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Abstract

Bonding agents play a crucial role in the effective sealing and retention of resin-based composite restorations, which have been increasingly placed and replaced by dentists in many countries around the world. In fact, direct adhesive restoration with composite resins has become the procedure of choice for the treatment of anterior and posterior teeth. However, long-term durability of those restorations may be compromised due to progressive loss of the integrity of adhesive interfaces. This means that no adhesive strategy is free from technique sensitivity. The specificity and proportion of different constitutive molecules, the interaction between them and substrates can differ greatly from one class of adhesive system to another, which can affect bond quality. Protocol simplification has been an inevitable trend that has boosted the use of self-etching and universal systems in adhesive dentistry. However, there is a lack of randomized clinical trials to prove the effectiveness of these systems. This chapter gives an overview of the most important issues in dental adhesion and adhesive systems, as well, discussing their composition and clinical use.

Keywords: dental bonding systems, enamel, dentin, hybrid layer, durability

1. Introduction

The advent of adhesion to hard tissues of the tooth was a turning point and featured a new era in the dental field. Historically, adhesive systems are classified in ‘generations’ according to their chronological appearance on the market. Nevertheless, this nomenclature lacks objectivity, as it does not categorize adhesives according to strict scientific-based criteria, leading to confusion and misinterpretation if clinicians assume a hypothetical best performance of the last generations. One of the classifications that best characterizes adhesive systems scientifically is that proposed by Van Meerbeek et al. [1], as it considers their effect on the smear layer and the number...
of steps involved in their application. Currently, etch-and-rinse, self-etch and universal adhesive systems are the three main strategies to promote adhesion of composite resins to dental substrates [2–4]. Phosphoric acid continues to be the elective approach to optimize enamel surface conditioning, whereas the best approach to bonding on the dentin surface is still a controversial issue, mainly because of structural heterogeneity and higher hydrophilicity of dentin [2].

The quality and stability of adhesive interfaces in enamel and/or dentin play a major role in the long-term clinical success of composite resin restorations. Three-step etch-and-rinse adhesive systems have been shown to perform well in both laboratory and clinical assays and are still seen as the gold standard among bonding systems [1, 5–8]. The trend in bonding in recent years has been towards simplification by combining the primer and bonding agent, the conditioner and primer or even all three components into a single solution. All contemporary adhesive systems contain various specific molecules in their formulation that perform identical functions and therefore share the same basic bonding mechanism. This mechanism relies on the replacement of inorganic tooth material by resin monomers that, upon in situ setting, become micromechanically interlocked in the microporosities created in the substrate [1–3]. However, the molecular chemistry, specificity, proportion of the incorporated ingredients and their interaction with different tooth structures vary greatly between adhesive systems, which affects the quality of the bond achieved with each system [5, 7, 9].

Self-etch adhesives were developed to overcome several shortcomings of the etch-and-rinse approach, in particular, the susceptibility to variations in the degree of dentin moisture and the differential between deep demineralization and resin infiltration. Major concerns have been expressed in the literature regarding interfacial ageing due to degradation of the bonded interface [10–13]. Only two-step self-etch adhesives, mainly those containing the 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) monomer in their composition, have evidenced dentin bonding effectiveness similar to the gold standard three-step etch-and-rinse adhesives. This has been attributed to the chemical interaction potential that contributes to a more durable and stable bonding [14, 15]. Despite that, the quality and durability of adhesion to enamel using self-etch adhesives is still a controversial issue, particularly for those presenting mild acidity [3]. The latest one-step all-in-one self-etch systems have shown an inconsistent and tendentiously weaker adhesive performance that depends more on their specific formulation. These systems are alleged to have several drawbacks, especially regarding the high hydrophilicity, which makes them act as permeable membranes, allowing water movement across the adhesive layer [3, 5, 7, 9, 13, 16]. In spite of the compromised in vitro and in vivo findings associated with the one-step self-etch adhesives, simpler and faster-use adhesive materials have been developed, taking over a large fraction of the adhesive dentistry market. Besides, they have gained popularity among clinicians, regardless of the scarce proof of clinical efficacy.

A new group or generation of dental adhesives has been more recently introduced and were classified as universal or multi-mode adhesives. They are more versatile, giving the professional the opportunity to decide which adhesive strategy to use: etch-and-rinse or self-etch, since they can be adapted to a specific clinical situation. They are essentially based on the ‘all-in-one’ concept of the already existing one-step self-etch adhesives and can be used as self-etch
systems, in association with previous enamel and dentin phosphoric acid etching or combined with a selective enamel etching mode. The in vitro literature seems to suggest that bond strength is improved by the use of multi-mode adhesives with prior acid etching only for enamel; this effect was not evident for dentin with the use of mild universal adhesives [4]. More research is needed to study and compare those adhesives with those currently regarded as gold standards, as there is still very little clinical evidence available along with short follow-up periods.

The main challenge for current dental adhesives is to provide a bond that is equally effective for a range of dental substrates of different natures, such as enamel, sound, caries-affected or sclerotic dentin. From the clinical point of view, when bonding to both enamel and dentin, selective etching of enamel followed by the application of a mild 10-MDP-based two-step self-etch adhesive to both etched enamel and non-etched dentin would be the best option for an effective and more durable bond to the dental substrate.

### 2. Adhesion

The advent of adhesion to hard tissues of the tooth defined a turning point and featured a new era in dentistry. The substrates more frequently available for adhesion in restorative dentistry are enamel and dentin. These mineralized substrates present distinct ultra-morphology and composition. Regardless of depth or where it is located, enamel has a crystal, homogeneous structure mostly formed by hydroxyapatite (HAp) (96%wt/86%vol HAp; 3%wt/12%vol water; 1%wt/2%vol organic matrix) [17]. For this reason, enamel is considered to be a relatively static and predictable substrate regarding adhesive procedures. Conversely, dentin is a vital organic substrate, inherently hydrated and heterogeneous (70%wt/50%vol HAp; 12%wt/20%vol water; 18%wt/30%vol organic matrix—type I collagen) [18, 19], which makes adhesive procedures more complex when compared to enamel, depending mostly on its chemical composition, its level of moisture and regional morphological variation [20]. On the other hand, dentin suffers morphological and biomechanical changes related to physiological and/or pathological processes that involve alterations within its crystal and tubular structure, which cause changes to its permeability and its interfacial adhesion profile [21].

Adhesion reflects the capacity of a substance to adhere to another and may be the result of different processes, which can be mechanical, physical and/or chemical. Adhesive systems enhance interfacial strengths that aim at keeping organic solid substrates closely attached to the restorative materials such as composite resins [22]. The contact established between the substrate—enamel or dentin—and the adhesive depends on the level of the superficial wettability of the substrate by the adhesive, which is characterized by the contact angle formed when a drop of adhesive disperses on the substrate surface. The smaller the angle, the greater is the adhesive wettability. Thus, for the contact angle to come as close to zero degree as possible (which determines its spontaneous spreading), the surface tension of the liquid must be lower than the surface energy of the substrate, in this way ensuring a greater level of wettability between both components [23]. Compounds with high surface levels include very hard crystal
structures with strong intermolecular strengths, as is the case with enamel. Conversely, the presence of an organic material, such as collagen, saliva components or organic resins provides less surface energy to their structure, similar to dentin [23, 24]. Hence, according to these concepts, it can be understood that adhesive wettability is potentially easier with enamel compared to dentin.

