UNIVERSIDADE FEDERAL DE PELOTAS

Faculdade de Odontologia

Programa de Pós-Graduação em Odontologia

Tese

Avaliação do desempenho e estabilidade de sistemas adesivos universais.

Carlos Enrique Cuevas Suárez

Pelotas, 2018

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Avaliação do desempenho e estabilidade de sistemas adesivos universais.

Tese apresentada, como requisito parcial, para obtenção do grau de Doutor em Odontologia (Materiais Odontológicos), Programa de Pós-Graduação em Odontologia, Faculdade de Odontologia, Universidade Federal de Pelotas.

Orientador: Prof. Dr. Evandro Piva

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Pelotas, 2018

Universidade Federal de Pelotas / Sistema de Bibliotecas
Catalogação na Publicação

S939a Suárez, Carlos Enrique Cuevas

Avaliação do desempenho e estabilidade de sistemas adesivos universais / Carlos Enrique Cuevas Suárez ; Evandro Piva, orientador ; Adriana Fernandes da Silva, Cesar Liberato Petzhold, coorientadores. — Pelotas, 2018.

185 f. : il.

Tese (Doutorado) — Programa de Pós-Graduação em Materiais Odontológicos, Faculdade de Odontologia, Universidade Federal de Pelotas, 2018.

1. Adesão. 2. Adesivos universais. 3. Revisão sistemática. 4. Biocompatibilidade. I. Piva, Evandro, orient. II. Silva, Adriana Fernandes da, coorient. III. Petzhold, Cesar Liberato, coorient. IV. Título.

Black : D151

Elaborada por Fabiano Domingues Malheiro CRB: 10/1955

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Data da defesa: 10/12/2018

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Dedico este trabalho aos meus pais,
José Ricardo e Ana Lucía;
e a minha irma, Andrea.

Agradecimentos

À Universidade Federal de Pelotas, na pessoa do seu Magnífico Reitor Prof. Dr. Pedro Hallal.

À Faculdade de Odontologia, na pessoa da Diretora Profa. Dra. Adriana Etges.

Ao Programa de Pós-Graduação em Odontologia, na pessoa da Coordenadora do Curso Profa. Dra. Tatiana Cenci. Ao ex coordenador, Prof. Dr. Rafael Ratto de Moraes e, especialmente ao ex coordenador Prof. Dr. Maximilano Cenci, quem facilitou a parte burocrática para conseguir o aceite no PPPGO.

Aos meus pais, José Ricardo e Ana Lucía, que tem sido a minha base desde o começo da minha carreira profissional, especialmente estes últimos três anos que tive que morar fora de meu pais. Agradeço pela sua enorme ajuda e paciência durante todo esse tempo, assim como pelos ensinamentos ao longo da minha vida. Sem dúvida nenhuma vocês fizeram um grande trabalho me mostrando o caminho do bem. Agradeço também a minha irmã Andrea por ter sido um exemplo profissional para mim, e essa capacidade tua para saber lidar com os problemas tem me deixado um grande ensino na minha vida. A vocês três, pai, mai e irmã, fico lhes devendo todo o que eu sou até agora.

Ao meu Orientador, o Prof. Dr. Evandro Piva, quem primeiramente devo agradecer por ter aceitado me orientar, a pesar de não me conhecer previamente. Para mim, você representa um exemplo de pessoa e de profissional, sempre disposto a tomar as coisas com muita calma e serenidade. Nunca vou esquecer as dicas (e piadas também) que você me disse. Obrigado pelos ensinos, tanto dentro quanto fora da quadra de futebol.

Aos Professores Doutores Adriana Silva, Rafael Guerra Lund, César Henrique Zanchi e Wellington Luiz Oliveira da Rosa. Obrigado pelos ensinos recebidos, assim como pelas oportunidades de trabalhar com vocês. Vocês contribuíram para meu crescimento profissional e pessoal.

Agradeço ao laboratório CDC-Bio, muito bem conduzido pelas técnicas Dra. Tatiana e Dra. Josyane, sempre dispostas a ajudar em qualquer metodologia. Guardarei boas lembranças da sua capacidade de trabalho em equipe.

Aos meus amigos de laboratório com que tive o grande prazer de trabalhar estes anos: Andressa, Cristina, Juliana, Katielle, Leina, Peterson e Verônica. Obrigado por ter me aceito como amigo e por ter me acolhido durante este tempo, fui muito afortunado de ter vocês no meu lado. Levo de cada um grandes lembranças e aprendizados. Sem sua presença, eu teria tido muitas dificuldades durante este tempo, grande parte deste trabalho foi desenvolvido com sua ajuda. Com certeza estarei incomodando vocês durante muito tempo.

Aos alunos de iniciação científica que tive a oportunidade de "desorientar": Valéria da Cunha Elias e Christian Schwarzbold. Valéria, obrigado pela paciência nos momentos mas difíceis, aprendi muitas coisas com você. Christian, a pesar de que trabalhamos pouco, tenho certeza absoluta da sua capacidade, você fica em boas mãos dentro do laboratório. Também agradecer a Gabriela Cardoso, quem a pesar de não ter trabalhado juntos diretamente, conseguimos fazer uma boa amizade.

Agradeco ao pessoal do Laboratório de Síntese Orgânica e Polímeros do Instituto de Química da Universidade Federal do Rio Grande do Sul (UFRGS), coordenado pelo Prof. Dr. Cesar Liberato Petzhold. De igual forma, quero agradecer ao Laboratório de Materiais da Faculdade de Odontologia da UFRGS, coordenado pelo Prof. Dr. Fabrizio Mezomo.

Durante a minha estadia no laboratório CDC-Bio, tive a oportunidade de receber à Alma e Abraham, alunos do Doutorado em Engenharia de Materiais (UAEH, México), a quens espero ter ajudado no desenvolvimento da sua tese de Doutorado. Vocês sabem que foi um grande prazer recebe-lhos. Obrigado amigos.

Agradeço também à Prof. Dra. Ana María Herrera González, pelo apoio e ensino desde o começo da mina carreira profissional. Obrigado por me permitir ser um colaborador dentro de su grupo de pesquisa, e pela amizade e confiança demonstrada durante todo este tempo.

Ao meu amigo Juan Pablo Aitkeen, você foi um grande presente que Pelotas me trouxe. Eu não conheço uma pessoa mais alegre que você. Amigo, o futuro é muito promissorio para você.

Durante o período de 2015/2 a 2018/1, tive uma bolsa de estudos outorgada pelo *Programa para el Desarrollo Profesional Docente para el Tipo Superior (PRODEP, México)*. De igual forma, durante o período 2018/2 fui beneficiado com uma bolsa de estudos outorgada pela Coordenação De Aperfeiçoamento De Pessoal De Nivel Superior (CAPES, Brasil).

Gostaria de agradecer à *Universidad Autónoma del Estado de Hidalgo*, instituição onde atualmente trabalho, por ter me outorgado as facilidades para poder relizar os estudos de Doutorado.

Finalmente, quero agradecer a todas as pessoas que de alguma ou outra forma facilitaram a minha estadia no Brasil durante este período. Muito obrigado!

“Vá então. Há outros mundos além deste”

(John “Jake” Chambers [ATN1; SK])

Notas Preliminares

A presente tese foi redigida segundo o Manual de Normas para trabalhos acadêmicos da UFPel, adotando o nível de descrição em capítulos não convencionais. Disponível no endereço eletrônico: <https://wp.ufpel.edu.br/sisbi/files/2017/05/Manual_Normas_UFPel_trabalhos_acad%C3%AAmicos.pdf> Acesso em: 23 de outubro de 2018.

O projeto de pesquisa referente a esta Tese foi aprovado dia 18 de dezembro de 2015, 2012, pela Banca Examinadora composta pelos Professores Doutores Evandro Piva (presidente), Claudio Martin Pereira de Pereira, César Henrique Zanchi e Rafael Ratto de Moraes (suplente).

Resumo

CUEVAS-SUAREZ, Carlos Enrique. **Avaliação do desempenho e estabilidade de sistemas adesivos universais.** 2018. <185f>. Tese (Doutorado em Odontologia). Programa de Pós-Graduação em Odontologia, Universidade Federal de Pelotas, Pelotas. 2018.

O objetivo deste trabalho, dividido em quatro estudos, foi investigar o desempenho e estabilidade de diferentes adesivos universais. Materiais e Métodos: No estudo 1 foi avaliada, através de uma revisão sistemática da literatura, a resistência de união imediata e a longo prazo de adesivos universais, comparando as técnicas de aplicação: condicionamento total e autocondicionante. O estudo 2 avaliou, através de uma revisão sistemática, a resistência de união *in vitro* de adesivos universais a diferentes substratos indiretos quando comparados com primers específicos para cada material. Para ambas revisões, dois revisores realisaram uma busca na literatura em oito bases de dados diferentes. Os dados foram extraídos e categorizados e as médias de resistência de união dos grupos considerados foram analisadas no programa RevMan 5.3.5. No estudo 3 foi analisada a viabilidade celular de diferentes marcas de adesivos universais e a sua relação com o tipo e a quantidade de substâncias lixiviadas em função do método de preparo de amostras utilizado. Foram testados quatro adesivos universais. As amostras foram preparadas usando três métodos diferentes: discos de forma cilíndrica feitos do próprio material, discos de papel de filtro impregnados com o sistema adesivo e discos de dentina bovina impregnados com o sistema adesivo. A técnica de *ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry* (UHPLC-QTOF-MS) foi utilizada para detectar substâncias lixiviadas. A viabilidade celular foi avaliada através do ensaio de proliferação celular WST-1. No estudo 4, diferentes sistemas adesivos foram caracterizados após a simulação de armazenamento (Shelf-life). O tempo de prateleira foi simulado armazenando os materiais em uma câmara climática por diferentes períodos de tempo usando o modelo de Arrhenius. O ensaio de avaliação de resistência de união à microtração (μTBS) foi realizado com base na ISO/TS 11405. O grau de conversão (GC) foi avaliado por meio de espectroscopia no infravermelho por transformada de Fourier acoplado a um dispositivo de refletância total atenuada. A quantidade de nanoinfiltração foi avaliada após identificação de prata amoniacal por intermédio da técnica de microscopia eletrônica de varredura em modo de electróns retroespalhados. Resultados: Para o estudo 1, a evidência *in vitro* sugere que a resistência de união dos adesivos universais pode ser melhorada usando a estratégia de condicionamento seletivo do esmalte. Os adesivos universais com pH suave parecem ser os materiais mais estáveis, tanto no modo de condicionamento total quanto no modo autocondicionante. Em relação ao estudo 2, pôde ser observado que os procedimentos de adesão em zircônia e resina composta indireta poderia ser mais simples usando apenas o adesivo universal, sem necessidade de um primer específico. Por outro lado, a capacidade dos adesivos universais para obter uma resistência de união adequada e durável em cerâmicas com alto conteúdo de vidro e

ligas metálicas é limitada. No estudo 3, de acordo com as evidências obtidas, a quantidade de sistema fotoiniciador lixiviado e o método de preparação da amostra têm um impacto significativo na viabilidade celular. Os resultados do estudo 4 mostraram que todos os adesivos avaliados apresentaram uma alteração significativa no seu desempenho após simulação do tempo de prateleira. De acordo com o protocolo de simulação de envelhecimento acelerado utilizado, para a maior parte dos adesivos avaliados, o período de vida útil estabelecido pelos fabricantes está superestimado. Conclusão: Para o uso em esmalte e dentina, é importante conhecer a categoria do sistema adesivo universal utilizado, com fim de determinar qual é o melhor protocolo de aplicação. Adicionalmente, a capacidade dos adesivos universais de obter uma resistência de união adequada e durável depende do tipo de material restaurador de uso indireto onde eles são aplicados. A interpretação dos resultados dos ensaios *in vitro* de proliferação celular deve considerar que a biocompatibilidade é afetada também pelo método utilizado. Por fim, a simulação do tempo de prateleira deve ser considerada como uma metodologia de rotina durante o processo de desenvolvimento e caracterização de sistemas adesivos universais.

Palavras-chave: adesão; adesivos; adesivos autocondicionantes; adesivos universais; revisão sistemática; biocompatibilidade; armazenamento; envelhecimento acelerado.

Abstract

CUEVAS SUAREZ, Carlos Enrique. **Performance and stability evaluation of universal adhesive systems.** 2018. <185p>. Thesis (PhD in Dentistry). Graduate Program in Dentistry. Federal University of Pelotas, Pelotas. 2018.

The objective of this work, divided in four studies, was to investigate the chemical-mechanical and biological performance of different universal adhesives. Materials and Methods: In the first study, it was evaluated whether the immediate and long-term bonding performance of universal adhesives would be improved by prior acid etching through a systematic review and meta-analysis. Study 2 evaluated, through a systematic review the *in vitro* bonding performance of universal adhesive systems to indirect substrates when compared to material-specific primers. For both systematic reviews, two reviewers performed a literature search on eight different databases. The data were extracted and categorized and the means of bond strength of the groups were analyzed using RevMan 5.3.5 program. In study 3, the cell viability of different universal adhesives and its relation with the type and amount of leached substances were analyzed according to the method of preparation of samples used. Four universal adhesives were tested. Specimens were prepared using three different methods: cylindrically shaped discs made from the material itself, filter paper discs impregnated with the adhesive system, and dentine bovine disc impregnated with the adhesive system. The ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS) technique was used to detect leached substances. Cell viability was assessed by the WST-1 cell proliferation assay. In study 4, different adhesive systems were characterized after shelf-life simulation. Shelf-life was simulated by storing the materials into a climate chamber for different periods of time using the Arrhenius model. The microtensile bond strength test (μTBS) was performed following the directions of ISO/TS 11405. The degree of conversion (DC) was evaluated by means of Fourier transform infrared spectroscopy coupled to an attenuated total reflectance device. The amount of nanoinfiltration (NL) was evaluated after identification of ammoniacal silver by means of the scanning electron microscopy in backscattered electron mode. Results: For study 1, the *in vitro* evidence suggests that the bond strength of mild universal adhesives can be improved by using the selective enamel-etch strategy. Mild universal adhesives seem to be the more stable materials, in both etch-and-rinse or self-etch strategies. Regarding study 2, it could be observed that the clinical procedure of luting zirconia and resin composite restorations could be simpler by using the single-bottle universal adhesives. Conversely, the ability of universal adhesives to achieve and adequate and durable bond strength to glass-based ceramics and alloys is limited. Study 3 demonstrated that the amount of photoinitiator system eluted and the sample preparation method seems to be determinant on the cell viability. The results of study 4 showed that the adhesives evaluated showed an significative alteration in their performance with progressive storage time. According to the accelerated aging protocol used, for most of the adhesive evaluated, the shelf-life period established by the manufacturers is

overestimated. Conclusion: when using on enamel or dentin, it is important to know the category of the universal adhesive system used, in order to determine which would be the best application method. Additionally, the ability of universal adhesives to achieve adequate and durable bond strength depends on the type of indirect restorative material where they are applied. On the other hand, interpretation of the results of in vitro biocompatibility tests should be done with caution, as they may vary depending on the method for the preparation of samples used. Finally, the simulation of the shelf time should be considered as a routine methodology during the process of development and characterization of universal adhesive systems.

Keywords: adhesion; adhesives; self-etch adhesives; universal adhesives; systematic review; biocompatibility; storage; accelerated aging.

Sumário

1 Introdução

O principal objetivo dos adesivos é proporcionar retenção entre materiais restauradores e os substratos dentais esmalte e/ou dentina (VAN LANDUYT et al., 2007). O mecanismo fundamental de ligação ao esmalte e a dentina é baseado em um processo de troca em que os minerais retirados dos tecidos duros dentais são substituídos por monômeros resinosos que após a polimerização, se tornam micromecanicamente entrelaçados nas porosidades criadas (VAN MEERBEEK et al., 2011).

Os sistemas adesivos usados atualmente podem ser classificados de acordo com a abordagem clínica em convencionais e autocondicionantes (MOSZNER; HIRT, 2012). A estratégia de adesão dos sistemas convencionais consiste em dois ou três passos. A utilização de adesivos de três passos requer condicionamento ácido prévio, em geral utiliza-se um gel de ácido fosfórico a 32-37%, um primer e um adesivo. Nos sistemas simplificados de dois passos, o segundo e terceiro passo (primer/adesivo) são combinados (MOSZNER; HIRT, 2012). Por outro lado, os sistemas adesivos autocondicionantes são baseados no uso de monômeros ácidos que são capazes de condicionar e infiltrar na dentina e/ou esmalte (MOSZNER; SALZ; ZIMMERMANN, 2005). Estes sistemas podem ser de um ou dois passos; os sistemas adesivos de dois passos incluem a utilização de um primer ácido, que condiciona o substrato (VAN MEERBEEK et al., 2011), já os sistemas autocondicionantes de passo único combinam o primer e o adesivo em um único frasco (ANUSAVICE; SHEN; RAWLS, 2014). Ainda, estes sistemas autocondicionantes podem ser classificados de acordo com sua acidez como “fortes” (pH <1), “moderadamente fortes” (pH = 1,5), “suaves” (pH > 2) e “ultra-suaves” (pH >2.5) (VAN MEERBEEK et al., 2010).

Atualmente os clínicos devem escolher entre esses dois tipos de sistemas adesivos. As evidências atuais apontam que uma adesão satisfatória à dentina pode ser obtida com a abordagem autocondicionante (BRESCHI et al., 2008; TJÄDERHANE, 2015). Entretanto, essa estratégia revelou algumas limitações na adesão ao esmalte (CARVALHO et al., 2012; MIYAZAKI et al., 2012). Portanto, o

condicionamento seletivo do esmalte em uma etapa separada com ácido fosfórico tem sido recomendado antes da aplicação de sistemas adesivos de tipo autocondicionante (ROTTA et al., 2007). Os adesivos “universais” ou “multimodo” foram introduzidos para serem usados em qualquer estratégia de adesão: condicionamento total, autocondicionante ou na técnica de condicionamento de esmalte seletivo (MUÑOZ et al., 2013). De maneira geral, eles são adesivos autocondicionantes de passo único que podem ser utilizados em conjunto com a aplicação prévia de ácido fosfórico (CHEN et al., 2015). Essa capacidade de multi-abordagem permite que os clínicos apliquem o adesivo em qualquer uma das estratégias de adesão descritas acima, dependendo da situação clínica específica e das preferências pessoais dos operadores (ALEX, 2015).

Uma revisão sistemática com meta-análise publicada pelo nosso grupo de pesquisa (DA ROSA; PIVA; DA SILVA, 2015) mostrou que a resistência de união dos adesivos universais é melhorada pelo uso do condicionamento prévio com ácido fosfórico no esmalte. Por outro lado, para a dentina, este efeito foi evidente apenas com o uso de adesivos universais classificados como ultra-suaves. Apesar deste resultado, umas das limitações relatadas nesta última revisão foi a escassez de estudos laboratoriais que avaliem a resistência de união a longo prazo após algum tipo de envelhecimento, assim como a falta de estudos clínicos randomizados que permitam corroborar os resultados encontrados pela revisão.

Por outro lado, os adesivos universais também podem ser utilizados para promover adesão entre diferentes substratos indiretos e materiais cimentantes resinosos (ALEX, 2015). Segundo o conceito de adesivo universal, os fabricantes incluíram na composição deles diferentes monômeros funcionais que melhoram a ligação química a diferentes substratos indiretos. Visto que existem no mercado, diferentes primers ou adesivos específicos projetados para promover a ligação entre cimentos resinosos e os diferentes substratos indiretos (SOARES et al., 2005; VARGAS; BERGERON; DIAZ-ARNOLD, 2011), o que pode dificultar que os clínicos escolham o sistema correto para situações específicas de adesão, o uso clínico de um adesivo para todos os substratos resulta muito conveniente.

A pesar desta evidente vantagem, há controversa em relação à combinação de vários componentes de diferentes naturezas químicas em um único frasco, especialmente em termos de eficácia e estabilidade (YOSHIHARA et al., 2016). A literatura científica demonstra inúmeros trabalhos avaliando o desempenho dos

adesivos universais em substratos indiretos, no entanto, a questão da eficácia clínica desses sistemas adesivos em relação aos diferentes primers especialmente projetados para ligação a cada substrato, ainda continua. Neste sentido, e devido à falta de estudos clínicos com acompanhamento a longo prazo, a revisão sistemática de estudos laboratoriais é uma abordagem para tentar responder a essa questão.

Visto um ponto de vista biológico, a introdução de novos produtos no mercado exige a garantia de que esses materiais possam ser usados com segurança em ambientes clínicos. Visto que a formulação dos adesivos universais consiste em misturas complexas de monômeros, solventes, ácidos orgânicos, fotoiniciadores e aditivos, como silano e clorexidina (CHEN et al., 2015), a introdução destes novos componentes pode alterar o comportamento biológico do complexo polpa-dentina. Nesse sentido, diversos estudos que avaliaram a viabilidade celular de adesivos universais já foram publicados, relatando resultados contraditórios sobre a sua biocompatibilidade (CATUNDA et al., 2017; ELIAS et al., 2015; JIANG et al., 2017; PUPO et al., 2017; VAN LANDUYT et al., 2015). Considerando que a biocompatibilidade dos materiais dentários é influenciada pela liberação de componentes que não se ligaram na cadeia principal da matriz resinosa (TOZ et al., 2017), a quantidade de substâncias não-reagidas que em entram em contato com as células desempenha um papel importante nos valores de viabilidade celular observados nos testes de biocompatibilidade.

Analisando os diferentes trabalhos acima mencionados, é evidente que procedimentos padrão ainda são necessários para avaliar com precisão a toxicidade real dos adesivos universais atuais, especialmente pela falta de conhecimento em relação a sua composição exata. Até o momento, o conhecimento exato com relação à quantidade e ao tipo de substâncias lixiviadas dos adesivos universais ainda é escasso.

Apesar da tentativa dos fabricantes de fornecer materiais mais versáteis e fáceis de usar, os sistemas adesivos do tipo autocondicionante apresentam problemas relacionados a mudanças na composição do material durante o período de armazenamento na prateleira (VAN LANDUYT et al., 2007). Inclusive, desde a introdução dos sistemas adesivos autocondicionantes no mercado, a estabilidade de prateleira desses materiais tem sido considerada como uma das suas principais limitações (MA, 2010). Para este tipo de adesivos, tem se relatado que a razão para não alcançar um desempenho satisfatório de adesão pode ser devida não apenas a

procedimentos clínicos incorretos, mas também à degradação dos componentes ou evaporação dos solventes (FUJITA; NISHIYAMA, 2006).

Na prática clínica, a vida útil dos adesivos é de extrema importância e os fabricantes sempre fornecem uma data de validade (geralmente 2 anos), após a qual se espera que o material exiba propriedades indesejáveis para sua correta aplicação (DONOHUE; APOSTOLOU, 1990). Neste contexto, diversos critérios têm sido propostos para determinar o que e como medir níveis aceitáveis de estabilidade (WOO et al., 1996), no entanto, estes critérios aplicam-se especificamente para avaliar a estabilidade dos medicamentos, o que pode não ser aplicável para materiais de alto desempenho como os adesivos universais, o que deixa clara a necessidade de estabelecer um protocolo específico com fim de determinar o prazo de validade de materiais odontológicos, monitorando a estabilidade de diversas propriedades deles ao longo do tempo.

Considerando o que foi anteriormente relatado, o presente trabalho visa investigar o desempenho e estabilidade de diferentes adesivos universais. Os objetivos específicos da presente pesquisa incluem:

1. Avaliar, através de uma revisão sistemática da literatura, a resistência de união imediata e a longo prazo de adesivos universais, comparando as técnicas de aplicação: condicionamento total e autocondicionante.
2. Revisar sistematicamente a literatura para avaliar a resistência de união *in vitro* de adesivos universais a diferentes substratos indiretos quando comparados com primers específicos para cada material.
3. Analisar a viabilidade celular de diferentes adesivos universais e a sua relação com o tipo e a quantidade de substâncias lixiviadas em função do método de preparo de amostras.
4. Caracterizar diferentes adesivos universais em função do seu prazo de validade após a simulação do tempo de prateleira.

2 Capítulo 1

Title. Bonding performance of universal adhesives: An updated systematic review and meta-analysis[1]

Short title. Bonding performance of universal adhesives.

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Keywords: Adhesives; Dental bonding; Dental materials; Systematic review.

Declarations of interest: None.

[1] Artigo aceito para publicação no periódico Journal of Adhesive Dentistry

2.1 Abstract

Purpose. To evaluate whether the immediate and long-term bonding performance of universal adhesives would be improved by prior acid etching through a systematic review and meta-analysis.

Materials and methods. Two reviewers performed a literature search up to April 2018 in eight databases: PubMed, Web of Science, Cochrane Library, SciELO, Scopus, LILACS, IBECS, and BBO. Only studies that evaluated the dentin or enamel bond strength of universal adhesives using a self-etch or etch-and-rinse strategy were included. Analyses were carried out using RevMan 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). A global analysis comparing self-etch or etch-and-rinse strategies and the influence of aging in bonding performance was performed with random-effects models at a significance level of $p < 0.05$.

Results. A total of 59 in vitro studies were included in the meta-analysis. The enamel bond strength of universal adhesives was improved by the etch-and-rinse approach ($p < 0.05$). In dentin, this effect was observed for ultra-mild and intermediately strong universal adhesives ($p < 0.05$). Irrespectively of the strategy employed, intermediately strong adhesives showed a decrease in bond strength after any type of aging. This effect was also observed for ultra-mild universal adhesives used in the etch-and-rinse approach ($p < 0.05$). Mild universal adhesives showed bond strength stability in both strategies ($p > 0.05$).

Conclusions. The in vitro evidence suggests that bonding performance of mild universal adhesives can be improved by using the selective enamel-etch strategy. Mild universal adhesives seem to be the more stable materials, in both etch-and-rinse or self-etch strategies.

PROSPERO: CRD42017079479

Keywords: Adhesive; Dental bonding; Dental materials; Universal Adhesives; Systematic review

2.2 Introduction

The current adhesive systems can be classified according to their adhesion strategy into etch-and-rinse or self-etch adhesives.[122] Etch-and-rinse adhesives are applied after complete phosphoric acid etching of the dental substrates (dentin and enamel).[75] On the other hand, the acid etching step is eliminated in the self-etching systems, as they contain monomers with acidic functional groups that simultaneously etch and prime the dental substrate.[65]

Actually, clinicians may choose between these two types of adhesive systems.[120] According to Van Meerbeek,[122] despite the high-product dependency, both types of systems have performed successfully both in laboratory and clinical research. The current evidence has pointed out that adequate bonding to dentin can be achieved with the self-etch approach.[10,107] However, this strategy has revealed some limitations in bonding to enamel.[15,62] The bond strength to enamel with self-etch adhesives was lower than etch-and-rinse systems.[122] Thus, selective enamel etching in a separate step with phosphoric acid has been recommended prior to application of self-etching adhesive systems.[90]

The "universal", "m ultipurpose" or "multimode" adhesives have been introduced to be used in any bonding strategy: etch-and-rinse, self-etch or selective enamel-etch.[67] They are essentially one-step self-etch adhesives that may be associated with phosphoric acid etching.[17] This multi-approach capability enables clinicians to apply the adhesive in any of the bonding strategies described above, depending on the specific clinical situation and the operators' personal preferences.[2] Additionally, one of the major concerns of the previous generation of one-step self-etch or 'all-in-one' adhesives systems was related to its increased nanoleakage after any type of aging and limited bond durability.[122] This compromised long-term performance was related to the presence of complex mixtures of hydrophilic and hydrophobic components within a single bottle.[118] As universal adhesives represent one type of one-step self-etch adhesives, the durability and stability of bonded interfaces created by these new adhesive systems continue to be questionable.

A previous systematic review and meta-analysis of our group[20] showed that bond strength was improved by the use of universal adhesives with prior acid etching for enamel. On the other hand, for dentin this effect was not evident with the use of

mild universal adhesives. Since the publication of our review, researchers have conducted new and more sophisticated studies in this research field. Also, there are also some concerns about the effectiveness and long-term durability of these adhesive systems. Therefore, the aim of this study was to evaluate whether the immediate and long-term bonding performance of universal adhesives would be improved by prior acid etching through a systematic review and meta-analysis. The hypothesis tested was that there would be no difference in immediate and long-term bond strength to dental substrates when using universal adhesives with the etch-and-rinse or self-etch strategy.

2.3 Materials and Methods

This systematic review was reported in accordance with the guidelines of the PRISMA statement.[63] The protocol was registered in the PROSPERO international database for systematic reviews (CRD42017079479). The research question was: does the etch-and-rinse strategy improve the immediate and long-term bond strength to dentin or enamel of universal adhesives?

2.3.1 Literature search

The literature search was systematically performed by two independent reviewers until April 11, 2018 (considering unlimited publication years). Eight distinct electronic databases were screened: PubMed (MedLine), ISI Web of Science, Cochrane Library, SciELO, Scopus, LILACS, IBECS, and BBO (Biblioteca Brasileira de Odontologia). The inter-examiner agreement was quantified using the kappa coefficient. The keywords and search strategy used in PubMed and adapted for other databases is listed in Table 1 (Supplementary information). The reviewers hand-searched the reference lists of included articles for additional papers. After the screening of articles, all studies were imported into Mendeley Desktop 1.17.11 software to remove duplicates.

