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Recent Advances in Contemporary Dental Adhesives

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Abstract: Dental adhesives are solutions of resin monomers that can make the resin/ tooth structure interaction achievable. Adhesive systems are composed of monomers with both hydrophilic groups that enhance wettability to the dental hard tissues and hydrophobic groups that allow the interaction and co-polymerization with the restorative material. Modification of adhesive materials is necessary to improve the longevity of resinous restorations and to obtain more stable resin-dentin bond through incorporation of active components into the adhesive system, treatment of the dentin surface prior to adhesive application, and modification of the bonding protocol.

Keywords: *Collagen crosslinking; MMPs; Hybrid layer; Dental adhesives; Adhesive degeadation.*

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I. Introduction:

Contemporary adhesive systems are unable to completely infiltrate the collagen network with resin monomers. The presence of water-rich spaces and unprotected collagen fibrils are responsible for nano-leakage within hybrid layers. Moreover, the unprotected collagen fibrils network will be subjected to enzymatic degradation. Therefore, modification of adhesive materials is necessary to improve the longevity of resinous restorations and to obtain more stable resin-dentin bond [1-4].

II. Classification of dental adhesives:

II.1. Classification according to generation:

1st generation: Etching dentin with 7% hydrochloric acid and GPDM (Glycerophosphoric acid dimethacrylate) was used for bonding to dentin.

2nd generation: The bonding adhesives were composed of BisGMA (bisphenol-glycidyl-methacrylate) and HEMA (hydroxyethyl methacrylate).

The 1st and 2nd generation dentin bonding agents chemically bonded to the smear layer rather than to the dentin tissue. Therefore, the bond strength was too weak leading to the poor clinical performance[1, 4].

3rd generation: Incorporation of hydrophilic primer that infiltrate and modify the smear layer. However, these adhesives do not eliminate marginal leakage [1, 4].

4th generation: Total-etch technique was introduced. Total-etch technique permits simultaneous etching of enamel and dentin[1, 4].

5th generation: The total-etch technique was simplified into two steps by combining primer and bonding resin into one application[1, 4].

6th generation: Self-etch adhesives two-step systems composed of self-etching primer solution and bonding agent [1, 4].

7th Generation: One bottle system contains etch, primer and bond [1, 4].

8th generation in 2010, voco America introduced voco futurabond DC, which may be used either as etch-and-rinse or as self-etch adhesives[1, 4].

II.2. Classification by mechanism of adhesion/clinical step:

II.2.1. Three-steps: These bonding systems are supplied as three bottles (etchant, primer, and bonding agent).

II.2.2. Two-steps 1: Bonding systems are supplied in two bottles, one consisting of etchant, and the other of the combined prime and bond formulation.

II.2.3. Two-steps 2: Bonding systems are supplied in two bottles, one containing a self-etching primer and the second the bonding agent.

II.2.4. One-step: Single bottle containing self-etching primer and bonding agent[4].

II.3. Classification according to adhesion strategy:

II.3.1. Smear layer removing adhesive systems:

These bonding agents completely remove the smear layer. Enamel and dentin are etched simultaneously using 37% phosphoric acid. After washing and drying the tooth surface, primer and bonding agent are applied either separately or in combination[5].

II.3.2. Smear layer modifying adhesive systems:

The bonding agents modify the smear layer and incorporate it in the bonding process. Enamel is selectively etched with 37 % phosphoric acid. After washing and drying the tooth, primer and adhesive are applied separately or in combination[5].

II.3.3. Smear layer dissolving adhesive systems (self-etch approach):

These agents partially demineralize the smear layer and the superficial dentin surface without removing the remnants of smear layer or the smear plugs. They use acidic primers which provide simultaneous conditioning and priming of both enamel and dentin. After this, adhesive is applied without washing the tooth surface[5].

II.4. Classification based on etching pattern:

II.4.1. Total etching technique:

The concept of total etching is the simultaneous etching of enamel and dentin. Total etching technique may either be as follows:

II.4.2. Self-etch system:

No separate etching and rinsing. The residual smear layer remnants remain within the bond. Depending on etching aggressiveness they are divided into:

- Strong Self-etch Adhesives (pH<1).
- Intermediate Self-etch Adhesives (pH ≈ 1.5).
- Mild Self-etch Adhesives (pH ≈ 2).
- Ultra Mild Self-etch Adhesives (pH≥2.5)[6].

III. Composition of dental adhesive:

a) Etchant:

In total-etch technique the etchant used is 35–37% phosphoric acid. The etchant in self-etch bonding agents is an acidic monomer that also serves as the primer.

b) Primer:

Primer is composed of hydrophilic monomers such as HEMA in a water-soluble solvent (acetone, ethanol, water) to promote good flow and penetration into hydrophilic dentin. Self-etch bonding agents utilize acidic primers.

c) Adhesive resin composed of two types of monomers:

Crosslinking hydrophobic monomers: Bis-GMA, TEGDMA, and UDMA.

Functional monomers:

10-MDP, phenyl-P and 4-META monomers with carboxylic and phosphate groups. These functional groups can ionically bond with calcium in hydroxyapatite providing satisfactory chemical bonding to dentin.

Meth acrylamides: Meth acrylamides have an amide (–CO–NH– or –CO–N–) group instead of an ester group (–CO–O–R–) as in conventional acrylates and methacrylates which promotes the formation of hydrogen bonds between the carboxyl and amide groups of the monomer with the carboxyl groups of collagen.

d) Fillers:

Recently nanofillers 0.5% to 40% by weight in the 8th generation adhesive systems. Fillers control handling, improve strength, and increase film thickness of the adhesive layer.

e) Solvent:

Solvents include acetone, ethanol, and water. Their main function is to promote good penetration of the monomers in the collagen network of the demineralized dentin, thus improve the diffusion ability of resin. Acetone evaporates quickly and requires the shortest drying time in the mouth. Ethanol evaporates more slowly and requires moderate drying time. Water evaporates very slowly and requires longest drying time. Bonding agents should be dispensed immediately before use to prevent premature evaporation of the solvent.

f) Photo-initiators:

Compounds that dissociate into free radicals upon absorption of light energy, such as camphorquinone (CQ) and 1-phenyl-1,2 propanedione (PPD).

g) Inhibitors:

Inhibitors (butylated hydroxytoluene) added to dental resins to scavenge free radicals originating from prematurely reacted initiators.

h) Modifiers:

Such as glutaraldehyde, (MDPB) monomer for antibacterial effect, and fluorine compounds[4, 5].

