Progress in Dental Adhesive Materials

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Abstract

There have been significant advances in adhesive dentistry in recent decades, with efforts being made to improve the mechanical and bonding properties of resin-based dental adhesive materials. Various attempts have been made to achieve versatility, introducing functional monomers and silanes into the materials' composition to enable the chemical reaction with tooth structure and restorative materials and a multimode use. The novel adhesive materials also tend to be simpler in terms of clinical use, requiring reduced number of steps, making them less technique sensitive. However, these materials must also be reliable and have a long-lasting bond with different substrates. In order to fulfill these arduous tasks, different chemical constituents and different techniques are continuously being developed and introduced into dental adhesive materials. This critical review aims to discuss the concepts behind novel monomers, bioactive molecules, and alternative techniques recently implemented in adhesive dentistry. Incorporating monomers that are more resistant to hydrolytic degradation and functional monomers that enhance the micromechanical retention and improve chemical interactions between adhesive resin materials and various substrates improved the performance of adhesive materials. The current trend is to blend bioactive molecules into adhesive materials to enhance the mechanical properties and prevent endogenous enzymatic degradation of the dental substrate, thus ensuring the longevity of resin–dentin bonds. Moreover, alternative etching materials and techniques have been developed to address the drawbacks of phosphoric acid dentin etching. Altogether, we are witnessing a dynamic era in adhesive dentistry, with advancements aiming to bring us closer to simple and reliable bonding. However, simplification and novelty should not be achieved at the expense of material properties.

Keywords: adhesives, bioactive materials, bonding, methacrylates, resins, etching

Introduction

Achieving optimal functional and esthetic outcomes while conserving as much tooth structure as possible has become an imperative in the era of contemporary adhesive dentistry. There is solid scientific evidence in the literature about the excellent clinical performance of composite restorations, whose integrity relies on the formation of hybrid layers (HLs) created by gold standard 3-step etch-and-rinse (ER) or 2-step self-etch (SE) systems (Van Meerbeek et al. 2020; Rodolpho et al. 2022). Nevertheless, failure of resin-based dental restorations still occurs (Fan et al. 2021), especially if adhesive protocols and indications for use provided by the manufacturers are not strictly respected (Demarco et al. 2012; Mazzitelli et al. 2022). Consequently, more user-friendly single-bottle/syringe materials, which should provide greater tolerance for potential errors during bonding and cementation procedures, were introduced to the dental market about a decade ago. Besides simplicity, the 2 main features of these materials, as claimed by the patent literature, are reliability—meaning that their performance is comparable to materials with a long track period, and versatility—implying that the same material may be used in various clinical situations and on different substrates, by inexperienced, as well as expert users, frequently without the need of substrate pretreatment. Their versatility is responsible for the addition of the attribute "universal" to materials such as adhesive systems and self-adhesive resin cements (Josic, Mazzitelli, Maravic, Comba, et al. 2022). In order to fulfill all 3 requirements—reliability, simplicity, and versatility—the chemical composition of these materials has undergone significant modifications through the introduction of various novel molecules. Modifications and improvements have also been introduced in the various stages of the adhesive procedures.

Considering that "universal" materials are relatively new, confusion and uncertainties regarding their actual reliability and versatility may arise in the scientific community and among dental clinicians. Accordingly, by analyzing the data

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from recent laboratory and clinical studies, this article will discuss the characteristics of materials and techniques considered to be of increasing interest in the world of adhesive dentistry.

Progress in Universal Adhesive Systems

Universal or multimode adhesives (UAs) represent the latest generation of adhesive systems with several advantages: 1) they can be used in ER, selective enamel etching (SEE), or SE mode, regardless of the extent of dentin moisture (Sebold et al. 2022), and 2) the presence of functional acidic monomers (i.e., 10-methacryloyloxy-decyl-dihydrogen-phosphate [10-MDP]) enables adhesion to various substrates such as composites, ceramics, and metal alloys (Tsujimoto et al. 2017). UAs can be classified based on their pH value into ultra-mild, mild, and intermediately strong (Table 1). In light of their modified composition compared to traditional ER and SE adhesive systems, UAs can also be divided into 10-MDP containing/free and silane incorporated/free materials (Table 1). The ability to form a chemical bond with dentin is dependent on the presence of functional monomers such as 10-MDP as they can chemically interact with the hydroxyapatite (HAp) crystals surrounding collagen fibrils in unetched dentin to form Ca-10-MDP salts that are resistant to hydrolysis and can, therefore, stabilize the adhesive interface over time. This phenomenon is known as "nanolayering" (Yoshida et al. 2012) (Fig. 1), and laboratory studies have suggested that 10-MDP–containing UAs exhibit superior properties when compared to adhesives containing other acidic monomers (Fehrenbach et al. 2021). Nevertheless, UAs' etching capacity to enamel remains limited, irrespective of the presence of 10-MDP, thus emphasizing the need to perform a separate acid etching step to ensure adequate bond strength to this tissue (Cuevas-Suarez et al. 2019; Fehrenbach et al. 2021).