Regardless of how the different adhesive systems work, they all have similar compounds. However, their relative proportion varies according to the different adhesive system classes. Overall, their basic composition contains acids, several monomers, organic solvents, polymerization initiators and inhibitors and, sometimes, some inorganic content, each having a specific function. Knowing the chemical properties of these components is fundamental in understanding the adhesive procedure as well as being able to predict its behaviour [9, 25]. Monomers are the most important components of an adhesive system, which is why they are considered as the key constituents of the system. Basically, two distinct monomer types can be distinguished: functional monomers, which generally exhibit hydrophilic properties and, according to the functional specific group, may workout distinct actions, such as increase the wettability of the substrate (e.g. hydroxyl ethyl methacrylate; HEMA); initiate tissue demineralization (e.g. phenyl-P); determine anti-bacterial properties (e.g. MDPB) [9, 25] and the cross-linking monomers with a hydrophobic profile which form the polymeric matrix of the adhesive responsible for its biomechanical behaviour and for its interaction and co-polymerization with the restorative material [9].

In 1955, Buonocore [26] pioneered and boosted the research in the adhesion field when he reported the successful use of 85% phosphoric acid to improve the mechanical retention of an acrylic resin on enamel, being considered the father of modern adhesive restorative dentistry. Gwinnett [27] was the first to analyse the adhesive interface on an electron microscope and reported the ability of the resin to penetrate into the prismatic irregularities of the enamel after acid etching, describing a new structure resultant from the hybridization of enamel and resin. In 1982, Nakabayashi et al. [28] showed that resins could also infiltrate phosphoric acid-etched dentine, forming a superficial structural layer composed of a demineralized dentine organic matrix infiltrated with resinous monomers, which they called a hybrid layer, providing a new insight into dentin bonding [28, 29]. Later, Van Meerbeek [30] described this structure in detail using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) and named it, the resin-dentin inter-diffusion zone.

The evolution of adhesive materials powered a change in the concept of cavity preparation based, nowadays, on a minimally invasive intervention coupled with maximal preservation of healthy dental structure [31]. Rotatory or manual instrumentation of the hard tissues produces organic and inorganic debris at their surface forming the so-called smear layer either in enamel (Figures 1 and 2) and dentin (Figures 3 and 4) [32–35]. On dentin, smear layer is a 1–2 μm adherent layer of debris composed of hydroxyapatite crushed aggregates, fragmented and denatured collagen, bacteria and their by-products [32, 34, 36]. Contiguously, the debris also occluded the orifices of the dentin tubules, identified as smear plugs, which may extend into the tubule to a depth of 1–10 μm [34]. Pashley [32] attributed two conflicting features to the smear layer. On one hand, the smear layer could act as a natural cavity protector by
obliterating dentin tubules and reducing dentin permeability; on the other hand, it could present an obstacle to in-depth diffusion of monomers and hinder effective bonding of resins to substrates. Consequently, choosing between adhesive systems that remove or dissolve the smear layer is still one of the major discussion topics in adhesion.

Figure 1. SEM image of ground enamel where the surface appears very rough, with grooves and covered with smear layer.

Figure 2. SEM image of fractured enamel showing the surface with a thick smear layer (sagittal view).

Figure 3. SEM image of prepared dentin where the surface is covered with smear layer and tubules are obliterated.
2.1. Adhesion strategies

Classification of adhesives is mandatory to provide an overview of the current field. The classification that best characterize adhesive systems was proposed by Van Meerbeek et al. [1] in 2003, as it considers the interaction mode with the substrate and the number of clinical application steps. Nowadays, two main adhesion strategies are identified: etch-and-rinse adhesive systems, which remove the smear layer and self-etching adhesive systems, which dissolve and incorporate the smear layer. A new group of materials called universal or multi-mode adhesive systems has recently been marketed. The main feature of these systems is that they can be applied according to different adhesion strategies (Table 1).

<table>
<thead>
<tr>
<th>Category</th>
<th>Technique (generation)</th>
<th>Etch</th>
<th>Priming</th>
<th>Adhesive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etch-and-rinse (ER)</td>
<td>Three steps (4th generation)</td>
<td>Phosphoric acid 32–40%</td>
<td>Primer</td>
<td>Adhesive resin</td>
</tr>
<tr>
<td></td>
<td>Two steps (5th generation)</td>
<td>Phosphoric acid 32–40%</td>
<td>Primer + adhesive resin</td>
<td></td>
</tr>
<tr>
<td>Self-etch (SE)</td>
<td>Two steps (6th generation)</td>
<td>Acidic monomers + primer</td>
<td>Adhesive resin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One step (7th generation)</td>
<td>Acidic monomers + primer + adhesive resin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Universal (U)</td>
<td>ER 2 steps</td>
<td>Phosphoric acid 32–40% (E+D)</td>
<td>Acidic monomers + primer + adhesive resin (E+D)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SE 1 step</td>
<td>Acidic monomers + primer + adhesive resin (E+D)</td>
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<tr>
<td></td>
<td>Selective etching</td>
<td>Phosphoric acid 32–40% (E)</td>
<td>Acidic monomers + primer + adhesive resin (E+D)</td>
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</tr>
<tr>
<td></td>
<td>enamel + SE dentin</td>
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E: enamel; D: dentin.
2.1.1. Etch-and-rinse adhesive systems

Etch-and-rinse adhesive systems can be applied in three or two steps, always using an initial acid-etching phase on both enamel and dentin. In the three-step systems, the acid etching and rinse step is followed by the intermediate application of a primer and ends with the application of a hydrophobic resin. For the simplified two-step etch-and-rinse approach, primer and resin are combined in a single bottle, which is why they are also known as one-bottle systems. Dental substrate etching is traditionally carried out with a gel of phosphoric acid at concentrations that vary between 30% and 40% (pH = 0.1–0.4), which is first applied to enamel and then to dentin, for a period of no longer than 15 seconds on dentin and no less than 15 seconds on enamel [33, 37].

Figure 5. SEM image of an enamel surface conditioned with 36% phosphoric acid. Different etching patterns can be observed either with dissolution of prism boundaries or dissolution of prism cores.

Figure 6. SEM image of an enamel surface conditioned with 36% phosphoric acid, showing hydroxyapatite crystallites forming a highly porous surface.

Phosphoric acid etching removes both the smear layer and approximately 10–50 μm of the enamel surface, creating a porous area with increased surface energy and wettability
This enables fluid resin dispersion into enamel microporosities by capillary attraction, forming macro and micro resin tags after polymerization. The macro-tags of resin fill the spaces around the enamel prisms, while the countless micro resin extensions cover each hydroxyapatite crystal individually. These micro-tags are probably the main contributors for enamel adhesion considering that they are numerous and provide a wide surface for adhesion. The enamel structure and composition are relatively homogenous regardless of the depth and location, the reason why it is considered a static and predictable substrate regarding adhesive procedures.