2.3.2 Study selection

Two reviewers independently assessed the titles and abstracts of all studies. The eligibility criteria consisted of selecting studies that evaluated dentin or enamel bond strength of universal adhesives in sound permanent teeth using self-etch or etch-

and-rinse techniques. Only studies that evaluated shear bond strength to enamel and microtensile bond strength to dentin were considered.[121] Case reports, case series, pilot studies, clinical trials, and reviews were also excluded. Only papers written in the English language were considered for this updated review. Full copies of all of the potentially relevant studies were assessed. Those that appeared to meet the inclusion criteria, or had insufficient data in the title and abstract to make a clear decision were selected for full analysis. The full-text papers were independently assessed in duplicate by two review authors. Any disagreement regarding the eligibility of the included studies was resolved through discussion and consensus by a third reviewer. Only papers that fulfilled all of the eligibility criteria were included.

2.3.3 Data extraction

The data were extracted using a standardized form in the Microsoft Office Excel 2016 software (Microsoft Corporation, Redmond, WA, USA), with all of the trial documents containing demographic data (year, country); outcomes evaluated, number of teeth, universal adhesive system used, predominant failure mode and composite used. If any information was missing, the authors of the included studies were contacted twice via e-mail to retrieve the missing data. If authors had not given any answer by two weeks after the first contact, the missing information was not included. For the articles that presented the information in graph formatting and for which the data could not be obtained from the authors, mean and standard deviation was calculated using WebPlotDigitizer 4.0 software (Austin, Texas, USA).

2.3.4 Quality assessment

The methodological quality of each included in vitro study was assessed by two reviewers according to the parameters of the previous systematic review.[20] The risk of bias of the article was evaluated according to the description it gave of the following parameters: random sequence generation, selective reporting, coefficient of variation, incomplete outcome data, blinding and other bias. The coefficient of variation (CV) of each article was calculated and classified as low, medium, high and very high.[16,89] Articles with low or medium CV were classified as low risk of bias, while articles with high or very high CV were classified as high risk of bias.

2.3.5 Statistical analysis

The meta-analyses were performed using Review Manager Software version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The analyses were carried out using a random-effect model, and pooled-effect estimates were obtained by comparing the standardized mean difference between bond strength values obtained using etch-and-rinse or self-etch approach. Bond strength comparisons were made considering the type of universal adhesive (ultra-mild, pH ≥ 2.5; mild pH ≈ 2; or intermediately strong, pH ≈ 1.5);[121] substrate (enamel or dentin) and methodology used. The comparisons were made to evaluate the immediate and long-term bond strength within each bonding approach (etch-and-rinse or self-etch) separately. Immediate bond strength was considered when the bond strength test was performed after storing the specimens for 24h in water at 37°C, while long-term bond strength was considered when the bond strength test was performed after storing the specimens for periods longer than 24h or after any thermocycling process.[43] A p-value < 0.05 was considered statistically significant. Statistical heterogeneity of the treatment effect among studies was assessed using the Cochran Q test and the inconsistency I^2 test, in which values above 50% were considered as indicative of substantial heterogeneity.

2.4 Results

2.4.1 Search strategy

A total of 9284 publications were retrieved in all databases. A flowchart outlining the study selection process according to the PRISMA Statement[63] is shown in Figure 1. The initial literature review identified 6366 records for initial examining. Of these, 6285 studies were excluded after reviewing the titles and abstracts, leaving a total of 81 studies to be examined by full-text reading. Of these, 23 were not included, because twenty-nine evaluated bond strength using a methodology different than enamel shear bond strength and dentin microtensile bond strength[3,5,47,51,53,64,85,92,94,101,102,110,13,112,116,126,18,21,24,30,31,33,46], two[36,87] did not evaluate bond strength and one[70] did not evaluate bond strength to sound dentin, thus in total 59 in vitro studies were analyzed in this review. The inter-examiner agreement was excellent (kappa coefficient = 0.84).

2.4.2 Descriptive Analysis

Ten different universal adhesive systems were evaluated in this review. The adhesives G-aenial Bond (GC, Tokyo, Japan) and Peak Universal Bond [Primer] (Ultradent, South Jordan, UT, USA) were considered intermediately strong (pH ≈ 1.5); the adhesives Futurabond M+® (VOCO, Cuxhaven, NI, Germany), Futurabond U® (VOCO, Cuxhaven, NI, Germany), Adhese Universal® (Ivoclar Vivadent, Schaan, Liechtenstein), Clearfil Universal Bond® (Kuraray, Okayama, Japan), OptiBond XTR® (Kerr, Orange, CA, USA), Prime&Bond® Elect (Dentsply Caulk, Milford, DE, USA) and Single Bond Universal (3M ESPE, St.Paul, MN, USA) were considered mild (pH ≈ 2); finally only the adhesive AllBond Universal® (Bisco, Schaumburg, IL, USA) was considered ultra-mild (pH ≥ 2.5). The main components of these universal adhesives are described in Table 2 (Supplementary Information).

Among the different methodologies used by the in-vitro studies included in this review (Table 3; Supplementary Information), 20[4,6–8,26,34,41,44,59,69,73,86,99,102-104,111,113-115] evaluated shear bond strength to enamel, 3[13,53,79] evaluated micro-shear bond strength to enamel, and 37[1,17,19,25,29,32,33,35,37,38,44,45,48,50,56-58,61,66-68,71,74,79,80,93,96-98,105,109,123,124,129–131] evaluated microtensile bond strength to dentin.

2.4.3 Meta-analyses

For the enamel shear bond strength (Figure 2a-b and 3a), the etch-and-rinse strategy improved the bond strength and differed significantly from the self-etch strategy for all universal adhesives systems before aging ($p < 0.05$). After aging, comparisons could be made for mild (Figure 2c) and intermediately strong (Figure 3b) universal adhesive systems, resulting in a difference between the bonding approaches, favoring the etch-and-rinse strategy ($p < 0.05$). In terms of stability within the etch-and-rinse (Figure 2d and 3c) or self-etch approach (Figure 2e and 3d), the meta-analysis showed that the bond strength remained stable after any type of aging for mild and intermediately strong adhesives.

With regard to dentin microtensile bond strength, the etch-and-rinse approach improved the bond strength for ultra-mild universal adhesives before aging ($p < 0.05$; Figure 4a). The meta-analysis of bond strength after aging also showed this tendency (Figure 4b). When used in the etch-and-rinse approach, the bond strength of ultra-mild

adhesives was impaired after aging processes ($p < 0.05$; Figure 4c), whereas when the self-etch strategy was used, the bond strength remained stable (Figure 4d).

For mild adhesives, etch-and-rinse approach was statistically similar to self-etch before aging in dentin (Figure 5a), and this behavior was observed after aging ($p > 0.05$; Figure 5b). The bond strength stability analysis revealed that both strategies remained stable after the aging processes (Figure 5c-d).

For intermediately strong adhesives, the etch-and-rinse strategy favored both the immediate (Figure 6a) and aged (Figure 6b) bond strength to dentin ($p < 0.05$). In terms of stability, bond strength was impaired after the aging processes in any of the bonding strategies analyzed (Figure 6c-d).

2.4.4 Quality assessment

According to the parameters considered in the analysis of in vitro studies, the majority of studies scored particularly poorly in the items selective reporting and blinding of the examiner (Figure 7; Supplementary Information). A low risk of bias was observed regarding for the items random sequence generation, coefficient of variation, incomplete outcome data and other bias.

2.5 Discussion

We conducted an updated a systematic review and meta-analysis regarding the bond strength of universal adhesives depending on the approach in which they were used: self-etch and etch-and-rinse based on literature published after 2015. Since that date, a considerable number of new articles evaluating the performance of universal adhesive systems have been published; our previous review included 10 studies and most of them reported only immediate bond strength, while this updated review included 59 studies involving universal adhesives with different pH and bond strength evaluation after different aging protocols.

In accordance with our previous systematic review,[20] the performance of universal adhesive systems was shown to be dependent on their pH, the substrate to which it was bonded (dentin or enamel) and adhesive strategy used: self-etch or etch-and-rinse. However, the new meta-analyses that could be performed in this update allowed to demonstrate that the stability in the bond strength to dentin of the multi-

mode adhesives depends largely on their pH. On enamel, irrespective of the pH of the adhesive system, bond strength was improved by the use of prior phosphoric acid etching. On the other hand, dentin bond strength of mild universal adhesives was not dependent on the adhesive strategy used, and these adhesives seemed to be the materials with better stability. Considering these factors, the hypothesis of this updated review was partially accepted.

Our findings regarding bonding to enamel corroborate that up to now the use of phosphoric acid continues to be the best achievable strategy to improve bond strength of universal adhesives.[120] The etching step with phosphoric acid produces macro and micro porosities on enamel surface resulting from the dissolution of the hydroxyapatite.[128] This process leads to an increase in surface area of the substrate, allowing the resin monomers to infiltrate into the enamel, resulting in the formation 'prism-like' resin tags after the polymerization process.[88] Conversely, self-etch adhesive systems contain acidic monomers that simultaneously condition and prime the dental substrates.[122] Nevertheless, self-etch adhesives are unable to etch enamel to the same depth as phosphoric acid,[27] resulting in lower enamel bond strength values,[76] that was also observed in our analysis. After aging no decreases were observed for both etch-and-rinse and self-etch approaches, suggesting that both techniques are capable to achieve enough strong bonds which could effectively seal off the water diffusion pathway through the tooth-restoration interface, limiting degradation of its components by hydrolysis.[22] From a clinical point of view, it seems that rather than presenting higher initial bond strength values, it is more desirable that an adhesive has a long-term bonding stability. This fact explains the reason why several randomized clinical trials have concluded that additional etching of the enamel margins is not critical for the overall clinical performance of two-step self-etch adhesives.[12,28,82,83]

Bonding to dentin is considered a more challenging scenario, due to the composition of this substrate.[120] Our results showed that the bond strength to dentin was affected by the bonding strategy and the pH of the adhesive used. The etch-and-rinse approach improved the bond strength to dentin of intermediately strong universal adhesives. When an etch-and-rinse approach is used, the acid-etching step solubilizes the mineral content of the dentin (including the smear layer) to some extent.[75] Subsequent application of the adhesive system results in monomers infiltrating into the

collagen network and replacing the water between the collagen fibrils.[78] After this, in situ polymerization leads to the formation of the so-called hybrid layer, which in combination with the presence of resin tags within the dentinal tubules, provides the composite restoration with micromechanical retention.[119] Irrespectively of the bonding strategy used, etch-and-rinse or self-etch, the dentin bond strength of intermediately strong universal adhesives was significantly impaired after any aging processes. These lower values are explained by the presence of unpolymerized monomers remaining after light activation, which continue to demineralize the dentin due to their high level of acidity, thus promoting dentin-adhesive interfaces with low hydrolytic stability and low stable chemical interactions with the collagen.[122] In addition, the dissolved calcium phosphates embedded within the interface are soluble and very unstable, which may weak the interfacial integrity.[122] Laboratory and clinical data have previously demonstrated the reduced bond durability and restoration longevity when strong self-etch adhesives were used on dentin,[9,23,95,117] this being one of the reasons why the literature has recommended that it is better to avoid their use.[122] In regards to the intermediately strong self-etch adhesives analyzed in this review, their inconsistent bonding performance to dentin could be correlated with higher rates of clinical failure, however the lack of evidence on the clinical performance of these types of adhesives prevented us from confirming this correlation, so this type of adhesives should be further studied.

Dentin bond strength of ultra-mild self-etch adhesives was also improved when using the etch-and-rinse strategy in both immediate and long-term analysis. Although the role of resin tags in bonding performance is still debatable,[55,100] a recent study demonstrated that ultra-mild self-etch adhesives did not form resin tags when used in the self-etch mode, but they did form tags when used in the etch-and-rinse mode.[124] Based on this, micromechanical interlocking achieved through good dentin hybridization, considering the presence of resin tags and hybrid layer, could be proposed to improve the bond strength of ultra-mild self-etch adhesives. Despite the beneficial effect of the etch-and-rinse approach on the immediate bond strength of ultra-mild universal adhesives, it should be noted that the application of phosphoric acid led to a decrease in the bond strength values after aging. A previous study has demonstrated that the phosphoric acid treatment prior to application of the single-step adhesive may impact adversely on long-term dentin bond durability.[39] The basis of this

behavior lies in the fact that phosphoric acid etching of dentin removes hydroxyapatite, which is essential to achieve chemical bonding.[40] Moreover, excessive drying of etched surfaces may lead to collapse of the collagen network, which prevents monomer penetration into the decalcified dentin.[81] Another explanation could be that impregnation of the collagen fibrils exposed after acid etching could increase the activity of different endogenous gelatinolytic/collagenolytic enzymes, such as matrix metalloproteinases (MMPs) and cysteine cathepsins,[108] that promote degradation of the hybrid layer.[106] In clinical terms, applying an universal adhesive using an etch-and-rinse approach transforms it into a two-step etch-and-rinse adhesive, leading to the limitations inherent to this type of bonding strategy itself. Actually, with regard to the etch-and-rinse approach, the two-step etch-and-rinse adhesives performed clinically less favorably than conventional three-step etch-and-rinse adhesives, and therefore, their use would be questionable.[84]

Bonding performance of mild universal adhesives to dentin was not dependent of the bonding strategy used, which suggest that these types of adhesives could be used in a multi-mode approach. Studies with mild self-etch adhesives have demonstrated that when applied, dentin is partially demineralized, leaving a substantial amount of hydroxyapatite crystals around the collagen fibrils.[122] Thus, self-etch adhesives could interact with dentin in two ways: micromechanical and chemical.[122] The micromechanical interaction occurs due to in situ polymerization of the monomers that infiltrated into the dentin tissue, in a manner similar to that occurring with conventional etch-and-rinse adhesives. Whereas, the chemical interactions occur due to ionic bonding between functional monomers of adhesive systems and calcium in the residual dentin hydroxyapatite.[14] Besides, after aging processes, it was also observed no differences when using either the etch-and-rinse or self-etch approach. Also, the majority of studies included in the meta-analysis demonstrated that bond strength of mild universal adhesives remained stable, irrespective of the technique used. The stability of universal adhesives has been related to the presence of the 10-MDP monomer[42,125] that forms a low-soluble, stable nanolayer together with deposition of MDP-Ca salts at the bond interface,[127] thereby increasing its mechanical strength and preventing its degradation over time. Clinically, using the etch-and-rinse approach for bonding to dentin has several disadvantages; thereby, it should be considered that the

best option for bonding to dentin using mild universal adhesives seems to be the self-etch strategy.

The present systematic review demonstrated the influence of pH on the immediate and long-term bonding performance of universal adhesives. These results should be interpreted with caution, due to the high heterogeneity observed in the different comparisons made, and the inherent limitations of laboratory studies that may not represent the clinical performance of materials evaluated. Although there is a high number of in vitro studies found, only a few clinical trials are already available in the literature that evaluated the bonding performance of universal adhesives, and the evidence available at present corresponded to short follow-up periods.[11,49,52,54,60,77,91] The available published data from these clinical trials suggested that the clinical performance of these adhesive systems did not depend on the bonding strategy in up to 36 months of evaluation. Despite this result, it was reported a less satisfying performance relative to marginal discoloration over time, and further clinical studies with longer follow-up periods are still needed.

Finally, although it is difficult to stablish a relationship between the bonding effectiveness measured in the laboratory with the clinical effectiveness determined by randomized clinical trials,[121] it must be pointed out that the generally superior laboratory data of the adhesives systems currently considered the “gold standard” can confirm their excellent clinical performance.[14,72] Since the main causes of failure of composite restorations are related to the occurrence of fracture and secondary caries, it seems that achieving a stable bonding interface, especially in the long-term, renders the restorative treatment more predictable in terms of clinical performance. Considering the results obtained in this review, the following recommendations to clinicians could be stated: a) when applied to dentin, prior acid etching before the use of intermediary strong and ultra-mild universal adhesives it is not recommended and, b) selective etching of enamel followed by the application of a mild universal adhesive currently appears to be the best choice to effectively achieve a durable bond to tooth tissues.

2.6 Conclusion

The in vitro evidence suggested that bond strength to dentin of universal adhesives was dependent on their pH. Bonding performance of mild universal adhesives could be improved by using the selective enamel-etch strategy. When applied in dentin, mild universal adhesives seem to be the materials with better stability in both etch-and-rinse or self-etch strategies. Furthermore, a significant decrease in the bond strength after any type of aging was observed with the use of intermediately strong adhesives, irrespective of the substrate or adhesion strategy used.

2.7 Clinical relevance

The general practitioners should be aware of the type of category to which their universal adhesive system belongs in order to know which would be the best application method.

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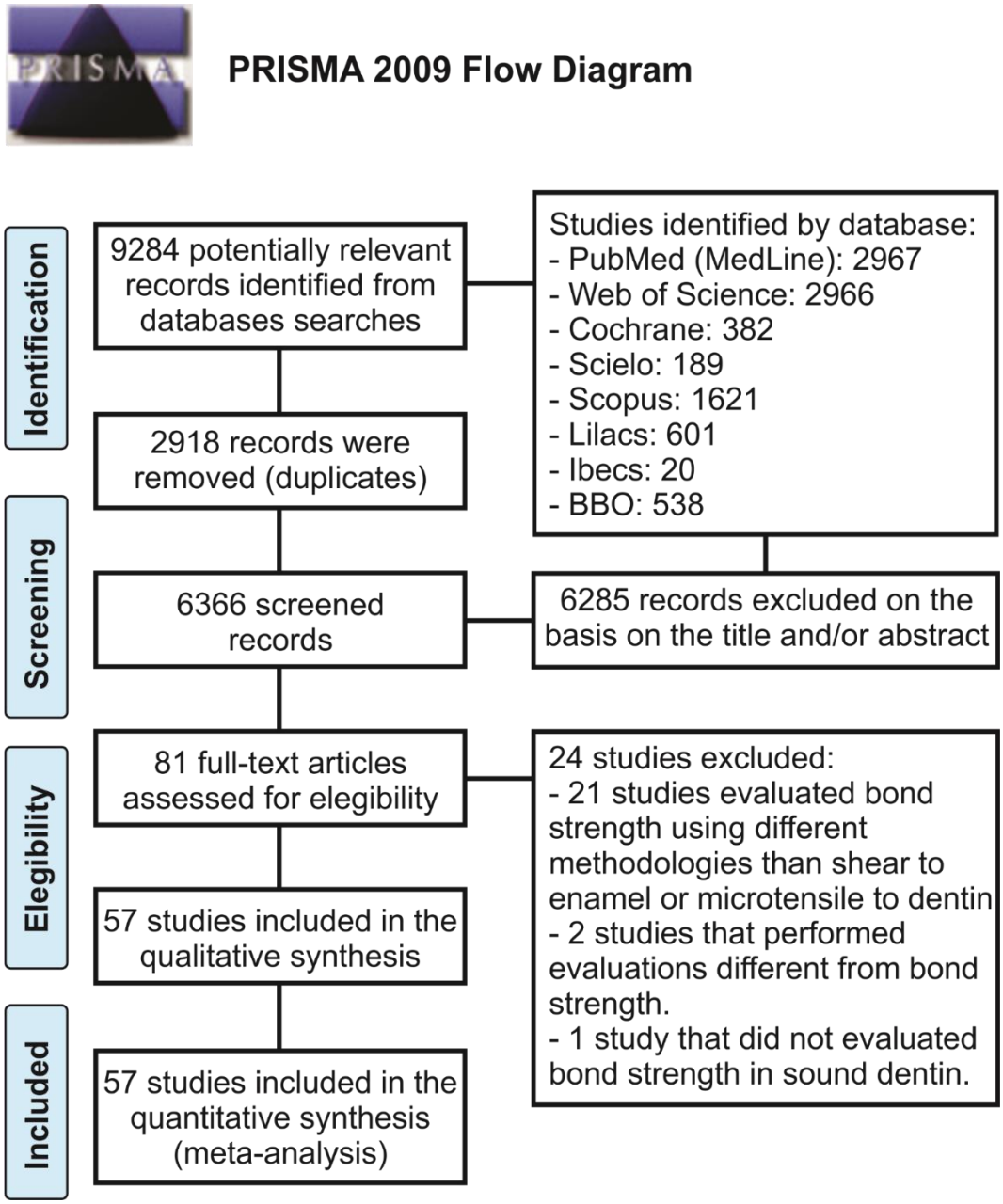

Fig. 1 Search flowchart according to the PRISMA Statement

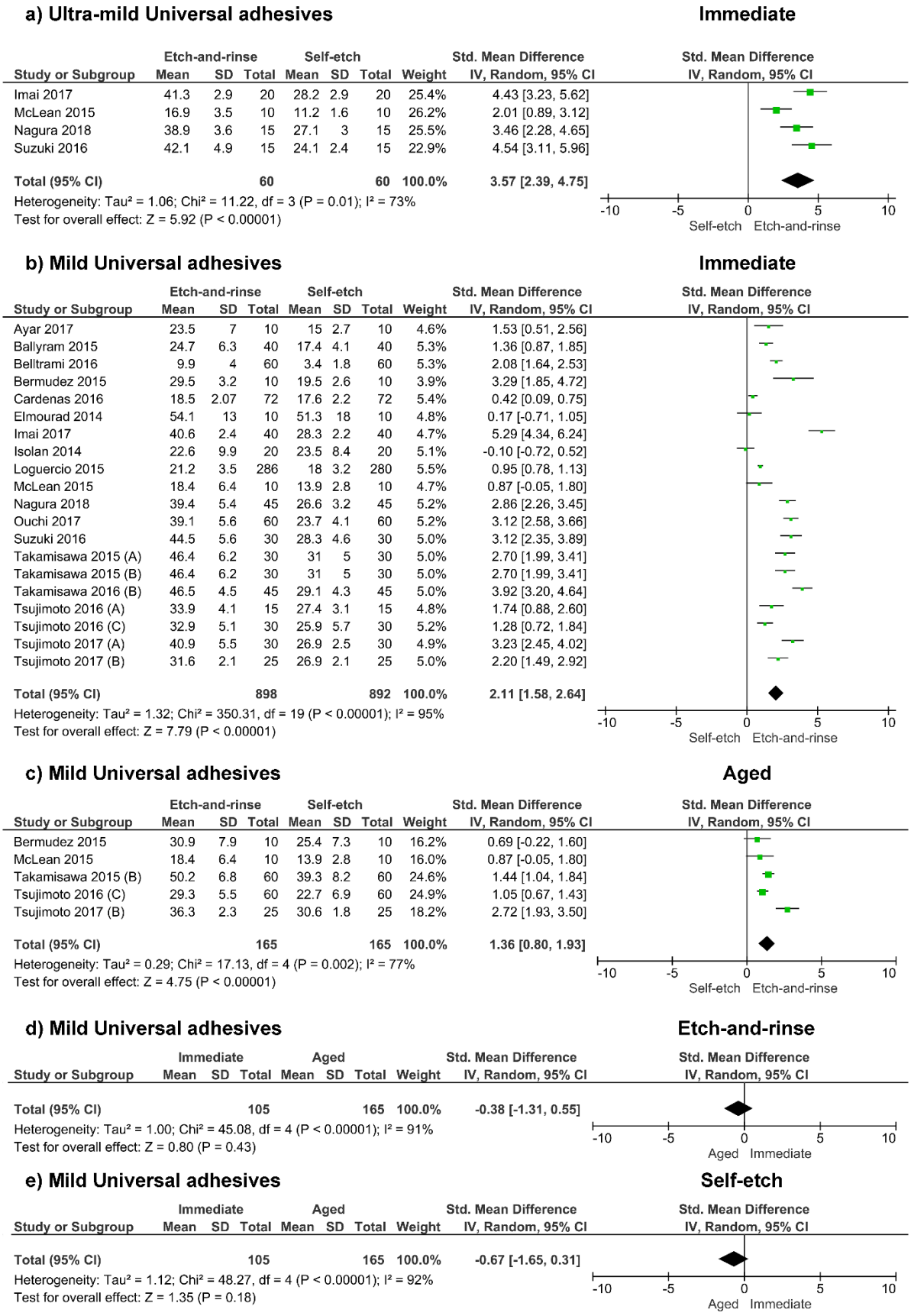

Fig. 2 Summary of findings of the meta-analysis comparing the shear bond strength of ultra-mild and mild universal adhesives to enamel.

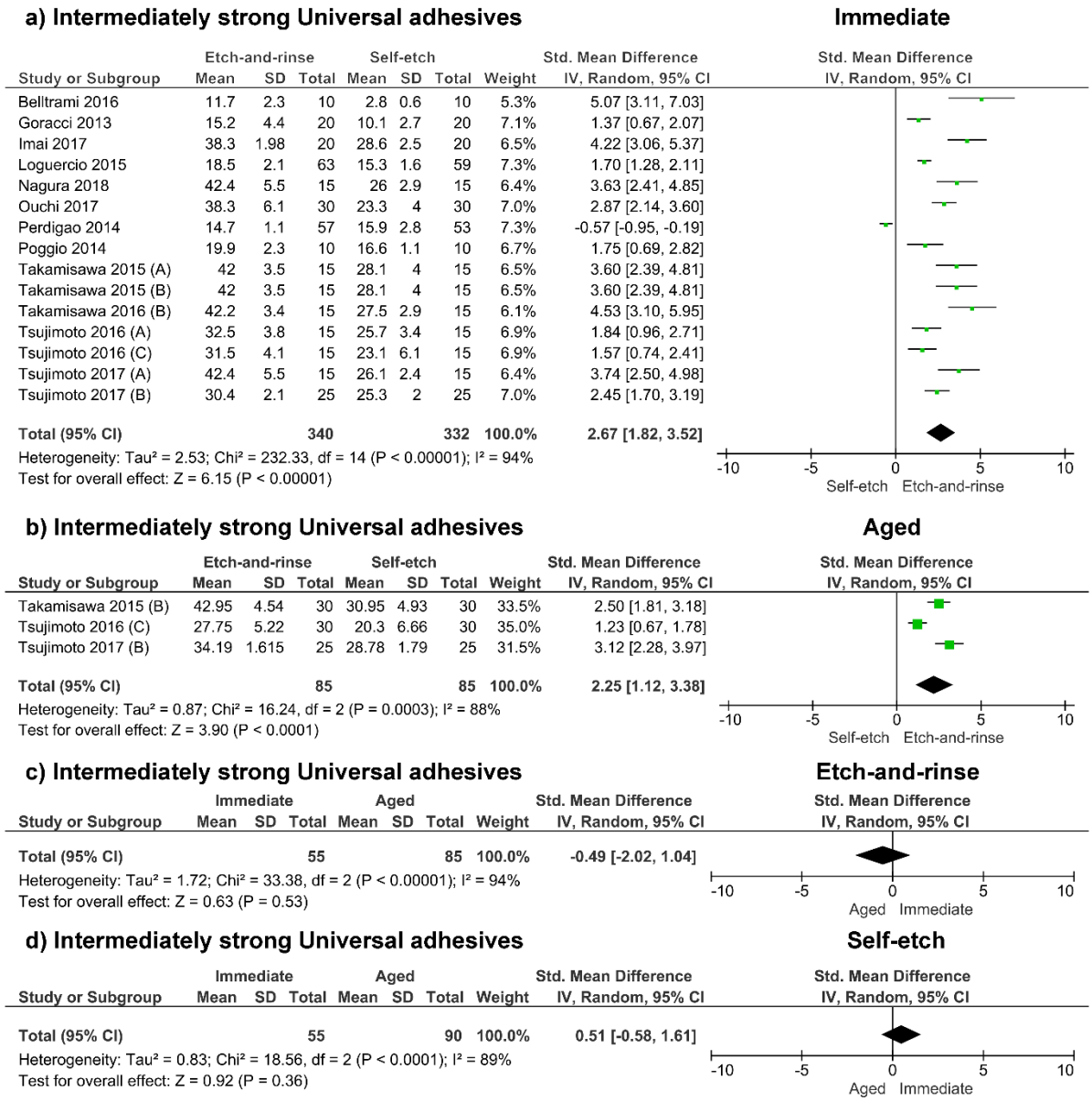

Fig. 3 Summary of findings of the meta-analysis comparing the shear bond strength of intermediately strong universal adhesives to enamel.