The expanded indications for their use (i.e., replacement of classical silane agents) require a delicate equilibrium between the various molecules within UAs, with minimal mutual interference. In addition, a higher pH value is also necessary in order to maintain silane stability, although this can also consequently decrease the etching capacity of the adhesive itself (Van Meerbeek et al. 2020). Currently, there are 4 commercially available silane-containing UAs that can be used for pretreatment of indirect restorations (Table 1). A recent meta-analysis suggested that conventional glass-ceramics pretreatment with hydrofluoric acid and a separate silane agent remains a gold standard, providing higher bond strength values when compared to silane-containing UAs (Lima et al. 2022). However, a recently introduced UA, not included in the previously mentioned study, contains additional silane coupling agents ([i.e., 3-(aminopropyl) triethoxysilane and γ-methacrylo xypropyltriethoxysilane; Table 1) that are more stable in an aqueous acidic environment. This adhesive achieved better results in bonding to glass-ceramics compared to its predecessor (Yao et al. 2021), with another benefit of being BPA (bisphenol A)–derivate free since it does not contain bisphenol A–diglycidylmethacrylate (Bis-GMA) (patent literature). Also, the chemical interaction and antagonistic effect between silane agents and 10-MDP must also be taken into consideration as the former can cause hydroxylation of zirconia and, consequently, alter the adsorption of 10-MDP, thus highlighting the importance of optimizing the percentage of silane incorporated within UAs (Ye et al. 2022).

As far as the data from randomized controlled clinical trials (RCTs) are concerned, the longest follow-up period demonstrating the good performance of composite restorations placed with UAs is 5 y (de Paris Matos et al. 2020). However, the clinical performance of UAs largely depends on the adhesive strategy, thus questioning their claimed versatility regarding the application mode in a clinical setting (Josic et al. 2021; Josic, Mazzitelli, Maravic, Radovic, et al. 2022). Indeed, a recent systematic review examining the clinical performance of composite restorations placed in noncarious cervical lesions concluded that the risk of postoperative sensitivity (POS) was higher when UAs are used in ER mode and that SE mode alone is not sufficient for providing adequate retention of composite restorations due to poor enamel demineralization potential (Josic et al. 2021). Therefore, the application of UAs in SEE mode was considered the most appropriate approach for minimizing risk of POS and achieving optimal retention in the medium-term period (up to 3 y of follow-up) (Josic, Mazzitelli, Maravic, Radovic, et al. 2022).

Progress in the Composition of Adhesive Materials

Monomers

UAs resemble SE adhesive systems in their composition as they contain hydrophobic monomers (i.e., Bis-GMA, triethyleneglycol-dimethacrylate [TEGDMA], and urethane dimethacrylate [UDMA]) that promote crosslinking with resin composites as well as hydrophilic monomers that can bind to the organic constituents of the tooth substrate (Table 1) (Papadogiannis et al. 2019).

Recently, the potential cytotoxic and estrogenic effect of BPAs motivated manufacturers to replace Bis-GMA in resin materials, leading to the introduction of a new methacrylate dendrimer, G(2)-isocyanatoethyl-methacrylate (G-IEMA), as a monomer in experimental BPA-free dental adhesive systems. G-IEMA is characterized by a star shape with 8 methacrylate groups and demonstrated interesting properties, leading to decreased nanoleakage expression when blended in experimental adhesives compared to commercially available Bis-GMA–based commercial ones (Vasconcelos e Cruz et al. 2019). However, the solubility and water sorption of these experimental formulations are comparable to commercial adhesives (Vasconcelos e Cruz et al. 2019), raising questions regarding the ability of dendrimers to improve the stability of the bonded interface and increase the durability of restorations in vivo.

The principal hydrophilic monomer in most UAs is hydroxyethyl-methacrylate (HEMA), which favors diffusion

Table 1. Composition of the Universal Adhesives Currently Available on the Dental Market Listed According to Their pH in Ascending Order.

