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Review

A Literature Review of Adhesive Systems in Dentistry: Key Components and Their Clinical Applications

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Abstract: The central aim of adhesive dentistry is to improve the compatibility between current adhesives and a range of substrates by employing diverse application techniques. Therefore, the overarching objective of this review is to offer a comprehensive analysis of dentin bonding systems, starting with an introduction to adhesion and a detailed overview of enamel and dentin structures, their histology, and the impact of dentin structure on resin–dentin bonding. It covers the mechanisms of resin–dentin bonding, including resin adhesive application, bonding mechanisms, and factors influencing efficacy. Further, this review explores the composition of resin adhesive systems, including acidic components, cross-linking monomers, solvents, and other critical elements. It also examines various adhesive strategies—etch-and-rinse, self-etch, and universal adhesives—highlighting their applications and advantages. The review extends to clinical applications of dental adhesion, including direct restorations, indirect restorations, and immediate dentin sealing (IDS), demonstrating the practical implications of adhesive systems in enhancing restoration longevity and performance. In conclusion, despite significant advancements, no gold-standard method for optimal adhesion exists. Each adhesive system has distinct strengths and limitations. The review emphasizes the importance of evaluating methods for achieving durable adhesion and staying current with technological advancements in adhesive systems. **Summary:** This review provides a thorough analysis of dentin bonding systems, delving into the structures and bonding mechanisms of both enamel and dentin. By exploring various adhesive systems and their components, it highlights the ongoing challenges in achieving optimal resin–dentin adhesion. The review also addresses the clinical applications of dental adhesion, including direct restorations, indirect restorations, and immediate dentin sealing (IDS), illustrating how different adhesive techniques impact clinical outcomes. It underscores the necessity for continuous innovation and assessment of adhesive systems to enhance long-term bonding effectiveness in clinical practice.

Keywords: adhesion; dental adhesive; dental bonding; dentin bonding agent; etch-and-rinse; self-etch; universal adhesive

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1. Introduction

Throughout the years, adhesive systems have undergone significant advancements in modern restorative dentistry. Historical reviews highlight the evolution of these materials and their impact on dental practice. For instance, early developments in adhesive technology laid the groundwork for current innovations, as detailed in works such as this review and another historical perspective [1–3]. Despite these advancements, challenges persist regarding the long-term durability of the resin–dentin bond interface, as noted in recent studies [1,3]. Bonding to enamel structure has become a predictable and well-established procedure [2], whereas bonding to dentin, due to its heterogenous structure and histology, is considered challenging [3,4]. Indeed, the attainment of optimal interdiffusion of the adhesive system within collagen fibrils and maintaining stability at the resin–dentin interface are critically significant [5]. As a result, it is fundamental to understand the mechanism of dentin hybridization during which an interdiffusion zone, also known as a hybrid layer (HL), is formed, leading to the development of micro-mechanical retention of the dental restoration [6]. Thereby, the HL is made up of residual hydroxyapatite (HAp), solvents, collagen, and resin monomers; its level of strength is ultimately influenced by each component's resistance to degrading occurrences [7,8].

During adhesion procedure, the mineral components are partially or totally removed by acidic monomers in self-etch (SE) or etch-and-rinse (ER) adhesive systems [9]. After the dentin and the enamel substrates have been totally etched with phosphoric acid (H_3PO_4), ER adhesives are applied, and thus the smear layer is removed [10]. On the contrary, the acid etching phase is removed for dentin with SE adhesives since they include monomers with acidic functional groups that concurrently etch and prepare the dental substrate [11]. Thus, the smear layer is modified and incorporated in the hybridized complex [12]. ER adhesive systems have two or three application step variations, whereas SE adhesive systems have one or two [9].

With regard to the ER adhesives, OptiBond FL (OBFL, Kerr Co., Orange, CA, USA), a three-step ER (ER III) adhesive, is recognized as one of the gold-standards of multiple bottle systems [10]. The adhesive used (OBFL) contains a highly hydrophobic bonding ingredient called glycerol-phosphate dimethacrylate (GPDM), which can chemically react with HAp in the etched and prepared enamel and dentin substrate to improve bond strength (BS) [13]. SE systems were then implemented, which eliminated on dentin the use of H_3PO_4 and the accompanying rinsing phase [9]. Clearfil SE Bond (CSE, Kuraray Noritake Dental, Tokyo, Japan) has been documented as the gold-standard in this class; the primer and the adhesive of this system consist of 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP), which interacts with calcium (Ca) to establish a strong and stable bond, hence forming nanolayers of 10-MDP–Ca [14]. Most recently, manufacturers have developed broader-ranging adhesive systems that can be utilized in both bonding procedures (ER and SE), in addition to the selective etching of enamel margins (SEE). The manufacturers propose that practitioners adopt bonding procedures based on their preferences and the type of tooth structure. This innovative set of dental adhesives, known as "multi-mode" or "universal adhesives" (UAs), is the newest version of dental adhesives [3,9,15]. Recent advancements also include the incorporation of nanoparticles in adhesive systems, which can significantly enhance the properties of adhesives. Nanoparticles improve the mechanical strength and durability of the bond by interacting at a microscopic level with the dental substrate [16].

Presently, these dentin bonding agents consist of monomers containing both hydrophobic and hydrophilic groups, along with polymerization modulators and relatively high levels of organic solvents [17]. These solvents serve as diluents and improve the spreading, wetting, and penetration of monomers into the micro-porosities of the exposed, acid-demineralized collagen network [18]. It is imperative to emphasize that the higher the content of solvent inside the polymer, the lower the resin–dentinal BS and the mechanical properties of a cured resin [19].

Supremely, any excess solvent should be evaporated from the dentinal surface through air-drying the applied adhesive before photopolymerization. The existence of residual solvent could jeopardize the photopolymerization of resin monomers, leading to compromised bond integrity and the formation of unwanted voids in the adhesive interface. These voids can perform as defect-initiator sites, delivering a trail for nanoleakage (NL) and producing a reduction in the BS [20,21]. Solvent evaporation can be accomplished by incorporating an evaporation period between the application and curing of the adhesive, or by employing air-drying techniques with a tooth-syringe [22]. Overall, the evaporation of solvent from an adhesive depends on several factors, including the type of the solvent, operator skills, tooth-syringe distance, type of monomer, and air temperature, all of which appear to affect the air-drying duration of an adhesive system [23].

Moreover, there are various strategies available to facilitate the removal of solvents and enhance the longevity of adhesive systems, including amplified light-curing time, prolonged application time, active bonding application, multiple adhesive layers, extended air-drying, and using warm air stream on the primer or the adhesive [24–40].

The issue is that until now, there has been no specific protocol for achieving stable and optimal adhesion of adhesive systems to dentin. Likewise, improvement in BS can be realized by means of several strategies, and thus, advocated by various previous studies [7,25,41].

Hence, this review aims to evaluate current dentin bonding systems, assess their strengths and limitations, and highlight the importance of staying updated with advancements for achieving optimal adhesion.

2. Enamel and Dentin—An Overview

A main objective of restorative dentistry is to bond restorative materials to enamel, dentin, or both [33]. Chemically, enamel structure is a highly mineralized crystalline substance comprising 95 to 98% inorganic matter by weight. The inorganic content of enamel relies on HAp, the largest mineral component, which is present at concentrations of 90–92% by volume, and its proper arrangement as enamel prisms to maintain its structure [42]. However, in the free spaces between the HAp crystals, a network of organic materials exists. A resilient mineral, formed by the interaction between minerals, collagen I fibrils, and other proteins, is present within dentin and bone. Despite this, enamel is much tougher due to being more mineralized than bone. Also, enamel does not contain collagen; though, when it matures, a small quantity of specialized matrix proteins is produced inside the enamel [43]. The remaining enamel constituents include an organic phase, which reports for about 1 to 2%, and water (3 to 4%), which accounts for about 4% by weight [44].

The rods of enamel are tightly packed and interlaced in a wavy pattern that extends from the dentinoenamel junction (DEJ) to the tooth's exterior surface. Aprismatic enamel has an optic axis approximately parallel to the enamel's surface, with an acid-resistant surface that protects against enamel degradation in the oral setting [45]. The DEJ, or transition zone between dentin and enamel, together with the enamel tufts made of hypomineralized crack-like defects, plays a crucial part in tooth resilience and preventing the cracks propagation [46]. Typically, enamel rods are positioned perpendicular to both the DEJ and the tooth surface. After the enamel has been treated with an acidic conditioner, the "ends of the enamel rods" onto the surfaces are exposed for the bonding agent [44,45]. However, the rods can be placed parallel to the interior surface of a tooth preparation, when the "sides of the enamel rods" are revealed following acid conditioning [44].

Dentin is essential in the clinical use of adhesive restorations. Dentin is a complex tissue, and although known to be highly mineralized, it has a lower mineral level (70 wt% mineral by weight and 45% by volume) and a higher organic composition (20 wt% organic phase by weight and 33% by volume), with water making up the remaining fraction. Despite being less mineralized than enamel, dentin has a higher mineral content than bone or cementum [45].

The morphology of dentin is very complex. Its microstructure is naturally well-oriented, containing several dentinal tubules occupied by odontoblast processes or their residues, with a density ranging between (19–45) $\times$ 1000/mm^2 and an average diameter of 0.8–2.5 μm [47]. Dentinal tubules spread through the whole dentin thickness, starting from the DEJ or the cementum to the pulp [21,48,49]. These tubules are bounded by two dissimilar dentinal phases: the intertubular dentin (ITD) and the peritubular dentin (PTD) [50]. The larger part of the dentin volume is surrounded by ITD, a composite containing type I collagen fibrils irregularly fortified with nanoplatelets of carbonated HAp [45]. This configuration makes the dentin tougher and stronger. The PTD contains no collagen and is more mineralized, harder, and stiffer than the bordering ITD [51,52].

An increase in the diameter of the dentinal tubules inside the deep dentin, along with the convergence point of the tubules toward the pulp chamber, results in an exponential surge in the dentin permeability when the dentin is prepared deeper [53]. Thus, in the superficial dentin, bonding is primarily intertubular, while in the deep dentin, bonding is mainly intratubular [54] (Figure 1).

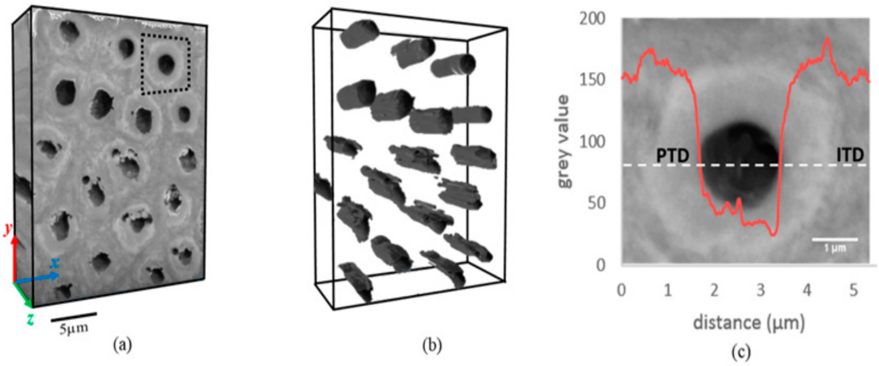

Figure 1. Three-dimensional (3D) focused ion beam-scanning electron microscopy tomography of a representative volume of dentin. (**a**) 3D reconstruction of the dentin structure composed of tubules. (**b**) 3D spatial distribution of dentinal tubules (dark grey). (**c**) The variation of grey scale values across the center of a representative single dentinal tubule (marked by the dashed region in image (**a**)) [47].

Enamel adhesion to dentin is very puzzling due to the high fluid content (10 wt%) present in the form of unbound and bound water, along with the extracellular protein content. Dentin, being hydrophilic, makes the infiltration of resin monomers unsuitable. However, an adequate resin–dentin bonding is possible with hydrophilic and amphiphilic resin chemistry only. The hydrophilic resin monomers might penetrate the demineralized surface of the dentin, rich in type I collagen fibrils, encasing the exposed dentinal matrix, then forming the so-called HL [4,55]. The hybridization of the dentin surface is the main mechanism for the micro-mechanical retention of bonding systems [56].

3. Histology of Enamel and Dentin Structures

Enamel is a dry substrate with no vital structures, making it closely perfect for forming a tight adhesive bond [3]. Ameloblasts are particular epithelial cells that generate enamel. During development, amorph matrix rich in proteins, acellular, and avascular ameloblasts cover the whole surface of the forming tooth, which is eventually occupied with ribbon-like crystals of carbonate-HAp. Away from the dentin, these crystals are arranged in rod and interrod spaces. Ameloblasts produce tight connections and membrane infoldings from the apical ends of the cells during the second phase of enamel maturation, altering the pH from moderately acidic to near-physiologic and allowing the matrix to crystallize [57].

The Retzius lines are the bands of enamel rods that emerge in a histologic slice of mature enamel. Strong Retzius lines are created following ameloblast traumas and are distinguished by uneven enamel crystal structures. Enamel is nearly devoid of soft organic matrix in its mature condition. The thickness of the enamel is thinner in the cervical region and thicker in the masticatory surfaces (incisal ridge and cusps) [58].

Mature enamel is composed of long, thin HAp crystal rods. The histological sections cannot assess its assembly as the crystals dissolve through decalcification, a process that allows cutting the teeth when making the specimen. Amelogenin, enamelin, and perlecan are three proteins found in enamel. The latter is found in the dental papilla and follicular intercellular gaps. The enamel epithelium and dental mesenchyme form the contact between dentin and enamel in the growing tooth. Coronal dentin is covered by enamel, while radicular dentin is covered by cementum [58,59].

Dentin is the major structure of the teeth, so understanding this complicated tissue in connection to resin–dentin bonding necessitates an outline of the dentinal organic matrix that is embedded in a collagen fiber mesh [60]. The extracellular organic dentinal matrix (ECM) is constituted generally of a three-dimensional (3D) network of fibrillar collagens, specifically type I collagen (90%) with traces of type V and III collagens [61]. The remaining ECM components are non-collagenous proteins, mostly proteoglycans. Dentin is found in the following substances: sialoproteins, phosphoproteins, bone morphogenic proteins, enzymes, and growth factors [62].

Collagen is thin (diameter = 1.5 nm) and lengthy (300 nm). The bordering collagens are shifted from one another by one-quarter of their length = 67 nm [63]. Fibrillar collagens (types I, II, III, V, XI, XXIV, and XXVII) predominate [64]. The three α chains possess N-terminal and C-terminal ends (Figure 2). The latter is associated with globular structure formation: the C-terminal propeptide.

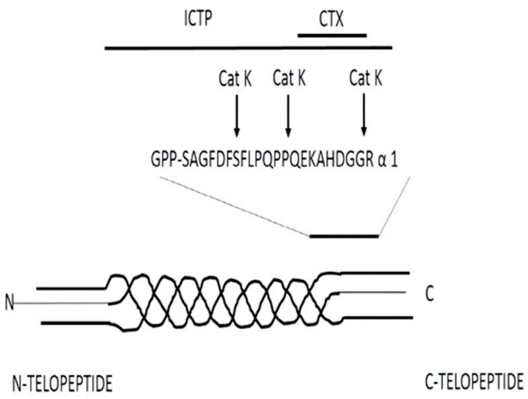

Figure 2. Orientation of type I collagen molecules in hard-tissues. N- and C-terminal ends of successive type I collagen fragments as specific biological markers of degradation. (Courtesy of Prof Umer Daood).

The Glycine-X-Y triplets of the chains then align to the N-terminus where the globular N-terminal propeptide generates a triple helix. The structure formed by the N- and C-terminal propeptides is called procollagen, which is subsequently converted into type I collagen [60,61,64] (Figure 3).

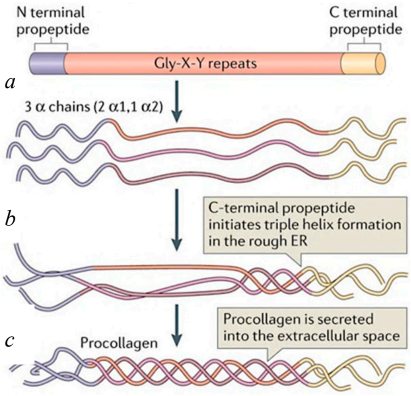

Figure 3. (**a**) Structure of the three chains α. (**b**) Initiation of the formation of the triple helix at the level of the C-terminal propeptide. (**c**) Representation of the structure of the procollagen triple helix. ER = Endoplasmic reticulum [61].

Bound water molecules occupied the voids inside and between the collagen fibers during the mineralization process of the dentin. Consequently, water is gradually substituted by minerals [64]. There was no evidence of resin infiltration in the mineralized dentin [60,64] (Figure 4).