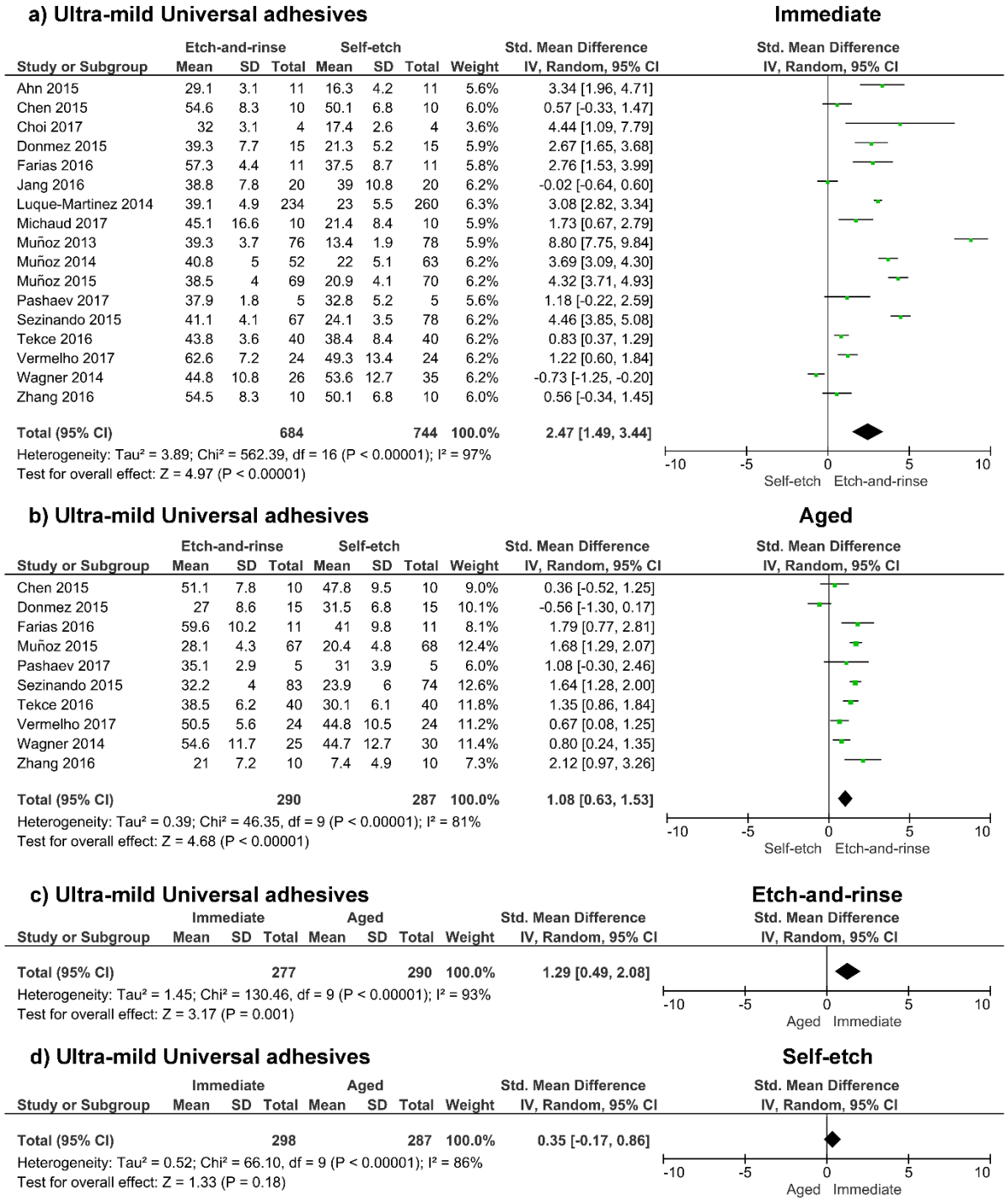

Fig 4. Summary of findings of the meta-analysis comparing the micro-tensile bond strength of ultra-mild universal adhesives to dentin using random-effects models.

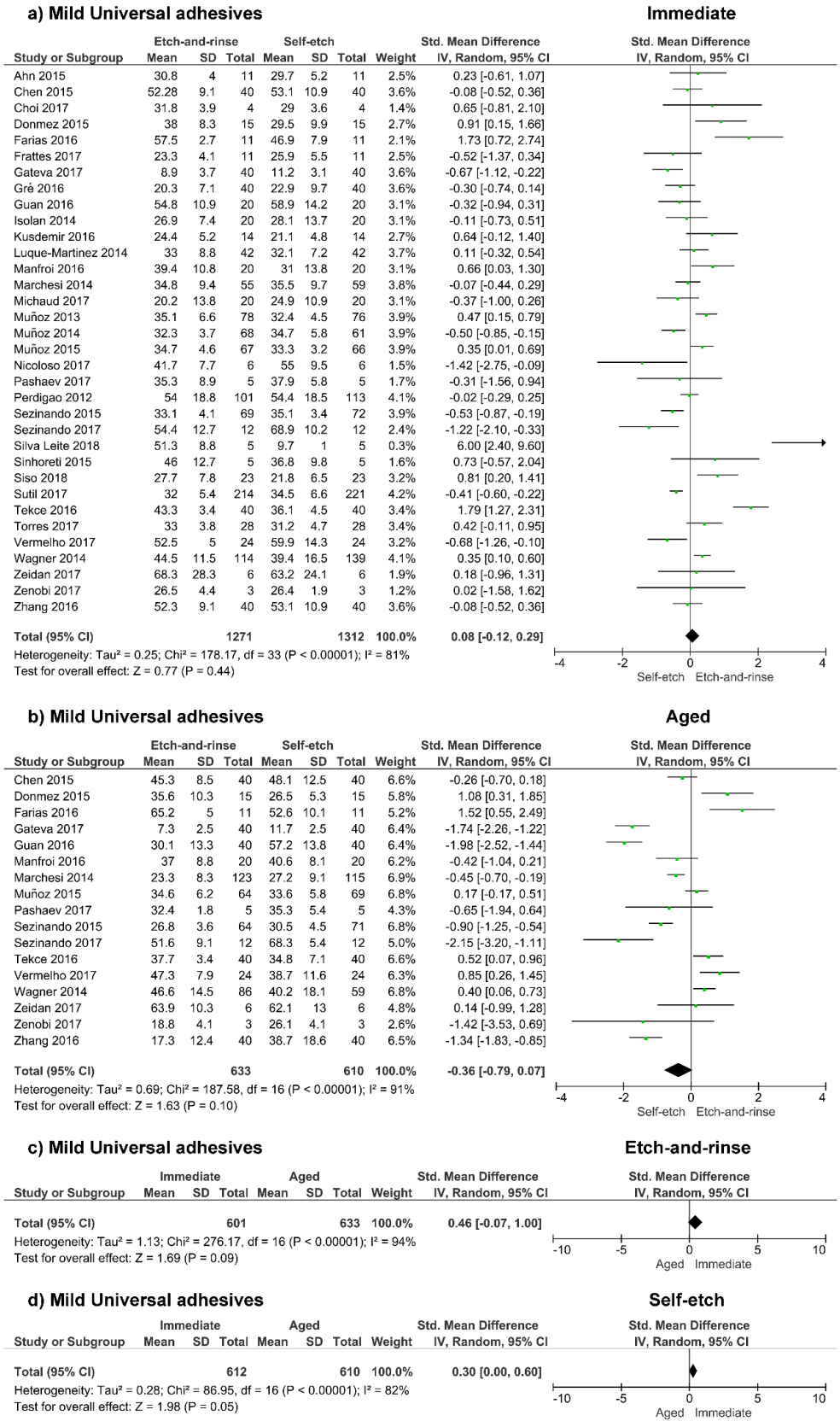

Fig 5. Summary of findings of the meta-analysis comparing the micro-tensile bond strength of mild universal adhesives to dentin using random-effects models.

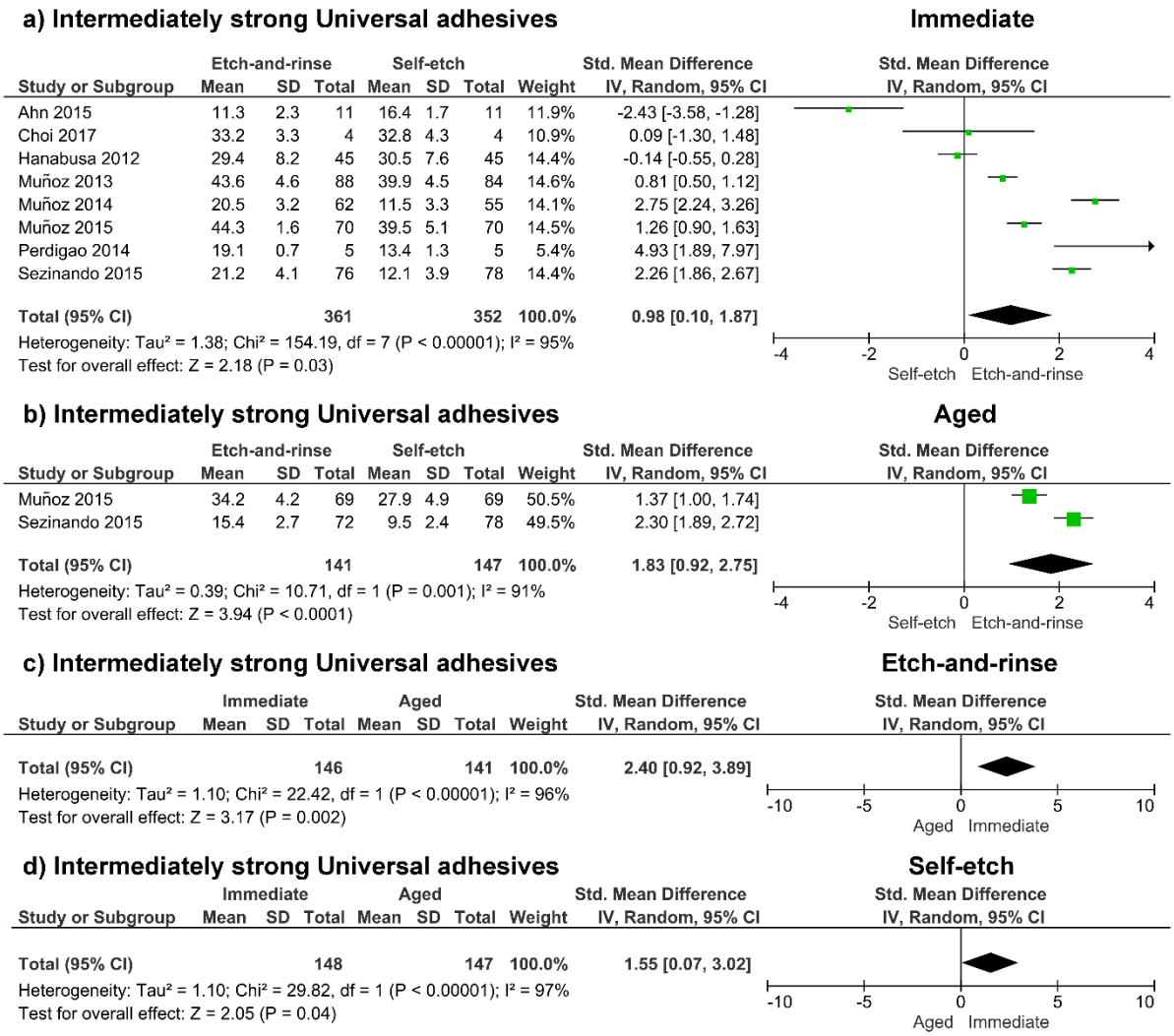

Fig 6. Summary of findings of the meta-analysis comparing the micro-tensile bond strength of intermediately strong universal adhesives to dentin using random-effects models.

Supplementary Data

Table 1. Search strategy used in PubMed (MEDLINE).

	Search terms
#1	(Universal adhesive) OR (adhesive, universal) OR (universal adhesives) OR (adhesives, universal) OR (Multimode adhesive) OR (multi-mode adhesive) OR (multimode adhesives) OR (multi-mode adhesives) OR (G Bond Plus) OR (Adhese Universal) OR (All-Bond Universal) OR (One-step Universal Dental adhesive) OR (One-step plus universal) OR (Peak Universal Bond) OR (Clearfil Universal Bond) OR (iBond Self Etch) OR (FuturaBond U) OR (Optibond XTR) OR (Optibond Universal) OR (Prelude One) OR (Prime&Bond Elect) OR (One Coat 7 Universal) OR (Universal bond) OR (Universal bonding agent) OR (multi-mode bond) OR (multimode bond) OR (multi-mode bonding agent) OR (multimode bonding agent)
#2	(Dental Bonding) OR (Bonding, Dental) OR (Dental Bonding, Chemically-Cured) OR (Chemically-Cured Dental Bonding) OR (Dental Bonding, Chemically Cured) OR (Dental Bonding, Self-Cured) OR (Dental Bonding, Self Cured) OR (Self-Cured Dental Bonding) OR (Chemical-Curing of Dental Adhesives) OR (Chemical Curing of Dental Adhesives) OR (Dental Bonding, Dual-Cure) OR (Dentin-Bonding Agents) OR (dental primer) OR (Dental Materials) OR (Materials, Dental) OR (Dental Material) OR (Material, Dental) OR (dental resin) OR (Dental Resins) OR (Resin, Dental) OR (Resins, Dental) OR (bonding interface) OR (adhesive) OR (Dentin-Bonding Agents) OR (Agents, Dentin-Bonding) OR (Bonding Agents, Dentin) OR (Agents, Dentin Bonding) OR (Dentin Bonding Agents)
#3	Search #1 AND #2

Table 2. Main components and classification of universal adhesives included.

Classification*	pH	Name	Manufacturer	Main components**
Ultra-mild	3.2	All-Bond Universal	Bisco, Schaumburg, IL, USA	Bisphenol A Diglycidylmethacrylate, Ethanol, MDP, 2-Hydroxyethyl Methacrylate.
Mild	2.7	Single Bond Universal	3M ESPE, St.Paul, MN, USA	2-Hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, Decamethylene dimethacrylate, ethanol, Silane treated silica, water, 2-propenoic acid, 2-Methyl-, reaction products with 1,10-decanediol and phosphorous oxide, copolymer of acrylic and itaconic acid, dimethylamino ethyl methacrylate, camphorquinone, dimethylaminobenzoato, 2,6-di-tert-butyl-P-cresol.
	2.5	Adhese Universal	Ivoclar Vivadent, Schaan, Liechtenstein	2-hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, ethanol, 1,10-decandiol dimethacrylate, Methacrylated phosphoric acid ester, camphorquinone, 2-dimethylaminoethyl methacrylate.
	2.5	Prime&Bond Elect	Dentsply Caulk, Milford, DE, USA	Acetone , Urethane Dimethacrylate Resin, Dipentaerythritol pentaacrylate phosphate, Polymerizable dimethacrylate resin, Polymerizable trimethacrylate resin.
	2.4	OptiBond XTR Primer	Kerr, Orange, CA, USA	Acetone, 2-hydroxyethyl methacrylate, ethanol.
		OptiBond XTR Adhesive	Kerr, Orange, CA, USA	ethanol, 2-hydroxyethyl methacrylate, 2-hydroxy-1,3-propanediyl bismethacrylate, Propylidynetrimethanol, ethoxylated, esters with acrylic acid, alkali fluorosilicates.
	2.3	Futurabond M+	VOCO, Cuxhaven, NI, Germany	Bisphenol A Diglycidylmethacrylate, Ethanol, Acidic adhesive monomer, catalyst.
	2.3	Clearfil Universal Bond	Kuraray, Okayama, Japan	Bisphenol A diglycidylmethacrylate, 2-hydroxyethyl methacrylate, ethanol, 10-Methacryloyloxydecyl dihydrogen phosphate, Hydrophilic aliphatic dimethacrylate, Colloidal silica, dl-Camphorquinone, Silane coupling agent, Accelerators, Initiators, Water.
	2.3	Futurabond U	VOCO, Cuxhaven, Germany	Bisphenol A diglycidylmethacrylate, 2-hydroxyethyl methacrylate, 1,6-hexanediylbismethacrylate, acidic adhesive monomer, urethanedimethacrylate, catalyst.
Intermediately strong	1.5	G-aenial Bond	GC, Tokyo, Japan	Acetone, dimethacrylate, phosphoric acid ester monomer, dimethacrylate component, photoinitiator, butylated hydroxytoluene.
	1.2	Peak Universal Bond Primer	Ultradent, South Jordan, UT, USA	Ethyl alcohol, methacrylic acid, 2-hydroxyethyl methacrylate
		Peak Universal Bond Adhesive	Ultradent, South Jordan, UT, USA	Ethyl Alcohol, 2-hydroxyethyl Methacrylate, Methacrylic Acid, Chlorhexidine di(acetate),

* Van Meerbeek, B, Peumans, M, Poitevin, A, Mine, A, Van Ende, A, Neves, A, et al.. Relationship between bond-strength tests and clinical outcomes. Dent Mater 2010;26:e100-e121. ** According to Manufacturers' MSDS

Table 3. Demographic and study design data of the included studies.

Study	Year	Country	Number of teeth (per group)	Primary Outcome	Secondary outcomes	Predominant failure mode	Universal adhesive used	Composite	Type of composite
Ahn	2015	Korea	42(2)	Dentin μTBS	Failure pattern	Adhesive	G-aenial Bond (GC, Tokyo, Japan) Single Bond Universal (3M ESPE, St.Paul, MN, USA) All-Bond Universal (Bisco, Schaumburg, IL, USA)	Filtek Z-250 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Ayar	2017	Turkey	60(10)	Enamel SBS	Failure pattern	Adhesive	Single Bond Universal (3M ESPE, St.Paul, MN, USA)	Valux Plus	Microhybrid
Ballyram	2015	Southafric	120(20)	Dentin SBS, Cut enamel SBS and Uncut enamel SBS	Failure pattern	Adhesive	Single Bond Universal (3M ESPE, St.Paul, MN, USA)	Filtek Supreme XTE (3M ESPE, Seefeld, Germany)	Nanocomposite
Belltrami	2016	Italy	160(10)	Enamel SBS			Single Bond Universal (3M ESPE, St.Paul, MN, USA) Futurabond M+ (Voco, Cuxhaven, Germany) Adhese Universal (Ivoclar Vivadent, Schaan, Liechtenstein) Clearfil Universal Bond (Kuraray, Okayama, Japan) GBU 500 (GC Corporation, Tokyo, Japan) Peak Universal Bond (Ultradent, South Jordan, UT, USA)	Grandio (Voco, Cuxhaven, Germany)	Nanohybrid

							OptiBond XTR (Kerr, Orange, CA, USA).		
Bermudez	2015	United States	120(20)	Enamel SBS	Failure pattern	Mixed	OptiBond XTR (Kerr, Orange, CA, USA).	Filtek Supreme Ultra (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Cardenas	2016	Brazil	63(24)	Enamel μSBS	Degree of conversion, Failure pattern, Enamel etching pattern	Adhesive	Clearfil Universal (Kuraray Noritake Dental, Inc, Tokyo, Japan) Futurabond U (VOCO, Cuxhaven, Germany) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Chen	2015	United States	200(10)	Dentine μTBS	TEM resin-dentin interfaces	Mixed	Prime&Bond Elect (Dentsply Caulk, USA) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco, Schaumburg, IL, USA) Clearfil Universal (Kuraray Noritake Dental, Inc, Tokyo, Japan) Futurabond U (VOCO, Cuxhaven, Germany)	TPH Spectra, Dentsply Caulk	Hybrid
Choi	2018	Korea	72(12)	Dentine μTBS	Failure pattern	Adhesive	G-Premio Bond (GC Corp., Tokyo, Japan) Single Bond Universal (SBU; 3M ESPE, St. Paul, MN, USA) All Bond Universal (Bisco Inc., Shaumburg, IL, USA)	Filtek Z250 (3M ESPE, St. Paul, MN, USA)	Microhybrid

Diniz	2016	Brazil	52(13)	Enamel μSBS	Failure pattern	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) Futurabond U (VOCO, Cuxhaven, Germany)	TPH (Dentsply, Petrópolis, RJ, Brazil)	Microhybrid
Donmez	2015	Turkey	8(1)	Dentine μTBS	Failure pattern	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco, Schaumburg, IL, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA) Aelite All Purpose Body (Bisco, Schaumburg, IL, USA)	Nanocomposite Microhybrid
Elmourad	2014	Saudi Arabia	90(10)	Enamel SBS	Failure pattern	Cohesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z250, 3M ESPE; St. Paul, MN, USA	Microhybrid
Farias	2016	United States	88(11)	Dentine μTBS	Failure pattern, Exent of resin infiltration inton dentine	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco, Schaumburg, IL, USA)	TPH3 (Dentsply Caulk,Milford,DE,USA)	Hybrid
Frattes	2017	Brazil	88(11)	Enamel and Dentin μTBS	Failure pattern AND SEM observation	Adhesive/Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Amelogen Plus (Ultradent Products; South Jordan, UT, USA)	Microhybrid
Gateva	2017	Bulgaria	60(20)	Dentin μSBS			Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Ultimate (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Goracci	2013	Italy	133(20)	Enamel and dentin SBS	Microleakage and SEM	Adhesive/Mixed	G-aenial Bond (GC, Tokyo, Japan)	G-aenial Universal Flo (GC, Tokyo, Japan)	Flowable composite

Gré	2016	Brazil	15(5)	Dentin μTBS	Failure pattern	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Guan	2016	Japan	45(8)	Dentine μTBS	SEM and TEM observation	Adhesive/Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) OptiBond XTR (Kerr, Orange, CA, USA).	Clearfil AP-X (Kuraray, Tokyo, Japan)	Microhybrid composite
Hanabusa	2012	Belgium	25(5)	Enamel and Dentin μTBS	Ultra-structural analysis (TEM)	Mixed	G-Bond Plus (GC, Tokyo, Japan)	Clearfil AP-X (Kuraray, Tokyo, Japan)	Microhybrid composite
Imai	2017	Japan	160(10)	Enamel SBS	Failure mode	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) AdheSE Universal (Ivoclar Vivadent, Schaan, Liechtenstein) G-Premio Bond (GC Corporation Tokyo, Japan)	Clearfil AP-X (Kuraray Noritake Dental, Tokyo, Japan)	Microhybrid
Isolan	2014	Brazil	50(5)	Enamel SBS and Dentin μTBS	Failure pattern	Adhesive - Adhesive/Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Opalis (FGM, Brazil)	Microhybrid composite
Jang	2016	Korea	24(4)	Dentin μTBS	Ultra-structural analysis (TEM)	Adhesive	All-Bond Universal (Bisco, Schaumburg, IL, USA) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z250, 3M ESPE; St. Paul, MN, USA	Microhybrid
Kusdemir	2016	Switzerland	18(3)	Dentin μTBS	Failure pattern	Adhesive/Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite

Loguercio	2015	United States	84(4)	Enamel μSBS	Etching pattern and in situ degree of conversion	Adhesive/Mixed	AdheSE Universal (Ivoclar Vivadent, Schaan, Liechtenstein) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) Clearfil Universal (Kuraray Noritake Dental Inc., Tokyo, Japan) Futurabond U (VOCO, Cuxhaven, Germany) G-Bond Plus (GC Corporation Tokyo, Japan) Prime&Bond Elect (Dentsply Caulk, Milford, DE, USA) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Luque-Martinez	2014	Brazil	140(5)	Dentin μTBS	Interfacial nanoleakage	Adhesive	All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) Prime&Bond Elect (Dentsply Caulk, Milford, DE, USA) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Manfroi	2016	Brazil	24(6)	Dentin μTBS	Failures and the adhesive interface analysis (SEM)	Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z250, 3M ESPE; St. Paul, MN, USA	Microhybrid
Marchesi	2014	Italy	60(15)	Dentin μTBS	Interfacial nanoleakage and MMP Expression	Adhesive (Cohesive in composite only with etch-and-rinse strategy)	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z250, 3M ESPE; St. Paul, MN, USA	Microhybrid

McLean	2015	Canada	60(5)	Enamel SBS	Failure pattern	Adhesive/Mixed	All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z250, 3M ESPE; St. Paul, MN, USA	Microhybrid
Michaud	2017	Canada	60(5)	Dentine μTBS			Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) OptiBond XTR (Kerr, Orange, CA, USA).	CompCore AF White (Premier Dental) CoreFlo (Bisco Inc., Schaumburg, IL, USA)	Dual-polymerizing foundation composite resin. Dual-polymerizing foundation composite resin
Muñoz	2015	Brazil	40(5)	Dentin μTBS	Nanoleakage	Adhesive/Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) Peak Universal Bond (Ultradent, South Jordan, UT, USA)	Opallis, FGM Produtos Odontológicos, Joinville, SC, Brazil)	Microhybrid
Muñoz	2014	United States	60(5)	Dentin μTBS	Nanoleakage and in-situ degree of conversion	Adhesive/Mixed	All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) G-Bond Plus (GC Corporation Tokyo, Japan) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Muñoz	2013	Brazil	40(5)	Dentin μTBS	Nanoleakage and in-situ degree of conversion	Adhesive/Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) Peak Universal Bond (Ultradent, South Jordan, UT, USA)	Opallis, FGM Produtos Odontológicos, Joinville, SC, Brazil)	Microhybrid

Nagura	2018	Japan	450(15)	Enamel SBS	Shear fatigue strength Surface free energy Failure mode	Adhesive	Adhese Universal (Ivoclar Vivadent, Schaan, Liechtenstein) All-Bond Universal (Bisco, Schaumburg, IL, USA) Clearfil Universal Bond Quick (Kuraray Noritake Dental, Tokyo, Japan) Gpremio Bond (GC, Tokyo, Japan) Scotchbond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Z100 (3M ESPE, St. Paul, MN, USA)	Microhybrid
Nicoloso	2017	Brazil	48(6)	Dentine μTBS	Failure mode	Adhesive/mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Ouchi	2017	Japan	90(7)	Enamel SBS	Failure mode	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) AdheSE Universal (Ivoclar Vivadent, Schaan, Liechtenstein) G-Premio Bond (GC Corporation Tokyo, Japan)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Pashaev	2017	Turkey	216(30)	Dentin μTBS	SEM observation	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)	Filtek Ultimate Universal Restorative (3M ESPE, St. Paul, MN, USA)	Nanocomposite
Perdigao	2014	United States	60(5)	Enamel μSBS and Dentin μTBS	Degree of conversion	Adhesive/Mixed	G-Bond Plus (GC Corporation Tokyo, Japan)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite

Perdigao	2012	United States	36(6)	Dentin μTBS	Ultra-morphologic evaluation	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z250, 3M ESPE; St. Paul, MN, USA	Microhybrid
Poggio	2014	Italy	100(10)	Enamel SBS	Failure patter and ARI	Adhesive	G-aenial Bond (GC Corporation Tokyo, Japan)	Grandio (Voco GmbH, Cuxhaven, Germany)	Nanohybrid
Sezinando	2015	United States	60(5)	Dentin μTBS	Nanoleakage	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) G-Bond Plus (GC Corporation Tokyo, Japan)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Sezinando	2017	USA	84(12)	Dentine μTBS	Failure mode and nanoleakage challenge	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z250, 3M ESPE; St. Paul, MN, USA	Microhybrid
Sinhoreti	2015	Brazil	20(5)	Dentin μTBS	Confocal microscopy		Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Silva Leite	2018	Brazil	30(5)	Dentin μTBS	Failure mode	Cohesive/mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Siso	2018	Turkey	20(5)	Dentin μTBS	Failure mode	Adhesive/mixed	Clearfil Universal Bond Quick (Kuraray Noritake Dental, Tokyo, Japan)	Clearfil AP-X (Kuraray, Japan)	Microhybrid
Sutil	2017	Brazil	96(8)	Dentine μTBS	Failure mode	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Suzuki	2016	Japan	45(15)	Enamel SBS	Shear fatigue strength and SEM	Adhesive. Mixed/Cohesive in enamel in	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid

						etch-and-rinse groups	Prime&Bond Elect (Dentsply Caulk, Milford, DE, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)		
Takamis awa	2015 (A)	Japan	90(15)	Enamel and Dentin SBS	Shear fatigue strength and SEM	For enamel: Adhesive For dentin: Adhesive/Mixed	G-aenial Bond (GC Corporation Tokyo, Japan) OptiBond XTR (Kerr, Orange, CA, USA). Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Takamis awa	2015 (B)	Japan	270(15)	Enamel and Dentin SBS	Shear fatigue strength and SEM	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) G-aenial Bond (GC Corporation Tokyo, Japan)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Takamis awa	2016 (B)	Japan	120(15)	Enamel SBS	Shear fatigue strength and SEM	Adhesive	Prime&Bond Elect (Dentsply Caulk, Milford, DE, USA) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) G-aenial Bond (GC Corporation Tokyo, Japan) OptiBond XTR (Kerr, Orange, CA, USA).	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Tekce	2016	Turkey	50(5)	Dentine μTBS	Failure mode and SEM observations of the interface	Adhesive/Mixed	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)	Filtek Ultimate Universal (3M ESPE, St.Paul, MN, USA)	Nanocomposite
Torres	2017	Brazil	112(14)	Enamel μTBS	Failure mode	Adhesive	Futurabond U (VOCO, Cuxhaven, Germany)		Nanohybrid

				Dentine μTBS			Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Grandio (Voco, Cuxhaven, Germany)	
Tsujimoto	2016 (A)	Japan	90(15)	Enamel SBS	Failure mode, surface free energy and SEM observations	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) G-aenial Bond (GC Corporation Tokyo, Japan)	Clearfil AP-X, (Kuraray Noritake Dental Inc., Tokyo, Japan)	Microhybrid
Tsujimoto	2016 (C)	Japan	135(7)	Enamel SBS	Failure mode, surface free-energy and SEM observations	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) AdheSE Universal (Ivoclar Vivadent, Schaan, Liechtenstein) G-aenial Bond (GC Corporation Tokyo, Japan)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Tsujimoto	2017 (A)	Japan	555(18)	Enamel SBS	Failure mode and surface characteristics	Adhesive	Clearfil Universal (Kuraray Noritake Dental Inc., Tokyo, Japan) G-aenial Bond (GC Corporation Tokyo, Japan) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z100 (3M ESPE, St.Paul, MN, USA)	Microhybrid
Tsujimoto	2017 (B)	Japan	100(25)	Enamel SBS	Surface Free Energy Measurements Failure mode	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) G-Premio Bond (GC Corporation Tokyo, Japan)	Clearfil AP-X (Kuraray Noritake Dental Inc., Tokyo, Japan)	Microhybrid
Vermelho	2017	Brazil	56(8)	Enamel μTBS	Ultramorphological dentin-resin	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Filtek Z350 (3M ESPE, St.Paul, MN, USA)	Nanocomposite

			48(8)	Dentine µTBS	interface TEM		All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)		
Wagner	2014	Germany	20(12)	Dentine µTBS	Resin penetration	Adhesive	Futurabond M+ (Voco, Cuxhaven, Germany) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA) All-Bond Universal (Bisco Inc., Schaumburg, IL, USA)	Grandio (Voco, Cuxhaven, Germany)	Nanohybrid
Zeidan	2017	Brazil	36(6)	Dentine µTBS	Failure mode - SEM observation	Cohesive in resin / adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	TPH3 (Dentsply Caulk, Milford, DE, USA)	Microhybrid
Zenobi	2017	Brazil	24(6)	Dentine µTBS	Failure mode - SEM observation	Adhesive	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Spectrum TPH (Dentsply, Petropolis-RJ, Brazil)	Microhybrid
Zhang	2016	United States	200(20)	Dentine µTBS	Failure mode - TEM observation	Mixed	All-Bond Universal (Bisco Inc., Schaumburg, IL, USA) Clearfil Universal (Kuraray Noritake Dental Inc., Tokyo, Japan) Futurabond U (Voco, Cuxhaven, Germany) Prime&Bond Elect (Dentsply Caulk, Milford, DE, USA) Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	TPH3 (Dentsply Caulk, Milford, DE, USA)	Microhybrid

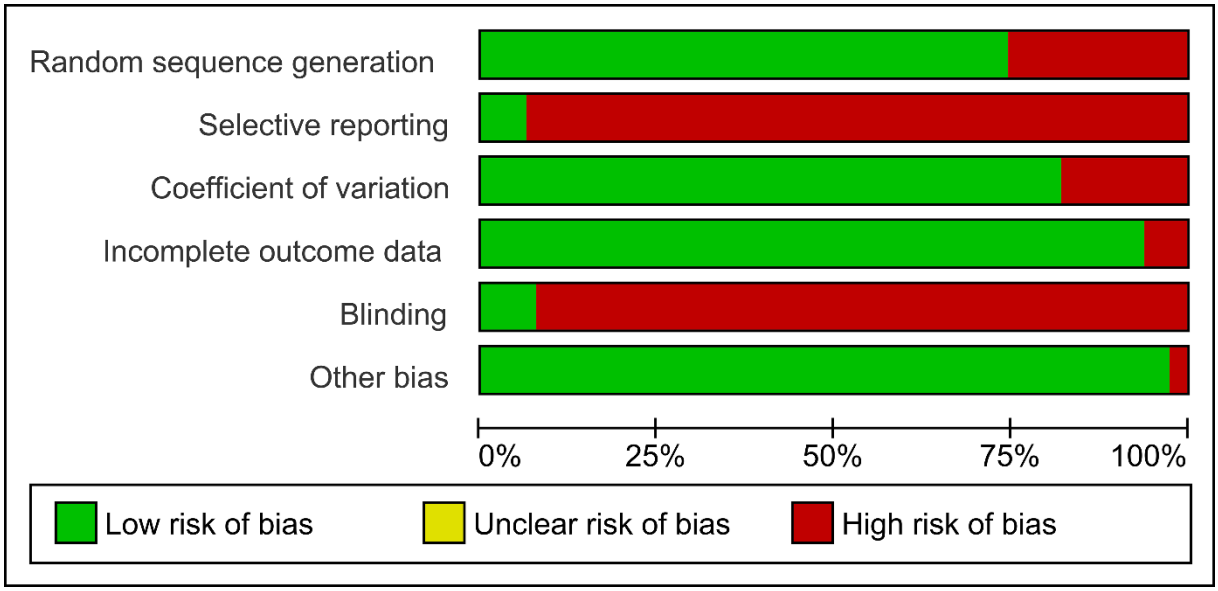

Fig. 7. Review authors' judgments about each risk of bias item for each included in vitro study

3 Capítulo 2

Bonding performance of universal adhesives to indirect substrates: a systematic review and meta-analysis[2]

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[2] Artigo formatado segundo as normas do periódico Dental Materials

Acknowledgments

This study was conducted in a Graduate Program supported by CAPES, Brazil. Author Carlos Enrique Cuevas-Suárez wants to thanks to PRODEP, México for PhD scholarship (DSA/103.5/15/6615).