Adhesive Trade Name(s)	pH	Methacrylates	Adhesion-Promoting Monomers		CHX	Silane	Initiators	Solvent Type	Delivery Form
			10-MDP	Other					
Peak universal (Ultradent Products)	1.2	HEMA	X	X	✓	X	NA	Ethyl alcohol	1-bottle
G2-BOND universal (GC Corporation)	Primer: 1.5 Adhesive: NA	Primer: Dimethacrylates Adhesive: Bis GMA UDMA	✓	4-MET GDMA	X	X	Primer: NA Adhesive: TPO	Water, acetone	2-bottle (primer + adhesive)
iBOND universal (Kulzer GmbH)	1.6–1.8	DUDMA	✓	4-META	X	X	NA	Water, acetone	1-bottle
G-PREMIO bond (GC Corporation)	1.8	X	✓	4-MET MDTP	X	X	NA	Water, acetone	1-bottle
One Coat 7 universal (Coltène)	2.0–2.8	DUDMA HEMA	✓	X	X	X	TPO	Water, ethanol	1-bottle
Optibond eXTRa universal (Kerr)	Primer: 2.2 Adhesive: NA	Primer: HEMA Adhesive: HEMA	X	Primer: GPDMA Adhesive: GPDMA GDMA	X	X	NA	Primer: Acetone, ethanol Adhesive: Ethanol	2-bottle (primer + adhesive)
Tokuyama universal bond (Tokuyama Dental America, Inc.)	2.2	Bond A: Bis GMA TEGDMA HEMA	X	Phosphate-monomer MTU-6	X	✓	NA	Water, acetone, isopropanol	2-bottle (Bond A + Bond B)
Clearfil universal bond quick (Kuraray Noritake Dental)	2.3	Bis GMA HEMA	✓	X	X	✓	NA	Water, ethanol	1-bottle
Futurabond U (VOCO)	2.3	Liquid 1: Bis-GMA HEMA UDMA Liquid 2: HEMA	X	GPDMA GDMA	✓	X	NA	Water, ethanol	2-bottle (Liquid 1 + Liquid 2)
All-bond universal (Bisco)	2.5–3.5	Bis-GMA HEMA	✓	X	X	X	NA	Ethanol	1-bottle
Prime&Bond active (DENTSPLY DeTrey)	2.5	Bisacrylamide 1 Bisacrylamide 2	✓	PENTA	X	X	NA	Water, Isopropanol	1-bottle
Adhese universal/ tetric N-bond universal (Ivoclar Vivadent)	2.5	HEMA Bis GMA DMAEMA	✓	X	X	X	CQ	Ethanol	1-bottle
Ambar universal (FGM)	2.6–3.0	UDMA HEMA	✓	X	X	X	CQ	Water, ethanol	1-bottle
CLEARFIL TRI-S BOND/ CLEARFIL S3 BOND PLUS (Kuraray Medical)	2.7	Bis-GMA HEMA	✓	X	X	X	CQ	Water, ethanol	1-bottle
Scotchbond universal/ single bond universal (3M, Oral Care)	2.7	Bis-GMA HEMA DMAEMA	✓	X	X	✓	CQ	Water, ethanol	1-bottle
Scotchbond universal plus (3M, Oral Care)	2.7	HEMA DEGDMA	✓	X	X	✓	CQ	Water, ethanol	1-bottle
ZIPBond universal (SDI)	3.0	Acrylic monomers	X	X	X	X	NA	Ethanol	1-bottle

4-MET, 4-methacryloxyethyl trimellitic acid; 4-META, 4-methacryloxyethyl trimellitate anhydride; 10-MDP, 10-methacryloyloxydecyl dihydrogen phosphate; Bis-GMA, bisphenol A–glycidyl methacrylate; CHX, chlorhexidine; CQ, camphorquinone; DEGDMA, diethylene glycol dimethacrylate; DMAEMA, 2-(dimethylamino)ethyl methacrylate; DUDMA, diurethane dimethacrylate; GDMA, glycerol-dimethacrylate; GPDMA, glycerol phosphate dimethacrylate; HEMA, 2-hydroxyethyl methacrylate; MDTP, 10-methacryloyloxydecyl dihydrogen thiophosphate; MTU-6, 6-methacryloyloxyhexyl 2-thiouracil 5-carboxylate; NA, Not available; PENTA, dipentaerythritol penta-acrylate phosphate; TPO, diphenyl (2,4,6-trimethylbenzoyl) phosphinoxide; UDMA, urethane dimethacrylate.

through the dentin collagen fibers, improving the adhesive wettability. HEMA also ensures the coexistence of hydrophilic and hydrophobic monomers in the same formulation, preventing phase separation phenomena. However, it can also lead to water sorption and hydrolysis of the adhesive layer (Munchow et al. 2014) and interfere with the interaction between 10-MDP and Ca, potentially impairing the formation of an adequate bond in 10-MDP–containing adhesives. Recently, acrylamide