**Figures 5 and 6** [35, 37–41]. This enables fluid resin dispersion into enamel microporosities by capillary attraction, forming macro and micro resin tags after polymerization [35, 38–40]. The macro-tags of resin fill the spaces around the enamel prisms, while the countless micro resin extensions cover each hydroxyapatite crystal individually. These micro-tags are probably the main contributors for enamel adhesion considering that they are numerous and provide a wide surface for adhesion (Figures 7 and 8) [1, 35, 38, 39]. The enamel structure and composition are relatively homogenous regardless of the depth and location, the reason why it is considered a static and predictable substrate regarding adhesive procedures [20].

**Figure 7.** SEM image of an enamel interface formed with a three-step etch-and-rinse adhesive, showing intra-prismatic resin-penetration and intra-crystallite impregnation.

**Figure 8.** Confocal laser scanning microscope image of an enamel interface formed with a two-step etch-and-rinse adhesive, showing intra-prismatic resin penetration.

Etching dentin surfaces with phosphoric acid leads to a complete removal of the smear layer and demineralizes the inter-tubular dentin from 3 to 5 μm deep, leaving a tridimensional microporous mesh of collagen fibrils exposed, practically devoided of hydroxyapatite and randomly arranged. It also removes the smear plugs, dissolves the peritubular dentin and...
opens the dentin tubules, which acquire a funnel shape, showing the collagen fibrils arranged in circles on the tubule walls. Intra-tubular demineralization can exceed the depth of the inter-tubular one reaching 6–7 μm in depth (Figures 9 and 10). Accordingly, as the inter-tubular distance decreases, deeper demineralization of dentin is expected [2, 24, 30, 33, 42, 43].

Figure 9. SEM image of a dentin surface conditioned with 36% phosphoric acid, showing complete smear layer removal and open dentin tubules.

Figure 10. SEM image of a dentin surface conditioned with 36% phosphoric acid, showing a detailed view of demineralized open tubules.

After dentin etching, practically the whole mineral content (~50 vol%) of the surface and subsurface is solubilized, removed and replaced by water. The addition of this water to the volume of water that is originally a part of this dental tissue (~20 vol%) results in a total of ~70 vol% of water that is dispersed around the 30 vol% of the collagen fibrils that remain anchored to the subjacent mineralized dentin. Literally, this leaves a collagen scaffold suspended in water [2]. The exposed collagen acts like a mesh with nanometric-size porosities of about 10–40 nm, that should be able to mechanically retain the fluid resin upon in situ polymerization [2, 44–46]. In fact, demineralized dentin becomes a highly hydrophilic substrate of difficult clinical manipulation regarding adhesive procedures, as these materials are extremely sensitive to the presence of water [12, 33, 47–49].
For etch-and-rinse adhesive systems, one of the more delicate steps relates precisely to the acid etching, rinsing and the drying phase [45]. After the acid is rinsed off, the procedures to dry the tooth should allow a low level of humidity at enamel while keeping the dentin hydrated to optimize the adhesion process. However, this is a difficult clinical task to achieve. Dehydration of the demineralized dentin leads to the collapse of the exposed collagen mesh, reducing or nullifying the spaces between the fibrils and preventing them from acting as channels through which monomers may penetrate and spread within [24, 44, 46].

The main aim of the priming step is to alter the hydrophilic dentin surface into a hydrophobic phase, which will ensure an increase on the dentin surface energy making this substrate an adequate receptor of the subsequent hydrophobic bonding resin, allowing a better wettability and efficient penetration in the exposed collagen network [42]. The primers, adhesion-promoting agents, contain amphipathic monomers dissolved in organic solvents such as acetone, alcohol and/or water. These monomers have hydrophilic properties with affinity for the exposed collagen fibrils and hydrophobic properties to enable co-polymerization with the adhesive resin [9, 23, 25]. The hydroxyl ethyl methacrylate (HEMA) monomer is the most frequently incorporated in primers. Its low molecular weight together with its hydrophilic nature not only enhances dentin wettability, but also potentiates re-expansion of the collagen network, improving bonding capacity of adhesive systems [46]. Furthermore, it enables dispersion of hydrophobic monomers as it keeps them in solution [9, 25, 46, 50].

For etch-and-rinse adhesives, the wet bonding technique is recommended as a routine procedure essential for dentin bonding [51], particularly important when primers containing acetone as a solvent are used [45, 51–53], as acetone molecules are incapable of establishing hydrogen bonds and encourage collagen re-expansion [46, 51, 54]. This technique consists of leaving the dentin moist in the post-conditioning phase, preventing the collapse of the collagen network, which is crucial in ensuring a suitable infiltration of the adhesive monomers throughout the nano-sized voids in the organic mesh [44, 46]. For this, excess water in the cavity must be removed with a dry sponge or a short air blast [55]. However, perception of how moist the dentin must be kept to ensure complete removal of water afterwards by solvents is quite ambiguous [45, 56]. If dentin presents an over-wet condition, excess water determines phase separation of the hydrophobic and hydrophilic components, resulting in the formation of blister and resin globules at the resin-dentin interface. This potentially weakens the resin-dentin bonds and is particularly more concerning when simplified systems are applied [47, 52, 55, 57]. On the other hand, when the dentin surface is excessively desiccated, the collapsed and altered collagen structure determines an incomplete inter-tubular resin infiltration. Interfaces are characterized by infiltrated areas along the dentinal tubules and superficially, forming a very fine hybrid layer delimiting an incompletely infiltrated sub-superficial hybridoid region, rich in collagen and susceptible to premature breakdown [47, 52, 53, 55].

The solvents should be able to displace all the water trapped within the collagen network on dentin, allowing monomers to inter-diffuse completely along the surface demineralization depth [9, 25, 55]. In order to optimize this process, the primer must be in contact with dentin for at least 15 seconds before drying [58, 59]. In addition, the primer should be actively rubbed on the dentin surface with disposable brushes to improve monomer inter-diffusion and solvent
evaporation, as an increase in mixture entropy and moieties kinetics is expected to occur [56, 60]. Afterwards, to complete primer application, a gentle air blast must be applied to promote evaporation of the remaining solvent. Nevertheless, the diffusion of monomers through the hydrated collagen decreases water vapour pressure, which may hinder its effective volatilization [9, 46]. Actually, the clinical time spent in this step seems insufficient to establish an effective solvent volatilization, even when a longer time period is allowed [61, 62]. Consequently, the residual presence of solvents associated with the centrifugal movement of dentinal fluid within the monomer hypertonic solutions may reduce the amount of monomers infiltrated in the collagen network. This may increase permeability of the adhesive layer and impair the conversion process of the monomers leading, ultimately, to the formation of more fragile and permeable polymers [2, 63, 64].

In three-step etch-and-rinse systems, an independent coat of a hydrophobic adhesive resin is applied to complete bonding procedure. In the simplified two-step systems, at least two layers of primer/bonding agent should be applied, whereby the first acts as a primer and the latter as bonding resin [2]. The diffusion of the adhesive resin throughout the inter-fibrillar collagen channels enables it to be micromechanically retained by hybridizing the inter-tubular dentin and tubule walls (Figures 11 and 12). This interpenetration enables a mixed structure to be formed, the hybrid layer, which is 4–6 μm thick and where collagen fibres and hydroxyapatite crystals become surrounded by a resin matrix, which is the main bonding mechanism to dentin [1, 24, 30, 40, 65, 66]. Funnel-shaped resin tags result from tubule wall hybridization, but their importance in the bonding process is a matter of speculation [66]. In fact, there is a drop in bond strength values in deep dentin where the number and size of tubules is greater and inter-tubular dentin occupies a minor fraction of the total bonding area [65, 67].