Declaration of Interest statement

Declarations of interest: none

3.1 Abstract

Objectives. To evaluate the *in vitro* bonding performance of universal adhesive systems to indirect substrates.

Data. A total of 45 studies were included in the qualitative analysis, and the meta-analysis was performed with 42 studies.

Sources. Two reviewers performed a literature search up to March 2018 in eight databases: PubMed, Web of Science, SciELO, Scopus, LILACS, IBECS, and BBO.

Study Selection. It was included studies that compared the bond strength of universal adhesives and well-established material-specific primers to indirect substrates: lithium disilicate ceramic, yttrium-stabilized zirconium dioxide ceramic, leucite-reinforced ceramic, feldspathic porcelain, polymer infiltrated ceramic material, resin composite and metal alloys. Analyses were carried out using RevMan 5.3.5. A global comparison was performed with random-effects models at a significance level of $p < 0.05$.

Results. Bond strength to glass-based ceramics and alloys was improved with the use of a specific-primer as separate step before the bonding procedures ($p < 0.05$). The bond strength to zirconium substrates was improved with the use of universal adhesives ($p < 0.05$). For bond strength to composite resin as indirect substrate, universal adhesives performed in a manner similar to that of the material-specific primer ($p > 0.05$).

Conclusions. The clinical procedure of luting zirconia and resin composite restorations could be simpler by using the single-bottle universal adhesives. Conversely, the ability of universal adhesives to achieve and adequate and durable bond strength to glass-based ceramics and alloys is limited.

Keywords

universal adhesives; glass-based ceramics; oxide-base ceramics; dental alloys; composites; systematic review.

3.2 Introduction

Several clinical situations lead to the indication for placement of indirect restorations, these include large cavities and/or failed direct restorations; posterior teeth with large interproximal cavities; missing teeth, and/or failed crowns requiring replacement, cases requiring improved esthetics, and cases requiring extensive rehabilitation.[1] The introduction of indirect materials with enhanced esthetics, increased fracture strength, biocompatibility and broader scope of clinical indications are some of the reasons why indirect restorations have increasingly been used.[2] Actually, the use of indirect procedures comprise a substantial portion of contemporary restorative treatments.[3]

One of the critical factors that influences the clinical success of indirect restorations is directly related to the cementation procedure.[4] According to the literature, the long-term success of this type of restorations is achieved when a strong and durable bond is obtained between the framework material-resin cement-dentin.[5,6] Contemporary luting techniques for bonding indirect restorations are based on the adhesive action of a resin cement which, after polymerization, bonds laboratory-made restorations to dental tissues.[7]

In this sense, the composition of material used for fabricating the restoration is another crucial factor associated with the longevity and clinical success of indirect restorations.[8] The chemical composition of the bonding system, and pretreatment of the internal surface of the restoration have an influence on the success of chemical interaction between the different substrates and the bond durability.[9,10] Based on this, manufactures have introduced specific primers or adhesives onto the market, designed to promote the bond between resin cements and indirect substrates, these include silane coupling agents for glass ceramic restorations, phosphate monomer-containing primers for polycrystalline ceramics and sulfuric monomer-containing primers for bonding alloys.[8,11]

The availability of such wide variety of materials makes it difficult for clinicians to choose the correct system for specific bonding situations. For example, in a recently published survey,[12] a high number of practitioners were found to use incorrect bonding techniques for the cementation of all-ceramic restorations, which could result

in reduced longevity of these types of restorations.[6] Situations such as these emphasize the need to indicate materials that help clinicians to simplify the conditioning of both the tooth and restoration surface. Based on this, new universal adhesives have been developed for use with multiple restorative materials.[13] They have different functional monomers in their composition which, according to the manufacturers, improve the chemical bonding to different indirect substrates.

Although the clinical use of a universal adhesive is very convenient, the combination of several components of different chemical natures into a one single bottle is controversial, especially in terms of effectiveness and stability.[14] Given this situation, the relevant clinical question continues to be whether or not these adhesive systems are as effective as the primers especially designed for bond to different substrates. Given the lack of clinical studies with long-term follow-up, the evaluation of laboratory studies is an approach to trying to answer this question. Therefore, the aim of this study was to systematically review the literature to evaluate the in vitro bond strength of universal adhesives to different indirect substrates when compared to material-specific primers. The null hypothesis tested was that there would be no differences in bond strength to different indirect substrates when using universal adhesives or a well-established material-specific primer especially designed for these purposes.

3.3 Materials and methods

This systematic review and meta-analysis was reported in accordance with the guidelines of the PRISMA statement.[15] The research question was: do the universal adhesives show bonding performance to different indirect substrates comparable with those of conventional well-established material-specific primers?

3.3.1 Literature search

The literature search was performed by two independent reviewers (CECS and RPV) until March 15th, 2018. The following eight electronic databases were screened: PubMed (MedLine), ISI Web of Science, Cochrane Library, SciELO, Scopus, LILACS, IBECS, and BBO (Biblioteca Brasileira de Odontologia). The search strategy used is listed in Table 1. The reviewers also hand-searched the reference lists of included

articles for identification of additional manuscripts. After the initial screening, all studies were imported into Mendeley Desktop 1.17.11 software (London, UK) to remove duplicates.

3.3.2 Study selection

Two reviewers independently assessed the titles and abstracts of all the manuscripts. Manuscripts for full-text review were selected according to the eligibility criteria: (1) evaluated the bond strength of universal adhesives and the well-established material-specific primers to following substrates: glass-based ceramics, oxide-based ceramics, polymer infiltrated ceramic material, indirect resin composite and metal alloys; (2) evaluated the bond strength of universal adhesives or well-established material-specific primers to the afore-mentioned indirect substrates with 2 antagonists: composite resin or composite cement; (3) included mean and standard deviation data in MPa on shear, microshear, tensile, and micro-tensile bond tests and; (4) published in the English language. Studies that involved different substrates other than those established in the inclusion criteria were not considered. Case reports, case series, pilot studies, and reviews were also excluded. Full copies of all of the potentially relevant studies were analyzed. Those that appeared to meet the inclusion criteria, or had insufficient data in the title and abstract to make a clear decision were selected for full analysis. The full-text papers were independently assessed by two authors. Any disagreement regarding the eligibility of the included studies was resolved through discussion and consensus by a third reviewer.

3.3.3 Data extraction

Data of interest from the manuscripts included was tabulated using Microsoft Office Excel 2016 spreadsheets (Microsoft Corporation, Redmond, WA, USA). These data included year of publication, country, substrate evaluated, universal adhesive system used, material-specific primer used, type of bond strength test, mean and standard deviation of the bond strength, number of specimens, type of composite used and storage conditions. Partially missing data were retrieved by contacting the corresponding authors via e-mail. If authors had not given any answer by one month after the first contact, the missing information was not included. For the articles that presented the information in graphic format and original data could not be retrieved

from the authors, mean and standard deviation was calculated using WebPlotDigitizer 4.0 software (Austin, Texas, USA).

3.3.4 Quality assessment

The methodological quality of each included in vitro study was assessed by two reviewers according to the parameters of the previous systematic review.[16,17] The risk of bias of the article was evaluated according to the description given of the following parameters: random sequence generation, selective reporting, coefficient of variation, incomplete outcome data, blinding and other bias. The coefficient of variation (CV) from each article was calculated and classified as low, medium, high and very high. [18,19] Articles with low or medium CV were classified as low risk of bias, while articles with high or very high CV were classified as high risk of bias.

3.3.5 Statistical analysis

The meta-analyses were performed using Review Manager Software version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The analyses were carried out using a random-effect model, and pooled-effect estimates were obtained by comparing the standardized mean difference between bond strength values obtained using the universal adhesive or the material-specific primer. Bond strength comparisons were made considering the indirect substrate used. Studies that evaluated the samples before and after aging processes, were analyzed separately. A p-value < 0.05 was considered statistically significant. Statistical heterogeneity of the treatment effect among studies was assessed using the Cochran Q test and the inconsistency I^2 test.

3.4 Results

A total of 8862 publications were retrieved in all databases. A flowchart that summarizes the study selection process according to the PRISMA Statement[15] is shown in Figure 1. After removing duplicates, the literature review retrieved 6851 manuscripts for initial examination. Of these, 6800 studies were excluded after reviewing the titles and abstracts. In total, 51 studies were examined by full-text reading. Of these studies, 6 were not included into the qualitative analysis: 2 studies did not use any experimental group with the use of a universal adhesive alone,[20,21]

and 4 studies did not evaluate the bond strength with the use of composite or resin cement.[22–25]. Of the remaining 45 studies, 3 were excluded from the quantitative analysis because the mean and standard deviation could not be retrieved,[26–28] totalizing 42 studies for the meta-analysis.

Seven different indirect substrates were considered in this review. These included lithium disilicate ceramic,[21,23,24,26,29–40] yttrium-stabilized zirconium dioxide ceramic,[21–23,25,28,33,38,41–54] leucite-reinforced ceramic,[21,55–57] feldspathic porcelain, [33,58] polymer infiltrated ceramic material,[20,59] resin composite[21,27,30,58,60–67] and metal alloys.[68–70] The characteristics of these studies are summarized in Table 2 (Supplementary material). The literature search identified other substrates, such as poly-oxymethylene[71] and polyaryletherketone[72,73], however, as a specific primer was not available for these substrates, they were not included in this review.

The universal adhesive systems included in this review were Clearfil Universal Bond® (Kuraray, Okayama, Japan), Single Bond Universal (3M ESPE, St. Paul, MN, USA), AllBond Universal® (Bisco, Schaumburg, IL, USA), Futurabond U® (VOCO, Cuxhaven, NI, Germany), iBond Universal (Heraus Kulzer GmbH, Hanau, Germany), Prime&Bond® Elect (Dentsply Caulk, Milford, DE, USA), Futurabond M+® (VOCO, Cuxhaven, NI, Germany), Adhese Universal® (Ivoclar Vivadent, Schaan, Liechtenstein), One Coat 7 Universal (Coltene, Altstätten, Switzerland) and Peak Universal Bond (Ultradent, South Jordan, UT, USA). Among the material-specific primers, the primers identified were for glass-based ceramic restorations, oxide-ceramic restorations, alloy restorations and composite restorations. The main components of the universal adhesives and material-specific primers included are described in Table 3 and 4 (Supplementary material).

A meta-analysis was performed with 42 in vitro studies. Separate analysis for each indirect substrate, lithium disilicate ceramic, leucite-reinforced ceramic, zirconia oxide, feldspathic porcelain, metal alloy and composite, were performed. When bond strength data were available after any type of aging processes, the meta-analysis was also performed. The main results of the datasets evaluated are shown in Figures 2-7.

Bond strength of resin composite to lithium disilicate ceramic substrate was analyzed both immediately and after aging (Figure 2). In both cases, the use of a

material-specific primer improved the bond strength ($p < 0.05$). The bond strength to leucite-reinforced ceramic showed that immediate bond strength was improved when a silane-based primer was used ($p < 0.05$), and this performance was maintained after aging (Figure 3). The analysis of immediate bond strength to feldspathic porcelain revealed that bond strength did not differ statistically when universal adhesive or silane-based primer were used (Figure 3). Relative to zirconia-based ceramics, the bond strength both immediate and after aging was improved with the use of universal adhesives (Figures 4 and 5).

Figure 6 shows the results relative to alloy surfaces. Immediate bond strength was improved with the use of a sulfur-containing primer ($p < 0.05$). This behavior was also observed for bond strength after the aging processes.

Bond strength to composite resin as indirect substrate was also evaluated (Figure 7). The meta-analysis demonstrated that the bond strength of universal adhesives was similar to that of the material-specific primer, both immediate and aged ($p = 0.11$). In all cases, high heterogeneity was observed in the analysis.

According to the parameters considered in the analysis of bias, the majority of studies were classified with high risk of bias only in the items *selective reporting* and *blinding*, while a low risk of bias was observed in the items *random sequence generation, coefficient of variation, incomplete outcome data* and *other bias* (Supplementary material).

3.5 Discussion

This systematic review and meta-analysis revealed that the bonding performance of universal adhesives as part of the luting processes in restorative indirect substrates differed among the substrates evaluated. For glass-based ceramics (lithium disilicate and leucite-reinforced ceramic) and alloys, the bond strength was improved when a material-specific primer was used for the bonding procedures. For oxide ceramics (zirconium oxide), the studies were able to demonstrate that the bond strength of resin cement or resin composite was improved when a universal adhesive was used instead of the material-specific primer. Finally, universal adhesives had the same performance as that of the material-specific primer when used for indirect

composite luting. Considering this, the null hypothesis of this study was partially rejected.

Adhesive cementation involves the use of an agent to promote bonding between the restorative material and the tooth structure,[8] which means that a bond should exist between the enamel or dentin and the cement, and between the cement and the internal surface of the restoration.[74] Irrespective of the material, an optimal bond could be achieved by roughening the intaglio surface of the restoration, a procedure that could be carried out by means of air abrasion, sandblasting, or etching with a hydrofluoric acid.[75] On the other hand, the application of a specific coupling agent on the pretreated surface improved the formation of chemical bonds between the components of the material and the cement.[76,77] Choosing between one or another mechanism, or a combination of both, depended on the chemical conformation and microstructure of each substrate.[75]

The adhesive cementation procedure for glass ceramic restorations was well defined, and involved etching with hydrofluoric acid and silanization.[8,75] Adhesive treatment of indirect restorations included the successive application of a bonding agent.[7,78,79] In an attempt to reduce the number of clinical steps, some universal adhesives have a silane coupling-agent incorporated into their compositions, and manufactures have claimed that direct chemical bonding to glass ceramic restorations can be obtained without the need of a separate ceramic primer.[80–82] This systematic review identified four universal adhesives that had a silane coupling agent included (Clearfil Universal Bond®, Single Bond® Universal, Futurabond U®, and Futurabond M+®) in their compositions. In the meta-analysis performed of glass ceramic restorations, only comparisons of studies that used these universal adhesive systems were included. The results of our review suggested that the silane contained in the universal adhesive was not as effective as the silane coupling agent applied as a separate step, for optimizing the ceramic resin cement bond.

The lower performance of universal adhesives when used as ceramic primers could be explained due to the low stability of silane coupling agent in the water acidic adhesive solution. In the presence of water, silane groups (-Si-CH_3) from the silane coupling agent hydrolyze into silanol groups (-Si-OH), which are capable of adsorbing and chemically bonding to glass.[83] After the hydrolysis process, silanol groups may undergo dehydroxylation and condensation to form a siloxane $(-O-Si-O)_n$ oligomer that

can no longer bond to glass.[14] The formation of oligomer depends mainly on the pH of the medium, the type of solvent and the environmental temperature, with this process being favored in acidic media.[84] It has also been demonstrated that an interaction between the different monomers contained in the universal adhesive might affect the coupling capacity of the silane content to silica, for example, the presence of BisGMA inhibits the condensation reaction between the silanol group and the substrate.[85]

An optimal cementation protocol for oxide based ceramics is still under controversial discussion.[86–89] The last systematic review performed about this topic concluded that mechanical pre-treatments, especially the ceramic coating, combined with methacryloyloxydecyl dihydrogen phosphate (MDP) containing primers yielded the highest long-term bond strength of composite cement to zirconia substrates.[90] The meta-analysis performed in the present review compared the bond strength values of zirconia oxide ceramics with those of resin composite or resin cement without considering the type of roughening process performed, by only evaluating the chemical bonding promoted by both MDP containing universal adhesives or primers. Our findings demonstrated higher bond strength values when universal adhesives were used instead of the material-specific primer. The superiority in the bond strength promoted by the universal adhesives may be explained due the presence of some functional components other than MDP.[50] Universal adhesives contain dimethacrylates and other additives that enhances the mechanical properties of the polymer and give it certain hydrophobicity, consequently improving the bonding properties, especially in the long-term.[91] In addition, the adhesive components of the universal adhesive reduce the contact angle between the zirconia surface and resin, resulting in a more intimate interaction, positively affecting the bond strength results.[92]

Strong adhesion between alloy surfaces and resin composites depends on micromechanical interlocking together with chemical bonding.[93] Aluminum oxide sandblasting has been proved to be the least expensive, most simple, and most effective method for creating micro-retention surfaces in dental alloys.[94] On the other hand, the chemical bonding results from phosphate and sulfur-containing functional monomers that are able to chemically bond to the surface oxide layer of dental alloys; while phosphate containing monomers promote adequate bond strength to base–metal

alloys, sulfur-containing monomers present a better bond to inert noble alloys.[76] At present, commercially available primers indicated for bonding metal alloys contain both phosphate and sulfur monomers, which guarantees adequate bond strength to any metal alloy.[95] According to the manufacturers' safety data sheet, none of the universal adhesives currently available include sulfur-containing monomers within their compositions, and this could be the reason why universal adhesives showed lower bond strength values than those of the alloy primers for bonding to alloy substrates.

Bonding of indirect resin composite restorations can be considered a challenging situation since the additional polymerization treatments used for enhancing their mechanical properties also reduce the number of residual-free carbon double bonds, limiting their potential for chemical bonding.[96,97] Several surface treatments have been proposed to improve the bond strength of resin cement or composite resin to these substrates, however the results are controversial and the advantage of using specific primers to improve chemical interactions with the indirect resin composite substrate components has not been clearly demonstrated.[98] The use of air-particle abrasion and additional silane treatment has been proposed to enhance the resin bond to laboratory-processed composites.[10] The evidence collected in this systematic review revealed that universal adhesives can promote bond strength to indirect resin composites similar to that of a silane coupling agent, as a separate step. The majority of the studies included in this comparison used Single Bond Universal as indirect composite primer, and the presence of a silane coupling agent in the composition of this universal adhesive could explain this behavior, however, as previously explained, the stability of the silane agent in this material is highly questionable. Instead of this, the absence of differences between the treatments compared could be attributed to the fact that after composite roughening, the silane coupling agent plays a minor role in improving the bond strength between composites.[98]

Finally, aged specimens of glass-based ceramics, oxide-based ceramics, alloys and composite substrates were analyzed. The analysis performed demonstrated performance of universal adhesives similar to that of non-aged specimens in the substrates evaluated. Despite this, the high incidence of pre-testing failures after aging processes is worth mentioning, when universal adhesives were used as glass-based ceramics primers, which emphasizes the importance of the presence of a silane coupling agent for bonding to these types of substrates. Conversely, it seems that the

universal adhesives achieved more durable bonding to zirconia, since the use of a material specific primer led to a high incidence of pre-testing failures.

From this review we were able to evaluate the best available in vitro evidence regarding the bonding efficacy of universal adhesives to indirect substrate. The results of our review should be considered with caution since high heterogeneity was observed in all the comparisons made. Future research must be conducted, especially well-conducted randomized controlled clinical trials, with the purpose of gaining better understanding of the performance of universal adhesives in the clinical success of indirect restorations.

3.6 Conclusions

The ability of universal adhesives to achieve adequate and durable bond strength to indirect substrates is limited, and depends largely on the substrate to which they are applied. The silane coupling agent incorporated into the universal adhesives did not seem to be very effective; and for glass-based ceramics, the use of a silane coupling agent in a separate step continues to be the gold standard for adhesive cementation to these substrates. This behavior could also be observed for the adhesive cementation of alloys, in which the alloy primer could not be - replaced by a universal adhesive, especially for adhesive cementation of precious alloys. Conversely, the clinical procedure of cementing zirconia and resin composite restorations could be demonstrated to be simpler and more efficient when using the single-bottle universal adhesives.

3.7 Formatting of funding sources

This work was supported by the Research Support Foundation of Rio Grande do Sul - Brazil (FAPERGS PRONEX # 16.0471-4) and National Council for Scientific and Technological Development (CNPq, Grant # 310879/2015-9).

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Table 1. Search strategy used in PubMed (MEDLINE).

	Search terms
#1	(Universal adhesive) OR (adhesive, universal) OR (universal adhesives) OR (adhesives, universal) OR (Multimode adhesive) OR (multi-mode adhesive) OR (multimode adhesives) OR (multi-mode adhesives) OR (G Bond Plus) OR (Adhese Universal) OR (All-Bond Universal) OR (One-step Universal Dental adhesive) OR (One-step plus universal) OR (Peak Universal Bond) OR (Clearfil Universal Bond) OR (iBond Self Etch) OR (FuturaBond U) OR (Optibond XTR) OR (Optibond Universal) OR (Prelude One) OR (Prime&Bond Elect) OR (One Coat 7 Universal) OR (Universal bond) OR (Universal bonding agent) OR (multi-mode bond) OR (multimode bond) OR (multi-mode bonding agent) OR (multimode bonding agent)
#2	(lithium disilicate) OR (lithium disilicate ceramic) OR (composite) OR (Y-TZP) OR (Zirconia) OR (CAD/CAM) OR (composite resin) OR (porcelain) OR (leucite-reinforced) OR (leucite-reinforced ceramic) OR (metal alloy) OR (metal-ceramic alloy) OR (alloy) OR (leucite-reinforced glass ceramic) OR (polycristalline zirconia) OR (glass ceramic) OR (polymer-infiltrated ceramic) OR (resin-glass ceramic)
#3	Search #1 AND #2

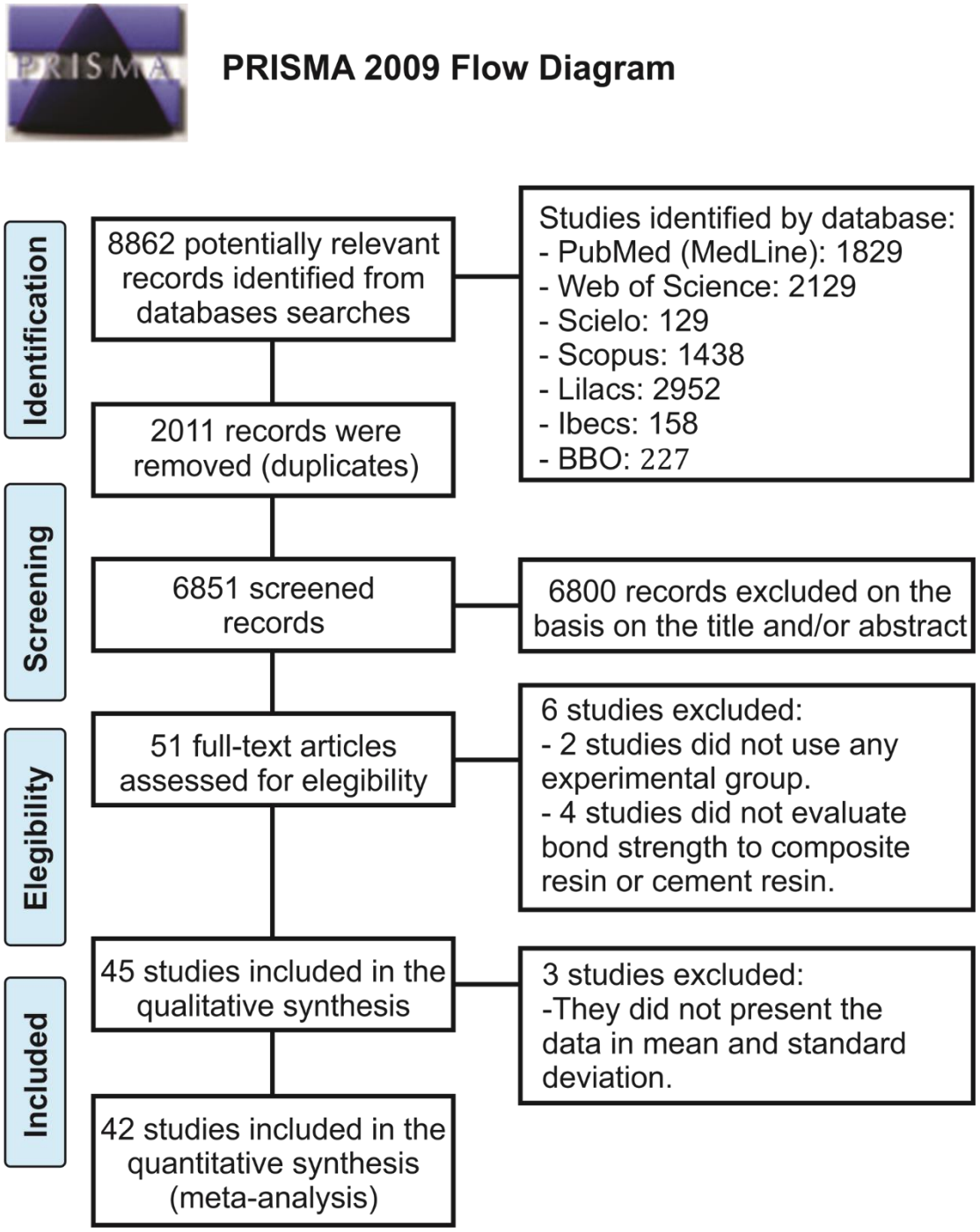

Fig. 1 Search flowchart according to the PRISMA Statement

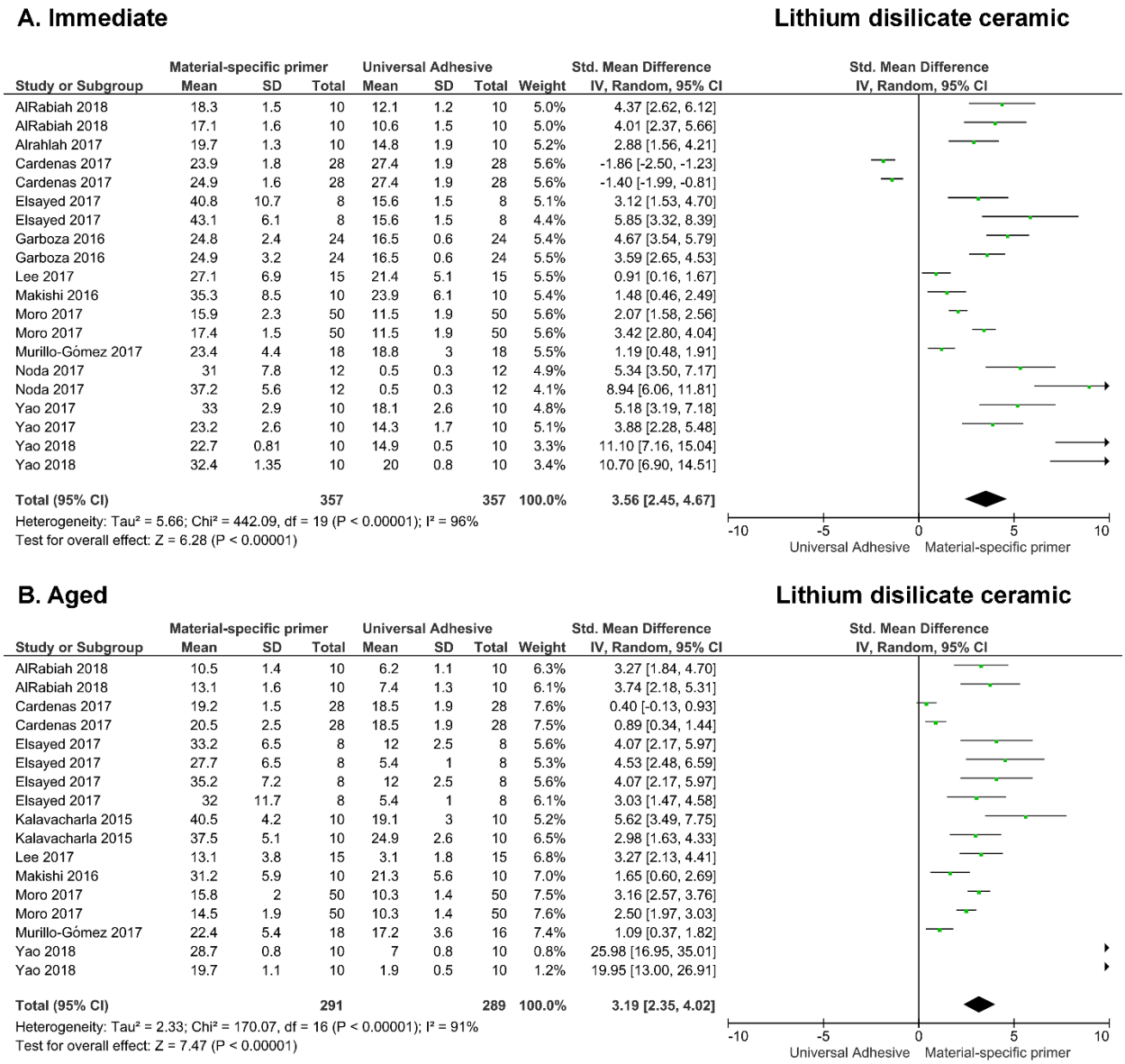

Fig. 2 Results for the analysis of the immediate (top) and aged (bottom) bond strength for lithium disilicate ceramics using random-effects models. Bond strength was improved using the material-specific primer ($p < 0.05$).