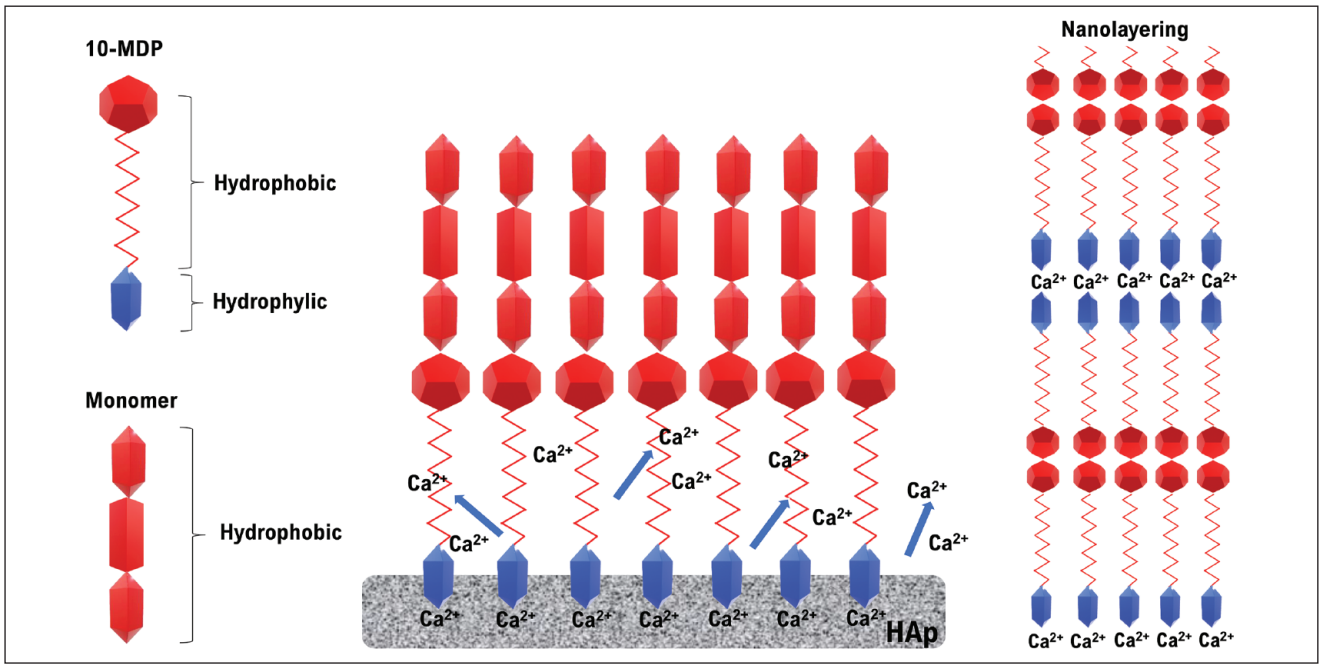

Figure 1. Schematic representation of the mechanism of interaction between 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) and hydroxyapatite (HAp). The 10-MDP etches mineralized tooth tissues, releasing calcium ions. It binds chemically on the hydrophilic end (through the hydroxyl groups of the phosphoric acid group) to the calcium ions from HAp, forming stable 10-MDP-Ca salts, while on the hydrophobic end (polymerizable methacrylate group), it binds chemically to monomers from the dental adhesive materials (central part of the figure). Owing to the affinity toward forming stable 10-MDP-Ca salts, 10-MDP molecules can also use calcium ions released by the etching of HAp to self-assemble into nanolayers within the hybrid layer (right side of the figure).

monomers have been used to replace HEMA in some adhesives (Table 1), resulting in higher bond strength values compared to other commercial UAs (Ahmed et al. 2019). Experimental acrylamide adhesives have been shown to stabilize the bonding interface in in vitro conditions simulating the oral environment (de Lucena et al. 2022) and are claimed to be more resistant in acidic environments (Fugolin et al. 2020) and promote collagen crosslinking and MMP inhibition. Nonetheless, clinical evidence of the superiority of acrylamides is still lacking.

The adhesion of UAs to the tooth structure is accomplished through the interaction between acidic monomers and hydrophilic functional groups (i.e., phosphate, phosphonate, and carboxylate) that have the ability to demineralize the tooth tissues. They can form chemical bonds between the dental substrate and restorative materials such as metals and ceramics (Chen et al. 2012). In addition to 10-MDP, other functional monomers such as dipentaerythritol penta acrylate monophosphate (PENTA-P), glycero-phosphate dimethacrylate (GPDM), 4-methacryloxyethyl trimellitic acid (4-MET), and 4-methacryloyloxyethyl trimellitate anhydride (4-META) have also been included in various formulations (Gary 2015; Dressano et al. 2020). 10-MDP is a phosphate ester monomer consisting of methacrylate and a PA group separated by a spacer group (Yoshihara et al. 2018). In addition to chemically bonding with HAp, 10-MDP can also establish hydrogen bonds with collagen molecules and inhibit dentinal matrix metalloproteinases (MMPs), thus preventing the hydrolytic degradation of collagen fibrils initiated by endogenous dentinal enzymes (Mazzitelli et al. 2022). This, in turn, enhances the longevity of the resin–dentin interface. However, 10-MDP can undergo hydrolytic degradation, leading to the search for substitutes with higher hydrolytic resistance. The most promising is 6-methacryloxy-2,2,3,3,4,4,5,5-octafluorohexyl dihydrogen phosphate (MF8P), which exhibit higher hydrolytic resistance (Van Meerbeek et al. 2020). However, no commercially available adhesives incorporate this monomer to date, making it difficult to evaluate its clinical potential.