Figure 11. SEM image of a dentin interface formed with a two-step etch-and-rinse system, showing the hybrid layer along with a wide number of resin tags.

In theory, the hybrid layer and resin tags should be extended to the same depth to which dentin demineralization occurred as a result of the acid etching step. However, even considering clinical procedures that prevent acid over-etching or collapse of the collagen network, an incomplete in-depth infiltration of dentin is often observed [2, 12, 47–49, 68]. This may be related to a combined interaction of factors, such as the presence of a superficial amorphous
phase at the demineralized dentin surface; the parallel arrangement of the collagen fibrils in relation to the surface and the presence of highly hydrated proteoglycans forming hydrogels in the spaces between fibrils [69]. These hydrogels act as filters for the molecules with a high molecular weight, such as dimethacrylates (Bis-GMA), allowing only smaller molecules such as HEMA to impregnate to a deeper level. In these conditions, the presence of linking monomers can be more restricted to the topmost part of the hybrid layer and, contrarily, its lower portion forms a more hydrophilic layer, susceptible to deterioration [2]. Indeed, the presence of a thin layer of water or hydrogel between the infiltrated bonding resin and the collagen fibrils, which are responsible for the formation of a hydrated network, was identified upon the use of the moist or water wet bonding technique (WWB). This hydrated network connects the resin tags to the base of the hybrid layer through the lateral ramifications of the dentin tubules and can spread throughout the whole thickness of the hybrid layer [2, 48]. Thus, the presence of hydrogels around the collagen fibrils may be responsible both for an infiltration differential and for phase separation of bonding components. This can lead to the presence of nano-sized porosities on bonding interfaces, impairing monomer conversion and mechanical properties development of the adhesive layer [63, 64] and reducing, consequently, its stability [2, 12, 70].

**Figure 12.** SEM image of a dentin interface formed with a two-step etch-and-rinse system showing the characteristic funnel-shaped resin tags with lateral anastomosis.

Deficient infiltration of the adhesive monomers leaves a strip of the collagen network in the hybrid layer incompletely impregnated, especially in the deeper areas, forming a microporous area characterized by the presence of sub-micrometric voids. This leads to the creation of hybrid layers that behave as semi-permeable membranes allowing water movements throughout the bonded interface even after adhesive polymerization. Those water pathways can be identified using the ammoniacal silver nitrate tracer under electron microscopy. The staining geometry observed determines different possible nanoleakage patterns running from a spotted to a reticular array that follow the discrepancy between dentin demineralization and adhesive impregnation along the resin-dentin interface [68]. Increased nanoleakage expression is more frequently linked to the use of two-step etch-and-rinse systems comparing to the three-step ones as they contain higher percentages of hydrophilic monomers and act as semi-permeable membranes after polymerization [2, 12, 47–49, 68]. Invariably, the progressive degradation of
the polymers and collagen increases the level of nanoleakage, inducing the presence of more fragile interfaces, which, in the long term, can compromise the durability of restorations [11, 12, 14, 15, 70–74].

The transactional effects of the different nanoleakage patterns result in the chemical degradation of the adhesive interfaces which follow a sequence of different phenomena, including water sorption of the polymers and the hydrolytic and enzymatic degradation of the unprotected collagen by matrix metalloproteinases (MMPs) and by cysteine cathepsins, particularly cathepsin K [3, 12, 70, 75]. Initially, the water sorption process leads to a swelling of the polymer and to the plasticization of the resin component that breaks the polymeric chains by splitting the ester linkages forming, in consequence, oligomers and monomers [76]. The ongoing deterioration of the polymer structure over time determines a change in its nuclear microstructure due to the formation of pores whereby degradation products are released, leading to a reduction of the polymer mass, which determines its solubility [72]. This inherent increase in porosity facilitates the movement of molecules, fluids, bacterial by-products and MMPs into and out of its structure, leading to a cumulative cycle of the water sorption rate and monomeric elution, which compromise polymer properties and the structural stability of the adhesive interface. Also, monomeric elution within the hybrid layer progressively exposes the collagen fibrils, which also become vulnerable to mechanical and chemical fatigue. Collagen depletion further debilitates the hybrid layer as porosities enlarge from a nanometric to a micrometric sized scale [12, 72, 75, 77–80]. Under occlusal function, resin composites may bend and allow compression of the water-filled voids in the degenerating hybrid layer, accelerating adhesive interface degeneration [81].

Researchers have focused attention on different molecules capable to inactivate or inhibit the action of the MMPs, which are responsible for collagen solubilization. Of these molecules, chlorhexidine has currently been the most studied [3, 75], with in vivo reports showing its ability in reducing the effects of hybrid layer degradation when a 2% chlorhexidine solution is applied for 60 seconds on the phosphoric acid etched dentin, before using an etch-and-rinse type bonding system [78, 79, 82]. It is also noteworthy that this procedure does not interfere with the immediate bond strengths of etch-and-rinse systems to the dentin substrate [71, 79, 82]. Consequently, along with its important antimicrobial activity, the application of chlorhexidine on etched dentin slows down the degradation of the exposed collagen fibrils, conditioning a more stable bonding interface in the long term.

Recently, the ethanol-wet-bonding (EWB) technique has been described as an alternative method to the water-wet-bonding technique, previously referenced. EWB relies on moistening demineralized dentin with ethanol and promote immediate hydrophobic monomer diffusion into dentin. The key question that nurtured the development of the EWB technique was whether it was possible to keep the demineralized dentin matrix saturated in ethanol without the occurrence of a simultaneous collapse of the collagen fibril while enabling hydrophobic monomer infiltration. This possibility was undertaken due to the convergence of the solubility parameters found between the substrate (ethanol and collagen) and the monomers solutions, determining their miscibility. For that, no phase separation is prone to occur [46, 83]. It was also verified that the EWB technique would cause a contraction of the collagen fibrils’ diameter
greater than the contraction of the volume of the collagen matrix resulting in a concomitant increase of the inter-fibrillar spaces and, consequently, an increased efficiency of monomeric infiltration [46, 84]. Indeed, some studies showed that the EWB technique applied to dentin optimizes the monomeric infiltration rate, improves the collagen matrix sealing, reduces permeability of the polymerized bonding layer, and minimizes water sorption by polymers forming more stable and less permeable bonding interfaces over time [2, 48, 84–86]. Despite this, the EWB technique cannot be optimized in a useful clinical time, as increasing concentrations of ethanol applied for long periods are required to ensure adequate dehydration of dentin [46, 83, 85, 86]. Because of this, a few simplified protocols were presented by using a two-concentration sequence or only one single solution of absolute ethanol to accomplish the process [83–85]. Nonetheless, no clinical study has confirmed the superiority of the EWB technique compared to the WWB technique [87, 88].