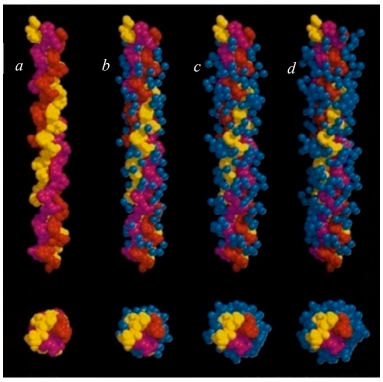

Figure 4. Representation of the progressive hydration of the collagen glycine–alanine peptide. Top row presents the perpendicular and the bottom row parallel view to the molecular axis at the same hydration level. (**a**) A view of the non-hydrated collagen, with the three peptide chains shown in different colors. (**b**) The first shell of water molecules (blue spheres), directly hydrogen-bonded to carbonyl, hydroxyl, or amide groups on the peptide surface. (**c**) The second shell of water molecules, hydrogen bond to the water in the first shell, demonstrating the filling of the superhelical groove. (**d**) The third shell of water molecules [64].

Interest in tooth adhesion is driven by the chemical interaction between the mineral platelets in hard tissues and the acidic monomers of SE and ER adhesive systems [33]. This process builds a channel for the resin to enter and enclose the collagen fibrils, enabling hybridization [3,9]. In the HL, the interfibrillar gaps between the collagen are adequately large (30 ± 11 nm) [8] which could simplify the penetration of small hydrophilic monomers such as bisphenol A-glycidyl methacrylate (Bis-GMA) (512 Da) and 2-hydroxy ethyl methacrylate (HEMA) (100 Da) [60]. A previous study proposes that molecules greater than 40 kDa were excluded from collagen water infiltration, while molecules smaller than 6 kDa in size diffused easily. While an obstacle occurs in the intrafibrillar space (1.26–1.33 nm), which is made of up to hundreds packed collagen molecules [65], other aspects should be taken into consideration such as the concentration (the ability of adhesive monomers to dislodge water from the collagen is restricted by their relative concentrations: water has a [55 mol/L] concentration, while co-monomers have a [3–4 mol/L] concentration) and viscosity (lower viscosity of monomeric bonding is obligatory to exhibit collagen water) [60,66] (Figure 5).

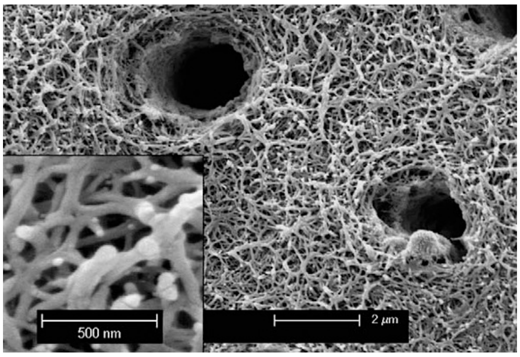

Figure 5. Scanning electron micrograph of acid-etched dentin showing two dentinal tubules containing remnants of peritubular dentin matrix. INSERT: High magnification of branching collagen fibrils (ca. 75 nm in diameter) separated by interfibrillar spaces that serve as channels for resin infiltrations during bonding [10].

Note that the hydrogen bonds between the collagen fibers are crucial for the hydration process, helping to prevent the collapse of the dentinal matrix before resin penetration [60].

4. Effect of Dentin Structure on Resin–Dentin Bonding

The main goal of any bonding agent is to achieve a firm and enduring adaptation of the restorative material to dental substrates [9]. The major challenge for any new dental adhesive is to be equally effective on both enamel and dentin surfaces [33]. To accomplish this goal, several obstacles must be overcome [9]. Bonding efficiently to the organic and wet dentin is a baffling task in adhesive dentistry. Nevertheless, bonding to enamel can be consistently achieved through the micro-mechanical interlocking of the resin tags (RTs) within the arrangement of micro-porosities of demineralized enamel, which successfully seals the margins of the restoration against leakage [3,7,33].

It has long been argued that the base of adhesion to dentin is imperfect [67]. On a nanoscale level, completely enveloping the collagen fibrils by monomers to fill up all the spaces is practically impossible [68]. Furthermore, methacrylic acid (MA)-based resin monomers are required for a higher possibility of penetration into the interfibrillar spaces of the collagen matrix because of this monomer's low viscosity and relative hydrophilic nature. However, this may lead to hydrolysis [69,70]. Ultimately, the presence of an exposed collagen, in addition to water empty spaces which are naturally present within the dentin collagen, can result in both hydrolytic and enzymatic degradation simultaneously [33,71]. These reasons led Bertassoni et al. [72] to determine that a suitable resin–dentin network is an important pre-requisite for a successful adhesion on a molecular level.

Acid etching is a process occurring as part of the mechanism of dentin binding. This procedure is used to demineralize between 5 and 8 µm of the ITD network in an effort to generate porosities at a nanoscale level in the collagen matrix. This results in the opening of dentin tubules, exposure of collagen fibers, and modification or elimination of the smear layer [3,10,17,73].

Thus, it is crucial to fully grasp the knowledge behind the behavior and properties of the smear layer in bonding mechanisms [74].

Role of the Smear Layer in Dentin Bonding

The production of the smear layer occurs while preparing the dental cavity. It manifests on the dentinal surface after the application of the instruments and is made up of varying debris and an altered morphology [75]. The resulting porous layer, with a thickness ranging between 0.5 and 7 µm, is comprised of saliva, water, HAp, bacteria, blood, and modified collagen [76]. The quality and thickness of the smear layer depend on the instrumentation used, the mode of use, the dentin site, and whether a splash of water is applied. A rougher surface is produced through diamond burs rather than carbide burs, and stronger friction is created by dry cutting than by wet cutting [75,77].

As soon as the layer binds to the dentinal surface, the entrance of the dentin tubules is plugged to a depth between 1 and 10 µm, effectively blocking any direct contact of materials with the dentinal substrate. The final layer is referred to as "Smear Plugs", which reduce the permeability of the dentin by 86% [78,79].

Addressing the issue created by the smear layer requires a certain level of etching prior to chemical adhesion to the dentinal substrate. There are two possible effective options:

- The full elimination of the smear layer with H_3PO_4 before bonding in an ER approach (smear layer-removal approach) [74].
- The application of bonding agents that can enter beyond the smear layer (various acidic primers are used), while integrating it following a SE approach (smear layer-modified approach) [80].

The bond to dentin depends on micro-mechanical interlocking in both processes [9,17].

In early generations, adhesives were bonded directly to the surface which is covered by the smear layer [81,82]. The BS of these adhesives in an in vitro setting is lower than 5 MPa, which might lead to clinical debonding [83]. The specimens appearing after debonding are classified mainly as a cohesive failure inside the smear layer due to the adhesive resin being hydrophobic which prevents it from entering through the debris zone [84].

In the initial phases of adhesive research, the most frequently used abrasive paper for generating a standard smear layer across dentin surfaces in research laboratories was 600-grit silicon carbide papers (SiC) (average particle size: 29 µm) [85–87]. Also, they are regularly employed by manufacturers before introducing a new adhesive system. Consequently, clinicians extrapolate these outcomes to clinical substrates, which are markedly different. For example, the smear layer generated by regular-grit diamond burs (average particle size: 100 µm) is denser, thicker, and rougher compared to that produced by 600-grit SiC [88]. Consequently, it can weaken the dentin bond, especially when SE adhesives are used [89,90], impacting material selection and, eventually, the quality of bonded resin restoration. Previous studies addressing such issues have recommended using coarser SiC, such as 180-grit (average particle size: 63 µm) [31,91–93], or 120-grit (approximately 125 µm in thickness) and 400-grit SiC (about 35 µm in thickness) for dentin preparation [94]. The aforementioned factors that contribute to the characteristics of the smear layer, and the smear layer's influence on the bond performance of adhesive systems should always be studied and highlighted.

5. Resin–Dentin Bonding

Following Oskar Hagger's groundbreaking work, Michael Buonocore emerged as a prominent advocate for adhesive technology in dentistry. Hagger, a chemist at De-Trey/Amalgamated Dental Company in London, UK, introduced Sevriton Cavity Seal in 1949, an acidic adhesive that interacted with the tooth surface on a molecular level. This innovative product earned Hagger the title of the true "Father of Modern Dental Adhesives", as his concept laid the foundation for subsequent generations of dental adhesives. Buonocore further advanced this field with his seminal research in 1955, demonstrating that enamel could be acid-etched to create an ideal surface for resin bonding. His work established enamel etching as a fundamental step in bonding procedures, revolutionizing dental practice and paving the way for the development of various adhesive systems that are now essential in restorative dentistry [30,33,95,96].

Dental adhesives have the following characteristics: they reduce marginal discoloration, minimize microleakage, reinforce the dentin or the enamel, preserve the tooth structure, and may even decrease postoperative sensitivity [97]. Indeed, years after Buonocore's work, significant progress has been made in the area of adhesives in restorative dentistry. The development and evolution of reliable enamel and dentin bonding agents is one such example [9,33,97].

Adhesive systems have progressed from the largely ineffective systems of the 1970s and early 1980s to the relatively successful ER and SE systems of today. The latest players in the adhesive marketplace are the so-called UAs [3,9,33].

This is the "cosmetic revolution" in dentistry, blossomed in large part due to dramatic advances in adhesive technology. In fact, the longevity and predictability of many if not most current restorative procedures are wholly predicated on the dentist's ability to bond various materials to tooth tissues [33]. Recent advances in the development of new bonding systems have resulted in higher bond strengths (BSs). Each adhesive system must be handled with careful attention to the details of application for maximal success [33,98].

5.1. Resin Adhesive Application

The field of application of adhesive systems is very large, and their contribution to the development of more conservative, aesthetic, and biocompatible therapies is obvious.

These systems are currently in widespread use and not limited to the following applications:

- Restoration of traumatic and carious lesions of classes I, II, III, IV, V, and VI.
- Repair existing restorations (amalgam, composite, crown).
- Bonding fractured fragments of anterior teeth.

- Sealing of cracks.
- Sealing pits and fissures.
- Desensitization of exposed root surfaces.
- Bonding of ceramic restorations (all-ceramic crowns, inlays, onlays, veneers).
- Improved retention of porcelain fused to metal crowns.
- Bonding of molded or prefabricated metal and fiber posts.
- Reinforcing fragile endodontically treated roots internally.
- Bonding of orthodontic brackets.
- Bonding splints in periodontology [99,100].

5.2. Mechanism of Adhesion

Adhesion occurs when two different molecules react upon being brought into contact as a result of a force of attraction between them [101]. The material used to cause adhesion is known as an "adhesive" and the substrate to which the adhesive is applied is named "adherent" [102,103].

Adhesion mechanisms that are normally used in dentistry are as follows:

1. Physical adhesion includes:
    a. Van der Waals interactions, which is the attraction among opposite charges on dipoles and ions.
    b. Dispersion forces, which is the interaction of induced dipoles.
    c. Hydrogen bond, an especially strong bond, can be involved in physical forces [101,104].
2. Chemical adhesion includes:
    a. Covalent bonding that includes sharing electrons between two molecules. It is a strong bond that liberates considerable amounts of energy. A covalent bond is existent in all organic compounds.
    b. Ionic bonding that includes a transfer of electrons from an atom to another, like the ion exchange adhesion mechanism observed in glass ionomer cements.
    c. Metallic bonding is the characteristics of the chemical bond of metals in which mobile electrons are exchanged among atoms in a typically stable crystalline assembly [101,104,105].
3. Mechanical adhesion includes:
    a. A diffusion of a material into another at a microscopic level. For instance, in composite resins the bonding includes the diffusion of resin into the enamel and the dentin substrates and the establishment of RTs [101].

After exploring the various adhesion mechanisms, suitable adhesion results are achieved by following these steps: dissolution of the smear layer from the enamel and dentin substrates; preservation of the collagen matrix; ensuring adequate wetting; effective monomer infiltration; photopolymerization within the tooth structure; and copolymerization with the resin composite matrix [102,106,107].

5.3. Factors Influencing Adhesion

5.3.1. Wetting

The adhesive, often a viscous fluid, is made of a material or film that joins two substrates and solidifies them [108].

The adherent is the initial support, material or substrate on which the adhesive is applied. The types of adherents are enamel, dentin, metal alloy, and ceramic material [79]. Indeed, the contact of the adhesive with the adherent depends on the wettability of the substrate and its surface free energy [108].

Wettability is the ability of a liquid to come into intimate contact with a solid. It is the phenomenon that controls the spread of a drop of liquid on the surface of a solid, when a drop of liquid is deposited on the surface of a solid; either the liquid spreads (on the so-called "wet" surface), or it forms a drop, making an angle of contact with the surface of the solid [109]. The wettability and the spreading velocity are also reliant on the chemical composition of adhesive agents [110]. As the viscosity of an adhesive increases, it becomes more challenging to achieve proper wetting of a substrate [111]. Wettability studies are generally based on the measurement of contact angles (CAs) as main data, which designates the degree of wetting when a solid and a liquid interact [112,113]. Small CAs lower than 90° (<90°) correspond to high wettability, while large CAs (>90°) correspond to low wettability [109]. The contact angle (CA) is defined as the angle formed by the intersection of the liquid–solid interface. Surface energy is also called surface tension or interface energy [109,112,114]. Surface tension is a force that exists at any interface between two different media (between a solid or a liquid and a gas). The tension between identical media—whether it is two solids, two liquids, or even between a liquid and a solid—is typically referred to as interfacial tension. This force is what enables a drop of water to resist spreading on paper or allows certain insects to walk on water, often associated with the concept of capillarity [109].

When dentin and enamel are demineralized by acid-etching, different changes in the surface energy of substrates could be observed. The surface free energy of enamel is improved, simplifying wettability [115]. Nonetheless, in dentin, the opposite will occur; while mineral is removed and collagen fibrils are exposed, surface free energy decreases [116]. To enhance the surface energy of dentin, it is essential to use an appropriate adhesive system that promotes good wettability [117].

Finally, for optimal adhesion, the adhesive must completely "wet" the surface to be bonded [79,108,109]. "Wetting" means that the adhesive flows and covers a surface to maximize the contact surface and the forces of attraction between the adhesive and the bonding surface. Complete wetting occurs at a CA of 0° and no wetting occurs at an angle of 180°. In order, for a liquid adhesive, to effectively wet a surface, the surface tension of the adhesive must be lower than the energy of the surface of the substrate to be bonded, or the energy of the surface of the substrate must be increased [108,109].

Micro-tensile bond strength (μTBS) of composite to dentin cavity floor has been shown to be affected by several factors, including dentinal tubule density, diameter, and sclerosis degree, as well as the presence of sclerotic dentin. Other influential factors encompass cavity preparation design, such as cavity shape and size, as well as the presence of bevels or chamfers. Additionally, the adhesive type and application protocol, the presence of contaminants like saliva or blood, and the method of polymerization can significantly impact μTBS values. Furthermore, factors related to substrate characteristics, such as dentin age, composition, and moisture content, play a crucial role in determining BS outcomes. Additional considerations include the presence of secondary caries, thermal and mechanical stresses, and the use of desensitizing agents or cavity liners [33,118,119].

5.3.2. Substrate Variations

The BS of composite resin on dentin near the pulp is generally 30–40% lower than that on superficial dentin [120]. Hence, the remaining dentin thickness plays an important role on the strength of dentin bonding agents [119]. It has been previously shown that the direction of dentin tubules can influence both the intrinsic wetness of the surface and BS. Bonding to parallel-oriented tubules (=occlusal wall) had higher μTBS than bonding to perpendicularly-oriented tubules (=gingival wall) [121]. Furthermore, permanent dentin has higher concentrations of phosphate (P) and Ca compared to primary dentin. Therefore, one might speculate that etching times for deciduous dentinal surfaces are typically shorter than those for permanent teeth. However, BS tends to be lower in primary teeth regardless of the different etching times applied compared to permanent teeth [122].

5.3.3. Dentin Humidity

One of the trickiest aspects of adhesive dentistry is maintaining proper moisture control [123,124], and one should consider that the average of oral temperature and relative humidity are approximately 30 °C and 80% correspondingly, with humidity varying from 74% to 94% [125,126]. In this manner, wetness of the dentin surface is an influencing factor that may affect bonding to dentin [127]. Successful adhesion to dentin could be negatively affected by both internal and external humidity.

The internal humidity of dentin comes from the dentinal fluid within the dentinal tubules. Therefore, interference with monomer infiltration into dentin and the polymerization of the resin could be observed. Thus, in order to simulate physiological bonding conditions, some authors have proposed conducting in vitro studies of bonding agents under hydrostatic pulpal pressure [128,129]. The various factors of external dentin humidity that could affect BS are numerous: blood, saliva, crevicular fluid, air humidity in the oral cavity, ambient air humidity, and water that could be contaminated from the air syringe [130].