Bioactive Compounds/Molecules

Current research is mainly focused on the development of bioactive compounds with antimicrobial and/or remineralizing properties, preventing the formation of recurrent caries at the tooth–restoration interface and, consequently, failure of the resin restorations (Demarco et al. 2012). Although caries development is largely dependent on the patient's oral hygiene and food habits, restorative materials might influence the formation of recurrent caries at the tooth–restoration interface (Nedeljkovic et al. 2015).

Chlorhexidine (CHX) is a popular MMP inhibitor and antimicrobial agent, mainly proposed as an extra-priming step for demineralized dentin, which is now included in some of the recent adhesive formulations with the same purpose (Breschi et al. 2020) (Table 1).

Silver nanoparticles have also been included at a concentration of 0.1% to 1% in experimental adhesive systems as they

exhibit excellent antimicrobial activity (Dressano et al. 2020) and good biocompatibility, exerting their action when released from the polymer.

Quaternary ammonium (QA) compounds are other antimicrobial agents that, on the contrary, have been incorporated into the resin monomer structure, forming the so-called quaternary ammonium methacrylates (QAMs). 12-Methacryloyloxy dodecylperidinium bromide antimicrobial monomer (MDPB) was the first QAM in a commercial adhesive and has been widely studied. MDPB can copolymerize with other monomers, while the QA group has antibacterial activity (Makvandi et al. 2018). Moreover, MDPB demonstrated a good inhibiting effect against MMPs. For this reason, the efforts of researchers have been directed toward the development of new QAMs, with mixed results (Breschi et al. 2018). Unlike MDPB, a monomethacrylate QAM, a recently developed group of antibacterial QA-based dimethacrylate monomers, was found to exhibit the advantage of creating crosslinking bonds with other monomers (Fanfoni et al. 2021). QA methacrylamides and acrylamides that combine significant antibacterial effects and good mechanical properties such as polymerization and bond strength have also been formulated (Fugolin et al. 2019).

Another interesting antibacterial compound is cetylpyridinium chloride (CPC), which was first incorporated in poly(2-hydroxyethyl methacrylate)/trimethylolpropane trimethacry late hydrogels but was then replaced with an inorganic compound loaded with CPC when it was found to be too prone to water sorption (Van Meerbeek et al. 2020).

Antimicrobial resistance is a potential problem associated with the use of antibacterial compounds, which, for instance, has been documented following the use of CHX and QAMs (Wang et al. 2018). In adhesive dentistry, antibacterial adhesives seek to halt bacterial proliferation at the restoration margins, although only bacteria that are in close contact with the bactericidal agent are killed. In case of resistance development, the outcome would be the loss of the adhesive bioactivity and protective effect against recurrent caries. The small thickness and limited exposure of the adhesive layer to the oral environment prevent the risk of massive oral dysbiosis caused by antimicrobial resistance.

A completely different approach involves the use of adhesives containing zwitterionic polymers (ZPs) such as poly (2-methacryloyloxyethyl phosphorylcholine) (MPC) that exhibit an inherent resistance to protein adhesion and inhibit biofilm formation. An adhesive containing a zwitterionic polymer (MPC) decreased the biofilm adhesion and showed antibacterial activity. Besides, MPC can increase the pH and induce neutralization of acids, reducing the risk of recurrent caries (Mangal et al. 2020). However, as higher pH values can also impair the etching and bonding abilities of UAs (Van Meerbeek et al. 2020), the role of ZPs in adhesive formulations must be investigated further.

Bioactive particles proposed as remineralizing agents include HAp, calcium silicates (CaSi), bioactive glasses (BAGs), and calcium phosphates (CaP). BAGs or CaSi particles promote mineral precipitation, replacing water from water-rich gaps in poorly infiltrated within the hybrid layer; improve the mechanical properties of the adhesive interface; and inhibit MMPs through electrostatic interactions (Braga and Fronza 2020). Ion-releasing particles associated with biomimetic analogues of noncollagenous proteins have been proposed to promote remineralization in completely demineralized dentin as they can guide apatite growth within the collagen matrix acting as stabilizers (Braga and Fronza 2020). The remineralizing properties may not only preserve the HL from hydrolytic degradation but might also allow the preservation of tooth structure by limiting deep carious tissue removal and minimizing the risk of pulp exposure. Although there is considerable in vitro evidence demonstrating remineralization of the hybrid layer, clinical evidence on the effects of these particles on bond strength is limited. One study with a follow-up period of 18 months evaluated the clinical performance of posterior restorations using adhesive systems containing BAGs and found no improvements in outcomes (Pintado-Palomino et al. 2019). For this reason, additional studies are required to include these remineralizing agents in commercial adhesives. Moreover, when the bioactive effect is exerted through ion release, the stability and integrity of the material over time become a significant concern.