IV. Failure of Resin-Dentin Bonding:

IV.1. Degradation of Resin-Dentin Bonding Interface:

IV.1.1. Degradation of Adhesive Resins:

Water within the hybrid layer and oral fluids (dentinal fluids and saliva) serves as a medium for the hydrolysis and leaching of resin adhesives leading to resin degradation and reduction of bond strength through different mechanisms[7, 8] :

- Water acts as a plasticizer between the polymer chains of the adhesives leading to the acceleration of matrix degradation[9].
- Human saliva contains cholesterol esterase and pseudocholinesterase, which act synergistically to degrade dimethacrylates[1].
- Methacrylate adhesives containing ester bonds are subject to chemical hydrolysis[1].
- Dental adhesive systems comprise both hydrophilic and hydrophobic components undergo phase separation phenomenon.

Phase separation phenomenon:

The hydrophobic monomers stay on the surface while the hydrophilic components infiltrate the interior of the hybrid layer producing heterogeneous resin layers. The hydrophilic domains have a limited degree of polymerization. Therefore, the poorly polymerized hydrophilic phase undergoes degradation more quickly[9, 10].

IV.1.2. Degradation of Collagen:

Degradation of collagen matrix by matrix metalloproteinases (MMPs) and cysteine cathepsins are among the major reasons for the failure of resin- dentin bond[1, 9].

- Matrix Metalloproteinase (MMP):

MMPs are produced by odontoblasts as they play an important role during dentine maturation, then they become inactive after the collagen matrix mineralization is completed. MMPs are Zn^{2+} and Ca^{2+} dependent endogenous proteases, Ca^{2+} ions preserve the structure of MMPs and Zn^{2+} ions are responsible for the enzyme activation. Acid-etching during dentin bonding and weak acids released by cariogenic bacteria can uncover and activate matrix-bound MMPs [2, 11].

- Cysteine Cathepsins:

Cysteine cathepsins (CTs) are expressed by mature human odontoblasts cells and pulpal tissues. There is synergistic activity between MMPs and CTs and they regulate the activities of each other. MMPs and CTs can attack type I collagen, the most abundant organic component of dentin matrix[1, 2].

IV.2. Incomplete Infiltration of the Resin Adhesives:

Incomplete infiltration of the adhesive in the collagen network is a result of the difference between penetration of the adhesive and action of the etching acidic agents leading to nano-leakage[9]. Moreover, incomplete resin infiltration leads to the activation of MMPs and CTs because the exposed dentin collagen becomes recognizable and available to MMPs and CTs[1].

IV.3. Mechanical Loading:

Masticatory forces can adversely affect the bonding interface leading to gap formation and marginal leakage around restorations. Moreover, exposed collagen fibrils due to incomplete infiltration of bonding resin are susceptible to creep or cycling fatigue during function. Additionally, surface strains of the adhesive layer facilitate the absorption of fluids and accelerates degradation of the adhesive[1].

IV.4. Microleakage:

When polymerization shrinkage and the associated contraction stresses of composite resins are higher than the bond strength, marginal gaps would form at the interface, resulting in microleakage. Bacteria and oral fluids can penetrate the tooth-composite interface. Bacterial collagenases may cause degradation of the hybrid layer and increase nanoleakage. Lactic acid produced by cariogenic bacteria can activate MMPs impairing resin-dentin bond durability[1].

V. Recent Advances in contemporary adhesives:

V.1. Incorporation of agents with anti-MMPs, remineralization, antibacterial, or reinforcing functions into adhesive systems.

V.2. Treatment of the dentin surface prior to adhesive application.

V.3. Modification of the Bonding Protocol.

V.1. **Incorporation of agents with anti-MMPs, collagen crosslinking, remineralization, or antibacterial functions into adhesive systems.**

V.1.1. Adhesives modified with anti-MMPs and collagen crosslinking Functions:

Applying MMPs inhibitors as a component of the adhesives may help to improve durability of adhesive restorations because they have the potential to decrease the degradation of the collagen fibrils within[1]. Several crosslinking agents have been suggested for protecting collagen fibers which were used as primers or incorporated into the adhesive formulation[12].

- Mechanism of action:

- Cationic-anionic reaction, cationic agents electrostatically bind to negatively charged catalytic sites of MMPs, blocking the active site.

- Chelating or formation of covalent bonds with zinc or calcium which leads to loss of catalytic activities of MMPs.

- Protein cross-linkers can induce changes in MMPs 3D structure and hinder molecular mobility which is essential for their enzyme activity. Moreover, they may stabilize collagen matrix and improve the mechanical properties of the hybrid layer, thus strengthening the resin-dentin bond.

- Crosslinking agents can crosslink proteases which interferes with their molecular mobility[1, 12].

V.1.1.1. Adhesives modified with synthetic anti-MMPs and collagen crosslinking Functions:

a) Glutaraldehyde:

Glutaraldehyde is a crosslinking agent with strong antibacterial activity. It contains two aldehyde groups at each end of the chain able to react with the amino groups of the collagen fibrils. Therefore, it stabilizes the collagen fibers in the hybrid layer and preserves the adhesive interfaces. Glutaraldehyde-containing bonding agents was introduced as a desensitizing agent for hypersensitivity treatment through denaturation of collagen in dentin, occlusion of dentinal tubules, and prevention of post-operative pain [2, 12, 13].