In an attempt to resolve the above-mentioned drawback, the use of rubber dam is required in restorative dentistry [131,132]. Thus, the humidity is reduced to a similar level as that of the ambient air, hence encouraging optimal and stable adhesion to the dentin [133]. It is imperative to state that the use of a rubber dam offers a dry field for improving the visibility and enhancing visual contrast [134]. Additionally, it is a low-cost material with a high effectiveness [135].

5.3.4. Configuration-Factor

The configuration-factor (C-factor, ratio between bonded and unbonded areas) is an influencing factor for dentin adhesion [136]. Numerous studies indicated that with an increase in C-factor, the BS decreases [137,138]. A rupture of dentin interface occurs when BS is lower than polymerization stress, and this process depends on the C-factor. Below 1, the interface could be preserved in a flat dentin, for example, with values above 2, failures at the adhesive interface could be more likely to occur. This is because the higher the confinement level, the lower the shrinkage stress that can be relieved by the flow of the free surfaces [139,140].

5.3.5. Age of the Patient (Sclerotic Dentin)

Sclerotic dentin is a clinically challenging binding substrate in which dentin has been physiologically and pathologically altered, relatively as the body's natural defense mechanism, or as a result of colonization by the oral microflora. It is also characterized by a partial or complete obliteration of the dentinal tubules by mineral deposits. Dentin becomes transparent and insensitive, while the surface of lesions appears smooth. The thickness of the sclerotic dentin layer is variable [141].

The sclerotic deposits which obliterate the dentinal tubules were always present after the acidic conditioning of the sclerotic dentin, resulting in minimal formation even of zero "tags". In addition, the sclerotic dentin area impregnated with resin was found to be thinner compared to normal dentin [142].

Another morphological alteration of sclerotic dentin is the formation of a hypermineralized layer on the surface. This layer resists etching agents, thereby preventing the formation of the HL, which is essential for the adhesion process [143]. To overcome the diffusion barrier, the use of a rotary instrument can be a solution to remove the hypermineralized layer, and thus obtain intertubular retention [144]. However, this method could be detrimental when the lesion is near the pulp.

All in all, adhesion to sclerotic dentin was lower than the normal dentin which ultimately influenced the longevity of restorations [142,143]. A recommendation has been done by Hedge et al. [144] suggesting that the optimal approach to restore such a lesion is by removing a thin layer from the surface of the hypermineralized dentin. This method effectively removes the adherent bacteria layer on the surface as well, facilitating better adhesion of the dentinal substrate.

6. Resin Adhesive Systems

6.1. Composition of the Adhesive Systems

A dental adhesive system's fundamental parts are as follows:

Etchant, presently H_3PO_4 at a concentration ranging between 30% and 40%. The common H_3PO_4 gels are thickened using silica microparticles, while some incorporate alternative thickeners like xanthan gum. To enhance the application precision and guarantee that all gel is rinsed out, a color dye should be integrated. Glycol is frequently used to increase wettability and lessen viscosity. The etchant is constantly washed from the dental surface [3,96,145].

A hydrophilic solution including resin monomers, organic solvent (alcohol or acetone), water, and stabilizers is used as a primer [9]. The hydrophilic groups enhance the dentin wettability, which is located in a humid setting. Primers have a similar role in dentin adhesives as they do in paints [3]. The primer binds to surfaces and generates a binding layer that prepares the surface for the paint, in this case, the bonding resin [3,9]. Because of its high hydrophilicity and solvent-like properties, HEMA is the popular primer used [33]. Primers are often not washed or cured after being applied to the tooth surface; they are just air-dried [3].

The bonding resin is a low-viscosity solvent-free (hydrophobic) resin that is placed over the primer and then polymerized [9]. The hydrophobic groups engage and copolymerize with the restorative material, increasing the stability and durability of dentin bonding by sealing the bonded interface against NL [3]. The hydrophobic resin enhances both the primer's polymerization rate and the mechanical assets of both the adhesive and the HL [3,146]. Adhesive systems with this independent bonding phase produce better results. Most adhesive resins are made up of hydrophobic dimethacrylates such as Bis-GMA, triethylene glycol dimethacrylate (TEGDMA), and urethane dimethacrylates (UDMA) [3,17].

Additional components were present in the composition of the adhesive systems including initiators [for a self-cure resin system with an initiator such as benzoyl peroxide, the polymerization process can be triggered using a photo-initiator system consisting of the photosensitizer (e.g., camphorquinone) and an activator (e.g., tertiary amine)], fillers (silica particles), and other ingredients (paraben used as antimicrobials, glutaraldehyde (GA) used as desensitizer, fluoride for prevention of secondary caries, and chlorhexidine (CHX) used to inhibit collagen breakdown) [15,33].

All in all, the chemistry of an adhesive system is clarified by the following formula M-R-X, where "M" is a methacrylate group that combines with the resin matrix, "R" is a spacer, and "X" is a functional group for adherence to dental surfaces [107].

6.1.1. Acidic Components

In the ER strategy, the etching agent applied is 35–37% H_3PO_4, with a pH fluctuating between 0.5 and 1 (Figure 6). This pH becomes superior than 1 for the SE strategy using acidic monomers resultant from the esterification of H_3PO_4. This acidic pH prepares both the enamel and the dentin substrates to receive the bonding agents [147].

On enamel, the etching phase cleans the enamel, creates a complex 3D microtopography at the surface of enamel, rises the enamel surface area accessible for bonding, creates micropores into which the resin mechanically interlocks (Figure 7), and increases wettability by exposing more reactive surface layer [104,148].

Three types of enamel etching patterns may be detected under a microscope [148–150] (Figure 8):

- Type I of etched enamel: privileged demineralization of the enamel prism core while keeping the prism periphery intact. The matching tags in this case are cone-shaped.
- Type II of etched enamel: the inter prismatic enamel is removed preferentially, leaving the prism cores intact. The matching enamel tags are cup-shaped.
- Type III of etched enamel: the pattern is less apparent, with portions that match type I and II patterns and others that bore no similarity to enamel prism [148–150].

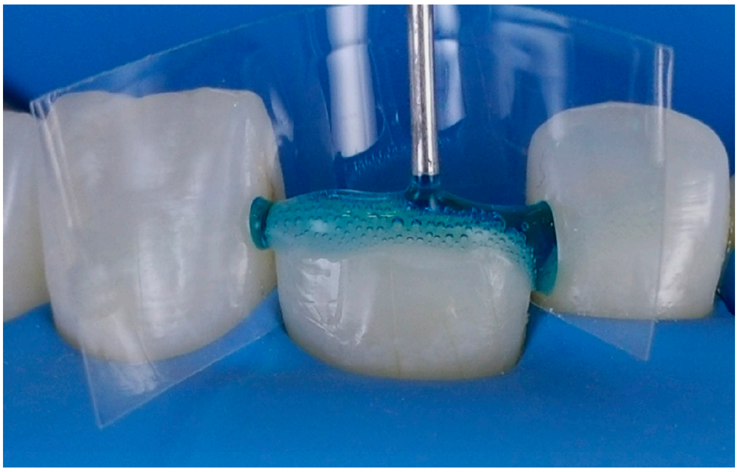

Figure 6. The formation of bubbles resulting from the chemical reaction between the acid and a mineral structure (positive sign of a chemical reaction). (Courtesy of Prof Louis Hardan).

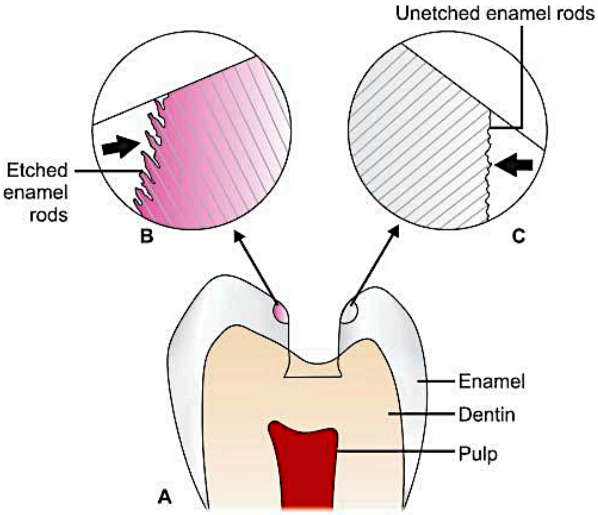

Figure 7. Difference in appearance of etched and unetched enamel rods. (**A**) A view of both etched and non-etched enamel. (**B**) Etched enamel rods. (**C**) Unetched enamel rods [148].

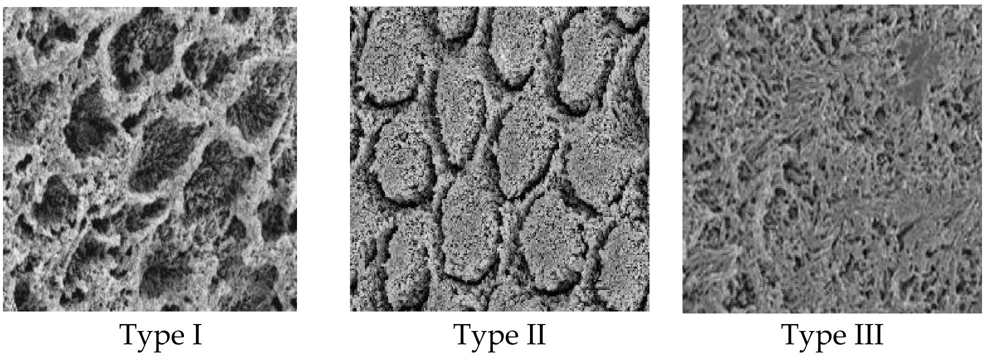

Figure 8. Types of etched enamel [79].

Various acids have been lately developed for demineralization including nitric acid, citric acid, and oxalic acids. These acids produce mild conditioning, hence for ER, the use of H_3PO_4 is recommended [148].

Acid etching with H_3PO_4 essentially creates a microporous layer, 5–50 µm deep, into which resin monomer flows [148,151]. This leads to a long-lasting enamel bond established by micro-mechanical interlocking of the resin and enamel. While H_3PO_4 cleans the enamel surface, it triggers salts precipitation on the etched surface; these salts might be eliminated more advantageously by means of rubbing the acid and rinsing it, delivering an ideal interface for the bonding [151].

Among the features that affect the acid etching on enamel substrate: the acid form (gel or liquid), the acid concentration and time of etched enamel, the acid type, the chemical type of enamel, the type of dentition (primary or permanent), and whether the enamel is demineralized or fluoridated [148,152].

On dentin, the etching stage removes or modifies the smear layer, and demineralizes 5–8 µm of the ITD matrix to create nanoscale porosities in the underlying collagen fibrillar matrix. Numerous acids or/and Ca chelators are used [153].

For acids: in operative dentistry, the most commonly used acid is 37% H_3PO_4 (Figure 9) in both liquid and gel forms. Although H_3PO_4 liquid has a lower pH, H_3PO_4 gel has a superior etching impact on dentin than liquid acid. This is due to the fact that gel acids stay on the tooth surface longer than liquid acids, and this contact time has a higher influence on dentin depth than pH. Acids not only eliminate the smear layer, but also open the dentinal tubules, expose the collagen network into which resin monomers infiltrate, and modify the dentin's wetness and permeability [148,154].

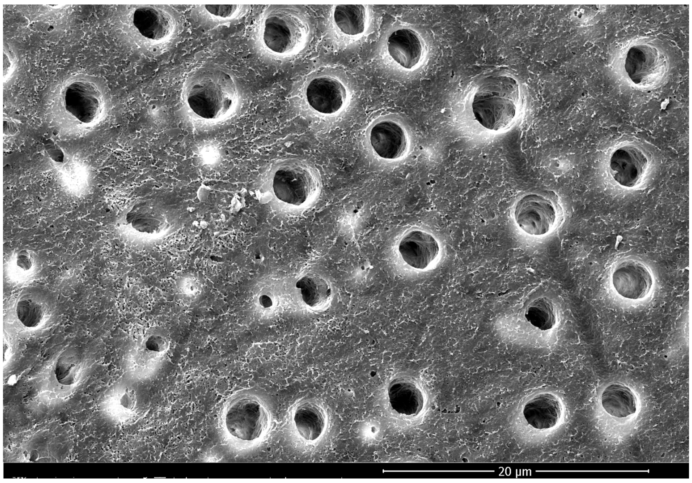

Figure 9. 37% orthophosphoric acid on dentin. (Courtesy of Prof Naji Kharouf).

There are many other acids used for conditioning the dentin like maleic acid, nitric acid, oxalic acid, citric acid, and hydrochloric acid [148].

For Ca chelators: these are used to remove and/or alter the smear layer while leaving the surface of dentinal layer undamaged. Ethylenediaminetetraacetic acid (EDTA) is the common chelator used [4,148].

Among the features that affect the acid etching on dentin substrate are the removal of cutting debris, the effective cavity preparation, the partial conditioning, and the formation of micropores [155].

As a result, the etching acid's form and pH are crucial. The degree and intensity of demineralization are induced by these variables. According to previous research, the primary variables influencing the dentin–conditioner interaction have been determined to be the acid content, osmolality, pH, and viscosity created by the thickening agents [156]. The dentist should clean the tooth surface and get it ready for bonding by using H_3PO_4 (liquid or gel). Compared to liquid acid, gel acid has advantages such as improved control during application and longer retention on the tooth surface [154] (Figure 10).

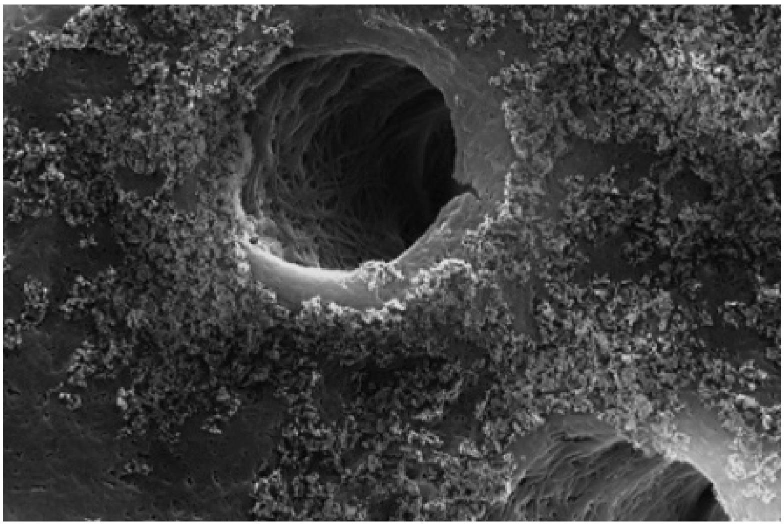

Figure 10. Higher magnification of dentin etched with phosphoric acid gel 37%. Amounts of small debris (silica) are clearly observed [154].

Since the advent of lasers in dentistry in 1960, there has been fast advancement, and the application field of lasers has grown dramatically [157]. The laser interacts with the target tissues through absorption, transmission, scattering, and reflection. Chromophores found in both soft and hard tooth tissues include hemoglobin, melanin, water, and HAp. The choice of laser is determined by tissue characterization since they have an affinity for specific wavelengths [158]. In addition to soft tissue applications, dentists frequently use lasers on dental hard tissues for cavity preparation, treating dentin hypersensitivity, caries removal, and surface conditioning [157]. Erbium lasers are often used for these hard tissue applications because their wavelengths are selectively absorbed by the HAp and water content of enamel and dentin. Another application for lasers is enamel and dentinal conditioning before the bonding process. On one hand, erbium lasers act on dentin by making a visible rough surface, opening dentinal tubules without a smear layer, and producing micro-irregularities caused by selective ablation of ITD [159]. Choosing the correct laser parameters is critical, since it may create changes in dentin collagen, which may have an unfavorable effect on adhesion. On the other hand, treating the enamel surface by means of an erbium laser produces an irregular, uneven surface that permits the adhesive to penetrate. As a result, the production of RTs enhanced the micro-mechanical retention [157]. Some studies have indicated that laser irradiation improves micro-mechanical retention by increasing surface roughness and surface area at the enamel-resin interface [160,161]. Prior investigation discovered that surfaces conditioned with erbium lasers or H_3PO_4 exhibit similar micro-irregularities [162]. Overall, there has been extensive research on the use of lasers in conjunction with or as an alternative to H_3PO_4 etching [158,163–165]. Although the ideal strategy for adhering to enamel and dentin remains unknown, clinicians prefer to employ H_3PO_4.

6.1.2. Cross-Linking and Functional Monomers

There are two main types of monomers: the functional monomers that correspond to the dentinal primers and the cross-linking monomers that correspond to the adhesive resin [48] (Figures 11 and 12).