Progress in Etching Strategies

Alternative Etchant Formulations

New etching materials and alternative etching techniques have been investigated extensively in an attempt to overcome the limitations of PA. Alternative etching approaches can be classified based on the composition of the conditioner and the etching technique (Table 2).

Dental etching plays a critical role as it lays the foundations for micromechanical retention and chemical interaction between the adhesive systems and dental substrates (Saikaew et al. 2022). Therefore, etchants should exhibit certain properties such as the ability to effectively remove the smear layer from the dental substrate, demineralize dentin without reducing Ca-content available for bonding at the adhesive interface (Stape et al. 2018), and possess antimicrobial and crosslinking properties so as to strengthen the adhesive interface and make it resistant to bacterial attack (Ren et al. 2018). Although no ideal etchant exists to date, encouraging results have been reported when using various innovative formulations.

Alternative PAic monomers and organic acids have been recently proposed to enhance the retention of UAs to enamel and dentin, being halfway between a PA etching and the acidic monomers of the SE adhesive systems. These materials demonstrated promising preliminary results with regard to bond strength (Sato et al. 2019; Yao et al. 2019; Baba et al. 2021).

The possibility of having a self-limiting etchant, which reduces the risk of dentin overetching, is also appealing. Recently, an experimental self-limiting zirconium-oxide conditioner was effective in maintaining the bond strengths to enamel and dentin over time while decreasing the dentinal host-derived MMP activity, in a material-dependent way (Yao et al. 2019; Mancuso et al. 2021; Ahmed et al. 2022).

Table 2. Schematic Representation of the Proposed Classification of Alternative Etchants and Etching Possibilities.

Materials
- I. Partial demineralization
  - Ia. Multi Etchant (Yamakin): Phosphoric acidic monomer (methacryloiloxy tetraethylene glycol dihydrogen phosphate, M-TEG-P), purified water, thickening agents, dye
  - Ib. Enamel Conditioner (Shofu): 40% organic acid, thickening agents, water, dye
- II. Self-limiting
  - IIa. Experimental zirconiuim oxynitrate conditioner (Ivoclar): $ZrO(NO_3)_2$, water, glycerol, fumed silica, polyethylene oxide
- III. Biomodifying
  - IIIa. Etch-37BAC (Bisco): 37% phosphoric acid, water, quaternary ammonium compounds, benzyl-C8-18-alkyldimethyl, chlorides, xanthic gum
  - IIIb. 2% Chlorexidine digluconate
  - IIIc. 2% Proanthocyanidins from grape seed extract
  - IIId. Chitosan: 0.1 g of chitosan (75%–85% deacetylated, 50–190 kDa; MilliporeSigma) in 0.2 wt% acetic acid
  - IIIe. BCE: β-tricalcium phosphate and monocalcium phosphate monohydrate powders mixed with citric acid (5 M)

Techniques
- I. Selective enamel etching (SEE)
  - Application of 35% to 37% phosphoric acid on enamel for 15 s and then water-rinsing
- II. Selective dentin etching (SDE) → "Short dentin etching"
  - Application of 32% phosphoric acid on dentin for 3 s and then water-rinsing for 5 s

Etchants can be further classified according to the mechanism of demineralization/conditioning on the tooth substrates. Etching techniques can be subdivided according to the dental substrate to be conditioned. The shift from the term *selective dentin etching* to *short dentin etching* is proposed to avoid confusion among researchers and clinicians.

Dentin etching with 35% PA tends to promote incomplete resin infiltration into the fully demineralized dentin and its collagen-rich organic matrix, resulting in the presence of denuded collagen fibrils at the bottom of the hybrid layer and degradation of the adhesive interface by MMPs. This led to the formulation of PAs containing MMP inhibitors (Vicente and Bravo 2008; Bernales Sender et al. 2020) and bioactive components (Ibrahim et al. 2019; Hass et al. 2021) as they represent a valid alternative for enhancing bonding performance.

Furthermore, the chelate-and-rinse approach involving dentin collagen crosslinkers (i.e., chitosan) that maintain the interfibrillar minerals, enhancing micromechanical retention and preventing collapse of the collagen matrix, has also been proposed (Gu et al. 2019). The possibility of performing the dry-bonding technique, as previously introduced with the SE strategy, would alleviate complications associated with the use of hydrophilic adhesives, thus potentially maintaining stability of the adhesive interface over time (Breschi et al. 2018; Van Meerbeek et al. 2020).