However, Glutaraldehyde has toxic, allergenic, and mutagenic effects. Direct incidental contact with mucous tissues, inhalation of glutaraldehyde evaporated from the adhesive should be considered as a source of irritation and allergic asthma both for dentist and patient[13].

Commercial Products:

- Gluma 2Bond bonding systems that contained 5% glutaraldehyde were the first adhesives that contained glutaraldehyde.

- Several other manufacturers also added glutaraldehyde to their adhesive formulation (Syntac, Vivadent; ProBond, DENTSPLY Caulk) [2, 13, 14].

b) Chlorhexidine (CHX):

CHX inhibits MMP and CTs proteolytic enzymes through cationic-anionic reaction of CHX which deforms MMPs molecules and prevents them from binding to substrates. In addition, CHX could bind Ca^{2+} and Zn^{2+} ions resulting in loss of catalytic activities of MMPs. Moreover, CHX is an antimicrobial agent that can inhibit bacterial proteolytic enzymes and can electrostatically bind to demineralized dentin[1, 2, 7]. Adhesive systems modified with CHX diacetate showed enhanced long-term stability of resin–dentine interfaces without affecting the bond strength[15].

Commercial product: Peak Universal Bond contains 0.2% chlorhexidine diacetate[14].

c) Zinc-Doped Adhesives:

MMPs-mediated collagen degradation activity is dependent on calcium (Ca^{2+}) and zinc (Zn^{2+}) ions concentrations and the Zn^{2+}/ Ca^{2+} ratio. Therefore, a relatively high concentration of Zn^{2+} may interfere with the MMP-mediated collagen degradation. The Zn^{2+} liberation from Zinc-doped adhesives will facilitate the formation of a ZnO rich layer that permits Ca and P deposits and further remineralization. For self-etching adhesives, Zn should be added into the bonding resins, and never in the primer containing MDP, as it forms Zn-MPD complexes that may interfere with chemical interaction of calcium/dentine and MPD dentin infiltration[1, 16, 17].

V.1.1.2. Adhesives modified with natural anti-MMPs and collagen crosslinking Functions:

a) Grape seed extract (GSE):

GSE is composed of proanthocyanidins (PA) which is a natural collagen cross-linker derived from polyphenols. PA can create hydrogen bonds between collagen fibrils. Moreover, electrostatic interactions occur between the

amide carbonyl group of collagens and the phenolic hydroxyl group of PA. This will increase the mechanical stability of the collagen matrix and improve the quality of the hybrid layer.

The incorporation of PA to an experimental adhesive did not show adverse effects on the immediate resin-dentin bond strength when its concentration was less than or equal to 2%. In addition, PA was incorporated into the etching solution and experimental primer to enhance the stability of bonding. However, there is a lack of long-term in vitro and in vivo studies on its stability; it may also stain the dentin brown [7, 12, 18].

b) Hesperidin (HPN):

HPN is a protein cross-linking flavonoid extract of citrus fruits. HPN has the capability of enhancing dentin remineralization. The effect of HPN on remineralization is related to its interaction with collagen providing stable collagen matrix for the remineralization process, since it acts as a scaffold for mineral deposition. HPN has been incorporated in Clearfil SE primer. Incorporation of HPN into Clearfil SE primer had a positive influence on the immediate resin-dentin bond strength, the hardness and elastic modulus of the interface[19, 20].

c) Quercetin:

Quercetin is a polyphenol abundantly found in in many plants and foods, such as onions, green tea, apples, and berries. Quercetin can inhibit MMP activity by zinc chelation because it has high affinity to metal ions. Quercetin increases the expressions of tissue inhibitor of metalloproteinase (TIMP). Quercetin suppresses prostaglandin-E synthesis by inhibiting the activity of cyclooxygenase-2 enzyme (COX-2) because the over-production of the COX-2 induces MMP release[2, 7, 21]. Quercetin has a crosslinks collagen by formation of hydrogen bonds, van der Waals forces, and electrostatic forces. Quercetin can induce dentinogenic differentiation of dental pulp cells and has an antibacterial effect by inhibiting the metabolic activity of *S. mutans*. Quercetin was incorporated into adhesive and used as pretreatment of etched dentin to improve the bond strength [22].

V.1.2. Adhesives with Remineralization Functions:

Remineralization of resin-dentin interfaces aims to replace water from water-rich resin-sparse regions of the hybrid layer with apatite crystallites. Moreover, cariogenic bacteria produce acids causing demineralization of the tooth structure and the tooth-restoration margins. Therefore, a new approach to stabilize resin-dentin bonding is to remineralize the hybrid layer to increase the mechanical properties of the dentin-resin interphase and protect the exposed collagen leading to inactivation of MMPs and CTs [1, 3].

The local alkalinization promoted by ion release (Ca^{2+}, Na^{+}) downregulates MMP activity that normally triggered in acidic conditions. In addition, Electrostatic interactions between MMP and CaP precipitates form high molecular weight, low-mobility aggregates, reducing enzymatic activity [3].

Dentin remineralization could be obtained through two approaches:

- Top-down remineralization (ion-based crystallization concept): In case of partially demineralized carious dentin, apatite crystallites left in the intrafibrillar regions serve as nucleation sites for calcium and phosphate ions precipitation, followed by epitaxial crystal growth. However, this approach may not be applicable for remineralization of completely demineralized dentin where seed crystallites are absent, e.g., in hybrid layers created by phosphoric acid etching or aggressive self-etch adhesives.

- Bottom-up (biomimetic) remineralization: Apatite precipitation in completely demineralized dentin is assisted by biomimetic analogs of non-collagenous proteins. These molecules serve as stabilizers for the mineral precursors and as templates to guide apatite growth in an oriented and hierarchically organized manner within collagen matrix. This strategy inhibits MMPs through biomimetic remineralization and prevents collagen degradation[3, 23-25].