A. Cross-linking monomers

All cross-linking monomers are hydrophobic, designed to stabilize the HL and interact with the overlying restoration material, as well as functional monomers. Acrylic systems are tasteless, colorless, and present an easy radical for polymerization reaction [166]. Different kinds of polymerizable groups, and hence resin systems exist:

- Acrylates ($–CH_2–CH=COO–$): compounds characterized by double bonds that exhibit higher reactivity than methacrylates, causing problems in shelf-life and biocompatibility, and containing an ester group [48].
- Methacrylates ($–CH_2–C(CH_3)=CH_2$): compounds containing acrylates (double bonds), methyl group ($–CH_3$), and ester group (Example: UDMA, Ethylene glycol dimethylacrylate, TEGDMA, or Bis-GMA) [167].

Both acrylates and methacrylates are susceptible to water degradation because of the presence of an ester group ($R_1–CO–OR_2$) in their formulations [69].

- Methacrylamides: compounds composed of a methacrylate group and an amide group ($R_1–CO–NH–R_2$) instead of an ester group [48].

Methacrylamides are more resistant to water degradation compared to methacrylates, primarily due to the presence of the amide group [49].

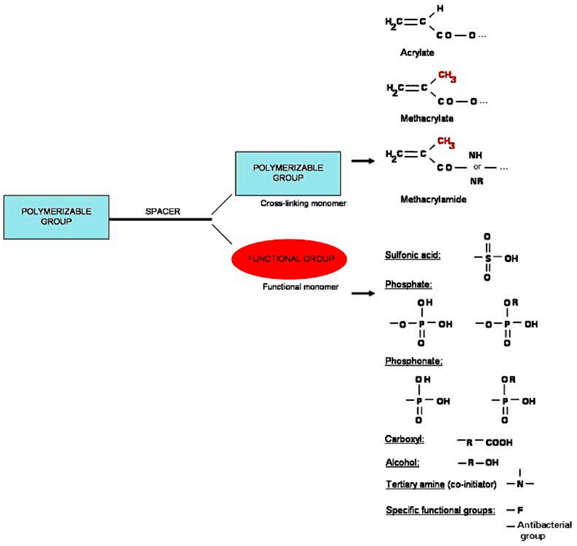

Figure 11. The typical configuration of cross-linking and functional monomers, with adhesive monomers commonly falling under the category of methacrylates [48].

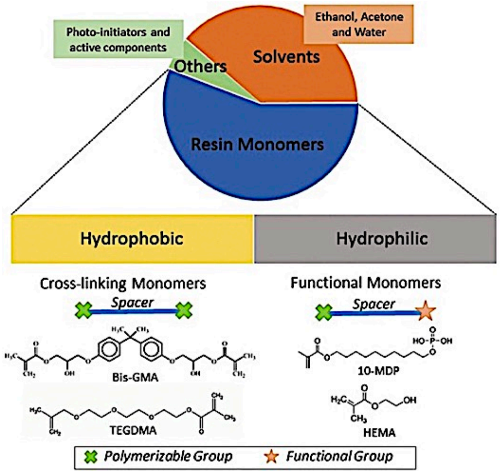

Figure 12. Composition of dental adhesives and examples of cross-linking and functional monomers used in contemporary adhesive systems [45].

B. Spacer

The spacer in dental materials plays a crucial role in determining various properties. It consists of an alkyl chain whose size corresponds to that of the monomers. Smaller monomers tend to be more volatile, while larger ones are less so. Additionally, the polarity of the spacer influences the solubility of the monomer in water. The presence of voluminous groups within the spacer can modify the reactivity of polymerizable or functional groups. Increasing the distance between methacrylate groups, for example, can enhance monomer reactivity. However, voluminous groups may also contribute to incomplete polymerization. Therefore, careful consideration of spacer characteristics is essential for optimizing the performance of dental materials including adhesive systems [48,166,167].

C. Functional monomers

Functional monomers serve several purposes in dental adhesives. Firstly, they improve wetting owing to their hydrophilic nature. Additionally, they function as adhesion-promoting agents, effectively enhancing BS to demineralized dentin [48]. In ER systems, functional monomers are tailored to match the dentinal primer, mainly aimed at enhancing the wettability of collapsed collagen. On the other hand, in SE systems, functional monomers, often termed SE primers, are acidic in nature. These acids demineralize dental surfaces and facilitate the smooth infiltration of the adhesive resin. SE systems are broadly categorized into two major families: those containing phosphorus groups (like 10-MDP, dipentaerythritol penta-acrylate phosphate (PENTA), and HEMA-P) and those containing carboxylic acids (such as 4-MET and 4-methacryloxyethyl trimellitate anhydride (4-META)) [48,86]. The acidity of these functional groups determines the etching aggressiveness, with sulfonic acid being the most aggressive, followed by phosphonic, phosphoric, carboxylic acid, and alcohol [168]. However, it is important to note that carboxyl and P groups are susceptible to water degradation [48]. This classification provides valuable insights into the diverse roles and properties of functional monomers in dental adhesive systems, aiding in the selection and optimization of adhesive formulations for clinical applications.

There are a variety of functional monomers in dental adhesive systems:

1. Pentamethacryloyloxyethylcyclohexaphosphazene monofluoride (Dentsply company): Monomer with five methacrylate-alkyl chains and a fluoride as a functional group [48].
2. N-phenylglycine glycidyl methacrylate and N-tolylglycine glycidyl methacrylate: Monomer with tertiary aromatic amine group [48].
3. Dimethylaminoethyl methacrylate (DMAEMA): Monomer with tertiary amine group [169].
4. Methacryloyloxydodecylpyridinium bromide (MDPB): Monomer patented by Kuraray company with antibacterial agent and a methacrylate group. This molecule is hydrophobic when compared to other hydrophilic functional monomers [170].
5. N-methacryloyl-5-aminosalicylic acid: Monomer patented by Kuraray company and presented in adhesive systems with a salicylic group (desensitizing outcome) [48].
6. MA: Monomer rarely used in adhesives due to its risk of allergic reactions [48].
7. Methyl methacrylate (MMA): Old monomer rarely used in adhesive formulation like MA monomer [48].
8. 4-META: Monomer with hydrophobic aromatic group, functional hydrophilic carboxyl groups, and demineralization assets. The adhesion capacity of 4-META has been well defined in the literature and depends on the interaction between the substrate and the carboxyl groups that substitutes P ions with Ca ions in HAp [17,33]. The resulting 4-META-Ca presents a low chemical stability [17,33,48]. This procedure is followed by the superficial dissolution of HAp due to the attack of hydronium ions resulting from the water protonation reaction with 4-META. After extracting Ca, P, and hydroxyl ions from the apatite surface, the solution turns out to be acidic, leading to the formation of dicalcium phosphate dihydrate precipitate [48]. Previous analysis showed that 4-META-Ca solubilized quicker than 10-MDP–Ca, which leads to decreased molecular stability [34]. This discovery supports the "Adhesion-Decalcification concept" (AD concept), which stipulates that the lower the solubility of Ca salt in the acidic molecule, the stronger and more stable the adhesion with the HAp substrate [17,34].

9. 4-MET: 4-META + water = 4-MET: Two carboxylic groups attached to aromatic groups with methacrylate group as polymerizable group [48].
10. 4-acryloyloxyethyl trimellitate anhydride: Patented by Shofu company (Kyoto, Japan), two carboxylic groups linked to aromatic groups similar to 4-MET except the presence of acrylate group instead of methacrylate group [48].
11. 11-methacryloyloxy-1,1′-undecanedicarboxylic acid: Monomer patented by Tokuyama company (Tokyo, Japan); information regarding this monomer in the literature is quite sparse, 10 carbon atoms comparable to 10-MDP, with a hydrophobic spacer [48].
12. Phenyl-P: Monomer with monohydrogen phosphate group [48].
13. HEMA-P: Monomer with methacrylated H_3PO_4–HEMA esters group [48].
14. HEMA: Monomer with low molecular weight (small size) and often utilized in several adhesive systems [171,172]. This hydrophilic monomer is frequently included in the formulation of adhesives because of its solvent like nature. It consists of a mixture of hydrophilic and hydrophobic polymers. Hydrophilic monomers are usually transported in a water-soluble solvent (acetone, ethanol, water) to encourage an adequate flow and a penetration in the hydrophilic dentin (to influence the strength of the resulting bonding), while hydrophobic monomers promote the chemical bond with resin layer [17,172,173]. This increases stability and helps in preserving hydrophobic and hydrophilic monomers in the mixture by reducing phase separation in the presence of water [174]. Adhesives lacking HEMA monomer might have issues related to phase separation [175]. Although HEMA has numerous positive attributes, it also has drawbacks. HEMA, both in the unpolymerized and polymerized state, certainly absorbs water from the underlying dentin through osmosis and from the outer oral environment [174]. Once polymerized, it can swell, discolor, and contribute to the hydrolysis of the adhesive interface (water blisters become entrapped in the adhesive layer) [48]. Finally, HEMA has been correlated with biocompatibility concerns, as it has been assigned rather substantial allergic potential, and even contributes to probable genotoxicity [176]. All in all, the most notable disadvantages of HEMA are as follow: low polymerization capacity, low mechanical strength, high water sorption, and critical biocompatibility in terms of allergic reaction. When the HEMA concentration declines beneath a critical level, phase separation will happen between the adhesive monomers and water, and a strong air-stream is needed to eliminate the water-containing droplets from the adhesives [177]. High amounts of HEMA might lessen the mechanical characteristics of the resulting polymer [178]. This will result in flexible polymers with inferior qualities. PolyHEMA is basically a flexible porous polymer (‘gel’). As such, high concentrations of HEMA in an adhesive may have deteriorating effects on the mechanical properties of the resulting polymer. HEMA also reduces the vapor pressure of water, and probably also of alcohol [48,178]. High amounts may therefore hinder good solvent evaporation from adhesive solutions. Like all methacrylates, HEMA is vulnerable to hydrolysis, especially at basic pH, but also at acidic pH [178]. Uncured HEMA also has the ability to lower the vapor pressure of water and can make evaporation more difficult through the air-drying stage [48]. The ideal HEMA concentration to obtain higher BSs in primer/adhesive is between 30–40% [179], and 5–25 wt% in single-bottle adhesives [17], though this can depend on the specific adhesive formulation. Despite its effectiveness, the use of HEMA remains controversial. Some studies have shown no significant differences between the clinical performances of HEMA-based and HEMA-free adhesive systems [180,181]. While other findings revealed clinically significant difference between HEMA and HEMA-free adhesive systems [182,183]. In current adhesives, manufacturers strive to significantly lower the HEMA contents or even substitute HEMA with other monomers such as methacrylamide monomer [33]. To conclude, it may be stated that in very favorable conditions, the presence or absence of HEMA monomer might not influence the clinical behavior of adhesive systems. However, it is critical to

have a thorough understanding of the advantages and limitations of HEMA to make informed decisions and select the best adhesive system based on the clinical situation.

15. 10-MDP: This monomer was patented by Kuraray (Kuraray Noritake, Tokyo, Japan) and introduced in 1981 (following 'CSE' Technical Information from Kuraray Noritake). 10-MDP is used in many UAs including All-Bond Universal (Bisco, Inc., Schaumburg, IL, USA), Adhese Universal (Ivoclar Vivadent, Schaan, Liechtenstein), G-Premio Bond (GC, Tokyo, Japan), Futurabond U (Voco, Cuxhaven, Germany), Clearfil Universal Bond (Kuraray Noritake, Tokyo, Japan), and Scotchbond Universal (3M ESPE, St. Paul, MN, USA) [184]. In addition, 10-MDP is a major constituent of SE adhesive systems, with a dihydrogen phosphate group qualified to bond the tooth substrate, long carbonyl chains that render this monomer hydrophobic, and a methacrylate group on the other side capable of bonding to methacrylate-based materials [185]. 10-MDP outperformed the other functional monomers studied in terms of chemical bonding potential. This monomer was documented to self-assemble into "nano-layering", a process focused on the deposition of 10-MDP–Ca salts with low solubility in order to obtain an optimum hybridization [186,187]. Each nano-layering involves two sublayers of parallel 10-MDP monomers placed in reverse direction. This monomer's methacrylate group is pointed inwards, allowing mutual co-polymerization among two contrasting monomers. Its functional P group is oriented outwards, collecting Ca released from dentin structure [184,185,188] (Figure 13).

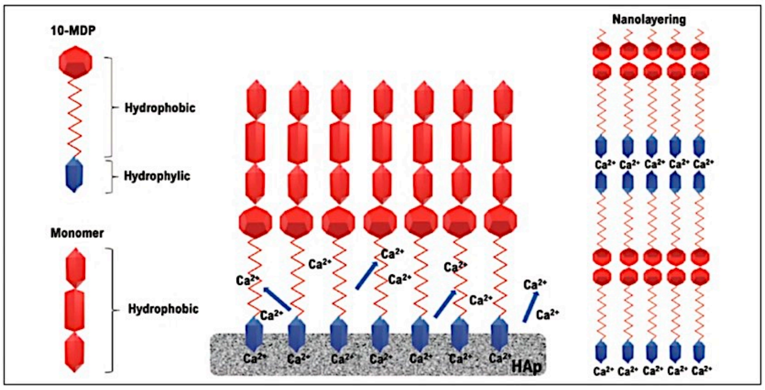

Figure 13. Nano-layering of 10-methacryloyloxydecyl dihydrogen phosphate–calcium salt [146].

The extended carbon-spacer group successfully reduces steric hindrance between the methacrylate and H_3PO_4 ester group while simultaneously providing hydrophobicity to decrease water sorption and enables parallel self-alignment of neighboring 10-MDP molecules during nano-layering [172]. Furthermore, the noteworthy etching influence makes 10-MDP distinctive among functional monomers, causing micro-retention and therefore permitting micro-mechanical interlocking, but also considerably releasing Ca from dentin as the driving force of 10-MDP nano-layering. Additional study is needed to determine the impact of nano-layering on adhesive interface stability [184]. Ca salts formed from the acidic molecule 10-MDP have higher chemical stability than 4-META. This could be explained by the fact that superficial HAp is dissolved by means of hydronium ions in the MDP, resulting in a higher concentration of Ca ions compared to 4-META. The nucleation and development of 10-MDP–Ca crystals on the HAp surface lead to a 4 nm layered structure made up of two MDP molecules. This nano-sized molecular alignment is not seen with 4-META when bonding to dentin. Bonding with 10-MDP is more solid and durable than the one created by 4-META and GPDM. However, the chemical interaction of the functional groups with the HAp crystals in enamel is not as effective as in dentin, likely due to the HAp crystal structure and/or size. This underscores the need for enamel acid etching prior to adhesive procedures using SE or UAs (SEE method) to enhance bonding effectiveness [17].

Inappropriate storage of some adhesives based on 10-MDP for a long period of time leads to the degradation of the MDP monomer [189]. The degradation proceeds via the hydrolysis of the functional group, producing compounds such as MA and 10-hydroxydecyl dihydrogen phosphate, which may eventually weaken the HL quality, due to poor monomer transport, penetration, and curing [17].

Variability in the bonding efficacy of several commercial 10-MDP-based adhesives was noticed [190,191]. The most logical explanation is a difference in chemical composition. BS was displayed to be dependent on the concentration of 10-MDP [36]. But in the presence of HEMA, even in a low concentration, the mechanical integrity of the nano-layers is reduced. For that reason, a HEMA-free adhesive system (like Prime & Bond Universal (PBU); Dentsply DeTrey GmbH, Konstanz, Germany) hypothetically has a stronger ionic binding potential compared to a HEMA-rich system.

MDP is durable in an oral environment due to its hydrolysis stability and more favorable for chemical bonding than 4-MET and Phenyl-P [17,192]. In addition, previous research demonstrated that zinc can be a competitor to MDP–Ca salts, not only HEMA or other components [193].

In 2017, Yaguchi et al. [194] suggested that UAs with less concentration of 10-MDP generate weak adhesion. Similarly, Fujita et al. [195] in 2018 indicated that the rate of 10-MDP–Ca salt formed by the demineralization of enamel and dentin relies on the components that are found in the commercial adhesive, rather than on the MDP and water concentrations.

In 2018, Yoshihara et al. [196] proposed that higher bonding effectiveness of 10-MDP must not only be attributed to their more intense chemical bonding to tooth substrate, but to its higher etching potential as well (by measuring the HAp-dissolving capacity). Other functional monomers (GPDM, Phenyl-P, 4-META) lacked this combination.

In 2018, Putzeys et al. [197] pointed out that the minimal toxic concentration of the functional monomer 10-MDP can stimulate an inflammatory response and suppress an odontoblastic differentiation.

In 2019, Zhou et al. [192] proved that HEMA-free adhesives are preferred since HEMA prevents the MDP-collagen protection.

