of change can be tracked and the buffering capacity quantified using our approach. The NMR chemical shift is extremely sensitive to small changes that most other methods cannot detect, making it an excellent probe for monitoring perturbations to the nucleus of interest. Here, the chemical shift of the carbonyl 13C in LA has been correlated with pH and monitored as a function of increasing concentration of monomer (Figure 4).

As can be seen in this plot, inclusion of HEMA, the monomer currently used in the methacrylate dentin adhesive, even at high concentration in the LA solution, has no impact on the pH of the solution, and it cannot buffer or neutralize LA. The addition of increasing amounts of 2-dimethyl-aminoethyl methacrylate (DMAEMA), which contains a basic amine, does however, shift the pH of the acidic LA solution making it more neutral. These data show that neutralization can be achieved by monomers such as DMAEMA and that the buffering capacity can be measured in a simple NMR experiment using LA as a probe [152].

VI. SUMMARY

In summary, the a/d bond can be the first defense against substances that may penetrate and ultimately undermine the composite restoration in vivo. In vitro and in vivo studies have suggested that several factors inhibit the formation of a durable a/d bond. These factors include: 1) water sorption and hydrolysis of the adhesive resin; 2) inadequate monomer/polymer conversion of the infiltrating adhesive; 3) incomplete resin infiltration; 4) incomplete solvent evaporation [78,86,182,183]; 5) enzymatic challenges within the cavity preparation [100]; 6) surface degradation by biofilms; and 7) substrate characteristics [76,78,161,184-187]. However, as indicated in a recent review of dental composite, the properties of the materials are one part of a complex problem [188]. The success of clinical restorations depends on a variety of factors including proper technique, appropriate materials and proper patient selection [188].

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RESUMO

Restaurações em resina composta apresentam elevada taxa de falhas, recorrência de cárie e maior necessidade de troca quando comparadas às restaurações em amálgama. A penetração de enzimas bacterianas, fluidos orais e da própria bactéria nas fendas existentes entre o dente e o compósito, enfraquecem a restauração e levam à recorrência de cárie e falhas. A margem gengival das restaurações em resina composta é particularmente vulnerável à cárie e, nesta margem, o adesivo e o selamento dentinário funcionam como a primeira barreira entre o dente preparado e o ambiente oral. O objetivo deste artigo de revisão é examinar os fatores físico-químicos que afetam a integridade e a durabilidade da interface de adesão adesivo/dentina e explorar como esses fatores agem sinergicamente para minar a restauração de resina composta. A revisão irá examinar as diversas possibilidades para solucionar esses problemas, bem como explorar como alterações na química dos materiais poderiam solucionar o impacto negativo do estresse físico-químico na interface adesiva com a dentina.

PALAVRAS-CHAVE

Revisão de literatura; adesão; interface dentina/restauração; integridade; durabilidade.

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