

Universal Adhesives in Clinical Dentistry

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ABSTRACT

Aim: This narrative review aims to present information on current adhesive strategies in operative dentistry and provide details on the status and adhesion potential of universal adhesives.

Background: Adhesive dentistry is a fast-developing field and plays an important role in clinical practice. The new adhesive bonding systems have been developed to simplify and enhance the adhesion between the resin restorative materials and the tooth surface. The bonding mechanisms of these adhesive materials depend on the tooth substrate and the mode of application.

Review results: Increasing demand for simplified adhesive systems and the need to use them in different clinical situations led to the development of new adhesive materials. Multifunctional universal adhesives have been developed in the last decade, becoming an addition to the well-accepted etch-and-rinse and self-etch (SE) adhesives. These adhesives have the versatility to be applied to dental hard tissues with any adhesion strategy and used with direct and indirect restorative materials. However, additional assessments are needed to ensure long-term durability and the versatility of universal adhesives on different surfaces.

Conclusion: Studies have confirmed that universal adhesives provide a better bond strength values and clinical durability with the SE application mode on dentin surfaces. For enamel surfaces, selective enamel etching is recommended to increase adhesive bonding performance.

Clinical significance: Universal adhesives are a promising new class of dental adhesives. However, it is important for clinicians to understand the limitations and correct management of these latest adhesive systems for clinical applications.

Keywords: Adhesion, Bonding, Review, Universal adhesive.

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INTRODUCTION

Adhesive dental materials have gone through substantial changes over the years and have been used in many fields of dentistry. Therefore, adhesion to dental hard tissues has gained great importance. The adhesion of restorative materials to dental tissues is mainly based on an exchange process in which the microporosities exposed by the removal of calcium compounds are replaced by resin to achieve a micromechanical interlocking with the tooth surface.¹

It has been proven that long-term enamel bonding is highly predictable and reliable compared to dentin bonding, primarily because of the morphological and histological differences between the substrates. The inorganic content of enamel is about 96% hydroxyapatite by weight and 4% water and organic material. However, dentin is about 70% hydroxyapatite by weight, 18% organic material, and 12% water.² These amounts vary depending on the tooth's age, depth of dentin, trauma, and pathology. While adhesion to enamel is reliable and based on hybrid interlocking with the microporosities created after acid etching the surface, adhesion to dentin is not reliable due to the heterogeneous structure of the tissue, which consists of a relatively high amount of water, organic content, and the presence of a smear layer.

To achieve a good adhesive interface with resin and tooth structure, it is important to develop a technique to

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penetrate and infiltrate the demineralized zone with resins that can be polymerized by either light curing or chemical curing. This thin layer of resin-infiltrated dentin is called the "hybrid layer,"³ which is a structure formed at the surface of dentin and composed of collagen, resin, and residual hydroxyapatite. The primary bonding mechanism to the tooth structure is micromechanical, but recent studies prove that it can happen on a chemical level with monomers as well as via ionic bonding of calcium in hydroxyapatite.^{4,5} The adhesion process with the tooth surface involves three main steps: Etching, priming, and bonding. Etching is achieved

with an acidic solution that demineralizes the tooth structure to create micro-retentive areas for resin flow. Solvents and hydrophilic monomers are the main ingredients of the primer that improve the wettability of the enamel/dentin surface and allow the replacement of the water present in the substrate with the resin monomers by expanding the collagen fibers of dentin. The bonding agent is the hydrophobic part of the bonding system that creates coupling with the resin-based restorative material.⁶ The strategies used to bond the adhesive to the hard tissues of teeth are classified according to their treatment of the smear layer and the number of application steps, such as the etch-and-rinse (ER) and self-etch (SE) approach.

Etch-and-rinse (ER) Approach

This approach involves a separate phosphoric acid etching step of enamel and dentin. The etching step removes the smear layer and demineralizes superficial dentin, exposing the hydroxyapatite-free dentin collagen network.⁷ There are three-step and two-step ER systems.