Alternative Etching Strategies

As previously indicated, the SEE strategy is considered suitable for when using UAs (Josic, Mazzitelli, Maravic, Radovic, et al. 2022) as the efficacy of PA in etching dentin is time dependent. The effect of reduced etching time on the bonding performance of UAs has been investigated, with reported outcomes that were similar to SE adhesives (Takamizawa et al. 2016). A reliable surface cleaning and no detrimental effects on adhesion forces have been observed after 3 s of dentin etching, following the "selective dentin etching" technique (Stape et al. 2018; Cavalheiro et al. 2020; Hardan et al. 2021). However, the authors of this review feel that the assigned name may be misleading to researchers and clinicians. We suggest *short dentin etching* as a more suitable term for etching times less than 15 s. This technique could mitigate the risk of inadvertent dentin etching while maintaining most minerals necessary for effective adhesion (Stape et al. 2018; Cavalheiro et al. 2020). However, etchant manipulation for such a short period of time can be clinically challenging, and further research is necessary to identify an etching technique that balances clinical needs with the preservation of HAp.

The viscosity of the etchant should also be taken into consideration when using one of the aforementioned strategies, as a more viscous product will allow selective application of the etchant, thus reducing the risk of mismanagement (Josic, Mazzitelli, Maravic, Radovic, et al. 2022).

Due to the variability of the dental substrate, which makes the PA etching highly unpredictable (Saikawe et al. 2022), it would be advantageous to possess a "universal etchant" capable of effectively etching enamel and dentin simultaneously. Such a material would prove useful in challenging clinical situations such as deep posterior proximal cavities where assessment of residual enamel and obtaining perfect bonding conditions can be difficult. The introduction of UAs with new formulations warrants further investigation of the mechanism that can be established between alternative etching strategies and these products.

Progress in Resin-Based Cements

Efforts to simplify resin-based materials have extended beyond adhesive systems and conservative dentistry into prosthodontics through the introduction of self-adhesive composite cements. Evidence suggests that the bond strength between these materials and the dental substrates, particularly enamel, is often inferior to that of their multistep counterparts (Ferracane et al. 2011). Therefore, self-adhesive cements that can also be used with prior application of a chemically compatible UA recommended by the manufacturer represent a suitable alternative and have recently been marketed (Table 3). In these cases, the UA can serve as a tooth tissue or restoration

Table 3. Detailed Compositions of Universal Cements.

Universal Cement's Name (Manufacturer)	3M RelyX Universal Resin Cement (3M, Oral Care)	PANAVIA SA Cement Universal (Kuraray Noritake Dental)	SoloCem (Coltène)
Chemical composition	*Base paste:* TEGDMA 2-Propenoic acid, 2-methyl-, 3-(trimethoxysilyl)propyl ester, reaction products with vitreous silica 7,7,9(or 7,9,9)-Trimethyl-4,13-dioxo-3,14-dioxa-5,12-diazahexadecane-1,16-diylbismethacrylate 2-Propenoic acid, 2-methyl-, 1,1′-[1-(hydroxymethyl)-1,2-ethanediyl] ester reaction products with 2-hydroxy-1,3-propanediyl dimethacrylate and phosphorus oxide Silane, trimethoxyoctyl-, hydrolysis products with silica t-Amyl Hydroperoxide 2,6-Di-tert-butyl-p-cresol HEMA Methyl methacrylate Acetic acid, copper(2+) salt, monohydrate. *Catalyst paste:* UDMA Ytterbium (III) fluoride Glass powder, surface modified with 2-propenoic acid, 2 methyl-3-(trimethoxysilyl)propyl ester and phenyltrimethoxy silane, bulk material TEGDMA L-Ascorbic acid, 6-hexadecanoate, hydrate (1:2) trimethoxy(octyl)silane, hydrolysis products with silica HEMA Titanium dioxide Triphenyl phosphite	*Paste A* 10-MDP Bis-GMA TEGDMA Hydrophobic aromatic dimethacrylate HEMA Silanated barium glass filler Silanated colloidal silica dl-Camphorquinone Peroxide Catalysts Pigments *Paste B* Hydrophobic aromatic dimethacrylate Silane coupling agent Silanated barium glass filler Aluminum oxide filler Surface treated sodium fluoride (less than 1%) dl-Camphorquinone Accelerators Pigments	TEGDMA DUDMA Bis-GMA HEMA Zinc oxide; ytterbium(III) fluoride 2,6-di-tert-butyl- 4-methylphenol 10-MDP dibenzoyl peroxide (BPO initiator) 4-META
Recommended adhesive resin	Scotchbond universal plus	CLEARFIL universal bond quick	One Coat 7 universal

The information on the composition of the materials was obtained from the manufacturers' websites and SDS documents.
4-META, 4-methacryloxyethyl trimellitic anhydride; 10-MDP, 10-methacryloyloxydecyl dihydrogen phosphate; Bis-GMA, Bisphenol A–diglycidylmethacrylate; DUDMA, diurethane dimethacrylate; HEMA, 2-hydroxymethacrylate; TEGDMA, triethyleneglycol dimethacrylate; UDMA, diurethane dimethacrylate.

conditioner without the need for other products. As these cements exhibit versatility of application mode similar to UAs and can be indicated for use on a variety of substrates, they should be considered the true "universal" resin cements (URCs), and this term should, therefore, be disambiguated throughout the scientific and commercial literature.