V.1.2.1. Bioactive glass (BAG):

BAG could be used as a source of calcium and phosphate ions that will subsequently crystallize into hydroxyapatite and induce remineralization of the resin-dentin interface. BAG has anti-microbial activity due to high pH in their environment due to the release of alkaline elements Na^+ or K^+ [1, 14]. The bioactivity of such BAG could be potentiated by doping with specific ions, such as Sr, Ag, F, and Cu. Fluoride (F)-doped BAG incorporated into adhesive resin have been demonstrated to have greater remineralization properties and MMP inhibition ability[3, 26].

Copper (Cu^{2+}) ions are considered a potent inhibitor of MMPs in human dentin. Cu doped BAG added to adhesive showed MMP deactivation and remineralization properties at the resin-dentin interface[1, 12]. Adhesives modified by Cu doped BAG are able to release Ca, Si, and Cu ions, which induce remineralization at adhesive resin-dentin interface, bind to specific sites on the exposed collagen fibrils and modify its spatial configuration protecting them from MMPs action, reduce the MMP enzyme activity, and induce formation of tertiary dentin or osteodentin structures along the walls of the pulp chamber [3, 26].

V.1.2.2. Amorphous Calcium phosphate nanoparticles (NACP):

NACP modified adhesives release Ca^{2+} and P^{3-} ions inside the water-filled voids in the hybrid layer which re-precipitate to form hydroxyapatite to mineralize the dentine and enamel and cause calcification of MMPs [1]. When collagen fibrils are completely demineralized, NACP could be used to achieve the biomimetic remineralization of adhesive resins. NACP bind with collagen and serve as a template when polyanions are incorporated around the NACP. This in vitro concept is not translated into clinical trials yet[25].

V.1.2.3. Hydroxyapatite:

HA nanorods in adhesives may biomineralize with the collagen network of tooth through hydrogen bonding between $COOH^-$, OH^-, and NH_2^- of the collagen network and OH^- group of the hydroxyapatite particles, achieving remineralization of the dentin at resin-dentin interface[1].

V.1.2.4. Dentin phosphoproteins Analogues:

Mineralization of dentin is a complex process regulated by the collagenous matrix mainly type I collagen, non-collagenous proteins (NCPs) such as dentin phosphoproteins (DPP), and minerals. Type I collagen defines the framework for mineral deposition and by itself is not sufficient to support nucleation of hydroxyapatite. DPP has a strong affinity for Ca^{2+} and are considered as nucleation sites within the collagen fibrils for mineral deposition initiation and propagation of hydroxyapatite crystals growth[27, 28].

Adhesives and primers modified with phosphoproteins analogues such as polyvinylphosphonic acid (PVPA), polyacrylic acid (PAA), polyaspartic acid, and sodium trimetaphosphate (TMP) show a promising potential for biomimetic remineralization of the hybrid layer through deposition of apatite crystals. Phosphoproteins analogues bind to collagen and serve as templates for specific calcium binding and apatite nucleation[25].

In biomimetic remineralization of resin–dentin bonds, a source of amorphous calcium phosphate (ACP) is required such as flowable composite or bonding agent containing (ACP)[25]. ACP and phosphoproteins analogues can move into collagen fibrils and slowly diffuse through any water-filled porosities within adhesives and hybrid layers (i.e., residual water in un-infiltrated dentin) and ``back-fill'' such defects with apatite crystals and calcify all dentin proteases as the matrix collagen remineralizes[29, 30].

V.1.3. Antibacterial Adhesive Agents:

Antibacterial bonding agents could combat biofilms and recurrent caries at the tooth-composite margins.

V.1.3.1. Quaternary Ammonium Salts (QAS):

QAS is a potent antimicrobial agent due to presence of positive quaternary amine charge (N^+) that interact with the negatively charged bacterial cell membrane leading to alteration of membrane permeability, disturbance of the bacterial surface electrostatic balance, and cytoplasmic leakage. Moreover, positively charged QAS can interact with the negatively charged extracellular polymeric substances (EPS) changing its physicochemical properties leading to reduction of the bacterial adherence. Finally, QAMs electrostatically bind to negatively charged catalytic sites of MMPs and CTs leading to inhibition of their activity and reduction of the demineralized dentin collagen degradation[1, 7, 31].

Commercial Products:

- ✓ MDPB monomer (e.g. Adper prompt L pop and Clearfil SE Protect Bond):

MDPB (12-methacryloyloxydodecy l-pyridiniumbromide) is an antibacterial monomer based on quaternary ammonium salts which provides bonding agents with long lasting antibacterial activity without releasing the antibacterial agent. Before polymerization, MDPB in primer acts as cavity disinfection. After curing it becomes immobilized by polymerization in bonding agents and covalently bonded to the polymer network[1, 5, 14]. Therefore, it is not leached from the hybrid layer and acts as a contact inhibitor against the bacteria that comes in direct contact with the polymer. MDPB-containing adhesive is promising to manage secondary caries, even root surface caries and active lesions. Clearfil SE Protect which contains 5% MDPB in the primer solution and fluoride in the adhesive resin, was the first antibacterial adhesive system to be commercialized [1, 5, 14].

- ✓ Benzalkonium chloride (BAC):

It is a cationic surface-acting agent with a quaternary ammonium group used as antimicrobial agent and surfactant. BAC-containing etchants can be used with E&R adhesives without affecting immediate bond strength to enamel or dentin. Bisco is already manufacturing the commercial 37% phosphoric acid with 1 wt% BAC[1, 7, 31].

V.1.3.2. Fluoride-releasing resin adhesives:

Fluoride-containing compounds are well known for their anti-caries effects because they enhance the formation of fluorapatite, accelerate remineralization, interfere the ionic bonds generated during biofilm formation, inhibit microbial growth and metabolism. Adhesives containing fluoride is superior for the hybrid layer strengthening and preservation of degradation of the resin dentine bond because F^- ions have been identified as MMP inhibitors through chelation of Ca^{2+} and Zn^{2+} and alteration of MMP structure[25, 32, 33].