In three-step ER systems, the smear layer is completely removed by etching the enamel and dentin with phosphoric acid. The separate application of a primer plays an important role in adhesion by preventing the collapse of exposed collagen and providing a good flow of the adhesive and penetration into hydrophilic dentin. The primer contains a hydrophilic monomer, such as 2-hydroxyethyl methacrylate (HEMA). The hydrophilic primer enables the resin adhesive to infiltrate the collagen network exposed by etching. The aggressive etching of the surface and penetration of the resin adhesive create thick hybrid layers in the dentin surface involving deep micromechanical interlocking.⁷ Two-step ER systems are characterized by applying a combination of primer and bonding agent in the same bottle, following a separate etching step of enamel and dentin. In this approach, to prevent the collapse of the collagen network, dentin should not be completely air-dried. Resin can hardly infiltrate into collapsed collagen, which can occur due to the absence of a separate priming step. The risk of collagen collapse makes this approach technique sensitive to dentin bonding and provides weaker resin–collagen interaction. In some published studies, the bond strength results of three-step ER appear to be higher than two-step ER.^{8,9} Although ER is the best approach for enamel, unprotected collagen fibrils can occur on etched dentin due to the incomplete infiltration of adhesive monomers and make the bonds prone to hydrolysis that leads to degradation over time.^{10,11}

Self-etch (SE) Approach

Self-etch (SE) adhesives use an acidic primer, which does not completely remove the smear layer. This approach limits the depth of the etched tooth structure and has the advantage of demineralizing and infiltrating the tooth surface simultaneously to the same depth. In general, the bonding approach of SE adhesive systems provides two different bonding mechanisms: Micromechanical interlocking and

chemical interaction of 10-methacryloyloxydecyl dihydrogen phosphate (MDP) with hydroxyapatite (HAp) of the surface. This chemical interaction reduces hydrolytic degradation by increasing the durability of resin–dentin bonds in the long term.¹² Some published studies also describe the presence of an acid-base resistant zone (ABRZ) beneath the hybrid layer in SE systems after an acid-base challenge. Because of the layer's resistance to acid challenges, it is assumed that it may play an active role in the prevention of caries attacks.^{13,14} SE adhesives can be two-step or one-step. Two-step SE adhesives require a separate acidic primer and hydrophobic resin application to enamel and dentin. However, one-step (all-in-one) SE adhesives combine the etchant, primer, and adhesive resin in one bottle. SE adhesives can be ultra-mild (pH > 2.5), mild (pH ≈ 2), intermediately strong (pH between 1 and 2), and strong (pH < 1), depending on their pH.¹⁵ Comparatively, the pH of 35% phosphoric acid for ER systems is about 0.7. Since the SE adhesives are not as effective as ER adhesives on enamel, selective enamel etching (SEE) prior to the application of SE adhesive is recommended.

Simplified adhesives (one-step SE and two-step ER) gained popularity among clinicians over time, which led to the development of new materials. However, there are still problems regarding the stability of the bonding, especially with dentin. These adhesives reduce the number of application steps as well as technique sensitivity.⁷ However, by combining the priming and bonding steps, the adhesives became less forgiving of application errors than other SE and ER adhesives. They are generally more hydrophilic, and this, due to incomplete polymerization and adhesive permeability, results in water sorption and degradation of the hybrid layer.¹⁶ Particularly, some studies confirm that one-step SE adhesives did not yield successful results in both clinical and *in vitro* studies.^{17–19}

Self-etch (SE) Adhesives and 10-MDP monomer

Simplified ER and SE adhesives have been shown to degrade over 5 years of *in vitro* testing due to collagen breakdown and degradation of polymer and silane coupling, respectively, while two-step SE with a 10-MDP monomer (which is further described below) resulted in a stable bond strength.¹¹ Therefore, clinically, three-step ER and two-step SE adhesives are shown to be more stable and have a more durable bonding performance compared to simplified adhesive systems.²⁰