2.1.2. Self-etching adhesive systems

In early 1990s, development of self-etching adhesives containing acidic primers as promoting monomers for direct bonding to the smear layer covered enamel and dentin introduced a new dental bonding technology [3]. These systems do not require a separate etching step as acidic monomers simultaneously etch and prime the dental substrate. Thus, all by-products arising from the demineralization process and from the dissolved smear layer become incorporated in the bonding interface [3, 45]. Self-etch adhesives simplified the bonding protocol as they require less operative steps and exhibit reduced technique-sensitivity, as the level of substrate moistness is no longer a critical issue of the bonding procedure [47, 89]. Also, as they do not fully remove the smear layer and the smear plugs, immediate surface rehydration secondary to dentinal fluid movement is prevented and reduced post-operative sensitivity is likely to occur [90, 91]. Another significant advantage pointed out to these systems relies in the fact that demineralization and infiltration phenomena take place simultaneously and to the same depth, which would ensure, theoretically, complete penetration of the adhesive leaving no sub-infiltrated demineralized areas [3]. However, interfacial nanoleakage identifying micro-porous areas within the hybrid layer have also been verified, rejecting the supposition of adhesive resin complete infiltration [10, 49, 50, 57, 89, 90, 92].

The composition of the self-etch adhesive systems is unique, as they contain high concentrations of water. They are basically formed by aqueous mixtures of acidic functional monomers (the so-called self-etching primers), generally phosphoric acid- or carboxylic acid-esters with a higher pH than that of phosphoric acid used in the etch-and-rinse bonding systems. Water acts as an ionizing medium for dissociation of acidic protons and dissolution of calcium ions, promoting the etching process, while preventing, simultaneously, the collapse of demineralized collagen fibrils [90, 93]. Other hydrophilic functional monomers and hydrophobic cross-linking monomers are also present in their formulation [3, 9, 25]. Co-solvents, such as ethanol or acetone are frequently added to form an azeotropic mixture with water in order to promote solvation of hydrophobic moieties and to ensure proper thinning, spreading and dentin wettability [25, 93, 94].
HEMA is a frequently added monomer as it is a low molecular weight water-soluble monomer that improves the miscibility and solubility of the polar and non-polar adhesive components. Besides, HEMA can also stabilize the collagen fibril network, improving the dentinal permeability, wettability and monomer diffusion [25, 50]. However, the presence of HEMA further increases the hydrophilic nature of self-etch adhesives, which encourage water uptake. Some studies have concluded that HEMA-rich systems attract water from the underlying dentin thanks to an osmotic time-dependent process, inducing the presence of water droplets on the surface of the adhesive layer that behaves as a semi-permeable membrane [47, 57, 92]. Those droplets can reduce the monomer conversion rate, weakening the mechanical strength of the adhesive and potentially jeopardizing bond durability [63, 64]. Thus, for HEMA-rich adhesives immediate light curing of the lining composite should be performed as soon as possible before water droplets arise at the adhesive surface. It was shown that delayed curing influenced bond strength adversely [57, 92]. HEMA-free self-etching adhesives were also developed. However, another problem has been detected related to a phase separation process. Once ethanol/acetone starts to evaporate, the solvent-monomer balance is broken, with water separating from the other adhesive components. This is particularly more critical in acetone-based adhesives as acetone volatilizes faster and severe changes in the water/acetone ratio are likely to occur [25, 50, 90, 95]. This phenomenon was easily identified using light microscopy by dispensing a drop of adhesive onto a glass plate. As the co-solvent starts to evaporate, many small water droplets start gradually to emerge in the adhesive layer. Spontaneous disappearance can happen, but takes several minutes and entrapment of the droplets upon light curing becomes more likely. This can compromise bond strength and increase interfacial degradation susceptibility [45, 50, 89, 96]. Thus, a very strong air-drying step is highly recommended for this kind of adhesives in order to blow the droplets out, leaving only a thin layer of bonding resin [45, 50], although this prerequisite is a less ambiguous instruction than ‘gentle air-drying’. This procedure seems effective on flat surfaces, but eliminating these droplets in the more complex cavity geometries may prove more difficult [3, 45, 50].

Self-etch bonding systems are classified as two-step and one-step adhesives. The two-step self-etching systems are based on the separate application of a hydrophilic self-etching primer followed by a hydrophobic bonding resin. One-step self-etching systems can be further subdivided into one- or two-component adhesives. In two-component systems, functional monomers are separate from water, increasing adhesive shelf life and hydrolytic stability, but additional and adequate mixing of both components is mandatory before clinical application. Single-component systems, also known as all-in-one adhesives combine all ingredients related to the acidic, priming and bonding functions into a single bottle [3, 45, 96]. This last group of one-step adhesives exhibits a complex mixture of hydrophilic and hydrophobic components that accounts for major shortcomings of the adhesion protocol [45, 89, 96].

The great variability reported to the performance of different self-etching adhesive systems can be attributed to several characteristics related to their composition and, particularly, to some properties of the functional monomers with respect to its acidity, hydrolytic stability and chemical interaction ability [5, 7, 9]. The composition and concentration of acidic resin monomers establish differences in the acidity and aggressiveness of self-etching systems and
determine their effect on smear layer dissolution and demineralization ability on ungrounded and ground enamel and dentin, determining distinct bonding interfacial ultra-morphology [3, 40, 41, 45, 47, 97–99]. Aggressiveness depends on the pH of the solution and self-etch systems can be categorized according to their pH into ultra-mild (pH > 2.5), mild (pH = 2), intermediately strong (pH between 1 and 2) and strong (pH ≤ 1) (Figures 13 and 14) [3]. As acidic monomers diffuse in depth they are gradually buffered by the mineral content of dental substrates, loosing progressively their etching ability [10, 94, 100].

Figure 13. SEM image of a dentin surface conditioned with an ultra-mild two-step self-etch adhesive, showing a lightly dissolved smear layer and obliterated tubules.

Figure 14. SEM image of a dentin surface conditioned with an intermediately strong one-step self-etch adhesive, showing incomplete smear layer dissolution and partially open dentin tubules.

Like etch-and-rinse systems, all self-etch adhesives warrants the three main bonding stages: etching, priming and bonding, ensuring micromechanical interlocking of resin monomers upon polymerization and consequent tissue hybridization [1, 3, 45]. Furthermore, some functional monomers evidence an additional chemical interaction potentiality with calcium hydroxyapatite, which seems to improve bond durability [3, 101–103]. In fact, functional acidic monomers as 10-MDP, phenyl-P or 4-MET are able to establish ionic bonds between their functional groups (phosphate, phosphonic or carboxylic group) and calcium of hydroxyapatite, but with different behaviours in accordance to the adhesion-decalcification concept [101].
According to this model, all acids are able to establish a chemical bond with hydroxyapatite calcium, but whether the produced molecule will remain bonded or will debond depends on the stability of the formed calcium salt, that is inversely related to the monomer acidity. Although phenyl-P, 4-META and phosphoric acid molecules strongly interact with calcium, the instability of the calcium phosphate/carboxylate compound formed implies ready debonding, resulting in a moderate to severe decalcification effect. On the contrary, 10-MDP forms a stable calcium-phosphate salt along with a shallow demineralization of the surface [101, 103].

Figure 15. SEM image of a dentin interface formed with an ultra-mild two-step self-etch adhesive, showing the hybrid layer along with short cylindrical resin tags.

Figure 16. SEM image of a dentin interface formed with a strong one-step self-etch adhesive, showing a thick hybrid layer along with enlarged resin tags.