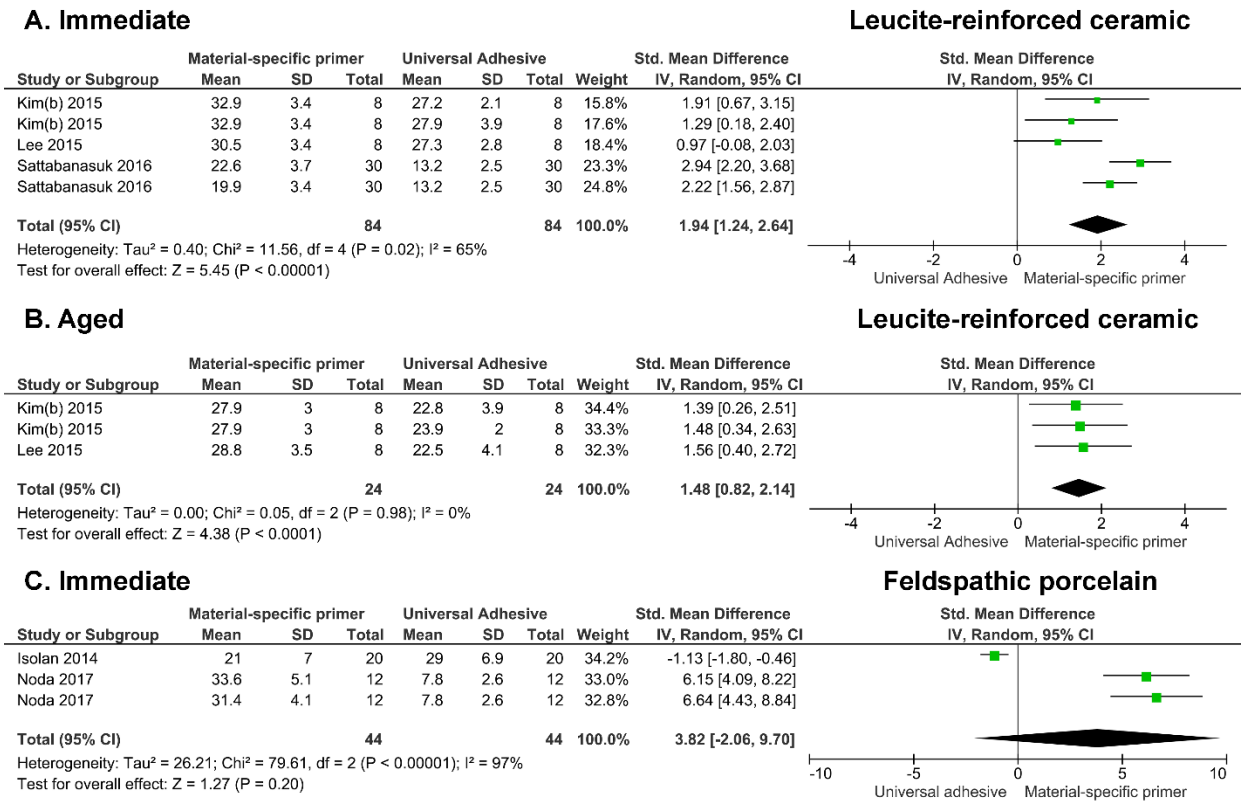

Fig. 3 Results for the analysis of the immediate (top) and aged (middle) bond strength for leucite-reinforced ceramic and immediate (bottom) feldspathic ceramic using random-effects models. The use of a material-specific primer improved the bond strength of resin composite to leucite-reinforced ceramic ($p < 0.05$). No differences were detected for feldspathic porcelain ($p = 0.20$).

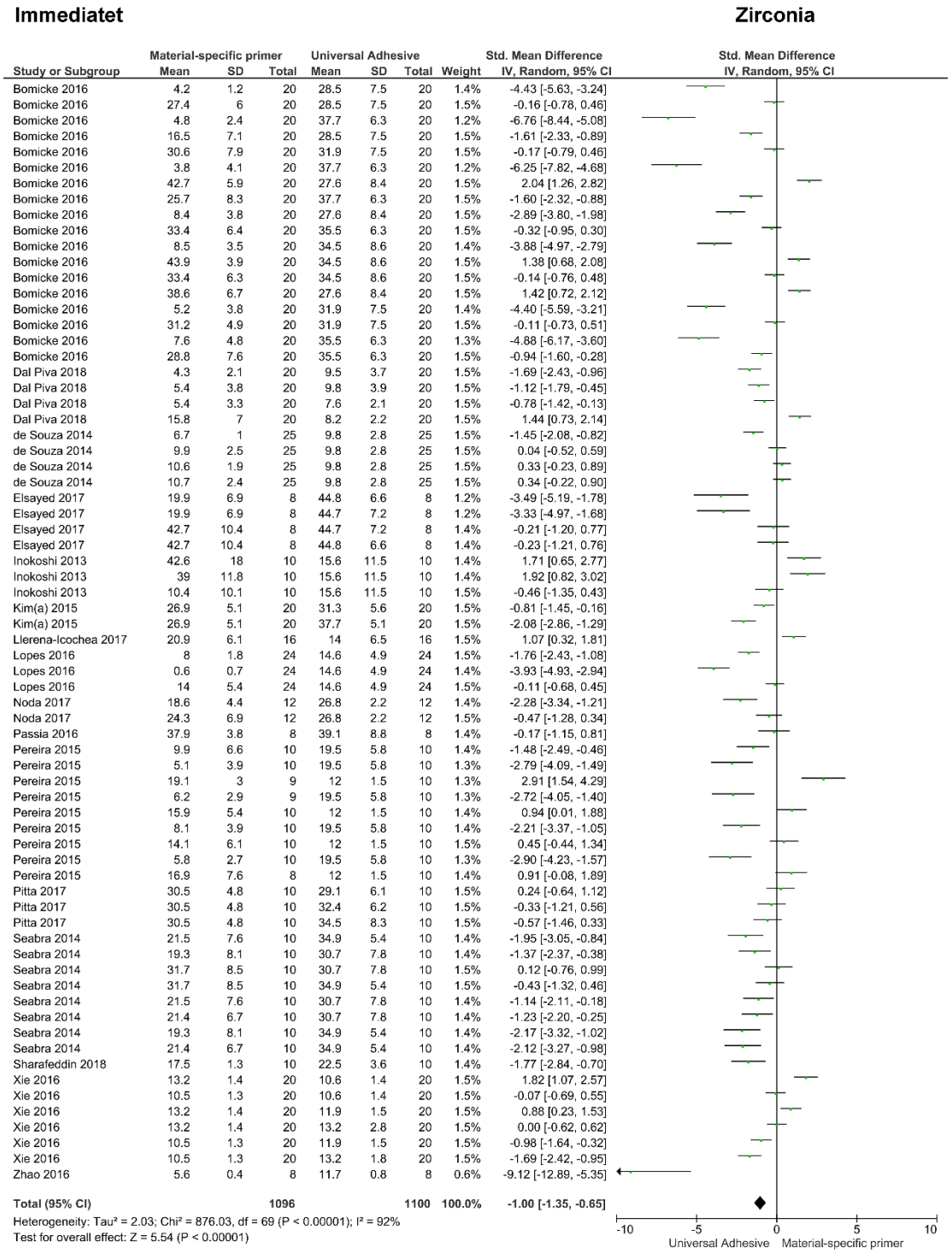

Fig 4. Results for the analysis of the immediate bond strength for zirconia using random-effects models. Bond strength was improved with the use of universal adhesive systems ($p < 0.05$).

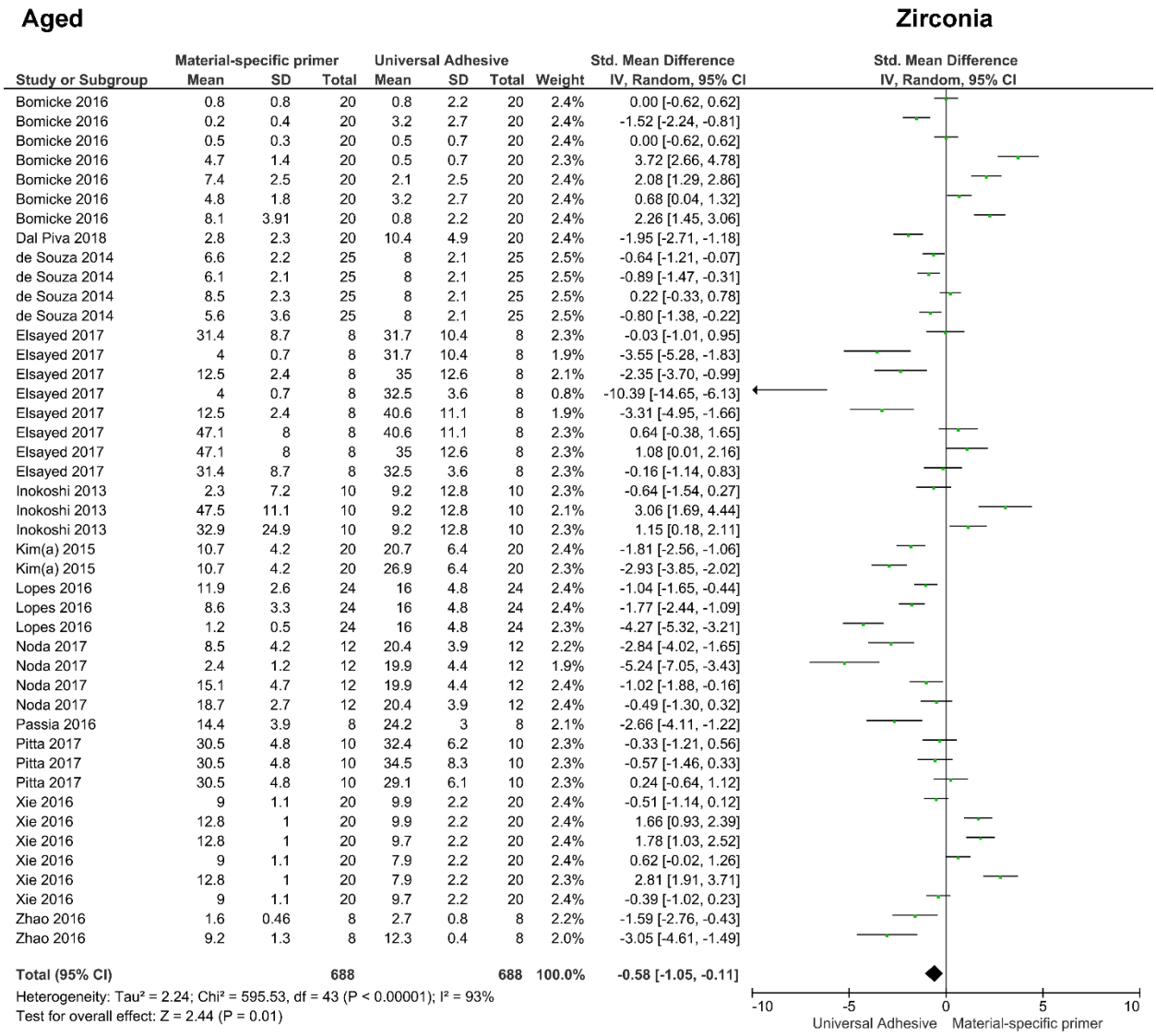

Fig 5. Results for the analysis of the aged bond strength for zirconia using random-effects models. Bond strength was improved with the use of universal adhesive systems ($p < 0.05$).

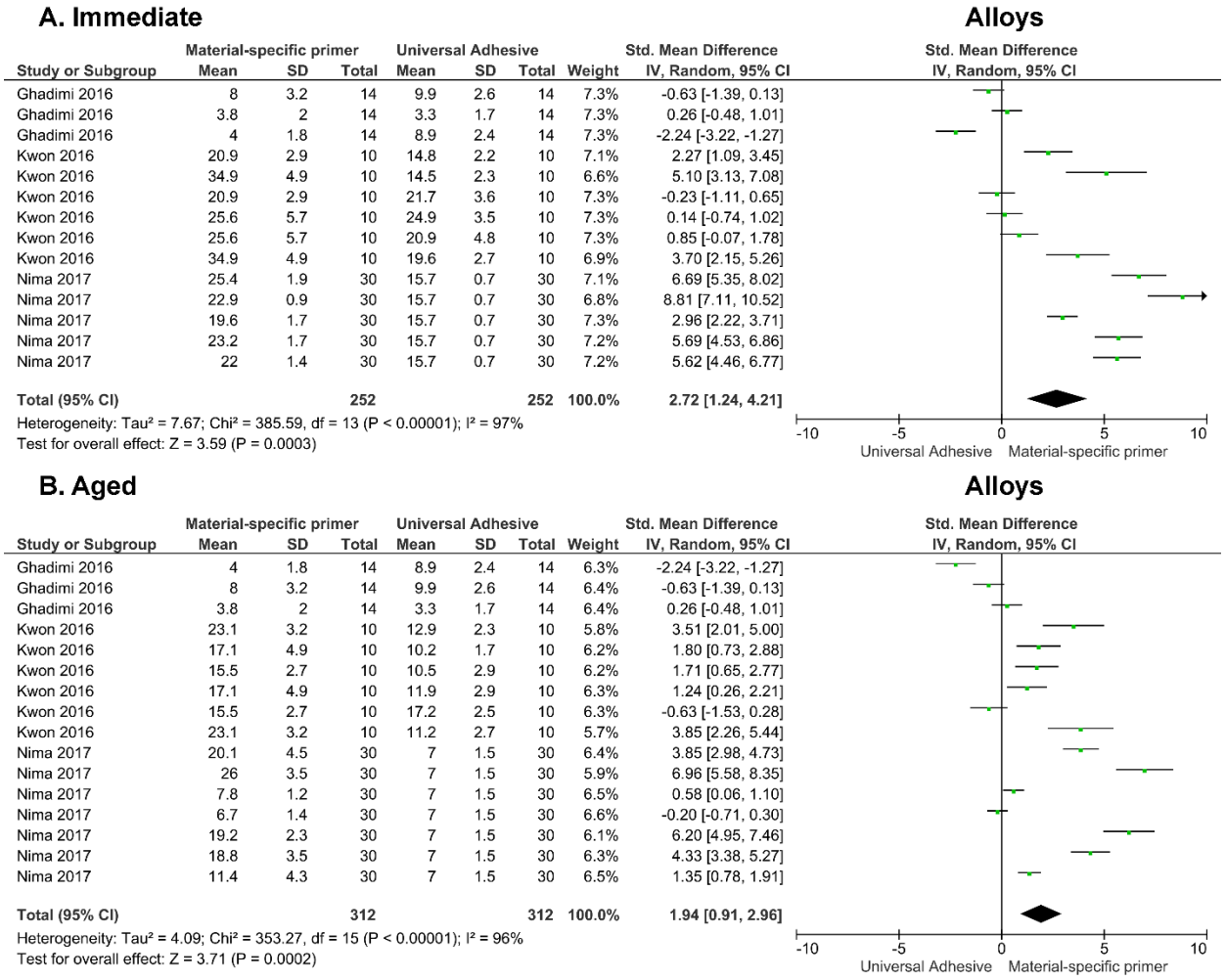

Fig 6. Results for the analysis of the immediate (top) and aged (bottom) bond strength for alloys using random-effects models. The use of the material-specific primer improved the bond strength of resin composite materials ($p < 0.05$).

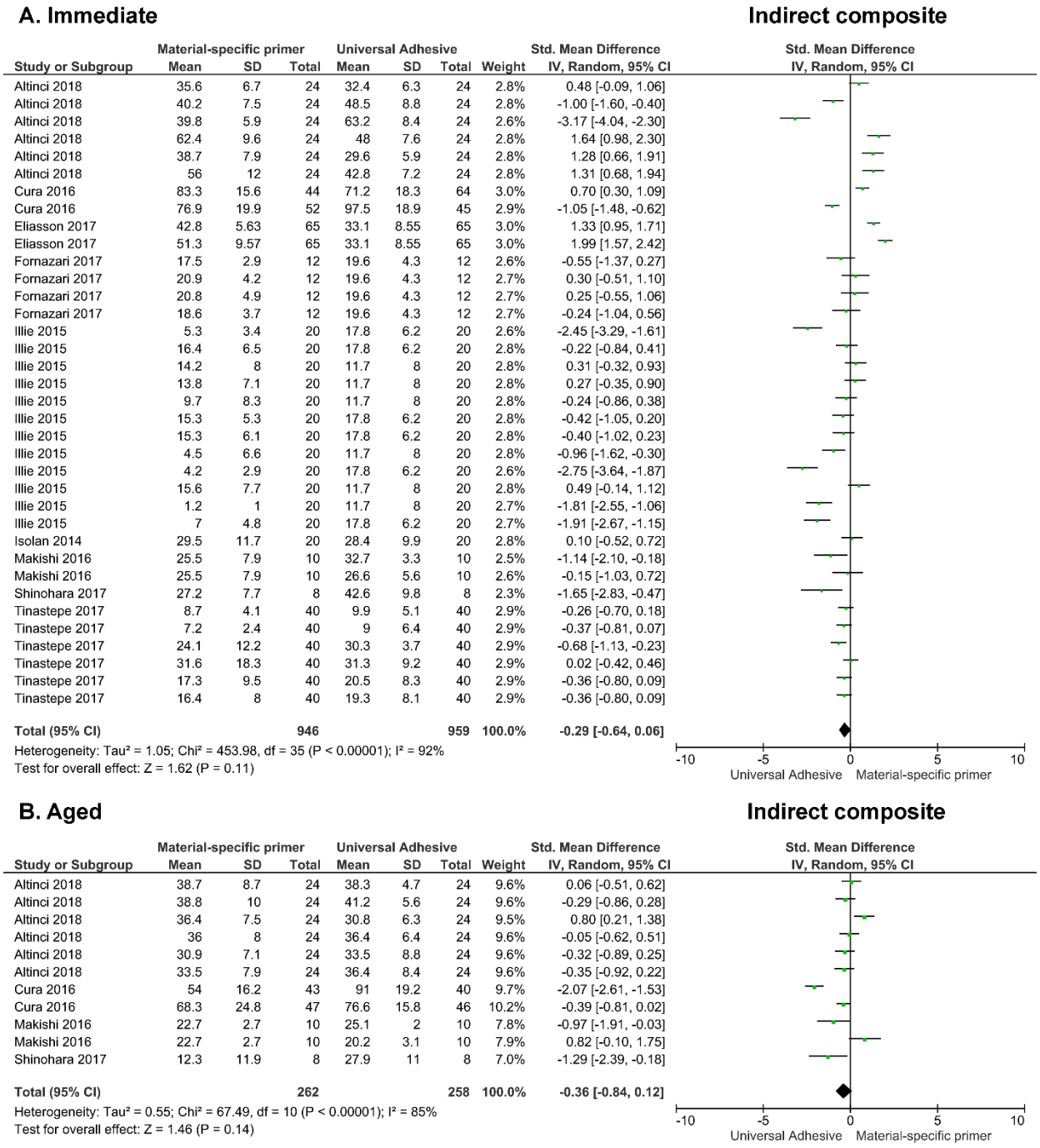

Fig. 7 Results for the analysis of the immediate (top) and aged (bottom) bond strength for indirect composites using random-effects models. No differences between universal adhesives and material-specific primers were detected ($p > 0.05$).

Appendices

Table A.1 Demographic and study design data of the included studies.

Study	Year	Country	Substrate	Bond Strength test	Storage conditions (immediate/aged)	Universal adhesive	Material-specific primer	Type of composite used
AlRabiah	2018	Saudi Arabia	Lithium disilicate ceramic	SBS	Distilled water at 37 °C for 24 h / Distilled water at 37 °C for 3 months and thermocycling (5000 cycles 5–55 °C/30 s dwell time)	Single Bond Universal (3M ESPE), All Bond Universal (Bisco), Futurabond U (Voco)	Silane (Ultradent)	Microhybrid composite resin (Tetric Ceram, Ivoclar Vivadent)
Alrahlah		Saudi Arabia	Lithium disilicate ceramic	SBS	Distilled water at 37 °C for 24 h	Single Bond Universal Adhesive (3M ESPE)	Monobond Plus (Ivoclar Vivadent)	Resin cement (Variolink Esthetic Dual Cure, Ivoclar Vivadent)
Altinci	2018	Finland	Composite	µTBS	Distilled water at 37 °C for 24 h / Thermocycling (6000 cycles 5–55 °C/30 s dwell time)	iBond Universal (Heraus Kulzer GmbH)	Signum Ceramic bond I (Heraus Kulzer GmbH)	Nano-hybrid composite (Venus Pearl, Heraus Kulzer GmbH), Hybrid composite (Z100, 3M ESPE) and Nanofilled composite (Filtek Supreme XTE, 3M ESPE)
Bomicke	2016	Germany	Yttrium-stabilized zirconium dioxide	TBS	Distilled water at 37°C for 72 h / Distilled water at 37 °C for 150 days and thermocycling (37,500 cycles 6.5–60 °C/45 s dwell time)	Single Bond Universal Adhesive (3M ESPE)	Clearfil Ceramic Primer (Kuraray Noritake Dental Inc.), Monobond Plus (Ivoclar Vivadent), Ceramic Bond (Voco)	Autopolymerizing composite resin (Rebilda SC, Voco)

Cardenas	2017	United States	Lithium Disilicate Ceramic	μSBS	Distilled water at 37 °C for 24 h / Distilled water at 37 °C for 1 year	Prime & Bond Elect (Dentsply Caulk), Single Bond Universal Adhesive (3M ESPE)	Monobond S and Monobond Plus (Ivoclar Vivadent)	Resin cement (Enforce, Dentsply Caulk, and RelyX Ultimate, 3M ESPE)
Cura	2016	Spain	Composite	TBS	Distilled water at 37 °C for 24 h / Distilled water at 37 °C for 6 months	Single Bond Universal (3M ESPE)	ESPE Sil (3M ESPE)	Resin cement (RelyX Ultimate, 3M ESPE)
Dal Piva	2018	Brazil	Yttrium-stabilized zirconium dioxide	μSBS	Distilled water at 37 °C for 24 h / Distilled water at 37 °C for 6 months and thermocycling (5000 cycles)	Singlebond Universal Adhesive (3M ESPE)	RelyX ceramic primer (3M ESPE)	Resin cement (RelyX ARC, 3M ESPE)
de Souza	2014	Canada	Yttrium-stabilized zirconium dioxide	μTBS	Distilled water at room temperature for 24 h / Distilled water at room temperature for 6 months	Single Bond Universal Adhesive (3M ESPE)	Experimental MDP-containing primer solution (Kuraray Noritake Dental Inc. Noritake Dental Inc)	Resin cement (RelyX Ultimate, 3M ESPE)
Eliasson	2017	Iceland	Composite	μTBS	Thermocycling (5000 cycles 5–55 °C/20 s dwell time)	Adper Scotchbond Universal Adhesive (3M ESPE)	Bis-silane (Bisco)	Nanofilled composite (Filtek Supreme XTE, 3M ESPE)
Elsayed	2017	Germany	Lithium Disilicate Ceramic and Yttrium-stabilized zirconium dioxide	TBS	Distilled water at 37 °C for 72 h / Thermocycling (7500 and 37,500 cycles 5–55 °C/30 s dwell time)	Single Bond Universal (3M ESPE), All-Bond Universal (Bisco)	Monobond Plus (Ivoclar Vivadent) Calibra Silane (Dentsply Caulk)	Resin cement (Variolink Esthetic Dual Cure, Ivoclar Vivadent; RelyX Ultimate, 3M ESPE and Duo Link, Bisco)

Fornazari	2017	Brazil	Composite	µSBS	Distilled water at 37 °C for 48 hours	Single bond Universal Adhesive (3M ESPE)	Ceramic Primer (3M ESPE), Monobond Plus (Ivoclar Vivadent)	Nanoparticled composite (Filtek Supreme Ultra Restorative Composite, 3M ESPE)
Garboza	2016	Brazil	Lithium disilicate	µSBS	Not informed	Singlebond Universal Adhesive (3M ESPE)	RelyX Ceramic Primer (3M ESPE)	Resin cement (RelyX ARC, 3M ESPE)
Ghadimi	2016	Iran	Stainless steel crowns	SBS	Thermocycling (1500 cycles 5–55 °C/30 s dwell time)	Singlebond Universal Adhesive (3M ESPE)	Alloy Primer (Kuraray Noritake Dental Inc. Noritake Dental Inc)	Microhybrid composite resin (Filtek Z250, 3M ESPE)
Ilie	2015	Germany	Composite	TBS	Thermocycling (10000 cycles 5–55 °C/20 s dwell time)	Singlebond Universal Adhesive (3M ESPE, St Paul, MN, USA)	Clearfil Ceramic Primer (Kuraray Noritake Dental Inc. Noritake Dental Inc), Tokuso Ceramic Primer (Tokuyama Dental Corp), Ceramic Repair System Kit: Monobond Plus + Heliobond (Ivoclar Vivadent) and Visio link (Bredent)	Nanoparticled composites (Clearfil Majesty Posterior and Clearfil Majesty ES 2, Kuraray Noritake Dental Inc. Noritake Dental Inc)

Inokoshi	2013	Belgium	Yttrium-stabilized zirconium dioxide	μTBS	Distilled water at 37 °C for 1 week / Cyclic tensile stress of 10 N at 10 Hz for 10,000 cycles	Scotchbond Universal (3M ESPE)	Monobond Plus (Ivoclar Vivadent), ZPRIME Plus (Bisco), Clearfil Ceramic Primer (Kuraray Noritake Dental Inc.)	Resin cement (RelyX Ultimate, 3M ESPE)
Isolan	2014	Brazil	Composite and feldspathic porcelain	μTBS for composite and SBS for feldspathic porcelain	Distilled water at 37 °C for 24 h	Scotchbond Universal (3M ESPE)	Silane (Dentsply Caulk)	Microhybrid composite resin (Opalis)
Kalavacharla	2015	USA	Lithium disilicate	SBS	Distilled water at 37 °C for 24 hours and thermocycling (10000 cycles 5–55 °C/15 s dwell time)	Scotchbond Universal (3M ESPE)	RelyX Ceramic Primer (3M ESPE)	Microhybrid composite resin (Filtek Z100, 3M ESPE)
Kim	2015	Korea	Yttrium-stabilized zirconium dioxide	μSBS	Distilled water at 37 °C for 24 hours / Thermocycling (10000 cycles 5–55 °C/25 s dwell time)	Singlebond Universal (3M ESPE), All-Bond Universal (Bisco)	Alloy primer (Kuraray Noritake Dental Inc.)	Resin cement (RelyX ARC, 3M ESPE)
Kim	2015	Korea	Leucite-renforced ceramic	μSBS	Distilled water at 37 °C for 24 hours / Thermocycling (10000 cycles 5–55 °C/25 s dwell time)	Singlebond Universal (3M ESPE), All-Bond Universal (Bisco)	RelyX Ceramic Primer (3M ESPE)	Resin cement (RelyX Ultimate, 3M ESPE)
Kwon	2016	Korea	Noble metal-ceramic alloys	SBS	Distilled water at 37 °C for 24 h / Distilled water at 37 °C for 7 days and thermocycling (10000 cycles 5–55 °C/30 s dwell time)	Singlebond Universal (3M ESPE), All-Bond Universal (Bisco)	M.L. Primer (Shofu Inc.)	Resin cement (Duo-Link, Bisco)
Lee	2017	Korea	Lithium disilicate ceramic	μSBS	Distilled water at 37 °C for 24 h / Thermocycling (10000 cycles 5–55 °C/24 s dwell time)	Singlebond Universal (3M ESPE)	Bis-Silane (Bisco)	Resin cement (NX3, shade clear, Kerr Corp.)