Universal Adhesives

Universal adhesives have been introduced to the market in recent years. They allow simpler and faster application by combining acidic primers and adhesives in their application process, like the one-step SE adhesives. The main advantage of the universal adhesives is the option of applying in ER, SE, or SEE modes, according to the clinicians' requirements. In addition, universal adhesives can bond to various materials in a predictable pattern that enables dentists to use them for the bonding of different restorative materials.²¹

Universal adhesives are classified as ultra-mild, mild, and intermediary strong, similar to SE adhesives.⁷ When universal adhesives are applied in the SE mode, their aggressiveness on the dental hard tissue varies according to the pH values of the acidic monomers.^{22,23} The acidic composition of SE adhesives affects the resistance of adhesives to aging.²⁴ The major difference between traditional one-step SE adhesives and universal adhesives is the presence of specific functional monomers that provide chemical bonding to calcium in hydroxyapatite. The most effective of these is a phosphate monomer, MDP.²⁵ The MDP monomer is found in the formulation of the gold standard two-step SE adhesive, Clearfil SE Bond (Kuraray Noritake Dental Co., Ltd. Tainai City, Japan). When the patent of this phosphate monomer expired in 2011, other manufacturers included MDP in their adhesives. The incorporation of this monomer into the other adhesive systems led to the arrival of universal adhesives into the adhesive marketplace. According to the adhesion-decalcification concept, MDP forms ionic bonds with calcium in hydroxyapatite crystals to form stable MDP-calcium salts. With the deposition of these salts, a nano-layer is formed on the outer surface of the hydroxyapatite crystals, and chemical bonding is achieved.²⁵

It has been found that this chemical bond formed with MDP is stable in water. This contributes significantly to the long-term durability of the resin-dentin interface by protecting the hybrid layer against hydrolytic degradation.^{15–24} A 13-year clinical study showed that restorations of noncarious cervical lesions using Clearfil SE Bond and without enamel etching were retained long-term in spite of marginal discrepancies.²⁶ The long-term clinical success of this adhesive can be linked to the chemical bond between calcium and MDP and the micromechanical retention caused by the minimal etching potential of MDP.²⁷

There is still a conflict of opinion concerning the choice of application mode for universal adhesives between clinicians. There are controversial results regarding the bonding strategies' effect on the bond strength of universal adhesives.^{22,28–30} It is well known that in ER mode, etched dentin cannot be fully penetrated by the resin and, consequently, leave exposed collagen fibers.³¹ Therefore, the hybrid layer becomes prone to hydrolytic and enzymatic degradation over time. The potential ionic bonding is also precluded by the removal of calcium.^{22,32–34} In SE mode, universal adhesives partially demineralize the dentin, and some hydroxyapatite remains between the collagen fibrils. Thus, these adhesives are bonded to dentin in two ways, micromechanical and chemical, like the conventional two-step SE adhesives.²² Therefore, the use of universal adhesives with the SE mode on dentin is recommended to optimize long-term bonding performance.²⁸

While the universal adhesives perform well on dentin in SE mode, they cannot create sufficient demineralization, and therefore, there is insufficient microporosity in enamel.¹⁰ Thus, SEE provides better micromechanical retention to enamel.^{22,35,36} A recent meta-analysis on the clinical behavior

of universal adhesives reported that the outcomes of restorations completed with SEE or ER were superior to those completed with SE and led to more predictable retention of composite resin restorations.^{37,38}