In 2021, Fehrenbach et al. [198] showed that adhesives including 10-MDP presented higher bonding capacity than materials formulated with other acidic ingredients, although this outcome was dependent on the type of mechanical testing, the nature of the substrate, the acidic content of the adhesive, and the application category of the adhesive.

In 2022, Jin et al. [199] demonstrated that adhesives based on 10-MDP preserve the collagen inside the HL by concurrently enhancing collagen's resistance to exogenous enzymes and hindering matrix metalloproteinases (MMPs) activity, both of which provide the durability of resin–dentin bonding.

In 2023, de Oliveira et al. [200] demonstrated that the combination of HEMA and 10-MDP monomers in self-etching adhesives had no effect on the clinical performance of restorations in terms of retention, postoperative sensitivity, and secondary caries incidence. However, this combination favorably affected the marginal adaption and marginal staining during the two-year follow-up.

16. GPDM: In 1949, Oskar Hagger invented the first adhesive technique by combining GPDM in a liquid cavity sealer with a chemically cured resin-based restorative substance (Sevriton®) [201]. GPDM is a monomer with two methacrylate groups linked by a short carbon spacer to one P acidic functional group. Due to the presence of two polymerizable methacrylate groups, GPDM can promote better polymer formation than 4-META, 10-MDP, and HEMA [17]. The hydrophilicity of GPDM aids in adhesive infiltration into the demineralized dentin due to having similar characteristics to HEMA monomer [13]. GPDM also enhances the interaction between the bonding agents and HAp, comparable in function to 4-META which forms an unstable GPDM–Ca salt. GPDM behaves in a decalcification route, but unlike 10-MDP, it does not expose collagen, but rather promotes the creation of a thick HL with exposed collagen. However, the variances in chemical bonding do not eliminate the actual

bonding effectiveness of adhesive systems comprising GPDM [13,17]. The interaction between GPDM and the co-monomers should be further assessed to gain a better understanding of the positive outcomes with regards to bonding durability of adhesive systems containing this monomer [17,33].

17. PENTA-P: This monomer is characterized by P ester monomers containing carbon=carbon double bonds and a P group [-OP(=O)(OH)$_2$]. When compared to 10-MDP functional monomer, the chain of PENTA is shorter. PENTA has five vinyl groups compared to one in 10-MDP monomer, and these four additional vinyl groups make PENTA more resilient to hydrolytic degradation [51,202,203]. Thus, when hydrolysis occurs and eliminates one vinyl group from the main structure of the monomer, four vinyl groups will still be present for the conservation of the P group. Accordingly, copolymerization to other monomers and adhesion to tooth structure happen at the same time [189,202]. This finding could be elucidated by a previous study which demonstrated that PENTA incorporated into the formulation of the adhesive Prime & Bond Elect (Dentsply Caulk, Milford, DE, USA) had more stability than 10-MDP, as the BS is maintained even at the end of its shelf-life. This is explained by the sustained connection between the four vinyl groups and the P group [202,204] (Figure 14).

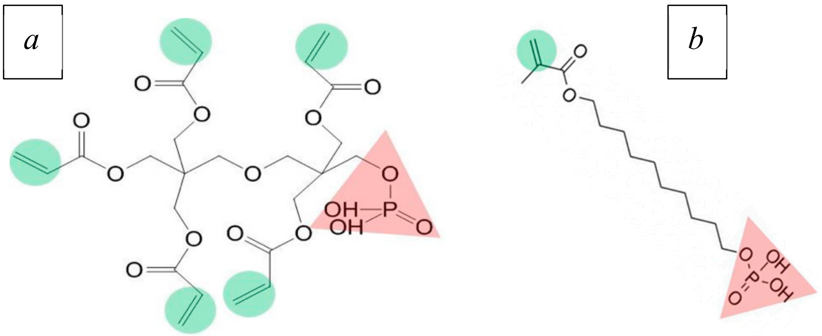

Figure 14. (**a**) Dipentaerythritol penta-acrylate phosphate has a more reliable bond than (**b**) 10-methacryloyloxydecyl dihydrogen phosphate-based adhesives. Reactive double bonds (circles) and acidic moieties (triangles) are marked [204].

Both MDP and PENTA monomers are acidic, so they react with the dental surface by adhering to Ca ions. Thus, these ions were integrated into HL by forming Ca-P complexes. PENTA monomer, unlike 10-MDP, is unable to show a nano-layer (like MDP–Ca salts) due to its massive structure, however, with five double bonds, and a hydrophilic core (unlike MDP, which is hydrophobic), this molecule is capable of improving the wetting process [205,206].

A difference in the interfacial interaction of each functional monomer has been designated in the AD concept that displayed the way molecules interact with HAp-based tissues [33]. This model displays that, primarily, all acids chemically bond to Ca of HAp (Phase 1). This primary bonding phase drives together with a release of hydroxide and P ions from HAp into the solution to achieve an electron neutrality. The stability of the correspondingly generated monomer–Ca salt determines whether the monomer will stay bonded (Phase 2, "adhesion route") or de-bond coupled with an abundant decalcification (Phase 2, "decalcification route") [33,207]. As an example, since 10-MDP–Ca follows the adhesion route while GPDM–Ca essentially follows the decalcification route, the 10-MDP–Ca salt is more stable than the GPDM–Ca salt [207].

Knowing that there is a large number of bonding agents in the dental market, it is challenging to choose the best version. Additionally, a number of these adhesives are introduced as modifications of previous iterations. Therefore, it is crucial to emphasize the features of each component inside the adhesive of choice for better performance. Moreover, the incorporation of various co-monomers (cross-linkers or adhesion promoters), catalysts, and solvents strongly altered the adhesive film properties, which affected the BS of the adhesive system [208].

6.1.3. Solvents

The wetting ability of adhesives is amplified by the addition of different solvents and hydrophilic monomers [26,171]. The former eliminates the water, which is present between the collagen fibers, and dissolves the amphiphilic resin which increases the surface tension. The main solvents used in adhesive systems are acetone, ethanol, and water, each with a different evaporation time [17].

It is important to recall that the air-drying method is more intricate and reliant on pressure, position, angle, distance, and time [209]. Collagen fibrils collapse as a result of this technique, which also reduces monomer penetration and produces weaker BSs. It is advisable to investigate a different, more regulated approach. One of these methods is the blot-drying method, which quickly eliminates extra water by using a foam pellet (tissue or a sponge) to ensure that adhesives penetrate well [22]. The adhesive should ideally be allowed to air-dry on the dental surface in order to remove any leftover solvent, as this could disrupt the polymerization of the resin monomers and leave unwanted voids in the adhesive interface that could serve as defect initiator sites and weaken the BS [210].

Solvent evaporation is a critical factor in determining the bonding effectiveness of modern adhesives [211]. Various factors need to be considered to effectively carry out this clinical step. In this regard, the clinician must take into account that the evaporation capacity varies throughout solvents, which is caused by the vapor pressure (mmHg) [17,212]. This pressure defines the point at which a liquid transforms into a gas [213]. The higher the vapor pressure, the more volatile the solvent is; that is to say, it evaporates more easily [49]. The capacity of solvents to attach to hydrogen is another crucial feature; this property permits collagen to expand again upon dehydration, hence enhancing resin dispersion and self-bonding [17] (Table 1).

Table 1. Properties of solvents commonly used in dental adhesives [17].

Solvent	Dipole Moment (D)	Dielectric Constant	Boiling Point (°C)	Vapor Pressure (mmHg 25 °C)	Ability to Form Hydrogen Bonds
Water	1.85	80	100	23.8	High
Ethanol	1.69	24.3	78.5	54.1	Medium
Acetone	2.88	20.7	56.2	200	Low
Tert-Butanol	1.7	12.5	82.4	46	Medium

Polar solvents play a crucial role in dental adhesive systems. They have the ability to form hydrogen bonds with their solutes, facilitating effective bonding.

Dipole moment is a measure of the separation of positive and negative electrical charges within a molecule. The Debye (D) is a unit used to express dipole moments. It is an indication of the degree of polarity of a molecule, with higher dipole moments demonstrating greater polarity. In summary, it measures how much a molecule's electrons are shared unequally between atoms, resulting in a partial positive charge on one end and a partial negative charge on the other. In the context of solvents, those with high dipole moments have strong polar properties, which make them effective at dissolving polar substances and enhancing interactions with other polar molecules, such as water [64]. Additionally, solvents with high dipole moments and excellent evaporation capacities exhibit good water-removing capabilities, which are essential for optimal adhesive performance. The hydrogen-bonding capacity of a solvent is particularly significant in re-expanding the shrunken demineralized collagen network after dehydration. Solvents with a higher affinity for forming hydrogen bonds can disrupt the stabilizing hydrogen bonds and other forces that maintain collagen in a shrunken state, thereby facilitating adhesive interactions [17,48].

However, dipole moments and hydrogen bonding are not directly proportional. Just because a molecule has a higher dipole moment (like acetone) doesn't mean it forms stronger hydrogen bonds. Acetone has a higher dipole moment than water but forms weaker hydrogen bonds because it lacks the strong electronegative atom-hydrogen bonds that water has (O-H bonds). So, while both dipole moments and hydrogen bonds are related to molecular polarity, their strength and presence depend on the specific molecular structure and the types of atoms involved [17,64].

The dielectric constant is the measure of a material's capacity to store electrical energy in an electric field. It is signified by the symbol ε (epsilon) and is a quantification of the degree to which a material can polarize in reaction to an external electric field. For solvents, the dielectric constant specifies the solvent's ability to reduce the strength of electrostatic forces between charged particles. Solvents with higher dielectric constants have a greater ability to stabilize charges and dissolve ionic or polar substances. In regard to the adhesive performance, solvents with higher dielectric constants can be beneficial because they are capable of effectively dissolving and removing water from the substrate, expediting the interaction between the adhesive and the substrate surface. Additionally, they aid in stabilizing the charged species within the adhesive, promoting better bonding and wetting [17].

The boiling point of a solvent is defined as the temperature at which the vapor pressure of the liquid is equal to the atmospheric pressure, leading to the transformation of a liquid into a gas. It is a crucial characteristic that determines the volatility and evaporation speed of the solvent [17,48].

Acetone is an organic solvent, has a high vapor pressure of 200 mmHg, but lacks an H-bonding capacity, evaporates quickly (evaporation temperature, 56.2 °C), and requires the shortest drying time in the mouth [17,26,209,214]. Acetone-based systems require and tolerate higher humidity levels without any loss of adhesion. Other systems, especially those based on ethanol, require a drier surface [26]. In acetone-based systems, the evaporation point of the water is lowered, while that of acetone is raised when acetone and water come into contact with dentin. This is known as the azeotropic phenomenon, which is defined as a mixture of two liquids that are distilled at a constant temperature and produce a set composition vapor at a certain pressure [215]. As a result, acetone and water evaporate, and the resin is able to pass through.

For this reason, acetone-based adhesives should not be brushed during their application in order to avoid their rapid evaporation before the infiltration of the resin monomers into the demineralized dentin [48,216]. It is important to note that achieving a moist surface does not imply tolerance to contaminants such as blood, gingival fluid, or saliva [17,48].

Acetone allows a mixture of polar and nonpolar chemicals due to its dipole moment and dielectric constant, which facilitates the formulation of single-bottle adhesives that contain hydrophobic and hydrophilic monomers [17,48,217,218]. However, due to its higher vapor pressure compared to ethanol, it is more volatile, necessitating higher solvent concentrations that lower monomer concentration and typically require the application of two or more bonding layers to achieve optimum BS [216]. In fact, reports have shown that acetone-containing adhesives have an inferior BS than ethanol-based solutions [215,219,220]. Additionally, acetone's higher volatilization compared to other solvents is likely to shorten its shelf-life and prevent certain manufacturers from using it [17].

Ethanol is a polar solvent, has a vapor pressure of 54.1 mmHg, average H-bonding capacity, evaporates more slowly (evaporation temperature, 78.5 °C) than acetone, and requires a moderate drying time [17,48,221,222]. When combined with substances like water, ethanol forms hydrogen bonds [222]. Even though this solvent has a higher vapor pressure than water, it cannot be completely eliminated from the dental adhesive within a clinically feasible time frame [221]. A prior investigation revealed that ethanol remained in the adhesive for 60 s after volatilization [223].

Dental adhesives' sorption, solubility, and curing rates can all be hampered by excessive ethanol [17,223]. According to Ye et al. [224], ethanol concentrations of 20% or below are optimal for adhesive systems since they have a lower resin viscosity and enhance molecular mobility and polymer conversion. Higher concentrations may impair the adhesive's mechanical qualities and encourage the phase separation of hydrophobic and hydrophilic constituents [225].

The dentinal collagen matrix could expand and become more rigid when ethanol is added, which makes it easier for monomers to penetrate the demineralized dentin's collagen network. Nonetheless, as ethanol's hydroxyl group esterifies carboxylic groups, it may interfere with the capacity of the acidified chains to etch the tooth surface when paired with monomers that have carboxyl groups such as 10-MDP. Therefore, ethanol is inappropriate for monomers with carboxylic acid moieties [17,48]. Furthermore, residual excess ethanol from air-drying may enhance the adhesive's water sorption and solubility, promoting hydrolytic breakdown and raising the risk of cytotoxicity for human dental pulp cells [225,226].

The single-bottle adhesives' hydrophobic and hydrophilic monomers may not separate as a result of the presence of ethanol. Also, the aqueous ethanol solution creates an azeotrope, which facilitates vaporization of the remaining water within the demineralized dentin substrate [29,227]. However, it is impossible to completely remove both bound and unbound water from the demineralized dentin [228], since ethanol vaporizes slower than acetone [29,229].

Water is strongly polar, has a vapor pressure of 23.8 mmHg, and high H-bonding capacity [10], but because of the low vapor pressure and high boiling temperature (100 °C) [230], water evaporates very slowly and requires the longest drying time [48]. Agreeing to Pashley et al. [10], water has a strong capacity to break hydrogen bonds between collagen fibrils, allowing for further resin infiltration and re-expansion. This is essential for the creation of a HL in ER adhesive systems. As was previously mentioned, this solvent's capacity to ionize the acidic monomers found in SE adhesives—which are in charge of the chemical adhesion of these systems—is another crucial feature [231]. However, due to water's low vapor pressure, it is difficult to completely remove this solvent from the adhesive layer. As a result, to facilitate the evaporation of such a solvent, it is advised to combine it with additional solvents (ethanol and acetone), resulting in an azeotropic mixture [232]. This leads to superior vaporization, which will increase the adhesive's degree of conversion and create a higher-quality of HL that will strengthen the bond [17].

Achieving the optimal moist state can be challenging, particularly when dealing with massive tooth cavities and the intraradicular space. As a result, new adhesive compositions were created to decrease the sensitivity of modern adhesives to moisture.

Certain materials enable proper dentin hybridization regardless of the substrate's moisture content. These adhesives often contain solvents other than water, ethanol, and acetone, such as tertiary butanol [233].

Tert-butanol, also known as 2-methyl-2-propanol, has a vapor pressure of nearly 26 mmHg that is close to the vapor pressure of water (46 mmHg) [17]. Compared to other alcohols, tert-butanol has a molecular chain with fewer hydrogen atoms and a superior molecular weight [234]. Contrary to ethanol-based systems, the molecular structure, which consists of four carbons and one alcohol group surrounded by three methyl groups, offers better stability and compatibility with both water and polymerizable resins [17,235]. Furthermore, due to tert-butanol's higher boiling point compared to acetone and ethanol, the dentin collagen matrix is prone to less shrinkage, the evaporation is slower, and the HL in dry or wet dentin is more resistant [17]. Although butanol-based adhesives are indicated for both "dry" and "wet-bonding" approaches, prior research indicates that BS is higher in wet dentin than in dry dentin [236]. The Dentsply company added tert-butanol (Tertiary butanol) to a two-step ER (ER II) adhesive (Prime & Bond Xp (Dentsply Sirona, York, PA, USA)) because of this solvent's similar vapor pressure to ethanol, which leads to better stability to the chemical reaction with the monomers [2,17].

Later on, Prime & Bond Universal (Dentsply DeTrey GmbH, Konstanz, Germany) was introduced and launched at IDS 2017. This adhesive, which contains a water solvent of 5–24.5% with a new co-solvent "isopropanol" (10–24.5%), was used [237]. Isopropanol has a boiling point of 82.3 °C (close to that of ethanol (78.5 °C)) [173], soluble in water at

25 °C [238], and a vapor pressure of 45.4 mm Hg. The polarity of isopropanol (0.546) is lower than that of alcohol and ethanol (0.654) [239]. The viscosity of isopropanol (2.4 mPa·s at 20 °C) is more than 400-fold lower than that of water (1000 Pa·s at 20 °C) and twice as high as that of ethanol. This may lead to diverse solubility, wetting, and evaporation properties when combined with water in more complex adhesive mixtures [240].

The following Table presents a solvent overview of common systems used in dental adhesives, including the respective pros and cons [204] (Table 2).