Lee	2015	Korea	Leucite-reinforced ceramic	μSBS	Distilled water at 37 °C for 24 h / Thermocycling (10000 cycles 5–55 °C/24 s dwell time)	Singlebond Universal (3M ESPE)	RelyX Ceramic Primer (3M ESPE)	Resin cement (RelyX Unicem U200, 3M ESPE)
Llerena-Icochea	2017	Brazil	Yttrium-stabilized zirconium dioxide	SBS	Distilled water at 37 °C for 24 h	Single Bond Universal (3M ESPE)	Signum Zirconia Bond (Heraeus Kulzer GmbH)	Resin cement (RelyX Ultimate, 3M ESPE)
Lopes	2016	Brazil	Yttrium-stabilized zirconium dioxide	μSBS	Distilled water at 37°C for 72 h / Distilled water at 37 °C for 6 months	Singlebond Universal Adhesive (3M ESPE)	Signum Zirconia Bond I + II (Heraeus Kulzer GmbH), MZ Primer (Angelus)	Resin cement (Duo-Link Dual-Syringe, Bisco)
Makishi	2016 b	Brazil	Lithium Disilicate Glass Ceramic and composite	μSBS	Distilled water at 37°C for 72 h / Distilled water at 37 °C for 1 year	All-Bond Universal (Bisco), Singlebond Universal Adhesive (3M ESPE)	RelyX Ceramic Primer (3M ESPE)	Resin cement (Duo-Link Dual-Syringe, Bisco)
Moro	2017	Brazil	Lithium disilicate	μSBS	Distilled water at 37 °C for 24 h / Thermocycling (10000 cycles 5–55 °C/20 s dwell time)	Singlebond Universal Adhesive (3M ESPE)	Rely X Ceramic Primer (3M ESPE)	Flowable resin (PermaFlo Pink, Ultradent)
Murillo-Gómez	2017	Brazil	Lithium disilicate glass ceramic	μSBS	Distilled water at 37°C for 24 h / Distilled water at 37 °C for 6 months	Singlebond Universal Adhesive (3M ESPE)	RelyX Ceramic Primer (3M ESPE), Clearfil Ceramic Primer (Kuraray Noritake Dental Inc. Noritake Dental Inc.)	Resin cement (RelyX Ultimate, 3M ESPE)

Nima	2017	Brazil	Nickel-Chrome Metal Alloy	μSBS	Distilled water at 37 °C for 24 h /Thermocycling (5000 cycles 5–55 °C/30 s dwell time)	Singlebond Universal Adhesive (3M ESPE)	RelyX Ceramic Primer (3M ESPE), Alloy Primer (Kuraray Noritake Dental Inc.), Universal Primer (Tokuyama)	Flowable resin (Filtek Supreme Ultra Flowable Restorative, 3M ESPE)
Noda	2017	Japan	Feldspathic ceramic, lithium disilicate ceramic and yttrium-stabilized zirconium dioxide	μSBS	Distilled water at 37 °C for 24 h /Thermocycling (5000 and 10000 cycles 5–55 °C/30 s dwell time)	Scotchbond Universal Adhesive (3M ESPE)	Clearfil Ceramic Primer (Kuraray Noritake Dental Inc.), Tokuyama Universal Primer (Tokuyama)	Resin cement (Clapearl DC, Kuraray Noritake Dental Inc.)
Passia	2016	Germany	Yttrium-stabilized zirconium dioxide	TBS	Distilled water at 37 °C for 72 h / Distilled water at 37 °C for 150 days and thermocycling (37,500 cycles 5–55 °C/30 s dwell time)	Singlebond Universal Adhesive (3M ESPE)	Monobond Plus (Ivoclar Vivadent)	Resin cement (RelyX Ultimate, 3M ESPE)

Pereira	2015	Brazil	Yttrium-stabilized zirconium dioxide	SBS	Distilled water at 37°C for 60 days	Singlebond Universal Adhesive (3M ESPE)	Alloy Primer (Kuraray Noritake Dental Inc.), MZ Primer (Angelus), Metal/Zirconia Primer (Ivoclar Vivadent), Monobond Plus (Ivoclar Vivadent), Z Prime Plus (Bisco), Signum Zirconia bond (Heraeus Kulzer GmbH)	Resin cement (RelyX ARC, 3M ESPE)
Pitta	2017	Portugal	Yttrium-stabilized zirconium dioxide	SBS	Distilled water at 37 °C for 72 h / Distilled water at 37 °C for 30 days and thermocycling (10000 cycles 5–55 °C/30 s dwell time)	Scotchbond Universal (3M ESPE), All-bond Universal (Bisco), Futurabond M+ (Voco)	Z-prime Plus (Bisco)	Resin cement (RelyX ARC, 3M ESPE; Bifix QM, Voco; Duo-link Universal, Bisco)
Rohr	2017	Switzerland	Polymer-infiltrated ceramic network	SBS	Distilled water at 37°C for 24h	Scotchbond Universal (3M ESPE)	Vitasil (VITA)	Resin cement (RelyX Ultimate, 3M ESPE)
Sattabanasuk	2016	Thailand	Leucite-reinforced ceramic	µSBS	Distilled water at 37°C for 24h	Singlebond Universal Adhesive (3M ESPE)	RelyX Ceramic Primer (3M ESPE)	Nanoparticled composite (Filtek Z350XT, 3M ESPE)
Seabra	2014	Portugal	Yttrium-stabilized zirconium dioxide	SBS	Distilled water at 37°C for 48h	All-Bond Universal (Bisco), Singlebond Universal Adhesive (3M ESPE)	Z-Prime Plus (Bisco)	Microhybrid composite resin (Filtek Z250, 3M ESPE)

Sharafeddin	2018	Iran	Yttrium-stabilized zirconium dioxide	SBS	Distilled water at 37°C for 24h	All-Bond Universal (Bisco)	Z-Prime Plus (Bisco)	Resin cement (Variolink N, Ivoclar Vivadent)
Shinohara	2017	Japan	Composite	SBS	Distilled water at 37 °C for 24 h / Thermocycling (10000 cycles 4–60 °C/60 s dwell time)	Singlebond Universal Adhesive (3M ESPE)	GC Ceramic Primer II (GC Corp.)	Microhybrid composite resin (Gradia Direct, GC Corp)
Tinastepe	2017	Turkey	Composite	SBS	Distilled water at 37°C for 24h	Singlebond Universal Adhesive (3M ESPE)	Ultradent silane (Ultradent)	Microhybrid composite resin (Filtek Z250, 3M ESPE)
Xie	2016	China	Yttrium-stabilized zirconium dioxide	SBS	Distilled water at 37 °C for 24 h / Thermocycling (20000 cycles 5–55 °C/30 s dwell time)	Single Bond Universal (3M ESPE), Clearfil universal bond (Kuraray Noritake Dental Inc.), All-bond universal (Bisco)	Porcelain Primer and Z-Prime PlusTM (Bisco)	Resin cement (Variolink N, Ivoclar Vivadent)
Yao	2017	China	Lithium disilicate ceramic	SBS	Distilled water at 37 °C for 24 h	All Bond Universal (Bisco), Single Bond Universal (3M ESPE), Adhese Universal (Ivoclar Vivadent), Clearfil Universal Bond (Kuraray Noritake Dental Inc.)	RelyX Ceramic Primer (3M ESPE)	Microhybrid composite resin (Charisma, Heraeus Kulzer GmbH)
Yao	2018	China	Lithium disilicate ceramic	SBS	Distilled water at 37 °C for 24 h / Thermocycling (10000 cycles 5–55 °C/30 s dwell time)	All Bond Universal (Bisco), Adhese Universal (Ivoclar Vivadent), Clearfil Universal Bond (Kuraray Noritake Dental Inc.), Single Bond Universal (3M ESPE)	RelyX ceramic primer (3M ESPE)	Microhybrid composite resin (Charisma, Heraeus Kulzer GmbH)

Zhao	2016	China	Yttrium-stabilized zirconium dioxide	SBS	Distilled water at 37 °C for 24 h / Distilled water at 37 °C for 30 days and Thermocycling (3000 cycles 5–55 °C/30 s dwell time)	Scotchbond Universal (3M ESPE)	Clearfil Ceramic Primer (3M ESPE), Z-Prime Plus (Bisco)	Resin cement (RelyX Ultimate, 3M ESPE and Duo-Link, Bisco)

SBS = Shear bond strength, μSBS = micro-shear bond strength, μTBS = micro-tensile bond strength, TBS = tensile bond strength.

Table A.2 Material-specific primers included in this systematic review.

Name	Manufacturer	Type	Uses*	Composition**
Ultradent Silane	Ultradent	Silane-based ceramic primer	Glass ceramics and composites	Methacryloxy propyl trimethoxy silane, isopropyl alcohol
Monobond Plus	Ivoclar Vivadent	Universal primer	Glass and oxide ceramics, metal, composites, fiber-reinforced composite	Methacrylated phosphoric acid ester, ethanol
Signum Ceramic bond	Heraus Kulzer GmbH	Silane-based ceramic primer	Silicate ceramics	Poly(oxy-1,2-ethanediyl), alpha-hydro-omega-[(1-oxo-2-propenyl)oxy]-ether, 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, tetramethylene dimethacrylate, diphenyl(2,4,6- trimethylbenzoyl)phosphine oxide.
Rely X Ceramic Primer	3M ESPE	Silane-based ceramic primer	Ceramic or metal restorations	Ethyl alcohol, water, methacryloxypropyltrimethoxysilane
Z-Prime Plus	Bisco Inc.	Zirconia, Alumina and Metal primer	Zirconia, Alumina and Metal restorations	Ethanol, BisGMA, 2-Hydroxyethyl Methacrylate, 10-methacryloyloxydecyl Dihydrogen Phosphate
AZ Primer	Shofu Inc.	Zirconia and Alumina primer	Zirconia and Alumina restorations	Acetone, 6-methacryloyloxyhexyl dihydrogen phosphate
Clearfil Ceramic Primer	Kuraray Noritake Dental Inc.	Full ceramic primer	Ceramic restorative, porcelain, Zirconia, Alumina, Lucite, Lithium Silicate and composites.	Ethanol, 3-trimethoxysilylpropyl methacrylate, 10-Methacryloyloxydecyl dihydrogen phosphate
Ceramic Bond	VOCO	Full ceramic primer	Ceramic, zirconia and composite	Organic acid, 3-trimethoxysilylpropyl methacrylate, acetone
Monobond S	Ivoclar Vivadent	Silane-based ceramic primer	Glass-ceramics, lithium disilicate glass-ceramics, composites and fibre-reinforced composites.	Ethanol, 3-trimethoxysilylpropyl methacrylate
Bis-silane	Bisco Inc.	Silane-based ceramic primer	Porcelain/Lithium Disilicate Restorations	Acetone, ethanol, 3-(trimethoxysilyl)propyl-2-methyl-2-propenoic acid

Calibra Silane	Dentsply Caulk	Silane-based ceramic primer	Ceramic, porcelain and composite inlays/onlays, crowns and veneers	Ethanol, acetone, 3-trimethoxysilylpropyl methacrylate
Alloy Primer	Kuraray Noritake Dental Inc.	Metal primer	Gold, base and semi-precious metals, titanium and other dental alloys.	6-(4-Vinylbenzyl-N-propyl)amino-1,3,5-triazine-2,4-dithione, 10-Methacryloyloxydecyl dihydrogen phosphate, acetone
Tokuso Ceramic Primer	Tokuyama	Silane-based ceramic primer	Glass-ceramics and composites	Ethanol, 3-trimethoxysilylpropyl methacrylate, methacryloxyalkyl acid phosphate
Visio link	Bredent	PMMA and composite primer	PMMA, artificial teeth and composites	Methyl methacrylate, pentaerythritol triacrylate, pentaerythritol tetraacrylate, diphenyl(2,4,6,-trimethylbenzoyl)-phosphineoxide
M.L. Primer	Shofu Inc.	Metal primer	Semi-precious metal, precious metal and non-precious metal	Acetone, phosphonate monomer, thioctic acid monomer
Signum Zirconia Bond	Heraus Kulzer GmbH	Zirconia oxide primer	Zirconia oxide surfaces	Acetone, 10-Methacryl-oxydecyl-dihydrogenphosphate, acetic acid, methylmethacrylate, diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide
MZ Primer	Angelus	Alloy, zirconia and alumina primer	Alloy, Zirconia and Alumina surfaces	Phosphoric acid 2-hydroxyethyl methacrylate ester, methacrylic acid, pyromellitic dimethacrylate, benzoyl peroxide, acetone
Beautibond Multi PR Plus	Shofu Inc.	Silane-based ceramic primer	Glass ceramics and composites	Ethanol, 3-trimethoxysilylpropyl methacrylate
Universal Primer	Tokuyama	Universal primer	Glass-ceramics (porcelain), oxide-ceramics (zirconia and alumina), metals (precious and non-precious) and resin materials including inorganic filler.	Ethanol, acetone, (1-methylethylidene)bis[4,1-phenyleneoxy(2-hydroxy-3,1-propanediyl)] bismethacrylate, 2,2'-ethylenedioxydiethyl dimethacrylate, 3-trimethoxysilylpropyl methacrylate, 6-methacryloxyhexyl-2-thiouracil-5- carboxylate, 2,6-di-tert-butyl-p-cresol, 2-propenoic acid 2-methyl- 2-hydroxyethyl ester phosphate, 1-methacryloxy-1,1-undecanecarboxylic acid.

Metal/ Zirconia Primer	Ivoclar Vivadent	Alloy, zirconia and alumina primer	Zirconium oxide and aluminium oxide ceramic or metal and metal-ceramic.	6-(4-vinylbenzyl-n-propyl)amino-1,3,5-triazine-2,4-dithione, 10-Methacryl-oxydecyl-dihydrogenphosphate, acetone
Vitasil	VITA	Silane-based ceramic primer	Glass-ceramics and composites	3-trimethoxysilylpropyl methacrylate, ethanol

* According to manufacturer.
** According to Manufacturers' MSDS

Table A.3 Main components of universal adhesives included.

Name	Manufacturer	Main components*
All-Bond Universal	Bisco Inc.	Bisphenol A Diglycidylmethacrylate, Ethanol, MDP, 2-Hydroxyethyl Methacrylate.
Single Bond Universal	3M ESPE	2-Hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, Decamethylene dimethacrylate, ethanol, Silane treated silica, water, 2-propenoic acid, 2-Methyl-, reaction products with 1,10-decanediol and phosphorous oxide, copolymer of acrylic and itaconic acid, dimethylamino ethyl methacrylate, camphorquinone, dimethylaminobenzoato, 2,6-di-tert-butyl-P-cresol.
iBond Universal	Heraus Kulzer GmbH	Acetone, 4-methacryloxyethyltrimellitic acid anhydride.
Adhese Universal	Ivoclar Vivadent	2-hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, ethanol, 1,10-decandiol dimethacrylate, Methacrylated phosphoric acid ester, camphorquinone, 2-dimethylaminoethyl methacrylate.
Prime&Bond Elect	Dentsply Caulk	Acetone , Urethane Dimethacrylate Resin, Dipentaerythritol pentaacrylate phosphate, Polymerizable dimethacrylate resin, Polymerizable trimethacrylate resin.
OneCoat 7 Universal	Coltene	Ethanol, urethane dimethacrylate,
Futurabond M+	VOCO	Bisphenol A Diglycidylmethacrylate, Ethanol, Acidic adhesive monomer, catalyst.
Clearfil Universal Bond	Kuraray Noritake Dental Inc.	Bisphenol A diglycidylmethacrylate, 2-hydroxyethyl methacrylate, ethanol, 10-Methacryloyloxydecyl dihydrogen phosphate, Hydrophilic aliphatic dimethacrylate, Colloidal silica, dl-Camphorquinone, Silane coupling agent, Accelerators, Initiators, Water.
Peak Universal Bond Primer **Peak Universal Bond Adhesive**	Ultradent	Ethyl alcohol, methacrylic acid, 2-hydroxyethyl methacrylate, 2-hydroxyethyl methacrylate. Ethyl Alcohol, 2-hydroxyethyl Methacrylate, Methacrylic Acid, Chlorhexidine di(acetate),

* According to Manufacturers' MSDS

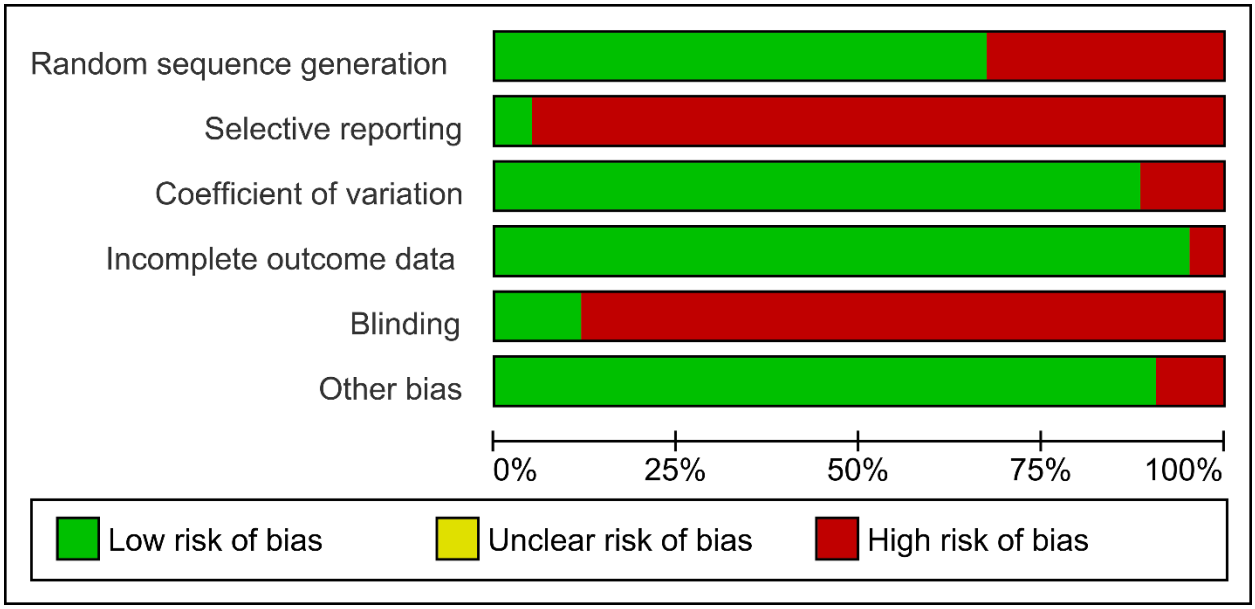

Figure A1. Review authors' judgments about each risk of bias item for each included in vitro study.

4 Capítulo 3

Cell viability related to unreacted substances of universal adhesives[3]

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[3] Artigo formatado segundo as normas do periódico Journal of Denal Research

4.1 Abstract

The objective of this study was to evaluate the elution of unreacted substances and the cell viability of four universal adhesives as a function of the sample preparation method used. Four universal adhesives were tested, Single Bond^{TM} Universal (SBU), Tetric® N Bond Universal (TBU), OptiBond® Universal (OBU) and OneCoat Universal (OCU). Specimens were prepared using three different methods: cylindrically discs (5x1mm) built from the adhesive material itself, filter paper discs (⌀ 5mm) impregnated with the adhesive system, and dentine bovine disc (5x1mm) impregnated with the adhesive system. UHPLC-QTOF-MS was used to detect unreacted substances after specimens' fabrication. The cell viability of the universal adhesives as a function of the sample preparation method, and of the different concentrations of each compound detected by the analytical method described, in their isolated form, were evaluated using the WST-1 assay. Two-way ANOVA and Tukey's test were used for statistical analysis. According to UHPLC-QTOF-MS analysis, signals for HEMA, BisGMA, CQ, EDAB, TPO, and UDMA were identified from the extraction media. When evaluated in the form of material discs, significantly higher amounts of CQ where detected in all universal adhesives evaluated ($p<0.001$). The cell viability was found to be significantly influenced by both universal adhesive type ($p<0.001$) and method of specimen preparation ($p<0.001$). All universal adhesives exerted a cytotoxic effect when evaluated in the material disc form, while when evaluated using paper disc or dentine disc, the cell viability values for all materials was close to 100%. Highest CQ concentrations detected in the material disc form were found to be cytotoxic against fibroblast cells ($p<0.05$) and could be related to the cytotoxic effect exerted by universal adhesives when evaluated in the material disc form. The amount of photoinitiator system eluted and the sample preparation method showed to be determinant on biocompatibility outcomes.

Keywords: Dental adhesive, Biocompatibility, Sample preparation, Photoinitiator composites; systematic review.

4.2 Introduction

One of the most recent innovations in the field of dental adhesives is the introduction of the so-called universal or multi-mode adhesives, which are intended to be applied using the self-etch, or etch-and-rinse techniques using the same single bottle of adhesive solution (Migliau 2017). The formulation of these universal adhesives comprises complex mixture of monomers, solvents, organic acids, photoinitiators, and additives, also some of these universal adhesives contain components to provide wider indications and applications, such as silane and chlorhexidine (Chen et al. 2015).

The introduction of these new components may alter the biological behavior of the pulp-dentin complex, and therefore, the introduction of these new or modified products requires the assurance that they can be safely used in clinical settings. In this sense, several studies evaluating the cell viability of universal adhesives has been published, reporting contradictory results about the biocompatibility of these materials (Elias et al. 2015; Van Landuyt et al. 2015; Catunda et al. 2017; Jiang et al. 2017; Pupo et al. 2017). Different outcomes are probably due to differences in sample preparation methods, cell lines, and application methods used in these studies, which evidences that standard procedures are still needed in order to accurately assess the actual toxicity of current materials.

Besides, it has been previously reported that the biocompatibility of dental materials is influenced by the release of unbounded components from the resin matrix as a result of incomplete polymerization (Toz et al. 2017). In this sense, the amount of unreacted substances eluted could play an important role in the cell viability values observed in the biocompatibility tests. To date, exact knowledge with regard to the quantity and type of unreacted substances eluted from universal adhesives is still scarce.

Accordingly, in the present study, the release profile of unreacted substances and the cell viability from polymerized universal adhesives as a function of the sample preparation method was evaluated. The null hypothesis tested was that different sample preparation methods will not affect the release profile of unreacted substances and the cell viability of universal adhesives.

4.3 Materials

4.3.1 Experimental design

In this study, the elution study of unreacted substances and cell viability was evaluated according to these factors: (1) universal adhesive system at four levels: Single BondTM Universal (SBU, 3MESPE, St. Paul, MN, USA), Tetric® N-Bond Universal (TBU, Ivoclar-Vivadent, Liechtenstein), OptiBondTM Universal (OBU, Kerr, Orange, CA, USA) and OneCoat 7 Universal (OCU, Coltène/Whaledent Inc., Cuyahoga Falls, OH, USA); and (2) sample preparation method at three levels: disc-shaped polymerized material, filter paper disc impregnated with the adhesive system, and dentin bovine disc impregnated with the adhesive system (Figure 1). The composition of the universal adhesives systems evaluated in this study is described in Table 1.

4.3.2 Ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS)

Sample preparation was performed using three different methods. All specimens were prepared into a laminar flow cabinet under sterile conditions. For photopolymerization, the Ultra Radii (SDI, Australia) LED photopolymerization unit (1000 mW/cm^2) was used. All the specimens were prepared by the same operator.

Method 1: Disc-shaped specimens (n=3; 5×1 mm) were prepared by filling silicon molds with the adhesive system. To fill the mold completely, 50 µL of the material were necessary. Previous to photoactivation, the materials were air-dried for 10s and covered with a Mylar® strip. Then, the materials were photoactivated during 10s for both sides. After photopolymerization, the specimens were removed from the silicon mold and the irregularities were removed using a scalpel blade.

Method 2: Filter paper discs (n=3; nº 5, Whatman cellulose filters, England) of 5 mm of diameter were made and sterilized in an autoclave (121 °C/30 min). The discs were embedded with 5 µL of each adhesive system and air-dried during 10s. Then, the impregnated discs were photopolymerized for 10s.

Method 3: Bovine dentin discs (n=3; 5x1 mm) were cut from the buccal surfaces using a water-cooled trephine drill. The discs were then wet-polished with 600-grit SiC abrasive papers for 1 min to standardize the smear layer and sterilized in an autoclave

(121 °C/30 min). Before bonding procedures, dentine discs were kept immersed in sterilized water for at least 30 min. Once the specimens were rehydrated, the excess of water was removed using absorbent paper and 5 µL of the adhesive system was rubbed for 10s to the dentin surface using a disposable dental brush, then the adhesive was air-dried and the material photoactivated for 10s.

Immediately after polymerization, the specimens were immersed in light-proof glass vials containing 99.5% water and 0.5% dimethyl sulfoxide at 37 °C for 24h. The extraction media and the incubation period used simulated the conditions of the subsequent cell viability assays. After the incubation period, all the extraction media were removed from the vials and transferred to different vials for the analysis.

Prior to the analysis of the extraction media, calibration curves for bisphenol A-glycidyl methacrylate (Bis-GMA), triethylene glycol dimethacrylate (TEGDMA), hydroxyl ethyl methacrylate (HEMA), urethane dimethacrylate (UDMA), camphorquinone (CQ), ethyl-4-dimethyl aminobenzoate (EDAB), monoacylphosphine oxide (TPO), bysacylphosphine oxide (BAPO), and diphenyl iodonium hexafluorophosphate (DPHIHF) were prepared, and standard chromatographs of each compound were obtained. Then, the analysis of eluted compounds released from the samples was carried out using a UHPLC-QTOF-MS system. The UHPLC (Shimadzu-Nexera x2) equipped with Shin-pack XR ODS III column (2.0 mm × 50 mm, 1.6 µm) at 40 °C and coupled to a QTOF-MS mass analyzer (Bruker Daltonics- Impact II) was used to separate and detect the compounds of interest. The QTOF-MS system was equipped with an electrospray ionization (ESI) source, operating in positive ionization mode. The mobile phase consisted of A: acetonitrile (0.1% formic acid) and B: aqueous phase (0.1% formic acid), The elution gradient started at 10% of A maintained for 2 min, increased to 90% in the next 8 min, and kept for 1 min. Then 90% A linearly decreased to 10% in 4 min, kept for 5 min. The flow rate was 0.3 mL/min−1 and the injection volume was 10 µL. The operation parameters of ESI were the following: capillary voltage, 4000 V; end plate offset, 500 V; nebulizer pressure, 4 bar (N2); drying gas, 9 L/min−1 (N2); and drying temperature, 200 °C. The QTOF-MS system was operating in broadband collision-induced dissociation (bbCID) acquisition mode and recorded spectra over the range m/z 50−1000 with a scan rate of 2 Hz. A QTOF-MS external calibration was performed before each injection with a sodium formate solution. Data treatment were processed with Data Analysis 4.2 Software. The

quantitative analysis was performed through the use of calibration curves and the qualitative analysis by comparing the retention time and the mass accuracy. Results were expressed as µg/mL.

4.3.3 Cytotoxicity assay

Sample preparation was performed following the same procedures performed in the UHPLC-QTOF-MS analysis. After specimens' preparation, the discs were placed in 24-well plates with DMEM (Dulbecco's Modified Eagle's medium) and stored at 37 °C at pH 7.2 for 24h following ISO standard (International Organization for Standardization 2009; International Organization of Standardization 2012). After the incubation period, this conditioned medium supposed to contain the eluate released to the culture medium.

4.3.3.1 Cell culture and WST-1 assay

The mouse fibroblast cell line (L929) was cultured at a density of 2×104 cells in 96-well plates containing DMEM media supplemented with 10% L-glutamine, 10% fetal bovine serum (FBS), penicillin (100 U/mL) and streptomycin (100 U/mL). Cells were incubated at 37 °C under 95% air and 5% CO2 for 24 h.