Despite their popularity due to the simplified application procedures, universal adhesives still have shortcomings and need improvement in their long-term durability as one-step SE adhesives. They contain both the hydrophilic and hydrophobic components in the same bottle. HEMA is frequently added to many of the commercial adhesives as an essential component. It is a hydrophilic monomer that facilitates infiltration and "wetting" of the demineralized dentin substrate.^{39,40} On the other hand, HEMA causes water accumulation at the interface, impairs polymerization, and makes the interface more susceptible to hydrolytic degradation and water sorption, which influences the long-term stability of the restoration.^{40,41} In addition, it is known that HEMA may give rise to allergic reactions.⁴² Today, manufacturers attempt to reduce the HEMA content or replace it with some alternative monomers, such as with different dimethacrylates.⁴³

The name "universal" also indicates that the adhesives can interact with different kinds of substrates in clinical applications. In general, universal adhesives are also recommended for the bonding of different restorative materials, such as silica-based ceramics, composites, zirconia, and noble and nonprecious metals, due to their improved composition with good chemical stability and mechanical properties at high temperatures. Adhesion of resin cements to glass ceramics, such as lithium disilicate, is achieved by hydrofluoric acid etch, followed by silane application. For the simplification of the indirect restorations' luting procedure, silane is included in the composition of some universal adhesives.⁴⁴ However, the acidic pH of universal adhesives reduces the bonding efficiency and stability of the silane, which is stable between pH values of 4 and 5.^{44,45} Another influence on the effect of silane is its interaction with different monomers in universal adhesives. For example, it has been reported that the silane in universal adhesives is not effective enough in cementation of glass ceramics. For this reason, it is recommended that additional silane should be applied before the use of a universal adhesive, even if it contains silane, to increase the bond strength of glass ceramics.^{45,46}

Some Clinical Advice for a Durable Bonding Performance with Universal Adhesives

Clinical preferences depend on the individual situation and desired treatment options. However, there is no one specific material that can fully overcome the clinical problems of adhesive procedures.⁴⁷

Clinically, several methods that are different from the manufacturer's instructions can be applied to increase the bond strength of universal adhesives to dentin. These application modalities include extended application time, a double-layer application, active application of the adhesive, and application of a hydrophobic resin layer.⁴⁷ Clinical and

in vitro evidence suggests that active application of the adhesive by rubbing increases demineralization and resin monomer penetration into the dentin collagen.^{48,49} This method is also recommended to increase the bonding to enamel when applied in SE mode.⁵⁰

Challenges in the durability of the one-step and universal adhesives are caused by the thin film thickness due to the relatively high solvent content and the high hydrophilicity of the adhesive layer.⁵¹ The application of an extra hydrophobic resin layer has been shown to increase the bond strength of universal adhesives applied in SE mode.^{52,53} The additional resin coating after the application of the universal adhesive converts the one-step SE system into a two-step SE system and a two-step ER system into a three-step ER system. Thus, better polymerization is provided, a thicker and more durable hybrid layer is obtained, and the interface is protected against water penetration.⁷ With the intention to increase the durability by a separate hydrophobic resin application, a new two-step HEMA-free adhesive system comprising a universal-adhesive-derived primer and a highly hydrophobic agent has been launched with promising *in vitro* results.^{54–56} The purpose of developing two-step universal adhesives was to separate the priming and sealing steps of adhesive bonding agent to obtain a thicker adhesive-resin film thickness.⁵¹

All the universal adhesives contain water in their composition. Water is required for ionization of the acidic monomers and to enable decalcification of the tooth structure. Since the residual water may cause hydrolytic degradation, the solvent evaporation step is critical for the universal adhesives. Most manufacturers recommend a solvent evaporation time of 5 seconds; however, this would be insufficient for the removal of residual water from the interface. It is recommended that a prolonged solvent evaporation time of 15 seconds should be used to increase the dentin bond strength.^{57,58}

Like all bonding agents, universal adhesives will have their adhesive ingredients evaporate if subjected to excessive storage time and repeated opening of the adhesive bottle, which may impair the bond strength over time.⁵⁹ Therefore, to reduce degradation over time and preserve shelf-life stability, it is recommended to store universal adhesives in a refrigerator and directly recap the adhesive bottle after use.⁶⁰

To summarize, universal adhesives stand out in many categories compared to older adhesives because of their versatility and wider spectrum of use. However, it is crucial for practitioners to understand that the correct management of the adhesive interface for placement of the latest dental restorative resin materials involves a precise knowledge of the substrates, materials, and clinical protocols. It should always be remembered that simplification of the procedure may have the disadvantage of deterioration in the quality of the interface and introduce technique sensitivity, which is important when working with simplified systems.