Ultra-morphological interfacial characteristics produced by self-etching systems depend both on their acidic aggressiveness and on their formulation. In general, strong self-etching systems with a more acidic pH, equal to or lower than 1, are associated with a high demineralization depth, determining an etching pattern typically approaching that of phosphoric acid. At the dentine level, a collagen mesh practically devoided of hydroxyapatite can be found. After micromechanical adhesive interlocking, a 2–5 μm thick hybrid layer is produced along with
resin tags, whose ultra-morphological features are very similar to those provided by etch-and-rinse systems. The demineralization action of intermediately strong self-etching systems, with a pH ranging from 1 to 2, allows the identification of two zones; a superficial one with complete dentine demineralization and a partially demineralized basal zone. The latter retains some mineral or hydroxyapatite content with the ability to form chemical bonds with functional monomers. Mild and ultra-mild self-etching adhesive systems, with a pH higher than 2, were shown to demineralize dentin only partially and superficially, leaving part of the smear layer and smear plugs intact and a substantial amount of hydroxyapatite crystals around collagen fibrils, keeping them encapsulated and protected. Still, their 0.2–1 μm demineralization depth creates a microporous dentin surface capable of micromechanically retaining adhesives through a hybridization process. However, the resulting hybrid zones show much lower thicknesses than those obtained by strong and intermediately strong self-etching systems or etch-and-rinse systems (Figures 15 and 16) [1, 3, 40, 45, 47, 65, 97–99]. On the other hand, hydroxyapatite within the hybrid layer act as a receptor for the additional chemical adhesion process [3, 101, 103].

![Figure 17](image)

**Figure 17.** SEM image of an enamel surface conditioned with a mild two-step self-etch adhesive, showing a shallow inter-prismatic etching effect.

One of the greatest challenges of using self-etching systems relates to their effectiveness on simultaneous adhesion to enamel and dentin [3]. Generally, more acidic self-etching systems have the ability to completely dissolve the smear layer and their depth of demineralization into the enamel is similar to that of phosphoric acid. Instead, as the acidic degree of the systems decreases, morphological features on enamel surfaces become shallower providing enamel etching patterns less homogenous, especially with mild and ultra-mild systems (Figures 17 and 18) [38–41, 104–106]. Additionally, enamel-resin interfaces of less acidic systems have also proven to form thinner and relatively non-uniform hybrid layers with scarce and poorly defined inter- or intra-prismatic resin extensions, when compared to more acidic systems (Figures 19 and 20) [35, 38, 39, 41, 106]. Since enamel contains a high mineral fraction and larger hydroxyapatite crystals than dentin, and because the demineralization potential of self-etching systems is more limited than that provided by phosphoric acid, it is possible that more hydrogen ions released from the adhesive are neutralized by the enamel smear, limiting their interaction with the subsurface enamel [35, 94, 100]. Different studies reported the unpredict-
ability of the performance of self-etching adhesives in intact enamel, presenting evidence that previous mechanical preparation by grounding enamel can potentiate the adhesion capacity of these systems [38, 98, 107–110]. Also, the use of a selective enamel etching approach with phosphoric acid in intact or ground enamel seem to increase the enamel adhesion potential of these systems [111–114].

Figure 18. SEM image of an enamel surface conditioned with an intermediately strong one-step self-etch adhesive, showing a moderate inter- and intra-prismatic etching effect.

Figure 19. SEM image of an enamel interface formed with an ultra-mild two-step self-etch adhesive, showing a very superficial resin-impregnation within demineralized enamel along with a thick layer of adhesive.

In order to increase the acidity of adhesive solutions, the contents of acidic monomers and water is increased, which make stronger self-etch systems with increased hydrophilicity, leading to higher water sorption, and consequently, decreased hydrolytic stability [96]. Several studies have shown that despite more acidic self-etching systems exhibit a good bond ability to enamel, they invariably behave much worse at the dentine level, in spite of forming thick hybrid layers. Notwithstanding, a similar performance was reported for many less acidic systems, especially single-step systems. Although it has been claimed that discrepancies between the depths of demineralization and resin infiltration should not occur with self-etching systems, silver nitrate staining has been reported along resin/dentin interfaces
produced by these systems, thereby challenging the original concept that no pathways for water movement would be present. More relevant in all-in-one systems, the resin/dentin interface function as a permeable membrane that allow water movement across the adhesive layer even after polymerization. Nanoleakage expression occurs within voids left in un-infiltrated areas of the hybrid layer, but also within the adhesive layers as water trees and water droplets, which have been linked with incomplete water and/or solvent removal and/or water sorption from the underlying hydrated dentin. Over time, bond strength and stability is invariably compromised [10–12, 14, 15, 47, 49, 50, 57, 72–74, 89, 90, 92, 98]. For many of these systems, nanoleakage expression have also been identified at the base of the hybrid layer, suggesting that mineralized dentine underlying the hybrid layer may undergo structural changes secondary to the adhesive procedure, becoming porous enough to retain water. This may be due to the progressive buffering of acidic monomers by the substrate, which gradually loses their etching ability. This may result in an increasingly irregular and sparse demineralization in depth, creating smaller open inter-fibrillar spaces at this level. These spaces may contain dissolution by-products, such as hydrolytically unstable calcium salts [100–102] that act as molecular sieves, preventing infiltration of higher molecular weight resin monomers and making deep areas more hydrophilic [10, 89]. Furthermore, accumulation of unpolymerized acidic monomers in this area due to the presence of water (either from the dentin substrate or from the adhesive system itself) may result in their hydrolysis, forming acidic reaction by-products, which may play an important role in subsequent dentin demineralization once the hybrid layer is formed [10, 92, 115].

Figure 20. SEM image of an enamel interface formed with an intermediately strong one-step self-etch adhesive, showing a moderate inter- and intra- prismatic resin-impregnation within demineralized enamel.

Similar to etch-and-rinse adhesive systems, for self-etching systems, the literature also favours systems applying a hydrophobic adhesive resin as an individualized step, that is, two-step self-etching systems. However, unlike three-step etch-and-rinse systems, which invariably report good clinical and laboratory outcomes, making them the gold-standard in adhesion, two-step etch systems report varying degrees of efficacy, mainly due to their different level of acidity and hydrophilicity. Still, applying a hydrophobic adhesive resin in an independent step is usually associated with higher bond strengths and hydrolytically more stable interfaces than
simpler systems containing a mixture of both hydrophobic and hydrophilic components [9, 11, 49]. In fact, one-step self-etching adhesive systems create thinner adhesive films, which is why their application in two or more layers or employing an additional single-step application of a hydrophobic resin was shown to improve their performance regarding bond strength and interface stability [80, 116, 117]. The application mode of self-etching systems on dental substrates can also influence its performance. Some studies have shown that active application of the acidic self-etching system primers can improve adhesion to dentin and enamel by improving depth of demineralization, infiltration and chemical interaction as it promotes a more effective contact of monomers at the surface [74, 106, 118].