Table 2. Solvent overview of common systems used in dental adhesives including the respective pros and cons [204].

Solvent	**Advantages**	**Disadvantages**
Acetone/Ketones [204,217,218]	- Low intrinsic viscosity - Easy removal	- Undesired solvent loss - Risk of interaction with other components
Ethanol/Primary Alcohols [204,221–223]	- Sufficient penetration - Evaporation/removal	- Side reactions (e.g., Michael-addition) - Low stability with acids
Water [204,230]	- Best dentinal compatibility - Essential for etching	- Lowers evaporation rate
Tert-Butanol/Secondary/Tertiary Alcohols [204,234]	- Limited/no side reactions - Acrylate compatibility - High stability with acids	- Increased matrix viscosity

In essence, solvents are chemicals that have the capacity to disperse one or more substances. They play a crucial part in removing moisture from the dental substrate during the evaporation procedure and are in charge of enhancing its infiltration throughout the demineralized matrix [241]. Accordingly, considering all the findings discussed, the solvent composition of adhesives and the substrate's moisture content are critical factors that affect the durability of adhesive interfaces over time, as well as the BS and bonding stability of resin-based restorations [2,7,9,241]. Adhesives based on water or ethanol are an excellent choice for bonding agents, yet their BS may quickly deteriorate. Adhesives based on acetone might work better in overly dry environments, but not on excessively moist substrates [17,33,233]. Tert-butanol-containing adhesives might be vulnerable to dry conditions when dentin hybridization is taking place [233].

6.1.4. Other Components

Some manufacturers include filler particles in their adhesive formulations to enhance the mechanical features of an adhesive layer (for example, Tetric N Bond Total Etch (Ivoclar Vivadent, Schaan, Liechtenstein), and Gluma 2Bond, (Kulzer GmbH, Hanau, Germany)). Others incorporate CHX into their adhesive solutions to improve bond stability by reducing adhesive bond deterioration (for example, Peak Universal Bond (Ultradent Products, Inc., South Jordan, UT, USA) and Futurabond U (VOCO GmbH, Cuxhaven, Germany)). Another chemical added by manufacturers to dental adhesives is GA, which helps in minimizing post-operative sensitivity and maintain the collagen fibers in the HL, improving durability (for example, iBond Total Etch (Heraeus Kulzer GmbH, Hanau, Germany)). To avoid secondary caries beneath restorations, companies use antibacterial agents in the adhesive formulation [33]. An example of an antimicrobial component incorporated in some adhesive agents is the Clearfil Protect Bond (Kuraray, Tokyo, Japan), which is MDPB-based. Cetylpyridinium chloride is also an extremely efficient broad-spectrum antibacterial agent. A further example is the use of fluoride inside FL-Bond II (Shofu, Kyoto, Japan) and Futurabond NR (VOCO GmbH, Cuxhaven, Germany). In addition, the use of polymerizing agents (for example, Camphorquinone (CQ)) is necessary to initiate the polymerization of dental adhesives. Certain producers incorporate dyes into their adhesives to facilitate uniform mixing of the ingredients and serve as an indicator throughout the process, with the resulting bond becoming colorless after curing (Universal Bond by Tokuyama company (Tokuyama Dental, Tokyo, Japan)). In general, the influence of these compounds on the performance of adhesive agents is still uncertain and should be considered in future studies [15,33].

In addition to the aforementioned components, the use of inorganic–organic additives have garnered significant attention for their ability to enhance bonding performance. These additives, particularly in the form of modifier monomers, have been shown to improve adhesion by creating a HL that reinforces the interface between the restorative material and tooth substrate. For instance, as highlighted in studies such as those by Tanaka et al. [242] and Ivanov et al. [243], inorganic–organic compounds contribute to the formation of durable bonds through chemical interactions with both the adhesive and the dentin. The incorporation of these additives results in improved mechanical properties, reduced shrinkage, and enhanced long-term stability of the adhesive interface. Future advancements in adhesive systems will likely continue to explore and optimize the role of these modifiers to further improve clinical outcomes in restorative dentistry.

Referencing critical elements, such as the use of fillers, is essential for comprehending their impact on the properties of the adhesive agent. One potential cause of debonding in dental restorations could be the low mechanical properties of the adhesive layer that bonds the dental substrate to the resin composite. Actually, among the substrates of this bonded area, the adhesive layer has the lowest modulus of elasticity. When subjected to masticatory forces, the adhesive layer experiences higher level of stress among the constituents. In general, stress that surpasses the intrinsic strength of an adhesive layer causes cracks, defects, or failure in the resin–dentinal bond [244].

Usually, adhesive agents do not include filler particles in their formulations [245]. However, from a theoretical viewpoint and in line with composite resin, adding fillers increases the mechanical assets of an adhesive layer [48]. This idea is known as the elastic cavity wall concept [244]. Previously, manufacturers incorporated variable quantities of glass filler particles (1–5 µm in diameter) in the hydrophobic bonding bottle of ER III adhesive systems [48,242,246]. These filled adhesives were loaded up to 40–50 wt%, such as OBFL (Kerr Co, Orange, CA, USA) and PermaQuick (Ultradent, South Jordan, UT, USA) adhesives [247]. Due to the fact that these densely filled adhesives performed exceptionally well in previous studies [248,249], the same method was applied to ER II adhesive systems and SE adhesive systems [250].

Hydrophobic resins are paired with priming and/or acidic monomers in simplified adhesive systems, preventing the inclusion of significantly large amounts of filler. For example, ER II adhesive systems comprise approximately 8.5–15 wt% of fillers (OptiBond Solo (Kerr Co, Orange, CA, USA); One-Step Plus (Bisco, Inc., Schaumburg, IL, USA)) [251,252], which is less than half of the quantity applied in ER III adhesive systems [49].

Instead of microfillers, nanofillers have been used in the adhesive agents [253]. Nanofillers have the ability to penetrate dentin tubules and the collagen network, thereby enhancing the strength of the adhesive layer [251]. Nanometer-sized silica (pure silicon dioxide) less than 20 nm is typically added as nanofiller [230]. Some ER II adhesive systems (Prime & Bond NT and XP Bond (Dentsply Sirona, York, PA, USA), Adper Scotchbond 2 XT (3M ESPE, St. Paul, MN, USA)) and one-step SE adhesive systems (SE I) (Clearfil S3 Bond (Kuraray, Tokyo, Japan), G-Bond (GC Corp, Tokyo, Japan)) include nanofillers in an amount typically ranging between 5 wt% and 10 wt% [48].

Investigations have denoted that simpler adhesives containing nanofillers might have superior mechanical features than unfilled bonding agents; nevertheless, such variations are considered material-dependent [254,255]. Moreover, studies have shown that adding nanofillers does not strengthen bonding to the dentin substrate [256,257]. A detailed examination yielded inconclusive outcomes when filled and unfilled adhesives were compared [258,259].

All in all, the purpose of fillers is to improve the mechanical and physical properties of adhesives. The nanoparticles are intended to increase the viscosity of the adhesive, so that it can be used in a single layer. They make it possible to obtain a sufficiently thick resin layer above the HL, since even if they do not penetrate the collagen network, the film they generate stabilizes the HL. This charged film creates an elastic buffer zone which decreases the stress generated by polymerization shrinkage. In addition, the presence of fillers would increase the wettability of the adhesive and facilitate the infiltration of monomers into the dentin [260,261]. However, adhesives become more viscous as filler levels increase (high filler amounts), compromising the wettability of dental substrates [242]. Though, a potential drawback of fillers not penetrating the collagen network is that the adhesive bond might rely more heavily on the mechanical interlocking and less on chemical interactions with the collagen, which could affect the overall durability and integrity of the bond over time. Furthermore, if the fillers are not sufficiently integrated with the collagen matrix, there is a risk of microleakage or weaker BS in the long-term [262].

Dental adhesive systems involve complex composites with features that are affected by the presence and quantity of each component. The type and ratio of monomers, solvents, and initiators employed have a direct impact on the enhancement of their physical-chemical characteristics as well as their bonding effectiveness with dental substrates. In this context, being aware of the components and their interaction is crucial not only for inventing novel materials, but also to correctly identify their therapeutic application in each clinical circumstance [17].

6.2. Etch-and-Rinse Adhesive Strategy

When it comes to adhesive agents, the dental practitioner has various options, each with its clinical considerations. Choosing an adhesive agent is a critical decision that will affect the procedure's long-term success. Therefore, knowing the classification of the contemporary adhesive agents will assist the general dental practitioner in making decisions [15]. In 2003, Van Meerbeek et al. [263] suggested two different strategies of adhesive systems according to the way they interact with the dental substrate, these being the ER technique and the SE technique. The ER technique necessitates etching followed by rinsing prior to their use, whereas the SE products are applied directly to the dental substrate without any prior treatment. This class includes all SE adhesive systems.

Each of these classes can either be applied in three or two steps for conventional adhesives requiring pre-etching, or in two or one step for SE adhesives [3,9].

Irrespective of the adhesive system used, the bonding process starts with acid treatment to remove or stabilize the smear layer [9]. Behind this layer, this acidic treatment affects the enamel and dentinal surfaces. This process makes micro-roughness favorable to the penetration and diffusion of resin monomers. An adherent interphase and an ideal seal between dental substrate and biomaterial restoration will be formed after photopolymerization [9,15,33]. Essentially, the primary consideration in dental adhesion lies in determining whether to replace demineralized HAp or entirely remove the resin [10,14].

According to previous research, the key component of adhesion to dental tissue is mostly micro-mechanical [4] (Figure 15).

However, additional chemical interactions may also contribute to bonding when the adhesive comprises functional monomers capable of connecting to the HAp [43,264]. This chemical component, whose short-term effect may be masked by the tenacity of the micro-mechanical anchorage, could play a significant role in the adhesion potential of certain low-acid self-etching adhesives and in the durability of bonded joints [4]. This simple ranking makes it possible to classify all the varieties of products currently marketed into four categories: ER III, ER II, two-step SE (SE II), and SE I [9,15,265] (Figure 16).

ER III was introduced in the early 1990s as a family of adhesive systems [266]. ER III materials were the first to allow the complete removal of the smear layer and are still considered the gold-standard for dentin bonding [33]. In this system, the three main components (etching agent, primer, and adhesive resin) are generally packaged in separate containers and applied sequentially [10].

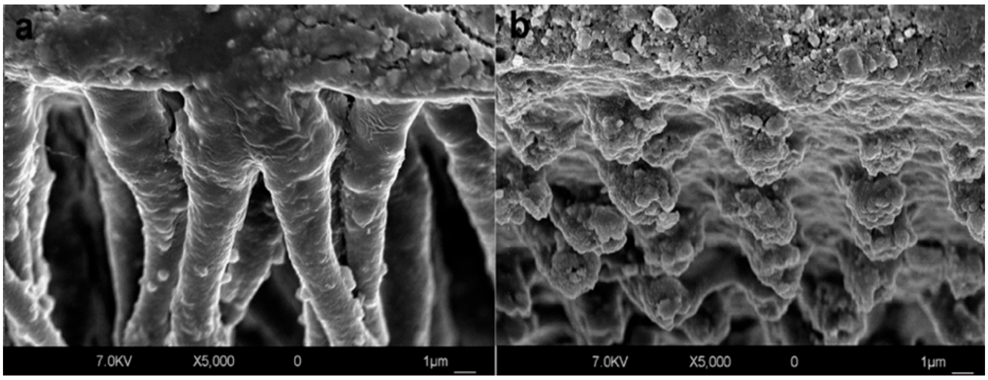

Figure 15. Micrographs of an (**a**) etch-and-rinse (ER) and (**b**) a self-etch (SE) adhesive system. Resin tags are clearly detectable in the ER adhesive systems (**a**), since they infiltrated dentin tubules funneled by the etching agent. SE adhesives often infiltrate no further than the smear layer and smear plugs, revealing a more homogenous morphology that is empty of long resin tags [4].

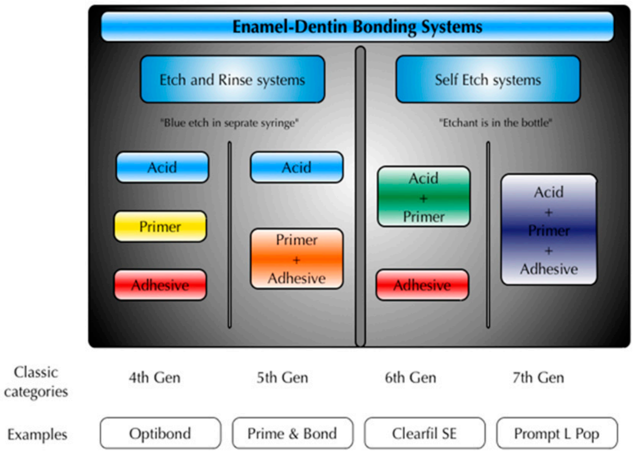

Figure 16. Classification of bonding systems [9].

This concept of total-etching of the ER III systems involves:

- Application of a solution or gel, usually H_3PO_4 (with a pH of 0.1 to 0.4), for a period of 15–30 s on the enamel and a maximum of 15 s on the dentin (a duration longer than 15 s will cause "over-etching") [33,267]. Etching agents are mostly colored gels (thickened by means of silica microparticles) that regulate the application and ensure that all the gel is rinsed off the tooth substrate [15].
- Copious rinsing (15 s and more) using an air/water spray to remove the residues that result from the chemical reaction between the acid and the minerals. However, the surface must remain moist in order to prevent collagen collapse. This is done using a dry applicator, absorbent paper points, or air that removes any excess humidity [9,10,266].
- Once the dentin is moist, the application of a hydrophilic primer solution on enamel and dentin in several layers will be necessary to infiltrate the exposed collagen network, followed by a slight air pump for 5 s to eliminate the solvent (depending on the solvent). Thus, the dentin will exhibit a glossy appearance [9,10].
- Application of adhesive resin on enamel and dentin, followed by the elimination of excess adhesive by a dry micro-brush. Afterwards, polymerization is done according to the manufacturer's recommendation. Thus, the HL is formed by the resin infiltrated surface layer on dentin and enamel. The purpose of the ideal hybridization for these adhesives is to gain high BSs [9], typically in the range of 20 MPa for both enamel and dentin substrates [262].

This system is very sensitive and requires a controlled etching technique, followed by an application of two or more components on both enamel and dentin [33]. However, they are very effective when used correctly, and are the most versatile of all adhesive generations, as they can be used for any bonding protocol (direct, indirect) or photopolymerization (self-cure, dual-cure). These systems are still the standards by which new systems are judged. Nevertheless, they can be very confusing and time-consuming with so many bottles and application steps [9,10,33].

Due to the complexity of ER III (All-Bond 2 and All-Bond 3 (Bisco, Inc., Schaumburg, IL, USA), Clearfil Liner Bond (Kuraray, Tokyo, Japan), Scotchbond Multi-Purpose and Adper Scotchbond Multi-Purpose Plus (3M ESPE, St. Paul, MN, USA), OBFL (Kerr Co, Orange, CA, USA), Syntac ClassicBond-it (Ivoclar Vivadent, Schaan, Liechtenstein), Permaquick (Ultradent, South Jordan, UT, USA), Amalgabond (Parkell, Edgewood, NY, USA), Gluma CPS (Heraeus Kulzer, Hanau, Germany), FL Bond (Shofu, Kyoto, Japan)), dentists sought a simpler adhesive solution. It is not just about the timing and number of bottles, but also the etching process, rinsing, and drying durations [9,33]. This marked a significant turning point in adhesive dentistry [266].

ER II systems were created in the late 1990s with a commercial focus on simplicity and speed of action, hence their general name of “single-component systems” or “one-bottle systems”. Notable products include Admira Bond, Solobond M, Polibond by VOCO (Cuxhaven, Germany); Excite, Excite DSC, Excite F, Single Layer Bond by Ivoclar Vivadent (Schaan, Liechtenstein); Optibond Solo Plus by Kerr (Orange, CA, USA); Prime & Bond 2.0, Prime & Bond 2.1 by Dentsply DeTrey GmbH (Konstanz, Germany); Prime & Bond NT, Prime & Bond XP by Dentsply Sirona (York, PA, USA); One Step, One-Step Plus by Bisco (Schaumburg, IL, USA); Single Bond Adper 2, Scotchbond1 by 3M ESPE (St. Paul, MN, USA); and Clearfil Liner Bond 2 by Kuraray (Tokyo, Japan) [9].

In addition, there was a need to improve the prevention of collagen collapse in demineralized dentin and minimize, if not completely eliminate, postoperative sensitivity. The most common simplification method is therefore the “one-bottle system” which combines the hydrophilic primer and the hydrophobic adhesive resin in a single bottle with a solvent, to be applied simultaneously to enamel and dentin after etching with 35 to 37% of H_3PO_4 (etching on enamel for 15 to 30 s and on dentin for a maximum of 15 s) [268].