REFERENCES

1. Summit JB, Robbins JW, Hilton TJ, et al. *Fundamentals of operative dentistry*. 3rd edition. Quintessence Publishing Co, Inc; 2006.
2. Gwinnett AJ. Bonding basics: what every clinician should know. *Esthetic Dent Update* 1994;5(2):35–41.
3. Nakabayashi N, Kojima K, Masuhara E. The promotion of adhesion by the infiltration of monomers into tooth substrates. *J Biomed Mater Res* 1982;16(3):265–273. DOI: 10.1002/jbm.820160307
4. Fukeygawa D, Hayakawa S, Yoshida Y, et al. Chemical interaction of phosphoric acid ester with hydroxyapatite. *J Dent Res* 2006;85(10):941–944. DOI: 10.1177/154405910608501014
5. Van Landuyt KL, Yoshida Y, Hirata I, et al. Influence of the chemical structure of functional monomers on their adhesive performance. *J Dent Res* 2008;87(8):757–761. DOI: 10.1177/154405910808700804
6. Ozer F, Blatz MB. Self-etch and etch-and-rinse adhesive systems in clinical dentistry. *Compend Contin Educ Dent* 2013;34(1):12–14, 16, 18; quiz 20, 30. PMID: 23550327.
7. Van Meerbeek B, Yoshihara K, Van Landuyt K, et al. From Buonocore's pioneering acid-etch technique to self-adhering restoratives. a status perspective of rapidly advancing dental adhesive technology. *J Adhes Dent* 2020;22(1):7–34. DOI: 10.3290/j.jad.a43994
8. Inoue S, Vargas MA, Abe Y, et al. Microtensile bond strength of eleven contemporary adhesives to dentin. *J Adhes Dent* 2001;3(3):237–245. DOI: 10.3290/j.jad.a7363
9. Kasahara Y, Takamizawa T, Hirokane E, et al. Comparison of different etch-and-rinse adhesive systems based on shear fatigue dentin bond strength and morphological features the interface. *Dent Mater* 2021;37(3):e109–e117. DOI: 10.1016/j.dental.2020.11.006
10. Pashley DH, Tay FR, Breschi L, et al. State of the art etch-and-rinse adhesives. *Dent Mater* 2011;27(1):1–16. DOI: 10.1016/j.dental.2010.10.016
11. Feitosa VP, Sauro S, Zenobi W, et al. Degradation of adhesive-dentin interfaces created using different bonding strategies after five-year simulated pulpal pressure. *J Adhes Dent* 2019;21(3):199–207. DOI: 10.3290/j.jad.a42510
12. Perdigão J, Lopes MM, Gomes G. *In vitro* bonding performance of self-etch adhesives: II—ultramorphological evaluation. *Oper Dent* 2008;33(5):534–549. DOI: 10.2341/07-133
13. Tsuchiya S, Nikaido T, Sonoda H, et al. Ultrastructure of the dentin-adhesive interface after acid-base challenge. *J Adhes Dent* 2004;6(3):183–190. DOI: 10.3290/j.jad.a9507
14. Inoue G, Tsuchiya S, Nikaido T, et al. Morphological and mechanical characterization of the acid-base resistant zone at the adhesive-dentin interface of intact and caries-affected dentin. *Oper Dent* 2006;31(4):466–472. DOI: 10.2341/05-62
15. Van Meerbeek B, Yoshihara K, Yoshida Y, et al. State of the art of self-etch adhesives. *Dent Mater* 2011;27(1):17–28. DOI: 10.1016/j.dental.2010.10.023
16. Breschi L, Mazzoni A, Ruggeri A, et al. Dental adhesion review: aging and stability of the bonded interface. *Dent Mater* 2008;24(1):90–101. DOI: 10.1016/j.dental.2007.02.009
17. Peumans M, Kanumilli P, De Munck J, et al. Clinical effectiveness of contemporary adhesives: a systematic review of current clinical trials. *Dent Mater* 2005;21(9):864–881. DOI: 10.1016/j.dental.2005.02.003