Although adhesive classification by categories regarding their clinical application is convenient and internationally accepted, adhesive behaviour depends much more on its composition and functional monomer specificity than on the category to which they belong [3, 5, 7, 9]. In fact, dentin bonding optimization with self-etching adhesive systems is associated with the presence of the 10-MDP monomer. This molecule has become the most promising acidic functional monomer for bonding, as it establishes readily and intensively an ionic bond with hydroxyapatite calcium and form a regular nano-layered structure on the dentin surface, within which calcium salts are deposited. The potentiality to chemically interact with interfacial hydroxyapatite is preponderant to achieve bond durability. The 10-MDP monomer was originally synthesized and patented by Kuraray (Osaka, Japan). The good in vitro and clinical outcome of the two-step self-etching systems containing 10-MDP, namely the Clearfil SE Bond and Clearfil Protect Bond, both developed by Kuraray may be partly attributed to the intense chemical adhesion established with tooth tissue [7, 15, 40, 89, 119–124]. Also, an acid-base resistant zone (ABRZ) formed beneath the hybrid layer after acid-base challenge was reported. Densely packed crystallites suggest that a hypothetical chemical reaction of hydroxyapatite and 10-MDP may take place in this area, enhancing resistance against demineralization from acid attack, which might play an important role in the prevention of secondary caries [125, 126].

Kuraray no longer holds the patent for 10-MDP, and many other manufacturers started to incorporate it into new adhesive formulations, including in many of the currently so-called universal or multi-mode systems [127–132].

2.1.3. Universal adhesive systems

It is clear that the trend in adhesive technology is to simplify bonding procedures by reducing application steps, shortening clinical application time and improving standardization [129]. Aiming at providing a single product for all situations, universal or multi-mode adhesive systems have been recently introduced and can be applied either with the etch-and-rinse or the self-etch mode. This multi-approach capability enables the clinician to apply an adhesive with the so-called selective enamel etching technique, which combines the advantages of an etch-and-rinse technique on enamel with a simplified self-etch approach on dentine [4, 132, 133].

The majority of universal adhesives are designed under the ‘all-in-one’ concept of the existing one-step self-etch adhesives, thus requiring water in their formulation to ionize hydrophilic acidic monomers [96]. Concerning etching capability, most universal adhesives present a ‘mild’
or ‘extra-mild’ profile [134]. It has been shown that adhesives within this pH range can be effective in bonding dentin. However, there is high concern about their behaviour when bonding to enamel [4]. Most often, phosphate esters are their primary functional monomer. Due to the high reported performance of the 10-MDP monomer, this specific molecule has been incorporated in a wide range of adhesives in this class. The 10-MDP molecule is an amphiphilic functional monomer with a long carbon chain backbone, which renders it fairly hydrophobic [9]. Additionally, stable MDP-calcium salts deposited in self-assembled nanolayers at dentin surfaces help to explain its high bond stability [103].

At present, there is only sparse literature reporting on the clinical efficacy of universal adhesives with short-term follow-ups. \textit{In vitro} studies indicate that these adhesives show similar adhesive performance in dentin, regardless of their application mode: etch-and-rinse or self-etch. However, when the self-etch mode is performed a more superficial interaction might reduce the risk of post-operative sensitivity and delay the inevitable degradation phenomenon, as chemical interaction is likely to occur [4, 129, 135]. Concerning the enamel substrate, the literature suggests that selective etching prior to the application of a mild universal adhesive is an advisable strategy to optimize bonding [4, 132, 135–137]. Nevertheless, the clinical use of phosphoric acid only on enamel margins without accidentally reaching dentin is challenging, especially if low-viscosity etchants are used.

After all, the increased versatility of universal adhesives has not followed the technological advances, which could help to overcome the flaws associated with previous generations of adhesives. Currently, adhesives with effective bioactive behaviours are still lacking [138]. In fact, a larger quantity of solvents and hydrophilic monomers in those adhesive formulations leads to a greater number of residual solvents to be entrapped in the adhesive layer, which may reduce dentin bond strengths, and increase the permeability of the adhesive layer after polymerization, reducing stability over time [129, 130]. Therefore, likewise one-step self-etch adhesives, several modified application techniques to overcome these problems are being evaluated, such as extending solvent evaporation time, applying adhesives actively with extended times on enamel, and placing an additional hydrophobic resin coating to optimize bonding [137, 139–142].

2.2. Research in adhesion

The limited durability of restorations mainly results from exposure of adhesive interfaces to the oral environment. These interfaces are permanently subjected to mechanical, chemical and/or thermal stimuli that can compromise its longevity in the short, medium or long term. The action of occlusal forces on adhesive interfaces as a result of a cumulative effect of masticatory cycles may induce tensions exceeding interfacial fracture toughness. This will determine a site for failure initiation, which can in turn, act as a local point of increased stress concentration, contributing to the progression and spread of the initial failure [13]. Temperature oscillations in the oral cavity may also induce repetitive contraction and expansion stresses at the tooth/resin interface, caused by differences between their thermal expansion coefficients. Such stresses may exacerbate the occurrence of interfacial cracks [143]. Additionally, biochemical hydrolytic and enzymatic breakdown can also potentiate interface degradation mechanisms,
in which both polymeric components and of collagen are enrolled. Finally, stresses developed during polymerization shrinkage of composite resins may also influence in adhesive interface failure [12, 13, 70].

The popularity of laboratory studies on adhesion is mainly associated with the speed with which new materials are emerging on the market, without a proper clinical evaluation of precursor systems, particularly in medium and long-term studies [6, 144]. Although in vitro studies cannot anticipate or replace results from clinical studies, they are an important step to compare and rank the adhesion potentiality. On the other hand, they are also useful to analyse distinct application variables that could hardly be tested in clinical studies due to both methodological details and ethics [7, 13, 145–148].

Currently, bond strength determination, micro-leakage assessment, quantitative marginal sealing evaluation and adhesive interfacial qualitative analysis are the most relevant experimental means to assess the performance of adhesive systems, particularly when associated with sample ageing methods [7, 145]. In vitro adhesion durability can be tested using different artificial ageing modes, namely water storage, thermal fatigue, mechanical fatigue, thermomechanical fatigue, enzymatic/chemical degradation among others [7]. However, most of these methods only mimics one of the factors involved in in vivo interfacial degradation, where all usually operate simultaneously [70]. Bond strength evaluation is a relatively simple method that allows testing different materials and/or techniques in a process where adhesive interfaces respond to an acute load. Dynamic experimental tests can potentially provide more relevant and realistic information to predict an adhesive behaviour, particularly when combined with complementary ageing procedures. Nevertheless, these methods demand considerably more technological investment and are time-consuming [7, 13, 16, 148–151].

Currently, one of the major issues discussed among researchers relates to the validation of in vitro tests results in order to determine whether they can correlate positively with clinical performance of adhesive restorations, i.e. to what extent is it possible to make clinical inference from the results of in vitro studies? In fact, several studies have evidenced that clinical results could be, in a very limited way, predicted by laboratory results [7, 145, 147, 148].

2.3. Adhesive protocols for clinical application: key steps

2.3.1. Etch-and-rinse systems

The three-step etch-and-rinse adhesive systems are considered as the gold standard for bonding to enamel and dentine because of their excellent performance in both in vitro and in vivo studies [1, 5–8].

Enamel etching by means of phosphoric acid results in a pattern of regular, deep demineralization with the overall production of interfaces with intensive inter- and intra-prismatic adhesive penetration along high and durable enamel bond strengths, which accounts for long-lasting clinical enamel marginal adaptation. Therefore, enamel conditioning with phosphoric acid is still considered as the gold standard procedure to optimize adhesion to this substrate [1, 3, 105, 120, 149, 150, 152].
However, resin-dentin interfaces proved to be much more unstable when etch-and-rinse adhesives are used. Dentin hybrid layer undergo degradation with time, more important for the two-step systems, even when ensuring an adequate enamel seal [11, 15, 71, 73, 78–80].