Their use is unlikely to be simple due to their low tolerance for handling. Furthermore, their performance is closely related to the moisture of the treated dentinal substrate. All ER II adhesives are incompatible with dual- and self-cured materials. This could be explained by the lower pH of the oxygen-inhibited layer, or the monomers in some simplified products, deactivating the tertiary amine in chemically cured composites [9,33,266].

Several long-term studies of ER II dental adhesives have shown high clinical bonding strengths (~25 MPa) [262]. Despite this, the resin–dentin bond is prone to water degradation. ER III adhesives are less prone to water degradation than ER II dental adhesives [9,266]. This is due to the high concentration of HEMA monomer inside the ER II. HEMA monomer should be added in higher concentrations to stabilize the mixture of ER II and to facilitate the infiltration of the self-priming adhesive inside the demineralized collagen fibrils [15].

The phenomenon of over-wetting in which water prevents the formation of a continuous adhesive seal, intensifies the importance of the issue of removing excess water from the surface of etched-and-rinsed dentin before applying the adhesive [269]. Conversely, a collapse of collagen can occur as a result of intense drying. The difficulty which the clinician now faces is finding the correct degree of dentinal moisture to provide optimal adhesive penetration [266]. Unfortunately, it is very difficult to control this state. Several techniques have been proposed for this purpose: progressive air-drying, elimination of excess water by simple aspiration with the saliva ejector, absorption of excess water by using wet cotton pellet or “micro-brushes” or drying the cavity with compressed air followed by rehydration by wet cotton [270]. ER II adhesives containing acetone are considered more sensitive to the moisture control of dentin than those containing alcohol [9,271].

ER adhesives, such as ER III and ER II, have several advantages [9,10,33]. They rely on an efficient diffusion-based bonding mechanism, enabling profound micro-mechanical interlocking at both the enamel and the dentin surfaces. The aggressive nature of the etchant, normally H_3PO_4, guarantees complete removal of the smear layer, thereby improving bonding performance. ER techniques are mainly effective for enamel bonding, with a recognized long-term adhesion durability. Specific ER adhesives, like ER III OBFL (Kerr Co., Orange, CA, USA) have a longstanding presence in the dental market, signifying reliability over more than two decades. Furthermore, independent clinical trials accomplished over 10 years acknowledge the persistent bond efficiency of ER adhesives, yet the outcomes may vary based on the product. But ER adhesives also present disadvantages. The aggressive nature of H_3PO_4 can result in excessive demineralization of the dentin, affecting its structural integrity. Complete dissolution of dentinal HAp and exposure of the collagen matrix can occur, necessitating the formation of a thicker HL within a limited clinical timeframe. This thick HL might be prone to microleakage, enzymatic degradation, and weak secondary chemical interactions, potentially destabilizing the long-term bond durability [10,15,33].

6.3. Self-Etch Adhesive Strategy

All SE systems contain a water component [33]. Water is needed to activate the ionization potential of their acidic functional monomers [9]. Thus, water is usually used as a co-solvent in SE adhesives, either alone or in combination with ethanol [14]. As they participate in the polymerization, the rinsing step is not required after their application, so they differ technically from ER adhesive systems [272].

Their acidic monomers may be derivatives of carboxylic acid groups (4-META) or P acid groups (Phenyl-P, 10-MDP, PENTA) [9,48]. They demineralize and simultaneously infiltrate both the enamel and the dentin substrates [33,273]. At the dentin level, the mineral phase of the smear layer is dissolved before superficially attacking the 5 μm of underlying mineralized dentin [8]. The Ca and P ions pass into the solution in the liquid adhesive. The carboxyl groups or phosphates of certain functional monomers can form chemical bonds with the dissolved HAp phases, contributing to an enhanced cohesion of the infiltrated resin after polymerization and probably to better resistance to hydrolysis of this zone [266]. The smear layer is not completely eliminated but infiltrated. After the polymerization process, the organic constituents of this layer are impregnated with the resin of the adhesive, as well as the collagen fibers of the treated dentinal surface [9]. The hybrid zone, therefore, contains both the proteins from the smear layer and those from the dentin [33]. Since the pH of the monomers is in the range of 0.8–2.5, the HL is thinner (0.5–1.5 μm for mild or moderate SE adhesives) than the one formed after H_3PO_4 etching ($pH < 1$), which is more acidic (5 μm for ER adhesives) [75]. Nevertheless, it is clear that adhesion to dentin does not depend on the thickness of the HL [274], nor the length of RTs [275].

The acidity of SE primers can be significant in terms of enamel efficiency and the durability of the bond they form [15,33]. In 2003, Van Meerbeek et al. [263] classified SE adhesives according to their acidity: primer and/or strong acid adhesives ($pH < 1$), intermediate ($pH = 1.5$), and those with weaker acids ($pH > 2$). Thus, there are self-etching systems that require the successive application of two different products (SE II) and others that require only one application (SE I) [9].

Usually, SE adhesive systems do not provide a selective demineralization of the enamel, similar to that with 35% H_3PO_4 [9]. Thus, SEE in a separate step with 35% H_3PO_4 has been recommended [190,276] (Figure 17).

SE II systems utilize a two-bottle approach, with the first bottle containing a self-etching primer and the second containing the adhesive resin [15]. The self-etching primer modifies the smear layer on the surface of the dentin and incorporates the products into the coating layer [266]. These systems were introduced in the latter part of the 1990s and early 2000s. They dissolve the smear layer when applied and do not require rinsing; thus, they sought to eliminate the etching step, or chemically include it in one of the other steps: acidic primer applied to the tooth first, followed by an adhesive (self-etching primer + adhesive) [9], or (self-etching adhesive): two bottles or one dose containing an acidic primer and adhesive; a drop of each liquid is mixed and applied to the dental substrate [277]. Obviously, the biggest advantage of this system is that their effectiveness seems less dependent on the hydration state of dentinal surface [9,278].

Figure 17. Selective enamel etching. (Courtesy of Prof Louis Hardan).

Unfortunately, early evaluation of these systems showed sufficient bonding to the etched dentin (41 MPa at 24 h), whereas bonding to enamel was less effective (25%) [9]. This could be related to the fact that they are constituted of an acidic solution with insufficient pH to etch the enamel properly, which is difficult to keep in place and must be continually refreshed [279]. In order to overcome this problem, etching the enamel first with traditional H_3PO_4 at a pH of less than 1.5 is preferred [45,280]. However, some of these products are slightly acidic, with a pH as high as 3.3 [9].

In addition, practitioners using this technique should be careful to confine H_3PO_4 only to enamel. Further etching of the dentin with H_3PO_4 could create a conflict, "over-etching", where the demineralization zone is too deep for the subsequently placed primers to penetrate completely into the demineralized dentin [9,278]. These systems are popular because they are easy to use, with a lower postoperative sensitivity. The reason that self-etching systems tend to minimize postoperative sensitivity is that the smear plugs in the dentinal tubule are left intact [33]. The benefit of SE II adhesives is that their effectiveness is less reliant on the level of dentin's moisture comparing to ER adhesives. Normally, SE II adhesives were described to have better bond stability when compared to SE I adhesives [15,33]. Further, SE II systems are classified into two types:

- Type I adhesives, which are self-etching primer and adhesive systems such as CSE (Kuraray Noritake Dental, Tokyo, Japan), Prelude SE (Danville Materials, San Ramon, CA, USA), and Ultradent Peak SE (Ultradent Products Inc, South Jordan, UT, USA). These adhesives have liquid components including a self-etching primer and an adhesive resin, which are applied separately to the tooth and are generally compatible with self-cured composites.
- Type II adhesive systems such as All-Bond SE (Bisco, Inc., Schaumburg, IL, USA), Brush&Bond (Parkell, Edgewood, NY, USA), Futurabond NR (VOCO America, Inc., Cuspis, CA, USA), Touch&Bond (Parkell, Edgewood, NY, USA), Adper Prompt L Pop (3M ESPE, St. Paul, MN, USA), and Xeno III (DENTSPLY Caulk, Milford, DE, USA).

They use a self-etching primer and adhesive that are mixed together prior to placement and are not compatible with self-cured composites [9,15,33].

Note that the enamel and dentin BS of SE II is lower compared to the ER III and ER II [9]. However, this might be controversial for other researchers [33,266].

SE I (all-in-one) adhesives were introduced in the late 1999 and early 2005 [9,266]. They contain a formulation that mixes a self-etching primer and an adhesive resin in a single bottle [49,278]. SE I systems are theoretically capable of etching and infiltrating both enamel and dentin. The self-etching primer creates a resin layer that bonds with the composite material through photopolymerization [15].

Clinically, this system is the easiest to use, and BS values are generally acceptable [9,262]. Despite the simplicity of the bonding operation, it was possible to eliminate the errors that could occur while mixing several separate components [33]. However, placing and incorporating all the chemistry required for an adhesive system into a single bottle, and keeping it stable for a reasonable period of time, is a significant challenge [9]. These acidic systems contain a significant amount of hydrophilic monomer in their formulations contributing to the increased permeability of the HL and may be subjected to hydrolysis and chemical decomposition [281].

In addition, once the SE I systems are placed and polymerized, they are mostly more hydrophilic than SE II systems; this condition forms water-filled channels that limit the depth of infiltration of the resin into the dental surface and leads to water infiltration from the dentin through the HL. This phenomenon creates voids with a poor sealing ability (Figure 18). The hydrophobic monomers contribute to more stable polymers [23].

SE I adhesives have proven to have the lowest initial and long-term BS of all the adhesives on the market. However, this can be considered a disadvantage [282]. In addition, they presented an incompatibility with self-curing resins and a reduction in shelf-life [15].

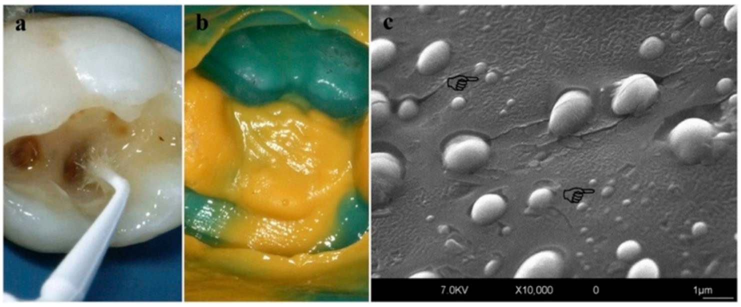

Figure 18. Illustrative steps of the in vivo analysis of the permeability of adhesives [283,284]. A cavity was prepared and bonded (**a**), and an impression of the cavity floor was obtained (**b**). After pouring a cast with epoxy resin, specimens analyzed under a scanning electron microscope revealed water droplets emanating from the adhesive surface (**c**). These droplets are the morphological evidence of water that seeped from the adhesive layer during the setting time of the hydrophobic impression material, forming major droplets as well as minor droplets (pointing finger) over the adhesive [267].

For instance, some of these products are: One Coat 7.0 (Coltene, Altstätten, Switzerland), Xeno IV (Dentsply Sirona, York, PA, USA), G-BOND (GC Corporation, Tokyo, Japan), OptiBond All-In-One (Kerr Corporation, Orange, CA, USA), Clearfil S3 Bond Plus (Kuraray Co., Ltd., Tokyo, Japan), Adper Easy One (3M ESPE Dental Products, St. Paul, MN, USA), Clearfill DC Bond (Kuraray Co., Ltd., Tokyo, Japan), Xeno DC IV (Dentsply Sirona, York, PA, USA), and Futurabond DC (VOCO GmbH, Cuxhaven, Germany) [9].

The SE I and ER II adhesives are simpler versions of the ER III and SE II adhesives [9,33]. It should be emphasized that simplified adhesives are user-friendly and have gained popularity as clinicians prefer easier-to-use dental materials [9,33]. Despite its ease of use and reduced technique sensitivity, the simplified adhesive approach has led to a decrease in effectiveness and durability [15]. Because of their hydrophilicity and the absence of hydrophobic bonding resin coating, cured adhesive films can act as permeable membranes, enabling water to move across the adhesive layer [9]. Based on the existing literature, dental adhesives with a hydrophobic bonding resin as the last stage of the clinical procedure, such as ER III adhesives and SE II adhesives, are more stable and provide longer-lasting restorations compared to their simplified equivalents [15,33]. Certain suppliers provide hydrophobic liners paired with the SE I adhesive (All-Bond SE/All-Bond SE liner (Bisco, Schaumburg, IL, USA)) [15].

Furthermore, simplified adhesives are not compatible with dual or chemically activated resin composites. Once chemical-cure and dual-cure resin composites are combined with simplified adhesives, leftover uncured acidic monomers from the cured adhesives' oxygen-inhibited layer (not covered by a hydrophobic bonding resin) come into direct contact with the composite material [285]. The acid deactivates the aromatic tertiary amines in the dual-cure or self-cure compound, preventing their polymerization [286–288]. This could become more troublesome if clinicians employ composites and adhesives from various suppliers. Some simplified adhesives are specifically designed to be used in conjunction with their patented dual-cure or self-cure composites, with the adhesive requiring independent photopolymerization (for example, Clearfil S3 Bond Plus/Clearfil DC Core Plus (Kuraray Co., Ltd., Tokyo, Japan)). Other SE bonding systems address the issue of incompatibility with self-cured or dual-cured composites by mixing the adhesive with a dual-cure or self-cure activator (for example, AdheSE/AdheSE DC (Ivoclar Vivadent, Schaan, Liechtenstein)) [15].

SE adhesives, including SE II and SE I, offer several advantages [9,15,33]. Mild SE adhesives achieve shallow hybridization of around 1 µm, allowing for easy resin diffusion in a short clinical period. This results in a high-quality HL rather than focusing on its thickness. The dentinal substrate is only moderately demineralized, permitting micromechanical interlocking. Limited collagen exposure makes it more resistant to enzymatic destruction. SE adhesives, especially SE II, have a proven track record, with products like CSE (Kuraray Noritake Dental, Tokyo, Japan) being reliable for over 20 years. Functional monomers like 10-MDP enhance chemical interactions and long-term bonding. Clinical evidence supports SE adhesives' long-term efficacy, with SE II adhesives showing a lower average annual failure rate (AFR) compared to SE I and ER adhesives. However, SE adhesives may have inadequate self-etching on enamel, requiring supplementary etching with H_3PO_4 for optimal retention. Additionally, smear layer interference can affect bonding, and the hydrolytic stability of 10-MDP, while efficient, is not perfect [33].

6.4. Universal Adhesives

Multi-mode universal bonding agents were released a few years ago, continuing the trend of simplifying adhesive methods [25]. This eighth-generation system can be employed with either ER, SE, or SEE procedures, relying on the clinical circumstances and the operator's personal preferences [9,41,172] (Figure 19). SEE is frequently indicated, and UAs can be used on either dry or wet dentin [15,267].

UAs have quickly gained popularity in clinical practice due to their ability to simplify and speed up the clinical bonding process by mixing the primer and adhesive resin in a single bottle [289]. Nonetheless, UAs are still viewed as adhesives that compromise efficiency for simplicity of use since:

- UAs integrate the primer and the adhesive resin, each with a distinct purpose, in a single application step [15].
- UAs generally contain less resin and more solvent compared to systems with separate primer and adhesive components. This formulation can impact the adhesive layer's thickness and its properties. The increased solvent content aids in better wetting and penetration of the adhesive into the tooth structure, but it may also lead to thinner adhesive layers after evaporation and curing, which could be prone to suboptimal polymerization [9,290].

- UA’s film thickness is usually less than 10 µm, influenced by air blowing pressure and time. This thin layer can result in suboptimal polymerization due to polymerization-inhibition by oxygen, suboptimal adhesive interface stabilization, and reduced ability to absorb stress from the restorative composite [33]. Both excessively thin and overly thick adhesive resin films can negatively impact BS, emphasizing the need for an optimal film thickness to ensure effective adhesion and durability [291].
- UAs are more hydrophilic and do not fully convert the adhesive surface to a hydrophobic situation [292,293].
- UAs absorb much more water and have lower hydrolytic resistance [294].

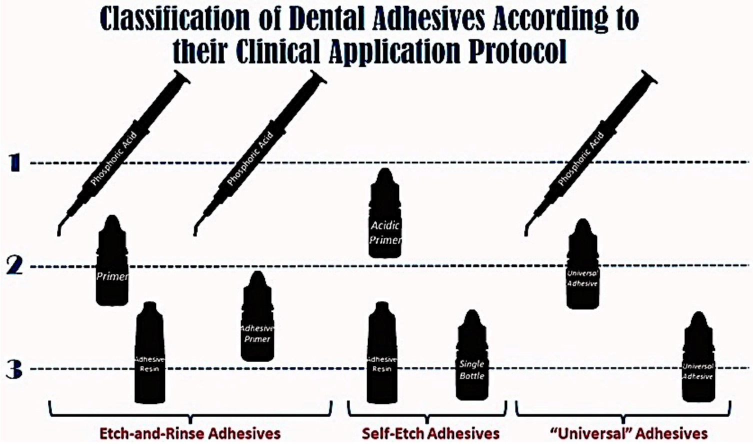

Figure 19. Classification of dental adhesive systems according to their protocol of clinical application (etch-and-rinse, self-etch, or “universal”; and one, two, or three steps) [289].