18. Brackett WW, Covey DA, St Germain. One-year clinical performance of a self-etching adhesive in class V resin composites cured by two methods. *Oper Dent* 2002;27(3):218–222.
19. Sarr M, Benoist FL, Bane K, et al. Bonding effectiveness of self-etch adhesives to dentin after 24 h water storage. *J Conserv Dent* 2018;21(2):142–146. DOI: 10.4103/JCD.JCD_257_17
20. Peumans M, De Munck J, Mine A, et al. Clinical effectiveness of contemporary adhesives for the restoration of non-carious cervical lesions: a systematic review. *Dent Mater* 2014;30(10):1089–1103. DOI: 10.1016/j.dental.2014.07.007
21. Alex G. Universal adhesives: the next evolution in adhesive dentistry? *Compend Contin Educ Dent* 2015;36(1):15–40. PMID: 25822403.
22. Cuevas-Suárez CE, da Rosa WLO, Lund RG, et al. Bonding performance of universal adhesives: an updated systematic review and meta-analysis. *J Adhes Dent* 2019;21(1):7–26. DOI: 10.3290/j.jad.a41975
23. Perdigão J, Swift EJ Jr. Universal adhesives. *J Esthet Restor Dent* 2015;27(6):331–334. DOI: 10.1111/jerd.12185
24. Fehrenbach J, Lacerda-Santos R, Machado LS, et al. Which self-etch acidic composition may result in higher dental bonds at the long-term? A network meta-analysis review of in vitro studies. *J Dent* 2022;126:104283. DOI: 10.1016/j.jdent.2022.104283
25. Yoshida Y, Yoshihara K, Nagaoka N, et al. Self-assembled nano-layering at the adhesive interface. *J Dent Res* 2012;91(4):376–381. DOI: 10.1177/0022034512437375
26. Peumans M, De Munck J, Van Landuyt K, et al. Thirteen-year randomized controlled clinical trial of a two-step self-etch adhesive in non-carious cervical lesions. *Dent Mater* 2015;31(3):308–314. DOI: 10.1016/j.dental.2015.01.005
27. Yoshihara K, Hayakawa S, Nagaoka N, et al. Etching efficacy of self-etching functional monomers. *J Dent Res* 2018;97(9):1010–1016. DOI: 10.1177/0022034518763606
28. Chen H, Feng S, Jin Y, et al. Comparison of bond strength of universal adhesives using different etching modes: a systematic review and meta-analysis. *Dent Mater J* 2022;41(1):1–10. DOI: 10.4012/dmj.2021-111
29. Elkaffas AA, Hamama HHH, Mahmoud SH. Do universal adhesives promote bonding to dentin? A systematic review and meta-analysis. *Restor Dent Endod* 2018;43(3):e29. DOI: 10.5395/rde.2018.43.e29
30. Assis P, Silva C, Nascimento A, et al. Does acid etching influence the adhesion of universal adhesive systems in noncarious cervical lesions? a systematic review and meta-analysis. *Oper Dent* 2023;48(4):373–390. DOI: 10.2341/22-067-LIT
31. De Munck J, Van Landuyt K, Peumans M, et al. A critical review of the durability of adhesion to tooth tissue: methods and results. *J Dent Res* 2005;84(2):118–132. DOI: 10.1177/154405910508400204
32. Cardoso MV, de Almeida Neves A, Mine A, et al. Current aspects on bonding effectiveness and stability in adhesive dentistry. *Aust Dent J* 2011;56 Suppl 1:31–44. DOI: 10.1111/j.1834-7819.2011.01294.x
33. Perdigão J, Araujo E, Ramos RQ, et al. Adhesive dentistry: current concepts and clinical considerations. *J Esthet Restor Dent* 2021;33(1):51–68. DOI: 10.1111/jerd.12692
34. Hanabusa M, Mine A, Kuboki T, et al. Bonding effectiveness of a new 'multi-mode' adhesive to enamel and dentine. *J Dent* 2012;40(6):475–484. DOI: 10.1016/j.jdent.2012.02.012