After 24h incubation, the culture medium was then replaced with equal volumes (200µL) of the conditioned medium which contained the eluate from each specimen. The plate was then incubated (37 °C, 5% CO2) for a period of 24 h. After this period, the medium was aspirated, and the WST-1 solution was applied. The plates were read in a spectrophotometer with a wavelength of 450 nm, where absorbance values were considered an indicator of cell viability.

Cell viability of HEMA, BisGMA, CQ and EDAB in their isolated form was also evaluated. Different concentrations (1000, 500, 250 and 100 µg/mL for HEMA; 5, 2.5 and 1 µg/mL for BisGMA; 100, 50, 25 and 10 µg/mL for CQ; and 10, 5, 2.5 and 1 µg/mL for EDAB) of each compound were diluted in 200 µL of DMEM and placed in a plate of 96-well plates containing mouse fibroblasts cells previously cultured. The plates were incubated for 24h in a humidified atmosphere of 5% CO2. The same protocol reported above was used to evaluate the cytotoxicity and to obtain the absorbance value.

4.3.4 Statistical analysis.

The statistical analysis was performed using the Sigma Plot 12.0 software. Two-way ANOVA analysis was conducted to evaluate the effect of the universal adhesive type and the method of sample preparation on the absolute compound elution data and the cell viability. Cell viability of different HEMA, BisGMA, CQ and EDAB concentrations were analyzed by independent one-way ANOVA tests. Post hoc multiple comparisons were performed using Tukey's test. A significance level of $\alpha=0.05$ was used for all analyses.

4.4 Methods Results

Figure 2 shows the amount of CQ, EDAB, HEMA and BisGMA eluted from the different universal adhesive systems as a function of the different methods of specimen preparation. When used in the form of material discs, all universal adhesives released significantly higher amounts of CQ, EDAB, HEMA and BisGMA ($p<0.001$), except for OCU, where the elution of HEMA was not significantly influenced by the method of specimen preparation ($p>0.05$), and where BisGMA was not detected. TPO and UDMA were only observed in the samples derived from OCU adhesive. For this material, the release of TPO was not dependent on the sample preparation method (1.24 µg/mL for dentin disc; 1.80 µg/mL for filter paper; and 1.23 µg/mL for disc-shaped specimen).

The cell viability of the four universal adhesives tested, as a function of the different methods of specimen preparation is presented in Figure 3. The cell viability was found to be significantly influenced by both universal adhesive type ($p<0.001$) and method of specimen preparation ($p<0.001$), and an interaction between these two variables was observed too ($p<0.001$). When evaluated in the material disc form, all universal adhesives promoted a cell viability lower than 50%, being the OCU adhesive the more cytotoxic material ($p<0.05$). When evaluated in the form of filter disc, all universal adhesives had cell viability values close to 100%. The same behavior could be observed when the cell viability was evaluated using the dentin disc model, except for OCU, which presented cell viability values around 80% ($p<0.05$).

Figure 4 shows the cell viability of HEMA, BisGMA, CQ and EDAB in their isolated form. For HEMA, only the 1000 µg/mL concentration demonstrated a significantly cytotoxic effect ($p<0.05$). None of the BisGMA concentration tested were considered cytotoxic. For CQ, only the 100 µg/mL concentration resulted in a

significantly higher cytotoxicity ($p<0.05$). For EDAB, the cell viability observed for al concentrations were around 80%, however, the differences observed between all concentrations were not significant ($p=0.074$).

4.5 Discussion

According to the results in this work, the concentration of unreacted substances eluted and the cell viability depended on the universal adhesive and on the sample preparation method used, and therefore, the null hypothesis was rejected.

The UHPLC-QTOF-MS technique was used to identify and quantify the unreacted substances in the extraction media. This technique is commonly used for pharmaceutical analysis which requires fast and high resolution separations with required sensitivity. The use of this analytical method demonstrated the presence of HEMA, BisGMA, CQ, EDAB, TPO and UDMA in the extraction media, and the concentration of such compounds varied accordingly to the method used for the specimen preparation. For CQ and BisGMA, the same pattern could be observed: irrespectively of the universal adhesive system, when the disc-shaped method was used, their concentration was significantly higher than the other two methods employed. For the other compounds, the release of unreacted substances showed different patterns. The release of EDAB for OBU and OCU was not significantly influenced by the sample preparation method. On the other hand, the release of HEMA was not dependent of the sample preparation method only for OCU adhesive.

Since the volume of material used for prepare the disc-shaped specimens (50 µL) was ten-fold higher than the volume used to prepare the filter or the bovine disc specimens (5 µL), the release of higher quantities of unreacted substances was expected. Nevertheless, it could be observed than other factors different than the volume used for sample preparation are involved in the elution profile. To cite an example, for TBU, the release of CQ for the disc-shaped specimens was roughly twenty-fold higher compared to what was observed with the other two methods, which was higher than the expected. For the other universal adhesives analyzed, the release of CQ had this behavior too. The differences in the amount of unreacted compounds released are probably due to the quantity of solvent that remains in the material when the disc-shaped specimen is used, even after the air-drying procedure. Since a greater

quantity of material was required to fabricate the specimens, the quantity of solvent was higher, and consequently, complete evaporation is more difficult, especially in water-based adhesives (Yiu et al. 2005). Therefore, the residual solvent could have compromised the material polymerization (Ogliari et al. 2008), increasing the leachability of the polymerization initiators and other unreacted substances (Jan et al. 2001).

Actually, the release of higher quantities of unreacted substances from disc-shaped specimens, could have an influence on the cell viability (Toz et al. 2017). When evaluated in the form of disc-shaped specimens, all universal adhesives tested promoted a reduction of cell viability by more than 30%, which according to ISO 10993-5, is considered a cytotoxic effect (International Organization for Standardization 2009). These results are in agreement with previous studies when extracts of polymerized disc-shaped specimens of universal adhesives where used to evaluate the cell viability against human pulp-derived cells (Van Landuyt et al. 2015; Pupo et al. 2017). When considering the type of universal adhesive, OCU presented the lowest cell viability values, this result could be due to the presence of TPO on the extraction medium from this material, since the use of this photoinitiator has been related to produce severe cytotoxicity when incorporated in adhesive systems (Van Landuyt et al. 2015; Manojlovic et al. 2017).

Contrary to the cell viability results obtained using the disc-shaped method, when the cell viability of the universal adhesives was tested using the paper filter or bovine dentin disc method, all the materials did not exert any cytotoxic effect against a mouse fibroblast cell line. The in-situ polymerization of adhesive systems into paper filter discs or dentine bovine discs to evaluate the cell viability has been previously explored, demonstrating contradictory results (Elias et al. 2015; Hass et al. 2016; Wegehaupt et al. 2016). For the one hand, it has been suggested the role of the dentin as a protecting agent against the self-etch adhesives, especially those with low pH values (Sun et al. 2016; Lee et al. 2016; Jiang et al. 2017). The presence of hydroxyapatite within the dentin structure has the ability to neutralize acidic components present in the self-etch adhesives, decreasing the acidic stimuli to cells (Wang and Spencer 2004). In regard to the use of filter paper as dentin substitute, despite that the filter composition is rather different from that of the dentin, it has been

used as dentin substitute for standardized dentin barrier tests, obtaining favorable outcomes (Kim et al. 2013).

In addition, it's worth mentioning that International Standard 7405:2008 specifies the test methods for the evaluation of biological effects of medical devices used in dentistry (International Organization of Standardization 2008). Such standard states that biocompatibility tests should be performed on materials in an "as-used state". Mean thickness of universal adhesives measured through SEM images varied from 9.75 to 13.83 µm, which means that the method usually used to perform most of the cell viability assays (test specimens prepared to a thickness of >1 mm) could not comply this requirement. Considering this statement, it seems that the use of a paper filter disc for sample preparation reflects better the conditions that are experienced in clinical use, and could be recommended for futures studies in an attempt to establish a standardized protocol for biocompatibility evaluation of light-cured adhesives systems.

Among the substances detected in the extraction media, HEMA, CQ, and EDAB were the only elutable substances detected in all samples from all adhesives evaluated. HEMA has been previously described as a monomer capable to induce apoptosis and genotoxic effects and to induce oxidative stress leading to cell death (Bolling et al. 2013; Krifka et al. 2013). Despite this, our study demonstrated that cell death observed in the disc-shaped specimens was not depend only for the effect of this compound, especially because the concentration detected by the UHPLC-QTOF-MS analysis resulted in a cell viability above 70% (Figure 3), in addition, the concentration of HEMA released was not depend of the sample preparation method for OCU. Thus, considering that CQ was the only substance detected in significantly higher amounts from the disc-shaped specimen, the presence of this compound could be directly related with the cytotoxic effect against fibroblast cells observed in this study. In an attempt to verify this, an independent cell viability assay was carried out to determine if the concentrations detected by the UHPLC-QTOF-MS analysis were enough to exert some cytotoxicity effect against a fibroblast cell line. According to the results (Figure 3), only the CQ at 100 µg/mL concentration could be considered as cytotoxic, while for others concentrations, resulted in a cell viability around 80%. Despite this, it is important to note that no one of the concentrations tested reached a cell viability close to the cell control, and some kind of cell injury could be caused. The

mechanism responsible for CQ is not well known, however, it has been reported to be dose-dependent (Chang et al. 2015). Considering the results, it is possible that the eluted components, especially the photinitiator system, that come into contact with the line cell have a synergism effect to promote a cytotoxic effect, and further studies should be conducted to verify this hypothesis.

Finally, it should be highlighted that the cell viability tests reported here were performed following the specifications provided by International Standard ISO 10993-5 (International Organization for Standardization 2009). Because the preparation method of the materials used for testing is critical, this procedure follows the International Standard ISO 10993-12 for sample preparation (International Organization of Standardization 2012). This standard specifies that the preparation of fluid extracts of the device materials is the most appropriate technique to provide test samples for determining the biological reactivity of possible eluted substances. The last statement assumes that the dimensions of the sample can be of any type, as long as a determined surface/volume extractions ratio were respected. However, it could be demonstrated that the dimensions of the samples had a significant impact on the cell viability results. Based on this, special attention must be paid when interpreting the results, in order that the cell viability assay is often used to determine the preliminary cytotoxicity of a material.

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Tables

Table 1. Main components of universal adhesives used.

Name	Manufacturer	Main components*	Adhesive layer thickness**
Single Bond™ Universal	3M ESPE, St.Paul, MN, USA	2-Hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, Decamethylene dimethacrylate, ethanol, Silane treated silica, water, 2-propenoic acid, 2-Methyl-, reaction products with 1,10-decanediol and phosphorous oxide, copolymer of acrylic and itaconic acid, dimethylamino ethyl methacrylate, camphorquinone, dimethylaminobenzoate, 2,6-di-tert-butyl-p-cresol.	9.75 (0.32) µm
Tetric® N-Bond Universal	Ivoclar Vivadent, Schaan, Liechtenstein	2-hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, ethanol, 1,10-decanediol dimethacrylate, Methacrylated phosphoric acid ester, camphorquinone, 2-dimethylaminoethyl methacrylate.	11.01 (0.27) µm
OptiBond® Universal	Kerr, Orange, CA, USA	acetone, 2-hydroxyethyl methacrylate, glycerol dimethacrylate, ethanol, glycerol phosphate dimethacrylate.	10.95 (0.34) µm
OneCoat 7 Universal	Coltène/Whaledent Inc., Cuyahoga Falls, OH, USA	Ethanol, urethane dimethacrylate, 2-hydroxyehtyl methacrylate.	13.83 (0.43) µm

* According to manufacturers' safety datasheet
** Measured through SEM images

Figures

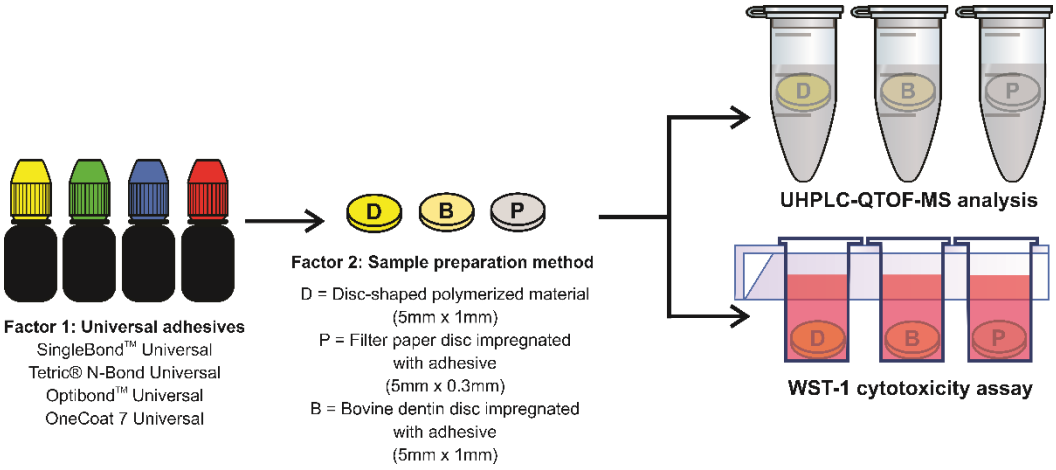

Figure 1 Schematic representation of the experimental design

Compound	M_w	*m/z* [$M+H^+$]	ion formula	ppm error
HEMA	130.14	153.05	$C_6H_{10}NaO_3$	0.6
BisGMA	512.59	513.25	$C_{29}H_{37}O_8$	2.7
CQ	166.22	167.11	$C_{10}H_{15}NaO_2$	0.1
EDAB	193.24	194.12	$C_{11}H_{16}NO_2$	0.7
TPO	348.37	349.13	$C_{22}H_{22}O_2P$	1.8
UDMA	470	471.27	$C_{23}H_{39}N_2O_8$	0.4

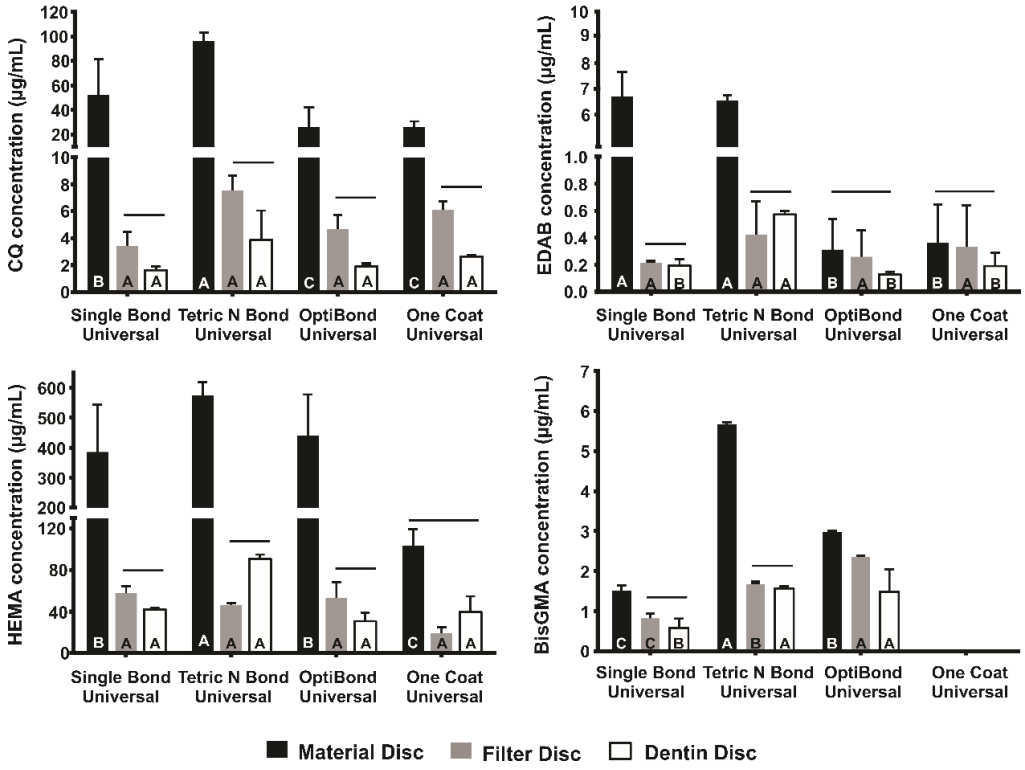

Figure 2 Amount of eluted CQ, EDAB, HEMA and BisGMA from the different universal adhesive systems as a function of the different methods of specimen preparation. Different letters indicate differences between universal adhesives within each sample preparation method. Columns under the same horizontal line indicate no differences between sample preparation method for each universal adhesive.

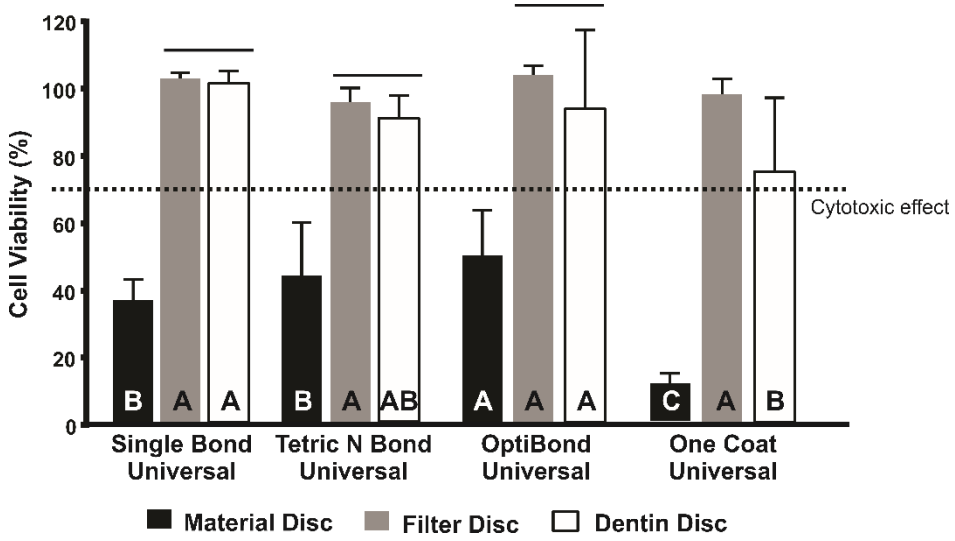

Figure 3 Cell viability of universal adhesives as a function of the sample preparation method used. Different letters indicate differences between universal adhesives within each sample preparation method. Columns under the same horizontal line indicate no differences between sample preparation method for each universal adhesive.

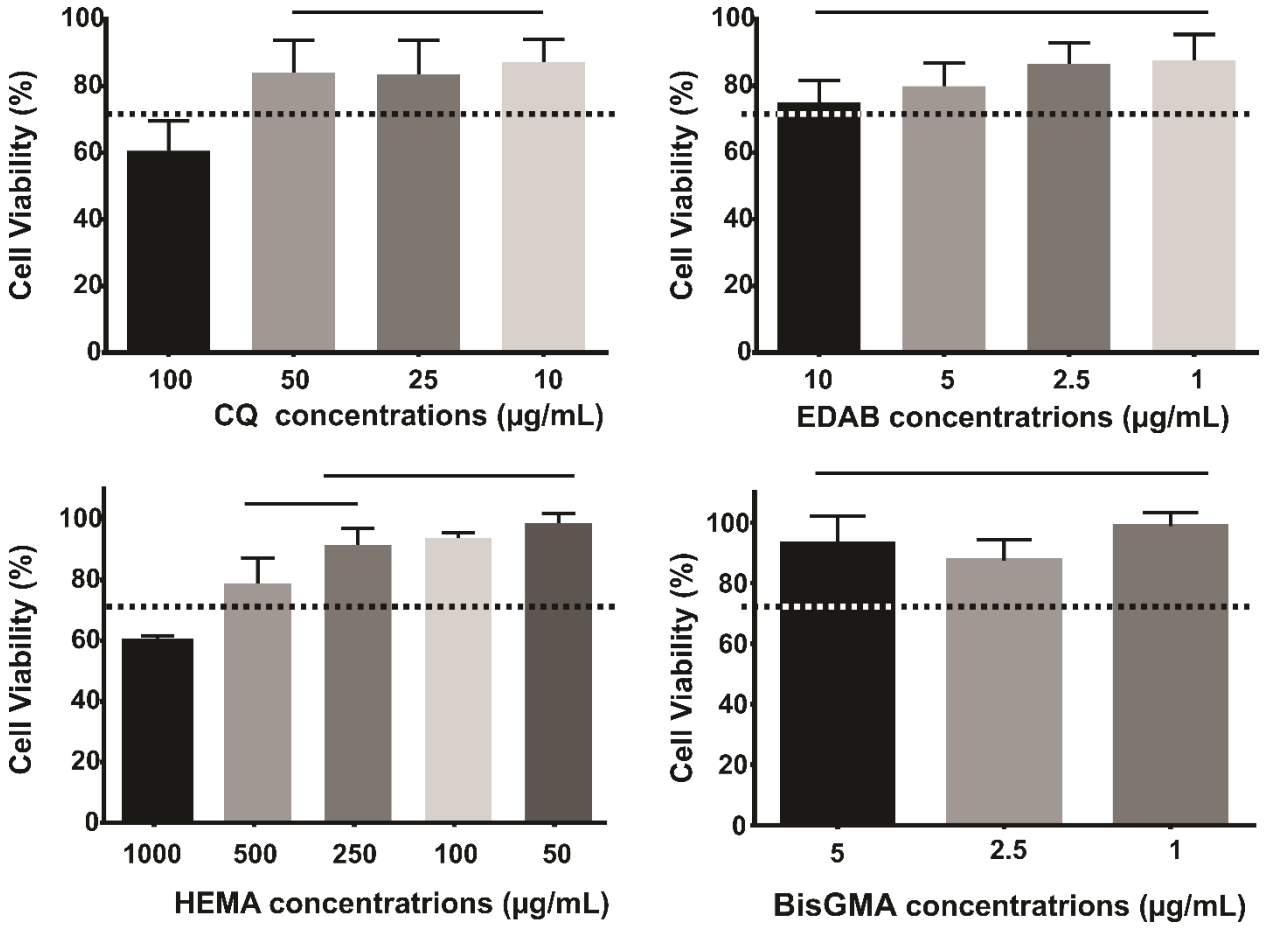

Figure 4 Cell viability of CQ, EDAB, HEMA and BisGMA as a function of its concentration. Columns under the same horizontal line indicate no differences between concentrations.

5 Capítulo 4

Impact of shelf-life simulation on bonding performance of universal adhesive systems[4]

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5.1 Abstract

The aim of this study was to evaluate the micro-tensile bond strength to dentin (μTBS), the degree of conversion (DC) and nanoleakage expression (NL) of five universal adhesives considering their expiry date (as-received, half-life and or end of shelf-life material) after shelf-life simulation. Five universal adhesives (Single Bond Universal, SBU; Tetric Bond Universal, TBU; OneCoat Universal, OCU; OptiBond Universal, OBU; and Prime&Bond Elect, P&B), two two-step self-etch adhesives (Clearfil SE, CSE; and AdheSE, ASE) and one two-step etch-and-rinse adhesive (Adper Singlebond 2, ASB) were evaluated. Shelf-life was simulated by storing the materials in an acclimatization chamber for different periods of time using the Arrhenius model. The μTBS was tested in accordance with the directions of ISO/TS 11405. DC was evaluated by means of Fourier transformed infrared spectroscopy. NL was evaluated after ammoniacal silver challenge. The significance level of $\alpha=0.05$ was used for all statistical analyses. The μTBS to dentin of TBU, P&B, ASE, and ASB adhesive systems remained stable throughout the shelf-life periods evaluated. On the other hand, the bond strength to dentin of SBU, OCU, OBU, and CSE decreased significantly after evaluation in the ‘half-life’ or ‘end of shelf-life’ condition ($p<0.05$). The number of adhesive and pre-testing failure modes increased when the materials were applied in their ‘half-life’ or ‘end of shelf-life’ condition ($p<0.05$). The degree of conversion decreased significantly after the periods of shelf-life simulation tested ($p<0.05$). OCU, ASE, and CSE adhesives showed significantly increased percentage of silver deposition within the adhesive layer. According to the accelerated aging protocol used, for most of the adhesive evaluated, the shelf-life period established by the manufacturers was overestimated. The use of bond strength tests in combination with a shelf-life simulation should be considered a routine procedure by manufacturers during the process of development of adhesive systems.

Keywords: dentin adhesive systems, product storage, accelerated aging.

5.2 Introduction

Adhesive systems are used to achieve adhesion to dental structures. The use of restorative materials in conjunction with the adhesive technique has become routine in dental practice today, especially because professionals prefer these materials because of their advantages such as aesthetics, improved adhesive properties, and conservation of dental structure, which, in turn, leads to strengthening the remaining dental structure [1].

The original multicomponent etch-and-rinse bonding systems have gradually been replaced by simplified, monocomponent self-etch adhesive systems that are more user-friendly [2]. One of the latest developments in adhesive dentistry was the introduction of universal adhesives, designed for application by means of both the etch-and-rinse technique and/or the self-etch technique using the same single bottle of adhesive solution [3]. Despite this attempt to provide more versatile and user-friendly materials, self-etch adhesives systems present a wide variety of problems related to changes in the composition of the material over the period of storage in a dental office due to hydrolysis or polymerization of the monomers, degradation of the additives (initiators/stabilizers), or evaporation of ingredients [4]. In order to minimize these effects, some manufacturers have recommended storage at low temperatures (below 10°C), despite this, the shelf-life and stability of these materials continues to be an important concern [5].

In dental clinical practice, the shelf-life of adhesives is extremely important. The reason for failing to achieve optimal bonding performance might not only be due to poor clinical procedures but also to the limited shelf-life of the single-step self-etch adhesives [6]. Based on this, manufacturers always stipulate an expiry date (commonly 2 years), after which the material is expected to exhibit undesirable physicochemical properties for its correct application [7]. In this context, various sets of criteria have been proposed to determine which are acceptable levels of stability and how to measure them; these include mechanical, optical, surface, and biological properties [8]. These criteria are specifically applied to assess the stability of medicinal products and although these may be useful as a starting point for establishing a set of criteria for assessing the stability of dental products, other variables should be evaluated, especially because the shipment, transport, and storage conditions of the materials for use in dentistry prior to clinical application are not always ideal.

Considering this, the aim of this study was to characterize five universal adhesive systems considering their expiry date after shelf-life simulation. The effect of shelf-life simulation on the micro-tensile bond strength to dentin, nanoleakage, and degree of conversion was explored. The null hypothesis tested was that the shelf-life simulation of adhesive systems would not affect the properties of micro-tensile bond strength to dentin, nanoleakage or degree of conversion of the materials evaluated.

5.3 Material and methods

5.3.1 Study design and accelerated aging protocol.

In this study, the micro-tensile bond strength, nanoleakage, and degree of conversion of five universal adhesives systems were analyzed considering the material condition (as-received, half-life and end of shelf-life) after different periods of shelf-life simulation. Five universal adhesives (Single Bond Universal, SBU; Tetric Bond Universal, TBU; OneCoat Universal, OCU; OptiBond Universal, OBU; and Prime&Bond Elect, P&B), two two-step self-etch adhesives (Clearfil SE, CSE; and AdheSE, ASE) and one two-step etch-and-rinse adhesive (Adper Singlebond 2, ASB) were evaluated. The composition of the adhesive systems evaluated in this study is described in Table 1.

The dental adhesive systems were characterized as soon as they were purchased on the online market and received, by considering them to be in 'as-received' condition. The materials were characterized as being in the 'half-life' and 'end of shelf-life' conditions after shelf-life simulation, by storing the materials in an acclimatization chamber at 40°C and 50% relative humidity for different periods of time. The period of time necessary to achieve the 'half-life' and 'end of shelf-life' condition was calculated individually for each adhesive system using the Arrhenius model [9], according to the following formula: $r = Q_{10}^{(RT-ET/10)}$

where r was the accelerated aging rate; RT the storing temperature recommended by the manufacturer; ET the storage temperature in the acclimatization chamber (40 °C) and Q_{10} the reaction rate coefficient (2).

The 'half-life' condition was considered after simulation of half of the shelf-life of the material (approximately 1 year considering the expiry date), and the 'end of shelf-

life' condition was considered once the adhesive reached the expiry date specified by the manufacturer (Table 2). For Single Bond^{TM} Universal, for example, the 'half-life' and 'end of shelf-life' conditions were reached after 4 and 9 weeks of storage in the climatic chamber, respectively.

5.3.2 Micro-tensile bond strength (μTBS) and failure mode analysis.

One hundred and twenty extracted bovine incisors were collected, cleansed of soft tissue, and stored in 0.5% Chloramine-T solution for seven days. Then, they were removed from the disinfectant solution, washed abundantly, and stored in distilled water at 4°C until use [10]. For specimen preparation, the root was sectioned, and their crowns were embedded in acrylic resin, allowing the buccal enamel surface to be exposed. Then, the enamel was abraded with an orthodontic grinder until exposure of a flat medium dentin surface. The exposed dentin surface was then wet-ground with P600 silicon carbide sandpaper for 30 seconds to standardize the smear layer. Dentin specimens were randomly divided into eight groups based on the adhesive system used. Subsequently, the specimens were divided into subgroups (n=5) according to the material condition: as-received, half-life and end of shelf-life.