Commercial Products:

Clearfil Protect Bond contains sodium fluoride (NaF) crystals which can release fluoride ions from the adhesive.

Clearfil Universal Bond Quick, Clearfil S3 Bond Plus, One Up F Bond Plus, Futurabond NR, OptiBond Solo and Reactmer Bond[14].

PEM-F in Xeno IV: PEM-F[1] is a monomer with a grafted fluoride functional group[5].

V.1.3.3. Surface pre-reacted glass ionomer (S-PRG) fillers:

Surface Pre-Reacted Glass-ionomer (S-PRG) fillers are synthesized by PRG (Pre-Reacted Glass) technology involving reaction between fluoroboroaluminosilicate glass and a polyacrylic acid solution. The S-PRG filler-containing adhesive can release various ions, such as aluminum (Al^{3+}), boron (BO_3^{3-}), fluoride (F-), sodium (Na+), silicon (SiO_3^{2-}

[1] pentamethacryloyloxy-ethylcyclohexaphosphazene- monofluoride

), and strontium (Sr^{2+}) in both neutral and acidic conditions. These ions have antimicrobial activity against various oral bacteria such as *S. mutans*.

Commercial products: FL-Bond II[34].

V.1.3.4. Silver nanoparticles (AgNPs):

Silver ions are the most widely explored antimicrobial agents which exhibit antibacterial, antifungal, and antiviral activity, as well as low toxicity and biocompatibility with human cells[1]. Polymers with Ag release a high number of ions initially losing their antibacterial activity in a short period. Thus, the synthesis and incorporation of nanometric Ag particles into the resin promoted polymers with a large reservoir of Ag ions, having ions releasing at a constant rate, allowing long-term antibacterial effects [24].

AgNPs cause rupture of cell membranes by contact with the silver metal surface leading to the uptake or ion penetration into the nucleus and formation of reactive oxygen species, and the inhibition of cell reproduction by interaction with DNA. Moreover, AgNPs inactivate the bacterial enzymes[14].

V.1.3.5. Chitosan:

Chitosan is known for being biocompatible and antibacterial agent that has several dental applications. The interaction between the positively charged chitosan and the negatively charged bacteria cell surface leads to the rupture of the cell membrane. Moreover, type I collagen has a capacity to form ionic complexes with chitosan, increasing the collagen strength. Chitosan was incorporated into dentin adhesives or used as a separate primer solution[14, 35]. However, chitosan may increase the hydrophilicity of the adhesive systems leading to formation of nano leakage within the hybrid layer. In addition, undesirable interaction between the adhesive systems with chitosan may compromise the function of chitosan as a cross-linking agent[12, 36].

V.1.4. Resin Matrix Reinforcement with Fillers:

V.1.4.1. Silicon dioxide nanoparticles (SiO_2 NPs):

Incorporation of SiO_2 nanoparticles (20 nm) improves mechanical properties of dentin bonding agents and provide elastic resin–dentin interface which may help to counteract stress resulting from polymerization shrinkage of the resin composite. Commercial product: Futurabond DC[37].

V.1.4.2. Zirconia nanoparticles:

Incorporation silanized ZrO_2 nanofillers into the primer or adhesive could enhance the bonding integrity and mechanical properties at resin-dentin interface, increase durability of the of the dentine-resin bond, and improve resistance to the hydrolytic process[38].

V.1.4.3. Carbon nanotubes:

Carbon nanotubes are extremely strong which were incorporated as fillers to adhesives to reinforce the resin matrix and thus the resin-dentine bond strength. The cylindrical hollow structure of nanotubes can act as a medium for the encapsulation of therapeutic molecules such as doxycycline, biomimetic agents, antioxidants, and collagen crosslinkers and then incorporated into an adhesive resin[9, 39].

V.1.4.4. Titanium oxide nanoparticles (TiO_2 NPs):

TiO2 NPs are effective against Gram-negative and Gram-positive bacteria and enhance stability of resin- dentin bond[40].

V.2. Treatment of the dentin surface prior to adhesive application:

V.2.1. Ethylenediaminetetraacetic acid (EDTA):

EDTA contains 4 carboxylic acid groups and acts by chelation of Zn^{2+} and Ca^{2+} ions. Application of EDTA before bonding agent application inhibits MMP activity and improves the removal of the smear layer and resin infiltration into the collagen matrix[12]. The benefits of EDTA pretreatment in dentin were also confirmed in a randomized clinical trial. A higher retention rate of composite resins was observed in non-carious cervical lesions bonded with a self-etch adhesive when the dentin was pretreated with EDTA 17% for two minutes[41, 42].

V.2.2. Tetracyclines:

Tetracyclines are antibiotics with cationic chelating properties. Chemically modified tetracyclines (minocycline and doxycycline) are considered broad-spectrum MMP inhibitors. Minocycline and doxycycline chelate Ca^{2+} and Zn^{2+} ions which play an important role in maintaining MMP structure and functional active sites. By binding to the zinc ion present on catalytic domain of the enzyme, modified tetracyclines can inhibit the MMPs by altering their conformation at the molecular level and thus blocking their catalytic activity in the extracellular matrix. The application of 2% MI, as dentin pre-treatment prevented the decrease in bond strength after storage for 6 months in artificial saliva[1, 7, 43].

V.2.3. Galardin:

Galardin is a synthetic MMP inhibitor which has a collagen-like backbone that facilitates its binding to the active site of MMPs and makes the antiproteolytic activity effective against MMPs. Pretreatment of dentin surface with Galardin resulted in high bond strength for a period of 12 months, even when used in low concentrations [7, 25, 44].