35. Beltrami R, Chiesa M, Scribante A, et al. Comparison of shear bond strength of universal adhesives on etched and nonetched enamel. *J Appl Biomater Funct Mater* 2016;14(1):e78–e83. DOI: 10.5301/jabfm.5000261
36. Suda S, Tsujimoto A, Barkmeier WW, et al. Comparison of enamel bond fatigue durability between universal adhesives and two-step self-etch adhesives: effect of phosphoric acid pre-etching. *Dent Mater J* 2018;37(2):244–255. DOI: 10.4012/dmj.2017-059
37. Josic U, Mazzitelli C, Maravic T, et al. The influence of selective enamel etch and self-etch mode of universal adhesives' application on clinical behavior of composite restorations placed on non-carious cervical lesions: a systematic review and meta-analysis. *Dent Mater* 2022;38(3):472–488. DOI: 10.1016/j.dental.2022.01.002
38. Ma KS, Wang LT, Blatz MB. Efficacy of adhesive strategies for restorative dentistry: a systematic review and network meta-analysis of double-blind randomized controlled trials over 12 months of follow-up. *J Prosthodont Res* 2023;67(1):35–44. DOI: 10.2186/jpr.JPR_D_21_00279
39. Moszner N, Salz U, Zimmermann J. Chemical aspects of self-etching enamel-dentin adhesives: a systematic review. *Dent Mater* 2005;21(10):895–910. DOI: 10.1016/j.dental.2005.05.001
40. Van Landuyt KL, Snauwaert J, De Munck J, et al. Systematic review of the chemical composition of contemporary dental adhesives. *Biomaterials* 2007;28(26):3757–3785. DOI: 10.1016/j.biomaterials.2007.04.044
41. Ahmed MH, Yoshihara K, Yao C, et al. Multiparameter evaluation of acrylamide HEMA alternative monomers in 2-step adhesives. *Dent Mater* 2021;37(1):30–47. DOI: 10.1016/j.dental.2020.10.002
42. Szczepanska J, Poplawski T, Synowiec E, et al. 2-hydroxyethyl methacrylate (HEMA), a tooth restoration component, exerts its genotoxic effects in human gingival fibroblasts through methacrylic acid, an immediate product of its degradation. *Mol Biol Rep* 2012;39(2):1561–1574. DOI: 10.1007/s11033-011-0895-y
43. Tauscher S, Angermann J, Catel Y, et al. Evaluation of alternative monomers to HEMA for dental applications. *Dent Mater* 2017;33(7):857–865. DOI: 10.1016/j.dental.2017.04.023
44. Perdigão J, Gomes G, Lee IK. The effect of silane on the bond strengths of fiber posts. *Dent Mater* 2006;22(8):752–758. DOI: 10.1016/j.dental.2005.11.002
45. Yao C, Yu J, Wang Y, et al. Acidic pH weakens the bonding effectiveness of silane contained in universal adhesives. *Dent Mater* 2018;34(5):809–818. DOI: 10.1016/j.dental.2018.02.004
46. Cuevas-Suárez CE, de Oliveira da Rosa WL, Vitti RP, et al. Bonding strength of universal adhesives to indirect substrates: a meta-analysis of in vitro studies. *J Prosthodont* 2020;29(4):298–308. DOI: 10.1111/jopr.13147
47. Hardan L, Bourgi R, Cuevas-Suárez CE, et al. Effect of different application modalities on the bonding performance of adhesive systems to dentin: a systematic review and meta-analysis. *Cells* 2023;12(1): DOI: 10.3390/cells12010190
48. Moritake N, Takamizawa T, Ishii R, et al. Effect of active application on bond durability of universal adhesives. *Oper Dent* 2019;44(2):188–199. DOI: 10.2341/17-384-L
49. Loguercio AD, Raffo J, Bassani F, et al. 24-month clinical evaluation in non-carious cervical lesions of a two-step etch-and-rinse adhesive applied using a rubbing motion. *Clin Oral Investig* 2011;15(4):589–596. DOI: 10.1007/s00784-010-0408-8