Although similar to their self-adhesive predecessors, formulations of these cements have been modified to improve the efficacy of polymerization and interaction with the cementation substrates. Some of the claims of the URC manufacturers regard the introduction of an amphiphilic redox initiator system, intending to initiate polymerization in the hydrophilic dentin with the same efficacy as observed in the hydrophobic portion of the adhesive layer. Furthermore, aryl sulfinate or aryl borate salts are added to dual-cured adhesive resin materials to allow synergistic activation of composite cement at the cement–tooth interface in an alternative polymerization strategy known as "touch-cure," introduced to improve the monomer conversion in areas with a scarce or no exposure to the curing light (Dimitriadi et al. 2021). From the available laboratory data, one of the URCs has a higher DC than its predecessors, lower total monomer elution, and a similar solubility when compared to several other multistep and self-adhesive cements (Aldhafyan et al. 2022), possibly corroborating the positive effects of the novel redox initiator. Contrarily, Vicker's hardness of this URC was lower, and shrinkage was higher compared to the same group of cements (Aldhafyan et al. 2021). In an effort to improve bonding efficacy, a mixture of prehydrolyzed and amino-functional silanes and a chemical polymerization activator were added to the formulation of the UA of 1 URC. In another representative of the group, a proprietary long-chain silane monomer was introduced in the base paste of the cement itself, which does not contain 10-MDP, enabling the preservation of its chemical structure (commercial literature). These modifications possibly underlie the demonstrated improvement of bonding properties to composite, ceramics, and zirconia compared to several competitors (Atalay et al. 2022; Rohr et al. 2022) when used in conjunction

with the recommended UA or a comparable bond strength in self-adhesive mode to a competitor that requires a separate silane application (Yoshihara et al. 2020). The performance of URCs is not only material group related but also material specific. While 1 URC demonstrated bond strength to coronal and radicular dentin comparable to multistep and self-adhesive resin cements (Josic, Mazzitelli, Maravic, Radovic, et al. 2022; Rohr et al. 2022), another performed comparably (Yoshihara et al. 2020) or worse than its predecessor (Oda et al. 2022) when used without the pertinent adhesive system. Similarly, while 1 URC system exhibited improved bond strength to composite blocks (Rohr et al. 2022), another demonstrated inferior outcomes when compared to a self-adhesive cement placed after a silane primer (Takahashi et al. 2022). Further, it is important to note that the bond strength of URCs to enamel is lower at baseline (Atalay et al. 2022) or after artificial aging (Rohr et al. 2022) compared to several multistep or self-adhesive resin cements.

As these materials are relatively new on the market, laboratory data are scarce, and clinical data are lacking. However, the available literature suggests that some of the mechanical properties of URCs are poorer than those of their predecessors, and the issue of poor bond strength to enamel has not yet been adequately addressed. As was the case with the UAs and self-adhesive cements, it may take several generations of URCs to reach their desired material and bonding properties.

Future Research and Concluding Remarks

Significant advances have indeed been achieved in terms of simplification and versatility of dental adhesive materials. Their reliability, however, remains questionable as long-term randomized clinical trials, as well as real-world data about the behavior of these materials, are still lacking. Moreover, there is a general discrepancy between the improvements in adhesion demonstrated by laboratory tests and the clinical performance of restorations. Comparison between newly introduced "universal" and "gold" standard materials in both laboratory and clinical studies should be encouraged, accompanied by a proper study design and standardization between the studies. It is also interesting to note that certain materials are examined to a greater extent than others, potentially due to the willingness and financial ability of their manufacturers to support research, and examination of a wider group of materials from each group is necessary to obtain valid and generalizable results.

All universal materials should not only possess the same/improved biomechanical and esthetic properties as their predecessors but also incorporate an additional property of bioactivity. The truly "universal" composite material of the future should ideally be suitable for use in both adhesive and self-adhesive mode, as well as exhibit mechanical properties that allow it to be used for cementation as well as a stand-alone restoration.

Author Contributions

M. Cadenaro, contributed to conception and design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; U. Josic, T. Maravić, contributed to design, data acquisition and interpretation, drafted and critically revised the manuscript; C. Mazzitelli, contributed to conception, data acquisition and interpretation, drafted and critically revised the manuscript; G. Marchesi, E. Mancuso, contributed to data acquisition and interpretation, drafted and critically revised the manuscript; L. Breschi, contributed to conception, data interpretation, critically revised the manuscript; A. Mazzoni, contributed to design, data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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