V.2.4. Carbodiimides:

Carbodiimides is a biocompatible synthetic crosslinking agent that can be easily rinsed from collagen without leaving any residual chemicals. They inhibit MMPs by inactivating the active sites and reducing their molecular mobility by creating a new peptide bond across adjacent peptides (MMPs crosslinking). Carbodiimides crosslink collagen without introducing additional linking groups as they activate the carboxylic acid groups of glutamic and aspartic acids that react with lysine or hydroxylysine to form amide crosslinking. Therefore, the resistance of cross-linked collagen matrices to degradation is improved. Carbodiimides' MMP inhibitory effect is much faster than its collagen cross-linking effect. This could be explained by the better accessibility of carboxyl and amino groups in MMPs than in collagen[7, 12, 43].

V.2.5. Natural Agents:

a) Grape seed extract (GSE)

b) Quercetin

c) Epigallocatechin-3-gallate (EGCG):

EGCG is a major green tea polyphenol which is considered as a natural inhibitor of MMPs through downregulation of MMPs expression and prevention of MMPs access to collagen chains. In addition, it stabilizes the collagen chain stable and increase the number of collagen crosslinks through the interaction of hydrogen molecules of galloyl groups. Treatment of the dentin surface with 0.1% EGCG aqueous solution before bonding agent application maintained the stability of the adhesive interface. However, EGCG at higher concentrations could interrupt the adhesive polymerization as it could be entrapped within the linear chains after curing interfering with the monomer conversion thereby affecting the bond strength[7, 12, 45].

d) Riboflavin (Vitamin B2):

Riboflavin is a crosslinking agent that produces free radicals when photo-activated in a spectrum ranging from ultraviolet (UV) to visible light (270 nm, 366 nm, and 445 nm). The free radicals create a strong covalent bond between the collagen fibers. However, the use of UV in the clinic is a concern as its safety is questionable. Moreover, additional light-curing steps are time consuming [7, 12, 29].

e) Sodium ascorbate (SA):

Sodium ascorbate is a bioavailable form of vitamin C. It is an antioxidant agent and inhibitor of MMPs. It stabilizes collagen and promotes collagen biosynthesis, but it lacks the cross-linking ability. Application of SA to dentin following bleaching reverse the compromised bonding that results from bleaching and improves the bond strength restoration [21, 43, 46].

V.2.6. Laser Treatment Prior to Bonding:

Laser irradiation of enamel/dentine may contribute to the success of dental bonding. Laser application to acid-etched dentin cause melting and occlusion of dentinal tubules and further reduce dentin permeability prior to the application of adhesives[47]. Laser irradiation after the application of bonding agent and before curing can cause fusion of adhesive and dentin. In addition, the increase in the temperature due to laser irradiation can result in enhanced penetration of adhesive, improved flow of adhesive on the surface and better evaporation of solvent[48].

V.2.7. Plasma Treatment Prior to Bonding:

Dentin treatment with non-thermal atmospheric plasma (NTAP) After acid etching improves bond strength and stability because carboxyl and carbonyl groups are grafted by the plasma application onto the dentinal substrate, which will enhance the chemical and mechanical interaction of the resin monomers through hydrogen bonding interaction between collagen fibrils and adhesive resins[9]. NTAP can increase interfacial bond strength by increasing the surface contact area with the collagen fibers allowing a higher interaction with the adhesive and penetration into the substrate[49, 50].

V.3. **Modification of the Bonding Protocol.**

V.3.1. Ethanol Wet Bonding:

Wet bonding technique is technically sensitive because excessive wetting or drying may adversely affect the bonding. The presence of water in the wet-bonding techniques may cause phase separation. Moreover, the collagen fibril network becomes suspended in water and complete penetration of resin will be hindered. Therefore, the ethanol-wet bonding concept was developed in etch-and-rinse (E&R) adhesive system to replace water with ethanol before the application of the adhesive[7, 51].

The miscibility of adhesive resin monomers in the ethanol-saturated dentin matrices is better than those in the water-saturated dentin matrices which allows intimate encapsulations of collagen fibrils with adhesive resin monomers[51]. Ethanol can inhibit MMPs by forming covalent bond between the MMP's catalytic zinc and the oxygen atom of the alcohol's hydroxyl group and denaturation of enzymes by removing water from the enzyme structure causing their denaturation[1, 7].

Disadvantages:

- Premature volatilization during clinical practice.

- Pretreatment with a series of increasing ethanol concentrations is time consuming and impractical for clinical operation.

V.3.2. DMSO Wet Bonding:

Dimethyl sulfoxide (DMSO) is an organic liquid that possesses stronger permeability and lower volatility than ethanol. The application of DMSO after acid-etching promotes formation of longer resin tags and increased infiltration depth into dentin improving the stability of the hybrid layer. This could be explained by the ability of DMSO to dissociate collagen fibrils into a sparser network, therefore; spaces occupied by resin monomer are increased. Moreover, hydrophilic, and hydrophobic monomers are dissolved in DMSO due to its amphiphilic nature, thereby reducing phase separation, and enhancing adhesive infiltration. DMSO blocks binding sites of MMPs with their substrate (dentin collagen) to hinder the interaction between them[10].

References:

1. Zhou W, Liu S, Zhou X, Hannig M, Rupf S, Feng J, et al. Modifying Adhesive Materials to Improve the Longevity of Resinous Restorations. Int J Mol Sci. 2019;20(3).

2. Münchow EA, Bottino MC. Recent Advances in Adhesive Bonding - The Role of Biomolecules, Nanocompounds, and Bonding Strategies in Enhancing Resin Bonding to Dental Substrates. Curr Oral Health Rep. 2017;4(3):215-27.

3. Braga RR, Fronza BM. The use of bioactive particles and biomimetic analogues for increasing the longevity of resin-dentin interfaces: A literature review. Dent Mater J. 2020;39(1):62-8.

4. Sofan E, Sofan A, Palaia G, Tenore G, Romeo U, Migliau G. Classification review of dental adhesive systems: from the IV generation to the universal type. Ann Stomatol (Roma). 2017;8(1):1-17.