50. Loguercio AD, Muñoz MA, Luque-Martinez I, et al. Does active application of universal adhesives to enamel in self-etch mode improve their performance? *J Dent* 2015;43(9):1060–1070. DOI: 10.1016/j.jdent.2015.04.005
51. Tang C, Ahmed MH, Yao C, et al. Experimental two-step universal adhesives bond durably in a challenging high C-factor cavity model. *Dent Mater* 2023;39(1):70–85. DOI: 10.1016/j.dental.2022.11.021
52. Sezinando A, Luque-Martinez I, Muñoz MA, et al. Influence of a hydrophobic resin coating on the immediate and 6-month dentin bonding of three universal adhesives. *Dent Mater* 2015;31(10):e236–e246. DOI: 10.1016/j.dental.2015.07.002
53. Ermis RB, Ugurlu M, Ahmed MH, et al. Universal adhesives benefit from an extra hydrophobic adhesive layer when light cured beforehand. *J Adhes Dent* 2019;21(2):179–188. DOI: 10.3290/j.jad.a42344
54. Katsuki S, Takamizawa T, Yokoyama M, et al. Influence of bonding agent application method on the dentin bond durability of a two-step adhesive utilizing a universal-adhesive-derived primer. *Eur J Oral Sci* 2022;130(3):e12868. DOI: 10.1111/eos.12868
55. Tsujimoto A, Fischer NG, Barkmeier WW, et al. Bond durability of two-step HEMA-free universal adhesive. *J Funct Biomater* 2022;13(3). DOI: 10.3390/jfb13030134
56. Yamanaka A, Mine A, Matsumoto M, et al. Back to the multi-step adhesive system: a next-generation two-step system with hydrophobic bonding agent improves bonding effectiveness. *Dent Mater J* 2021;40(4):928–933. DOI: 10.4012/dmj.2020-272
57. Luque-Martinez IV, Perdigão J, Muñoz MA, et al. Effects of solvent evaporation time on immediate adhesive properties of universal adhesives to dentin. *Dent Mater* 2014;30(10):1126–1135. DOI: 10.1016/j.dental.2014.07.002
58. Awad MM, Alrahlah A, Matinlinna JP, et al. Effect of adhesive air-drying time on bond strength to dentin: a systematic review and meta-analysis. *Int J Adhes Adhes* 2019;90:154–162. DOI: 10.1016/j.ijadhadh.2019.02.006
59. Mazzitelli C, Maravic T, Sebold M, et al. Effect of shelf-life of a universal adhesive to dentin. *Int J Adhes Adhes* 2020;102:102673. DOI: 10.1016/j.ijadhadh.2020.102673
60. Iliev G, Hardan L, Kassis C, et al. Shelf life and storage conditions of universal adhesives: a literature review. *Polymers (Basel)* 2021;13(16). DOI: 10.3390/polym13162708