**KEY STEPS:**

**Do not etch dentin for more than 15 seconds** [33, 37, 44].

*Why?* Longer exposure of phosphoric acid on dentin can cause collagen denaturation and increase the demineralization depth, which can negatively affect the subsequent dentin hybridization process.

**Leave the dentin surface moist before applying primer (three-step) or adhesive (two-step), particularly when acetone-based systems are used** [46, 52–54, 153].

*Why?* Desiccation of the demineralized dentin leads to the collapse of the exposed collagen mesh, reducing or nullifying the spaces between the fibrils due to spontaneous establishment of inter-peptide hydrogen bonds. This reduces dentin permeability and monomer infiltration is hindered.

**In case of excessive dentine desiccation, surface rehydration is mandatory and should be performed with water** [46, 54].

*Why?* Water is a strong polar protic solvent and it has been shown to be the most efficient solution in the re-expansion of collapsed collagen.

**Actively apply the primer/adhesive solution for at least 15 seconds to the demineralized dentin** [56, 58–60].

*Why?* This is the time needed to allow solvents to act as water-chasers. Active application improves monomer diffusion and solvent evaporation before the light-curing step.

**Promote extended solvent evaporation time** [56, 58–60, 154–156].

*Why?* The residual presence of solvents reduces the amount of infiltrated monomers in the collagen network and impairs monomer conversion.

**For two-step etch-and-rinse adhesives, place two or more coats of the primer/bonding solution and polymerize each separately** [2, 61, 62, 64].

*Why?* The second layer act as a bonding resin and increases the thickness of the adhesive layer. This produces an area of greater flexibility and elasticity that can absorb some of the shrinkage stresses raised during composite resin polymerization.

### 2.3.2. Self-etch systems

Two-step self-etch adhesive systems, particularly those containing 10-MDP in their composition, are considered as the gold standard when it comes to bonding dentin, because of their excellent performance in both *in vitro* and *in vivo* studies [7, 15, 40, 89, 119–124].

However, the behaviour of self-etching systems largely depends on their composition, aggressiveness and hydrophilicity. Hence, even within the same category there is a wide
variability of the reported results regarding bond strength and adhesion durability [1, 3, 5, 7–9].

KEY STEPS:

Etch enamel separately with phosphoric acid, particularly for mild or extra-mild self-etch systems [1, 5–8].

Why? As the acidic degree of self-etch systems decreases, morphological features on enamel surfaces become shallower providing enamel etching patterns less homogeneous and producing non-uniform hybrid layers with scarce and poorly defined inter- or intra-prismatic resin extensions. Phosphoric acid increases the efficacy of self-etching systems in bonding to the enamel, which is particularly more important in unground or intact enamel.

Apply self-etch adhesives by actively scrubbing them vigorously onto the surface [38–41, 104, 105].

Why? Active rubbing improves bonding performance to enamel and dentin as it promotes solvent evaporation, depth of demineralization, infiltration and chemical interaction due to a more effective contact of monomers with the surface.

For one-step self-etch adhesives, apply more than one adhesive coat and/or place a separate hydrophobic coating resin [74, 106, 118].

Why? Applying a greater number of layers and/or the extra placement of a hydrophobic resin in a single step has been found to improve the laboratory performance of these systems regarding bond strength and interface durability.

For HEMA-rich systems, promote accelerated composite resin build-up and polymerization [80, 116, 117].

Why? HEMA-rich systems exhibit enhanced capacity for water absorption from the underlying dentine. This is due to a time-dependent osmotic process that induces the presence of water droplets on the surface of the adhesive layer. Clinically, polymerization of the first composite resin increments must take place in the shortest time possible.

For HEMA-free systems, promote strong air-drying of the adhesive surface [47, 57, 92].

Why? Systems without HEMA undergo phase separation after solvent evaporation (ethanol/acetone) and droplets of water gradually rise to the surface and can be retained if adhesive polymerization starts immediately. Clinically, a strong air-drying step is highly recommended in order to blow the droplets out, leaving only a thin layer of bonding resin.

2.3.3. Universal systems

In essence, universal adhesives are single bottled, no mix all-in-one systems with a ‘mild’ or ‘extra-mild’ etching profile provided by acidic functional monomers. They present broader applications and can be used under different bonding strategies, adapting the most appropriate to each specific clinical situation. However, increased versatility of universal adhesives has
not followed the technological advances, which could help to overcome the flaws associated with previous generations of adhesives [25, 45, 50, 89, 90, 95, 96].

**KEY STEPS:**

**Etch enamel selectively with phosphoric acid** [129, 130, 138].

*Why?* The low acidity of most of these systems leads to a very superficial enamel demineralization pattern and phosphoric acid increases the efficacy in bonding to this substrate.

**Use the self-etch mode to optimize dentin bonding** [4, 132, 135–137].

*Why?* Dentin etching with phosphoric acid demineralizes it extensively and may restrict the chemical bonding potential of hydroxyapatite calcium and the phosphate-based monomers.

**Increase solvent evaporation time** [4, 129, 135].

*Why?* Extended evaporation time reduces residual water and/or solvent and may improve the performance of universal adhesives.

**Apply the adhesives by actively scrubbing them vigorously onto the surface** [139].

*Why?* Active rubbing improves bonding performance to enamel and dentin as it promotes solvent evaporation, depth of demineralization, infiltration and chemical interaction due to a more effective contact of monomers with the surface.

**Apply a separate hydrophobic coating resin** [137, 142].

*Why?* The additional placement of a hydrophobic resin in a single step has been found to improve the laboratory performance of these systems regarding bond strength and interface durability.

### 3. Conclusions

Nowadays, dental adhesives are used for a wide range of clinical applications. Undoubtedly, the current concept of minimal-invasive dentistry was determined by a significant improvement in the dental adhesive technology. Nevertheless, the increasing development of different types of dentin/enamel adhesives creates uncertainty among clinicians about which type to use in daily practice for a specific clinical situation.

Not only is it mandatory to rigorously follow the recommended protocols for adhesive procedures due to their inherent technical sensitivity, but also it is critical to select the correct adhesive strategy as a function of the restorative materials to be used and the substrates taking part in the process. Etch-and-rinse adhesive systems perform better on enamel and two-step self-etching systems containing 10-MDP seem to be more suitable for bonding to dentin. Therefore, an etch-and-rinse approach may be more appropriate to establish adhesion in cavities of anterior teeth, particularly in situations where enamel prevails over dentin. In posterior cavities, a selective enamel etching with phosphoric acid followed by the active
application of a 10-MDP-based two-step self-etch adhesive to both enamel and dentin is probably the better strategy to achieve, currently, optimal restoration durability.

Future perspectives in the adhesion field include the development of molecules or strategies to reduce the flaws of bonding systems that yield resin-dentin bonds prone to degradation. The use of therapeutic bioactive ion-releasing restorative materials that initiate nucleation and growth of the newly formed mineral within micro- and nano-sized voids is currently one of the main issues of research. Nevertheless, multicentric clinical studies should be encouraged to support incoming laboratory data, in order to point out if these new or modified approaches may effectively provide increased restoration longevity.

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