5. Hamdy TM. Modifications of dental adhesive systems. F1000Research. 2017;6.

6. Kakar S, Goswami M, Kanase A. Dentin Bonding Agents I: Complete Classification—A Review. World Journal of Dentistry. 2011;2:367-70.

7. de Moraes IQS, do Nascimento TG, da Silva AT, de Lira L, Parolia A, Porto I. Inhibition of matrix metalloproteinases: a troubleshooting for dentin adhesion. Restor Dent Endod. 2020;45(3):e31.

8. Tezvergil A, Pashley DH, Mutluay M. Long-Term Durability of Dental Adhesives. Current Oral Health Reports. 2015;2.

9. Amin F, Fareed MA, Zafar MS, Khurshid Z, Palma PJ, Kumar N. Degradation and Stabilization of Resin-Dentine Interfaces in Polymeric Dental Adhesives: An Updated Review. Coatings [Internet]. 2022; 12(8).

10. Zhang Z, Li K, Yang H, Yu J, Huang C. The influence of dimethyl sulfoxide on resin–dentin bonding: A systematic review. International Journal of Adhesion and Adhesives. 2022;113:103037.

11. Perdigão J, Araujo E, Ramos RQ, Gomes G, Pizzolotto L. Adhesive dentistry: Current concepts and clinical considerations. J Esthet Restor Dent. 2021;33(1):51-68.

12. Hardan L, Daood U, Bourgi R, Cuevas-Suárez CE, Devoto W, Zarow M, et al. Effect of Collagen Crosslinkers on Dentin Bond Strength of Adhesive Systems: A Systematic Review and Meta-Analysis. Cells. 2022;11(15).

13. Van Landuyt KL, Snauwaert J, De Munck J, Peumans M, Yoshida Y, Poitevin A, et al. Systematic review of the chemical composition of contemporary dental adhesives. Biomaterials. 2007;28(26):3757-85.

14. Sebold M, André CB, Sahadi BO, Breschi L, Giannini M. Chronological history and current advancements of dental adhesive systems development: a narrative review. Journal of Adhesion Science and Technology. 2021;35(18):1941-67.

15. Stanislawczuk R, Pereira F, Muñoz MA, Luque I, Farago PV, Reis A, et al. Effects of chlorhexidine-containing adhesives on the durability of resin–dentine interfaces. Journal of Dentistry. 2014;42(1):39-47.

16. Toledano M, Osorio R, Osorio E, Cabello I, Toledano-Osorio M, Aguilera FS. A zinc chloride-doped adhesive facilitates sealing at the dentin interface: A confocal laser microscopy study. J Mech Behav Biomed Mater. 2017;74:35-42.

17. Toledano M, Toledano-Osorio M, Hannig M, Carrasco-Carmona Á, Osorio MT, García-Godoy F, et al. Zn-containing Adhesives Facilitate Collagen Protection and Remineralization at the Resin-Dentin Interface: A Narrative Review. Polymers (Basel). 2022;14(3).

18. Chen H, Sun G, Wang H, Yu S, Tian Z, Zhu S. Effect of collagen cross-linkers on dentin bond strength: A systematic review and network meta-analysis. Front Bioeng Biotechnol. 10. Switzerland: Copyright © 2023 Chen, Sun, Wang, Yu, Tian and Zhu.; 2022. p. 1100894.

19. Islam S, Hiraishi N, Nassar M, Yiu C, Otsuki M, Tagami J. Effect of natural cross-linkers incorporation in a self-etching primer on dentine bond strength. J Dent. 2012;40(12):1052-9.

20. Islam SM, Hiraishi N, Nassar M, Sono R, Otsuki M, Takatsura T, et al. In vitro effect of hesperidin on root dentin collagen and de/re-mineralization. Dent Mater J. 2012;31(3):362-7.

21. Gotti VB, Feitosa V, Sauro S, Sobrinho L, Leal F, Stansbury J, et al. Effect of Antioxidants on the Dentin Interface Bond Stability of Adhesives Exposed to Hydrolytic Degradation. The journal of adhesive dentistry. 2015;17.

22. Porto ICCdM, Rocha ABdB, Ferreira IIS, de Barros BM, Ávila EC, da Silva MC, et al. Polyphenols and Brazilian red propolis incorporated into a total-etching adhesive system help in maintaining bonding durability. Heliyon. 2021;7(2):e06237.

23. Ye Q, Spencer P, Yuca E, Tamerler C. Engineered Peptide Repairs Defective Adhesive-Dentin Interface. Macromol Mater Eng. 2017;302(5).

24. Dressano D, Salvador MV, Oliveira MT, Marchi GM, Fronza BM, Hadis M, et al. Chemistry of novel and contemporary resin-based dental adhesives. J Mech Behav Biomed Mater. 2020;110:103875.

25. Tjäderhane L, Nascimento FD, Breschi L, Mazzoni A, Tersariol IL, Geraldeli S, et al. Strategies to prevent hydrolytic degradation of the hybrid layer-A review. Dent Mater. 2013;29(10):999-1011.

26. Jun SK, Yang SA, Kim YJ, El-Fiqi A, Mandakhbayar N, Kim DS, et al. Multi-functional nano-adhesive releasing therapeutic ions for MMP-deactivation and remineralization. Sci Rep. 2018;8(1):5663.

27. Suzuki S, Sreenath T, Haruyama N, Honeycutt C, Terse A, Cho A, et al. Dentin sialoprotein and dentin phosphoprotein have distinct roles in dentin mineralization. Matrix Biol. 2009;28(4):221-9.

28. George A, Hao J. Role of Phosphophoryn in Dentin Mineralization. Cells Tissues Organs. 2005;181(3-4):232-40.

29. Miletic V, Sauro S. Bonding to Tooth Tissues. In: Miletic V, editor. Dental Composite Materials for Direct Restorations. Cham: Springer International Publishing; 2018. p. 199-218.