UAs have a pH range of 1.5–3.2 and are classified as ultra-mild (pH > 2.5), mild (pH < 2), or intermediately strong (pH between 1 and 2) [41]. To create suitable UAs, extremely precise functional and cross-linking monomers with multifunctional properties are necessary [276,295]. They must be able to react with a variety of substrates, co-polymerize with resin-based restorations and cements, and have a hydrophobic property to prevent water sorption after polymerization. Furthermore, they must be hydrophilic in order to “wet” the dentinal substrate, which has a high water content [172]. Also, they must be acidic enough to be effective in a SE technique while not being highly acidic for successful polymerization [287]. The initiators of dual- and self-cure resin cement are interrupted in the case of UAs with high acidity.

Some manufacturers also claim that UAs can be used as adhesive primers for zirconia, alloys, ceramics, and composites in indirect restoration applications [15,295]. Additionally, a direct relationship occurs between the pH and the compatibility of UAs with cements and composites made from self- or dual-cure resin. The company says that some UAs are compatible with dual-cure and self-cure composite materials. As a simplification, the more acidic the adhesive, the less compatible it is with the self-cure mode of the dual-cure resin-based materials [287,296]. This is mainly due to the acid deactivation of aromatic tertiary amines which play a fundamental role in the chemical curing mechanisms of these materials [297]. To alleviate this difficulty, numerous UAs, when used in conjunction with this mode, require the inclusion of a separate “activator” (typically arylsulfinate salts) that should be mixed with the UAs if using an amine-containing cement [172]. The thickness of the polymerized adhesive film must be minimal to avoid interfering with the seating of indirect restorations. Scotchbond Universal Dual Cure Activator (Scotchbond Universal, 3M ESPE, St. Paul, MN, USA), One Coat 7 Activator (One Coat 7 Universal, Coltene, Altstätten, Switzerland), and Clearfil DC Activator (Clearfil Universal Bond Quick, Kuraray Noritake Dental Inc., Okayama, Japan) are examples of the aforementioned activator. However, some UAs like All-Bond Universal (Bisco, Inc., Schaumburg, IL, USA) do not use a separately applied activator, due to their compatibility with self-curing materials. Indeed, this adhesive (All-Bond Universal with a pH = 3.2) is less acidic (not usable as SE on dentin) than other UAs (2.0 < pH < 3.0) [298].

UAs are not to be confused with SE I single-bottle or "all-in-one" systems. These adhesives have distinct chemical compositions characterized by the presence of carboxylate or P monomers. The most used monomer is 10-MDP. Nevertheless, UAs contain a variety of additional functional monomers, including GPDM, PENTA, 4-MET, and 4-META [15].

The acidic monomer 10-MDP, which had been utilized by one SE adhesive system (CSE (Kuraray Noritake Dental, Tokyo, Japan)) for years, was incorporated to UAs once the patent expired [34]. The pioneering product of this category, Scotchbond Universal by 3M ESPE in St. Paul, MN, USA, featured 10-MDP [299]. This was followed by numerous adhesive systems made by different manufacturers. This 10-MDP monomer proved to generate a stronger and more stable bond with the tooth structure than the acidic monomers previously employed [34]. These UAs facilitate both micro-mechanical retention and chemical bonding with the dental substrates [15,172]. 10-MDP has a high affinity for HAp and forms chemical bonds with apatite crystallites via ionic bonding. The concentration of 10-MDP differs across UAs. It has been demonstrated that the higher the monomer concentration, the higher the adhesive's BS [15].

UAs strengthen adhesion to ceramic restorations. Indeed, UAs with 10-MDP improve adhesion to zirconia [300–303] and indirect resin-based composites [304]. On the other hand, UAs have proven incapable of replacing silane-based primers for glass ceramics such as lithium disilicate ceramics [305–307].

This class of adhesive systems should also include water in their formulation to dissociate acidic monomers and to make the SE procedure possible [287]. One of the many dilemmas confronted by chemists in evolving UAs is that water can degrade the chemistry of these systems, contribute to monomer separation, reduce shelf-life, and thus pose a challenge during evaporation [287,308]. In a previous study, Tsujimoto et al. [308] stated that UAs with 10–15% of water (Scotchbond Universal (3M ESPE, St. Paul, MN, USA) and Prime & Bond active (Dentsply DeTrey GmbH, Konstanz, Germany)) are optimal for lowering the impact of surface wetness, while adhesives with more than 25% (G-Premio Bond (GC Corporation, Tokyo, Japan) approximately 25%) of water content and adhesives with water content < 3 vol% (All Bond Universal (Bisco, Inc., Schaumburg, IL, USA)) experience phase separation. In the air-drying step, residual water may cause inadequate polymerization of the adhesive, increase hydrolysis after polymerization, and generally degrade the adhesive surface [23]. The addition of ethanol or acetone to UAs formulations increases resin wetting, infiltration of dental tissues, water elimination, and evaporation during the drying process [309].

Some UAs also state that they can be used instead of silane coupling as agents for bonding to silica-based ceramics (feldspath, lithium disilicate, etc.) [309]. Nonetheless, indirect restorations showed stronger bonding efficacy when silane and bonding resin were applied independently, resulting in a superior BS to an etched glass-based ceramic substrate after one year of water storage [304].

Several silanes are extensively utilized in the industry. Those silanes contain one or more atoms of silicone. However, silane used for the adhesion of silica-based ceramic in dentistry, known as 3-methacryloxypropyltrimethoxysilane, is primary applied after etching of substrate with hydrofluoric acid. Before incorporating silane directly into the universal bonding agent, the treatment mentioned was the optimal choice. This advancement in UAs allowed for its use without the need for a separate application of a silane solution [172]. In application, UAs including silane simplified the adhesion procedure, but this has presented an unforeseen issue. The chemicals found in the adhesive might compromise the stability of the silane and hinder its performance. This problem, along with the manufacturers' belief that the chemical interaction of silane when used with silica-based ceramics is drastically inhibited when merged with all other monomers present in UAs, has prevented some manufacturers from adding silane to their formulations [172,310]. Preceding investigations [298,311] suggested that the incorporation of resin monomers such as MDP or Bis-GMA (used in UAs) in silane solutions considerably reduces the effectiveness of adhesion and chemical interaction of silane to silica-based lithium disilicate when compared to pure silane groups. Thus, it was previously advised that a bond to the silicate-based ceramic can be achieved by etching the porcelain with hydrofluoric acid, then applying the pre-hydrolyzed silane (e.g., RelyX™ Ceramic Primer (3M ESPE, St. Paul, MN, USA), Porcelain Primer (Bisco, Inc., Schaumburg, IL, USA), Ultradent Silane (Ultradent Products, Inc., South Jordan, UT, USA)), which is free of added monomers or resins (pure silane) [172]. Another study revealed the instability of silane mixed with the acidic species in UAs. Thus, the application of silane coat to acid etched glass ceramics was proposed [312].

Most UAs are commercialized in a single bottle [9]. Nonetheless, there are two-bottle UAs designed to improve performance by separating specific components. For example, the G2-Bond Universal (GC Corporation, Tokyo, Japan) is a two-bottle universal bonding agent in which the primer and bonding ingredient are in different bottles and applied independently from standard SE II adhesives [299,313–315]. The G2-Bond Universal (GC Corporation, Tokyo, Japan) features Dual-H technology, allowing the adhesive to transition smoothly from hydrophilic to hydrophobic properties, optimizing adhesion to both tooth and composite. Unlike traditional adhesives, G2-Bond Universal (GC Corporation, Tokyo, Japan) is HEMA-free, enhancing the bonding layer's durability by making it extremely hydrophobic and less prone to water sorption and deterioration. This composition reduces the risk of gap formation and microleakage, leading to superior long-term performance [299]. Similarly, Tokuyama Universal Bond (Tokuyama Dental Corporation, Tokyo, Japan) and LuxaBond Universal (DMG America LLC, Englewood, NJ, USA) are two-bottle systems, but the contents are meant to be blended before use. The separation of acidic monomers and ceramic primers in these two-bottle systems prevents the deterioration of silane coupling agents, thereby preserving their adhesive properties and extending their shelf-life [15,70,202].

HEMA is the main hydrophilic monomer in most UAs. HEMA can disrupt the interaction between 10-MDP and Ca, thereby impeding the establishment of a sufficient bond in 10-MDP-containing adhesives [15]. The presence of HEMA in the same bottle with both hydrophilic and hydrophobic components may result in water sorption and hydrolysis of the adhesive layer, reducing universal bonding adhesion durability [276]. According to previous studies, UAs are material-dependent, and long-term research is still needed to assess the stability of resin–dentin interfaces generated by modern UAs [3,316].

UAs' clinical performance is heavily influenced by the adhesive strategy, calling into doubt their claimed adaptability in terms of application method in a clinical situation [15]. Several systematic reviews examined which application mode (SE vs. ER) was most effective for adhering to dentin and enamel. When utilizing mild adhesives, resin–dentin bonds were similar, but when using ultra-mild adhesives, they were significantly different (favoring the ER strategy) [276,317,318]. Furthermore, data suggests that SEE with H_3PO_4 prior to the application of UAs is an appropriate method for the amelioration of adhesion [15].

To enhance the performance of UAs, several factors must be considered. Firstly, ensuring complete solvent evaporation is crucial, as all adhesive systems use solvents like acetone, ethanol, water, or a combination of them. Inadequate evaporation can lead to incomplete polymerization of the resin, NL, and reduced BS. Extending air-drying times beyond the manufacturer's recommendation or using a warm air stream can help mitigate these issues [27,40,319]. Secondly, proper clinical technique is essential. UAs typically suggest scrubbing the adhesive for at least 20 s, followed by adequate drying and curing with a high-quality light. Adherence to these guidelines is vital for optimal results [33,172].

Additionally, checking the expiry date is important as bonding agents can degrade over time, particularly when exposed to high temperatures. Refrigeration can help maintain their efficacy, but adhesives should be brought to room temperature for at least 30 min before use [320]. Frequent bottle openings can also lead to solvent evaporation, so storing UAs in a refrigerator and securely recapping them after each use is recommended [70].

Studies have shown that the bonding performance of some adhesives decreases towards the end of their shelf-life, while others remain stable, emphasizing the need for careful shelf-life management. Furthermore, HEMA-free formulations using methacrylamides can contribute to an extended shelf-life [70,202].

Reading and following the specific instructions for each adhesive system is also critical, as different systems have unique placement and handling requirements [278]. Pre-etching with mildly acidic UAs can improve enamel BS but not dentin BS [321]. Lastly, the viscosity of the adhesive matters; applying two coats of very thin UAs can achieve the highest BS, while a single coat of more viscous adhesive is sufficient [322].

The advantages and disadvantages of UAs are summarized as follows:

Advantages:

- Suitable for ER and SE adhesives, as well as SEE, making them highly versatile [9].
- In SE mode, there is a potential for chemical interaction with HAp, thus, dentin margins are properly sealed [323,324].
- Application of this class of adhesives in SE mode with a scrubbing technique enhances the BS to enamel substrate [325].
- Keeping the dentin moist when employed in ER mode is not essential [9,324,326].
- Suitable for a wider range of restorative procedures [172].
- Used as zirconia primers [172].
- The Product Research and Evaluation by Practitioners Panel, a research group, reviewed the handling characteristics of UAs and determined that potentially all UAs scored highly for simplicity of use [327,328].
- Patient and operator factors may have a greater impact on restoration longevity than the adhesive used. When using UAs in clinical settings, isolation with a rubber dam is recommended, and moisture control is crucial. However, the reduced number of steps and the associated time savings may also be considered important advantages [124,324,329].

Disadvantages:

- UAs do not propose etching dentin, necessitating a separate enamel acid-etching process. This increases clinical application time [172]. Clinical investigations have shown that the SE method has a lower retention rate than ER and SEE on enamel [330].
- UAs must be mixed with a dual-cure activator when used with self- or dual-cure composite materials, including build-up materials and resin cements with aromatic tertiary amines in the initiator system [331,332].
- When H_3PO_4 is used to etch dentin, they do not effectively seal the margins [333].
- UAs, like traditional SE I adhesives, can act as permeable membranes following polymerization. This allows fluids to pass through the adhesive layer and degrade the resin–dentin contact via hydrolysis [9].
- Solvent evaporation time must be extended to prevent water entrapment and NL [334].
- The addition of silane to the adhesive solution does not increase BS to glass-matrix ceramics. Thus, a separate silane solution must be employed for better adhesion to glass-matrix ceramics [312].

7. Clinical Applications of Dental Adhesion

Dental adhesion is crucial in various restorative procedures, including direct restorations, indirect restorations, and immediate dentin sealing (IDS).

In direct restorations, adhesive techniques bond composite materials to tooth structures, enhancing esthetics and function. Studies such as those by Manauta et al. explore stratification concepts for anterior teeth using predefined enamel thickness and dentin shades [335,336], while Paolone addresses substrate considerations for direct composites [337]. Indirect restorations involve bonding pre-fabricated restorations like crowns and inlays to prepared tooth structures. Research on indirect restorations includes studies on the fracture resistance of different materials and preparation designs, such as the investigation by Comba et al. of lithium disilicate and polymer-infiltrated ceramic network restorations [338], and the comparison by Vichi et al. of factory-crystallized silicates for monolithic metal-free restorations [339]. Immediate dentin sealing (IDS) is another critical application of dental adhesion. IDS involves applying an adhesive resin immediately after cavity preparation and before the placement of an indirect restoration. This technique helps to protect the dentin from dehydration and bacterial contamination, improving the overall BS and longevity of the restoration. IDS is supported by various studies that emphasize its role in enhancing adhesive performance and ensuring a better seal against microleakage [340–342].

These clinical applications underscore the importance of adhesion in ensuring the success and durability of different restorative techniques.

8. Conclusions

Adhesive agents have advanced beyond technique simplicity, and their current progress is prompted by versatility. To aid decision making, general dentists ought to remain up-to-the-minute on the ever-changing adhesive agents. Adhesive dental agents are commonly classified into three categories: ER, SE, and UAs. ER adhesives are available in three-step and two-step varieties, whilst SE adhesives are available in two-step and one-step versions. The pH of SE adhesives has a considerable effect on their bonding ability. UAs provide versatility by allowing dentists to choose an application method (ER, SE, or selective-etch) dependent on the substrate and clinical scenario. ER adhesives generally have high bond effectiveness. They still demand cautious technique and may be sensitive to dentin moisture levels. SE adhesives are popular among clinicians due to their superior efficiency and lessened method sensitivity. UAs offer an array of benefits of both processes, combining the advantages of ER and SE adhesives. However, the efficiency of UAs on dental hard tissues and indirect restorative materials is material dependent, as some adhesives are not intended to adhere to all types of restorative materials.

Recognizing each category's features and limitations is crucial for successful bonding and dental restorations. Ongoing adhesive research and enhanced performance will help to advance the field of adhesive dentistry. As a result, practitioners need to stay up-to-date.

Companies have been making continuing progress in the development of innovative dentin adhesives with the goal of easing the process and improving clinical outcomes, which correlates to their stability with time and BS efficiency. Even though simplicity of adhesive systems has been linked to a loss of effectiveness, efforts have been made to advance the chemistry of the latest adhesives.

It is unclear if adhesives have reached a clinical performance level that can still be enhanced, particularly given the established higher efficiency of gold-standard adhesives. Perhaps clinicians are unaware that it has achieved a success rate exceeding 90% of what can be achieved with dental adhesion. To clinically differentiate adhesives in terms of bonding implementation, a substantially longer follow-up is now required to detect differences in their clinical outcomes across the most recent adhesive generations, even when compared to previous gold-standard multi-step adhesives. The new adhesive solutions can also be ascribed to their capacity to reduce or eliminate postoperative sensitivity, improve marginal seal, reduce microleakage, and increase resin flow into the fissure. The evolution of functional monomers with a strong and stable chemical affinity to HAp is unquestionably a beneficial direction in the pursuit of enhancing dentin adhesion.

The challenge lies in the absence of a gold-standard approach for achieving stable and optimal adhesion of adhesive systems to dentin. Moreover, numerous researchers have proposed various methods to enhance BS. Importantly, the rationale behind this review was to achieve superior and long-lasting adhesion of resin composite to dental tissues, with a focus on developing cost-effective, user-friendly, and efficient adhesive systems.

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