30. Abuna G, Feitosa VP, Correr AB, Cama G, Giannini M, Sinhoreti MA, et al. Bonding performance of experimental bioactive/biomimetic self-etch adhesives doped with calcium-phosphate fillers and biomimetic analogs of phosphoproteins. Journal of Dentistry. 2016;52:79-86.

31. Tjäderhane L, Nascimento FD, Breschi L, Mazzoni A, Tersariol ILS, Geraldeli S, et al. Strategies to prevent hydrolytic degradation of the hybrid layer—A review. Dental Materials. 2013;29(10):999-1011.

32. Zhang D, Li S, Zhao H, Li K, Zhang Y, Yu Y, et al. Improving antibacterial performance of dental resin adhesive via co-incorporating fluoride and quaternary ammonium. Journal of Dentistry. 2022;122:104156.

33. Nikaido T, Takagaki T, Sato T, Burrow MF, Tagami J. Fluoride-Releasing Self-Etch Adhesives Create Thick ABRZ at the Interface. Biomed Res Int. 2021;2021:9731280.

34. Nomura R, Morita Y, Matayoshi S, Nakano K. Inhibitory effect of surface pre-reacted glass-ionomer (S-PRG) eluate against adhesion and colonization by Streptococcus mutans. Scientific Reports. 2018;8(1):5056.

35. Diolosà M, Donati I, Turco G, Cadenaro M, Di Lenarda R, Breschi L, et al. Use of methacrylate-modified chitosan to increase the durability of dentine bonding systems. Biomacromolecules. 2014;15(12):4606-13.

36. Baena E, Cunha SR, Maravić T, Comba A, Paganelli F, Alessandri-Bonetti G, et al. Effect of Chitosan as a Cross-Linker on Matrix Metalloproteinase Activity and Bond Stability with Different Adhesive Systems. Marine Drugs [Internet]. 2020; 18(5).

37. Mishra A, Koul M, Upadhyay VK, Abdullah A. A Comparative Evaluation of Shear Bond Strength of Seventh- and Eighth-Generation Self-etch Dentin Bonding Agents in Primary Teeth: An In Vitro Study. Int J Clin Pediatr Dent. 2020;13(3):225-9.

38. Almutairi B, Binhasan M, Shabib S, Al-Qahtani AS, Tulbah HI, Al-Aali KA, et al. Adhesive bond integrity of silanized zirconia nanoparticles in polymeric resin dentin bonding agent. An FTIR, SEM, and micro-tensile experiment. International Journal of Adhesion and Adhesives. 2022;114:103069.

39. Feitosa SA, Palasuk J, Kamocki K, Geraldeli S, Gregory RL, Platt JA, et al. Doxycycline-Encapsulated Nanotube-Modified Dentin Adhesives. Journal of Dental Research. 2014;93(12):1270-6.

40. Zaharia ZC, Oancea OR, Gabor GAG, Negruțiu NM-L. New Trends in Dental Adhesion—A Systematic Review. Timisoara Medical Journal. 2020;2020(1).

41. Martini EC, Parreiras SO, Gutierrez MF, Loguercio AD, Reis A. Effect of Different Protocols in Preconditioning With EDTA in Sclerotic Dentin and Enamel Before Universal Adhesives Applied in Self-etch Mode. Operative Dentistry. 2017;42(3):284-96.

42. Luque-Martinez I, Muñoz MA, Mena-Serrano A, Hass V, Reis A, Loguercio AD. Effect of EDTA conditioning on cervical restorations bonded with a self-etch adhesive: A randomized double-blind clinical trial. Journal of Dentistry. 2015;43(9):1175-83.

43. Singh P, Nagpal R, Singh UP. Effect of dentin biomodifiers on the immediate and long-term bond strengths of a simplified etch and rinse adhesive to dentin. Restor Dent Endod. 2017;42(3):188-99.

44. Nagpal M, Taneja S, Kumar M, Dudeja C. Evaluation of the effect of natural versus synthetic matrix metalloproteinase silencers in preservation of dentin collagen and long-term bond strength of total etch adhesive. J Conserv Dent. 2020;23(3):221-6.

45. Neri JR, Yamauti M, Silveira FDd, Mendonça JS, Carvalho RMd, Santiago SL. Influence of dentin biomodification with epigallocatechin-3-gallate on the bond strength of self-etch adhesive: Twelve-month results. International Journal of Adhesion and Adhesives. 2016;71:81-6.

46. Ismail EH, Kilinc E, Hardigan PC, Rothrock JK, Thompson JY, Garcia-Godoy C. Effect of Two-minute Application of 35% Sodium Ascorbate on Composite Bond Strength following Bleaching. J Contemp Dent Pract. 2017;18(10):874-80.

47. Benitez Sellan PL, Zanatta RF, Gomes Torres CR, Tian F-c, Bergeron BE, Niu L-n, et al. Effects of calcium-phosphate, laser and adhesive on dentin permeability and bond strength. Heliyon. 2020;6(5):e03925.

48. Kasraei S, Yarmohamadi E, Ranjbaran Jahromi P, Akbarzadeh M. Effect of 940nm Diode Laser Irradiation on Microtensile Bond Strength of an Etch and Rinse Adhesive (Single Bond 2) to Dentin. J Dent (Shiraz). 2019;20(1):30-6.

49. Passos IDAG, Marques JDN, Câmara JVF, Simão RA, Prado MD, Pereira GDDS. Effect of non-thermal argon plasma on the shear strength of adhesive systems. Polímeros. 2022;32(1):e2022012.

50. Awad MM, Alhalabi F, Alshehri A, Aljeaidi Z, Alrahlah A, Özcan M, et al. Effect of Non-Thermal Atmospheric Plasma on Micro-Tensile Bond Strength at Adhesive/Dentin Interface: A Systematic Review. Materials (Basel). 2021;14(4).

51. Rajesh P, Chakravarthy D, Pugal N, S.N P, Lnu V. Contemporary Dentin Bonding Agents-A Review. Journal of Scientific Dentistry. 2018;8:13-9.