The adhesive systems were applied according to the manufacturers' instructions (Table 2), universal adhesives were applied in the self-etch mode. After the bonding procedures, resin composite build-ups (Filtek^{TM} Z250, 3M ESPE, St. Paul, MN, USA) were constructed in 3 increments of 2mm each and each layer was polymerized for 30 seconds. Light-curing procedures were performed using a LED photopolymerization unit Radii-cal (SDI Limited, Victoria, Australia). After immersion in distilled water at 37°C for 24 hours, the specimens were sectioned using a slow-speed diamond saw (Isomet Saw 1000 Precision, Buehler Ltd., Lake Bluff, IL, USA) to obtain resin-dentin sticks with a cross-sectional area of approximately 0.9 mm^2

After storage in distilled water at 37 °C for 24h, the sticks were individually fixed to a tensile testing device with cyanoacrylate glue and the μTBS was tested in a mechanical universal test machine (DL 500, EMIC®, Pinhais, PR, Brazil), at a crosshead speed of 1 mm/min with a 100N load cell. The fractured portions of the specimens were observed under a light microscope at 40x magnification to classify failures as adhesive, cohesive within dentin, cohesive within composite or mixed failures. For each tooth, the results obtained of the five sticks tested were averaged,

and the mean obtained was then used for statistical purposes. Specimens with pre-testing failures were included in the tooth mean value; for this purpose, the average value between zero and the lowest bond strength value obtained in each tooth was used [11].

5.3.3 Nanoleakage evaluation

Three resin-bonded sticks from each tooth were not tested in μTBS and were prepared for nanoleakage evaluation. The sticks were subjected to an ammoniacal silver nitrate solution challenge following the protocol described by Tay et al [12]. Subsequently, silver-impregnated specimens were polished with wet 600, 1000, 1200, 1500, 2000 and 2500 grit silicon carbide sandpaper for 60 seconds, followed by 1 and 0.25 μm diamond paste (Buehler Ltd., Lake Bluff, IL, USA) using a polishing cloth. The sticks were ultrasonically cleaned, air dried, mounted on stubs, and coated with gold-palladium. Adhesive-dentin interfaces were analyzed by scanning electron microscopy operated in the backscattered mode (JSM - 6610LV, Jeol, Tokyo, Japan). Three images were captured of each resin–dentin bonded stick. The relative percentage of nanoleakage was measured in all images using the ImageJ software (v 1.0i, National Institute of Health, USA). The mean nanoleakage percentage of all sticks from the same tooth was averaged for statistical purposes.

5.3.4 Degree of conversion

The degree of conversion was evaluated using real-time Fourier transformed infrared spectroscopy (Prestige21; Shimadzu, Tokyo, Japan) equipped with an attenuated total reflectance device. Previously, 10 μL of each adhesive system was transferred to a small plastic receptacle and air-dried for 30 seconds to remove solvents. After solvent evaporation, the material was placed on the diamond crystal. A spectrum was captured before and after the polymerization process. The degree of double bond conversion was obtained considering the height of the absorption band (% of absorbance) corresponding to the υC=C aliphatic bond at 1638 cm^{-1}, and as an internal standard, the height of the absorption band (% of absorbance) corresponding to the υC=C aromatic bond at 1609 cm^{-1}. Each test was performed in triplicate.

5.3.5 Statistical analysis

Statistical analysis was performed using the Sigma Plot 12.0 software. The data were analyzed to test the assumption of normal distribution and homogeneity of variance. Two-way ANOVA was conducted to evaluate the effect of the adhesive system and shelf-life simulation on the micro-tensile bond strength to dentin. The frequency of failure mode for each adhesive system was analyzed by the Chi-Square test. For each adhesive system, independent One-way ANOVA and Kruskal-Wallis tests were performed to evaluate the effect of the period of shelf-life simulation on the nanoleakage and degree of conversion. Post hoc multiple comparisons were performed using the Tukey test. For each adhesive system, additional linear regression analyses between micro-tensile bond strength, the degree of conversion, or nanoleakage and the shelf-life period, were performed. A significance level of $\alpha=0.05$ was used for all analyses.

5.4 Results

Table 3 shows the μTBS to dentin of the adhesives system used considering their period of shelf-life simulation. Two-way ANOVA revealed that there were significant differences in μTBS to dentin according to the type of adhesive system ($p<0.001$) and the period of shelf-life simulation ($p=0.003$). There was also a significant interaction effect between these two variables ($p<0.001$). The bond strength to dentin of TBU, P&B, ASE, and ASB adhesive systems remained stable during the shelf-life periods evaluated ($p>0.05$). On the other hand, the bond strength to dentin of SBU, OCU, OBU, and CSE decreased after the evaluation in the ‘half-life’ or ‘end of shelf-life’ condition. Linear regression analysis showed a significant correlation between μTBS average according to the period of shelf-life simulation for OCU, OBU and CSE ($p<0.05$).

Figure 1 summarizes the failure mode distribution among the adhesive systems considering their period of shelf-life simulation. The number of adhesive failure mode and pre-failure tests increased when the adhesive systems were applied in their ‘half-life’ or ‘end of shelf-life’ condition. For all materials, the variability in the frequency of different failure modes according to the period of shelf-life simulation was statistically significant (Chi-Square test, $p>0.05$).

The degree of conversion values are shown in Table 4. Except for P&B, the degree of conversion changed after the end of shelf-life period of shelf-life simulation ($p<0.05$). A significant correlation between the degree of conversion and the period of shelf-life simulation was observed for all the materials, except for CSE.

With regard to nanoleakage, OCU, ASE, and CSE adhesives showed significantly increased percentage of silver deposition within the adhesive layer ($p<0.05$) after shelf-life simulation. For these materials Linear regression analysis revealed a significant correlation between this variable and the period of shelf-life simulation (Table 5).

5.5 Discussion

In this study, the characterization of several adhesive systems according to a protocol of accelerated aging, simulating different shelf-life periods of the materials, was performed. The results obtained suggested that most of the evaluated properties were affected after shelf-life simulation, and these changes were material-dependent. Considering this, the null hypothesis tested was partially rejected.

The micro-tensile bond strength test is currently recommended as the best method to evaluate the bond strength of adhesive systems, and its considered useful for preliminary evaluation as a pre-clinical test [11]. According to Table 3, SBU, OCU, OBU, and CSE adhesives had a significant decrease in bond strength values after the shelf-life simulation, especially when evaluated in their end of shelf-life condition. This decrease in the bond strength values could be related to the chemical composition of these materials. According to the manufacturer's safety data sheet, SBU and CSE materials are formulated with 10-Methacryloyloxydecyl dihydrogen phosphate (10-MDP), while OBU has glycerol phosphate dimethacrylate (GDMA-P) in its composition. On the other hand, although this was not specified for OCU, one of the above-mentioned monomers was probably used in its formulation. According to previous data, ester based adhesive formulations with acid pH values are very prone to undergoing hydrolysis [13,14]. Consequently, free methacrylic acid, ethylene glycol, other alcohol derivatives, and free phosphoric acid are formed [15]. This hydrolytic phenomenon changes the chemical composition of the adhesive over the period of storage in the

warehouse or dental office, affecting its properties and impairing the bond strength between substrates [16].

Surprisingly, TBU and P&B universal adhesives maintained their bond strength values after simulation of the shelf-life period, even after evaluation in their ‘end of shelf-life’ condition. The P&B universal adhesive contains dipentaerythritol penta-acrylate phosphate monomer (PENTA-P) in its composition. The degradation mechanism of PENTA-P monomer is unknown, however, it could be hypothesized that, unlike the 10-MDP adhesive monomer, the presence of five vinyl groups within its chemical structure could make it more resistant to hydrolytic degradation. Thus, when hydrolysis occurs and breaks a vinyl group off the main structure of the monomer, four vinyl groups still remain available to maintain the connection to the phosphate group, which allows copolymerization with the other monomers, and at the same time, adhesion to the tooth structure [17]. With regard to TBU universal adhesive, since it has a relatively high pH about 3 [18], it is possible that the degradation rate of the methacrylated phosphoric acid ester on which this material is based is slower than it is in the other materials. As the hydrolysis of ester bonds into acidic aqueous media depends on how acidic the materials is, it seems that the use of self-etch adhesives with relatively higher pH could lead to materials with high shelf-life stability.

On the other hand, ASE and ASB adhesives showed bond strength stability among the shelf-life periods evaluated. This result was not surprising since ASE material is formulated with the use of patented acrylamide hydrolytically-stable monomers [19]. Because of their physical-chemical-stability, acrylamides have been proposed as an alternative to conventionally used methacrylates, mainly for purposes of increasing the shelf-life of dental adhesive formulations [20]. Amide bonds are more resistant to hydrolytic degradation since they are susceptible to hydrolysis phenomena only under circumstances of very low pH and/or temperatures above 100 ^{o}C [14,21]. On the other hand, ASB is an etch-and-rinse ethanol-based adhesive that does not contain water in its composition, and also has an elevated pH value. These conditions represent a more ‘friendly’ environment in which the hydrolysis of methacrylate monomers is not supposed to occur. Indeed, ethanol-based etch-and-rinse adhesives have demonstrated shelf-life stability [15].

With regard to the degree of conversion analysis, excepting for P&B and ASE, all materials showed a significant decrease in DC after shelf-life simulation. The degree

of conversion is a feature that is largely influenced by the type and concentration of the photoinitiator system. Although it was not specified in some of the safety data sheets, most of the materials used in this study were based on the CQ/EDAB photoinitiation system. Some studies have demonstrated that in acidic environments, the effectiveness and stability of this photoinitiator system was low [22,23]. On the one hand, an acid base reaction occurs between the acidic monomers and the amines, preventing the amine from acting as a polymerization coinitiator [24]. On the other hand, the amine-acidic monomer interaction can neutralize the acidic functional monomer, impairing its ability to form stable bonds with the hydroxyapatite of the dentin substrate [22]. Indeed, the reduction in the bond strength values after the shelf-life simulation observed in this study, could also have occurred as a result of this neutralization process.

Contrary to results found in the remainder of the adhesive systems, ASE not only maintained stability in terms of the degree of conversion, but the values also increased when the material was evaluated in its end of shelf-life condition. As explained before, ASE contains methacrylamide monomers with a phosphonic acid moiety as functional group. Methacrylamides are more resistant to hydrolysis than esters, and maintenance of the degree of conversion values is expected. In addition, recent studies have demonstrated [25,26] that polymerization of acrylamides initiated with CQ/EDAB is enhanced when alkyl phosphonic acid moieties are added, which could also could explain the findings obtained in our study.

Nanoleakage was used as an indirect method to evaluate the quality of the resin-dentin bonds. Nanoleakage expression represents the location of defects within the adhesive layer that might serve as the pathway for degradation, especially after any type of aging [27]. In this study, SBU and P&B, showed no increase in nanoleakage expression after shelf-life simulation. The presence of a polyalkenoic acid co-polymer within SBU composition is related to the ability to interact with calcium in hydroxyapatite [28], consequently, this feature has been used to explain the optimal long-term performance of polyakenoic-based materials [29]. Similarly, the P&B adhesive showed no increase in the nanoleakage expression, even when it was evaluated in its end of shelf-life condition. It should be highlighted that P&B was the only HEMA-free adhesive tested, and probably the absence of this monofunctional monomer enhanced the cross-linking density of the adhesive layer, decreasing water permeation [30]. On the

other hand, the presence of HEMA has been related to inhibition of the nanolayering chemical bonding mechanism of the 10-MDP monomer, which could increase the nanoleakage [31]. Despite these promising results, it is worth mentioning that for both adhesives, the increase in the number of the adhesive type of failures, and the increase in the percentage of pre-testing failure after simulation of the shelf-life period, suggested some type of degradation.

This study investigated the degradation profile of universal adhesive systems simulating three different periods of shelf-life using controlled temperature and humidity conditions. Furthermore, the conditions used in this study could be considered adverse, but they may be not uncommon during transportation and storage of the product, and the manufacturers should take into account the possible effect of these variables on the stability of the materials to enable them to determine an adequate expiry date. Moreover, the present findings suggested that humidity could also play an important role in the shelf-life stability of dental adhesives. As the range of humidity in which the materials should be stored is not informed by manufacturers, more research should be conducted to determine the effect of this variable on the rate of degradation of the components on which these materials are based.

5.6 Conclusions

The performance of adhesives systems after shelf-life simulation was material-dependent. The adhesive systems evaluated lost their bonding ability with progressively longer storage time, and according to the accelerated aging protocol used in this study, the shelf-life period established by the manufacturers could be overestimated. Shelf-life simulation with controlled temperature and humidity conditions should be considered a routine procedure during the process of development and evaluation of adhesive systems.

5.7 References

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Table 1. Main components of adhesives system used.

Name	Manufacturer	Main components*
Single Bond™ Universal (SBU)	3M ESPE, St.Paul, MN, USA	2-Hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, Decamethylene dimethacrylate, ethanol, Silane treated silica, water, 2-propenoic acid, 2-Methyl-, reaction products with 1,10-decanediol and phosphorous oxide, copolymer of acrylic and itaconic acid, dimethylamino ethyl methacrylate, camphorquinone, dimethylaminobenzoate, 2,6-di-tert-butyl-P-cresol.
Tetric® N-Bond Universal (TBU)	Ivoclar Vivadent, Schaan, Liechtenstein	2-hydroxyethyl methacrylate, Bisphenol A Diglycidyl Ether Dimethacrylate, ethanol, 1,10-decandiol dimethacrylate, Methacrylated phosphoric acid ester, camphorquinone, 2-dimethylaminoethyl methacrylate.
OneCoat 7 Universal (OCU)	Coltène/Whaledent Inc., Cuyahoga Falls, OH, USA	Ethanol, urethane dimethacrylate, 2-hydroxyehtyl methacrylate.
OptiBond® Universal (OBU)	Kerr, Orange, CA, USA	acetone, 2-hydroxyethyl methacrylate, glycerol dimethacrylate, ethanol, glycerol phosphate dimethacrylate.
Prime&Bond Elect ® (P&B)	Dentsply Caulk, Milford, DE, USA	Acetone, Urethane Dimethacrylate Resin, Dipentaerythritol pentaacrylate phosphate, Polymerizable dimethacrylate resin, Polymerizable trimethacrylate resin.
AdheSE® (ASE)	Ivoclar Vivadent, Schaan, Liechtenstein	Primer: phosphonic acid acrylate, bis-acrylamide derivative. Bond: Bisphenol A Diglycidyl methacrylate, 2-hydroxyethyl methacrylate.
Clearfil SE Bond 2 (CSE)	Kuraray Noritake Dental Inc.	Primer: 2-hydroxyethyl methacrylate, 10-Methacryloyloxydecyl dihydrogen phosphate, Hydrophilic aliphatic dimethacrylate, dl-Camphorquinone, Accelerators, Water, Dyes. Bond: Bisphenol A Diglycidyl methacrylate, 2-hydroxyethyl methacrylate, 10-Methacryloyloxydecyl dihydrogen phosphate, Hydrophobic aliphatic dimethacrylate, Colloidal silica, dl-Camphorquinone, Initiators, Accelerators.
Adper™ Single Bond 2 (ASB)	3M ESPE, St.Paul, MN, USA	Ethyl alcohol, Bisphenol A Diglycidyl methacrylate, silane treated silica, 2-hydroxyethyl methacrylate, glycerol 1,3-dimethacrylate, copolymer of acrylic acid and itaconic acids, water, diurethane dimethacrylate, diphenyliodonium hexafluorophosphate, ethyl 4-dimethyl aminobenzoate

*According to Manufacturers' MSDS

Table 2. Main information and application directions of adhesive systems used.

Material	Batch #	Shelf-life percentage*	Expiration date	Storing conditions	Application procedure
SBU	645031	15%	Nov-18	2°C / 25°C	Apply with rubbing for 20 s. Air dry for 5 s. Light-cure for 10 s.
TBU	V25219	20%	Oct-18	2° C / 28°C	Apply with rubbing for 20 s. Air dry for 5 s. Light-cure for 10 s.
OCU	H62762	15%	Apr-19	4°C / 8°C	Apply with rubbing for 20 s. Air dry for 5 s. Light-cure for 10 s.
OBU	6371589	25%	May-19	2°C / 8°C	Apply with rubbing for 20 s. Air dry for 5 s. Light-cure for 10 s.
P&B	170505	15%	May-20	2°C / 8°C	Apply with rubbing for 20 s. Air dry for 5 s. Light-cure for 10 s.
ASE	V01867 (Primer) V03476 (Adhesive)	15%	May-18 Jul-18	2°C / 28°C	Apply primer with rubbing for 15s and leave for other 15s. Dry with a strong stream of air. Apply bond and disperse with a very weak stream of air. Light-cure for 10s.
CSE	670203 (Primer) 6L0329 (Adhesive)	10%	Nov-18	2°C / 8°C	Apply primer and leave for 20 s. Air dry with a mild air stream. Apply bond and disperse using an air stream. Light-cure for 10 s.
ASB	N855670	15%	Feb-20	21°C / 24°C	Apply Scotchbond etchant to dentin. Leave in place for 15 s. Rinse for 10 s. Blot excess water leaving tooth moist. Apply 2 consecutive coats of adhesive. Air dry for 5 s. Light-cure for 10 s.

* Percentage of shelf-life considering the expiration date when the material was characterized in the ‘as-received’ condition.

Table 3. Microtensile bond strength to dentin of the adhesive systems evaluated after different periods of shelf-life simulation [mean(±SD)].

	Period of shelf-life simulation		
Group	As-received	Half-life	End of shelf-life
Single Bond™ Universal	^{A} 36.48 (9.61) a	^{A} 35.01 (5.30) a	^{B} 25.90 (5.82) ab
Tetric® Bond Universal	^{A} 30.35 (8.58) a	^{A} 28.78 (7.23) ab	^{A} 26.67 (6.25) a
One Coat 7 Universal	^{A} 16.62 (3.18) b	^{A} 14.35 (6.12) c	^{B} 7.73 (4.72) c
OptiBond® Universal	^{A} 31.39 (3.81) a	^{B} 19.86 (7.23) bc	^{B} 18.59 (4.40) bc
P&B Elect®	^{A} 14.36 (5.46) b	^{A} 17.06 (1.85) bc	^{A} 12.97 (7.89) bc
AdheSE®	^{A} 18.00 (3.97) b	^{A} 21.38 (5.43) bc	^{A} 20.60 (5.61) bc
Clearfil SE	^{A} 36.61 (8.58) a	^{B} 22.34 (3.45) bc	^{B} 16.29 (4.46) bc
Adper™ Single Bond 2	^{A} 36.54 (5.56) a	^{A} 30.00 (2.16) ab	^{A} 28.69 (6.95) a

Similar capital superscript letters (comparisons in same row) and lowercase letters (comparisons in same column) indicate no significant differences. ($p < 0.05$).

Table 4. Degree of conversion of the adhesive systems evaluated after different periods of shelf-life simulation [mean(SD)].

	Period of shelf-life simulation				
	As-received	Half-life	End of shelf-life	Linear regression	
				R^2	p
Single Bond™ Universal	^{A} 88.29 (0.08)	^{B} 83.92 (0.34)	^{C} 64.04 (1.21)	**0.876**	**<0.001**
Tetric® Bond Universal	^{A} 87.10 (1.70)	^{B} 74.29 (1.43)	^{B} 76.45 (3.05)	**0.523**	**0.028**
One Coat 7 Universal	^{A} 92.41 (0.16)	^{B} 73.83 (2.57)	^{C} 65.41 (1.39)	**0.934**	**<0.001**
OptiBond® Universal	^{A} 74.89 (0.95)	^{B} 79.82 (0.71)	^{B} 82.36 (1.56)	**0.854**	**<0.001**
P&B Elect®	^{A} 88.39 (1.4)	^{A} 81.88 (6.37)	^{A} 88.63 (3.35)	-	n.s.
AdheSE®	^{A} 67.96 (4.38)	^{AB} 78.50 (0.26)	^{C} 77.38 (2.37)	**0.483**	**0.038**
Clearfil SE*	^{A} 63.36 (0.58)	^{A} 65.14 (4.00)	^{B} 52.01 (1.44)	**0.537**	**0.025**
Adper™ Single Bond 2	^{A} 86.97 (0.35)	^{B} 82.24 (2.47)	^{B} 80.86 (1.56)	**0.639**	**0.010**

Common corresponding capital superscript letters (A–C) in a given row indicate no significant differences. *Analyzed using Kruskal-Wallis test. NS= not significant

Table 5. Nanoleakage of the adhesive systems evaluated after different periods of shelf-life simulation. [mean(SD)].

	Period of shelf-life simulation				
	As-received	Half-life	End of shelf-life	Linear regression	
				R^2	p
Single Bond™ Universal*	^{A} 4.52 (3.76)	^{A} 6.11 (1.77)	^{A} 5.29 (3.01)	-	n.s.
Tetric® Bond Universal	^{A} 2.99 (2.62)	^{A} 8.99 (6.23)	^{A} 9.54 (2.07)	-	n.s.
One Coat 7 Universal	^{B} 1.61 (2.03)	^{AB} 6.27 (5.44)	^{A} 14.13 (0.60)	**0.763**	**0.002**
OptiBond® Universal*	^{AB} 6.84 (2.21)	^{B} 3.80 (1.32)	^{A} 10.34 (1.04)	-	n.s.
P&B Elect®	^{A} 5.75 (4.91)	^{A} 6.16 (2.40)	^{A} 5.44 (2.69)	-	n.s.
AdheSE®	^{B} 2.61 (0.66)	^{B} 5.09 (0.43)	^{A} 12.60 (3.31)	**0.807**	**<0.001**
Clearfil SE	^{C} 1.52 (0.15)	^{B} 5.53 (0.95)	^{A} 12.61 (0.63)	**0.962**	**<0.001**
Adper™ Single Bond 2	^{A} 0.31 (0.21)	^{A} 3.28 (2.33)	^{A} 3.70 (0.66)	**0.533**	**0.025**

Common corresponding capital superscript letters (A–C) in a given row indicate no significant differences. *Analyzed using Kruskal-Wallis test. NS= not significant

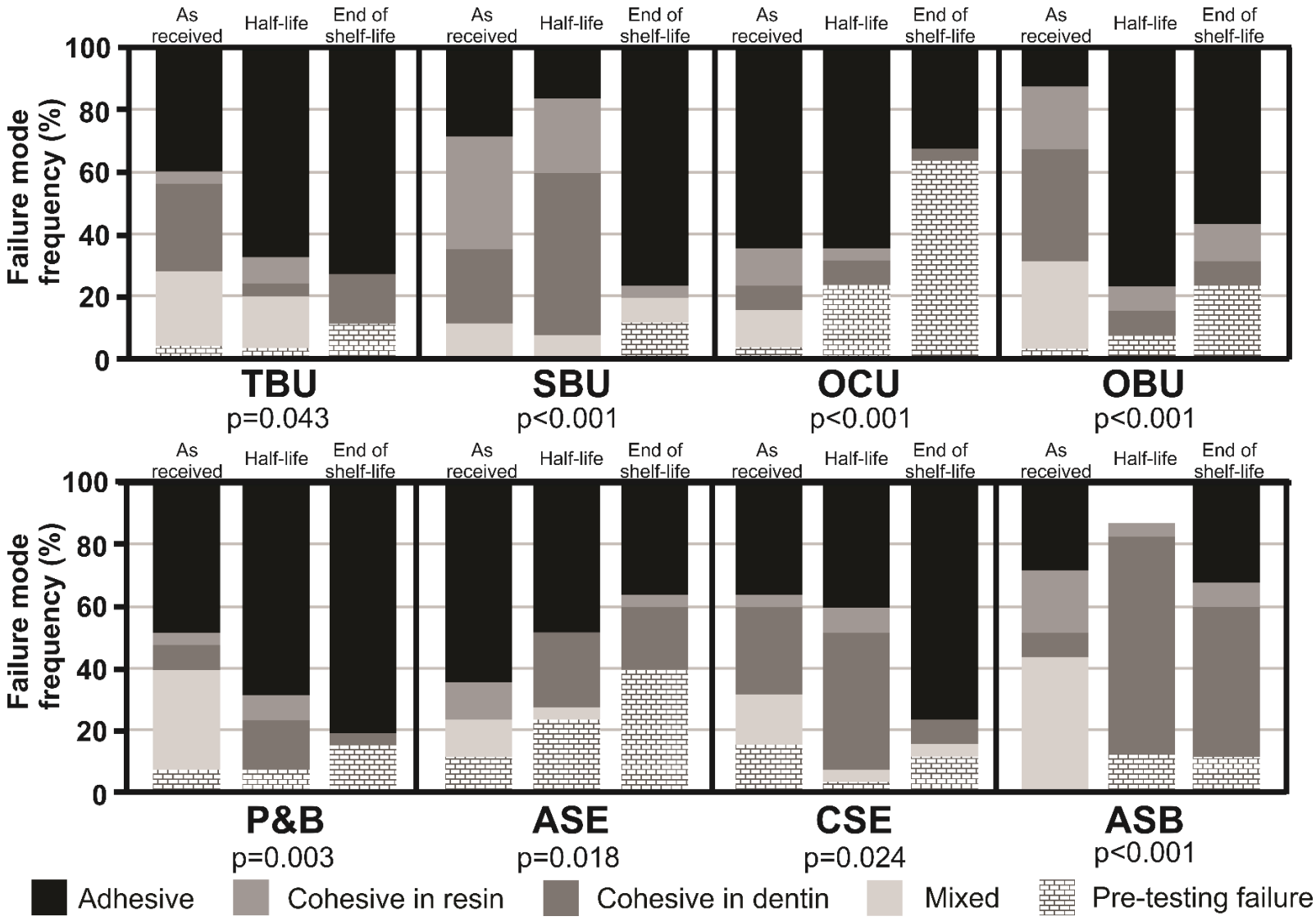

Figure 1. Failure mode distribution of the adhesives systems evaluated after μTBS.

Supplementary Material

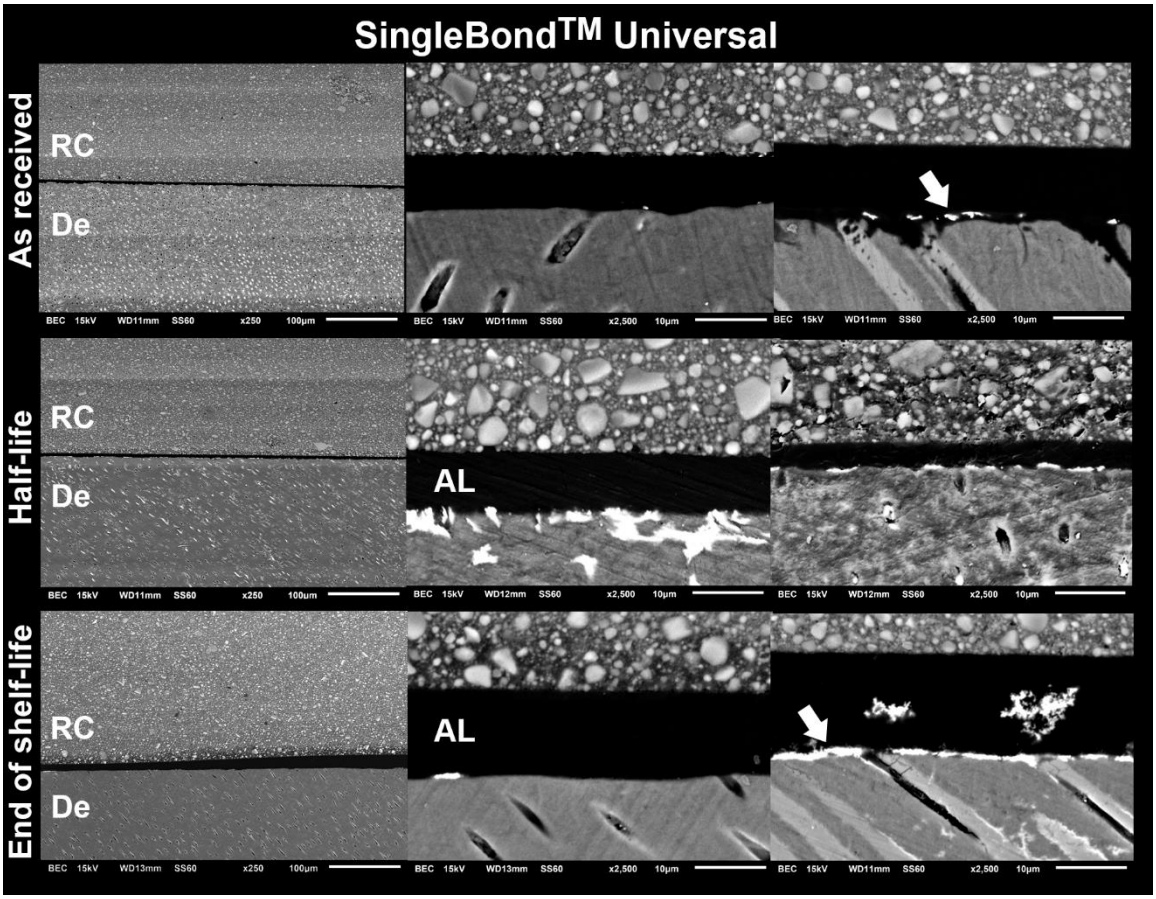

Figure S1. Representative backscatter SEM images of the resin-dentin adhesive interfaces of SBU. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage). Pointers suggesting “water trees”

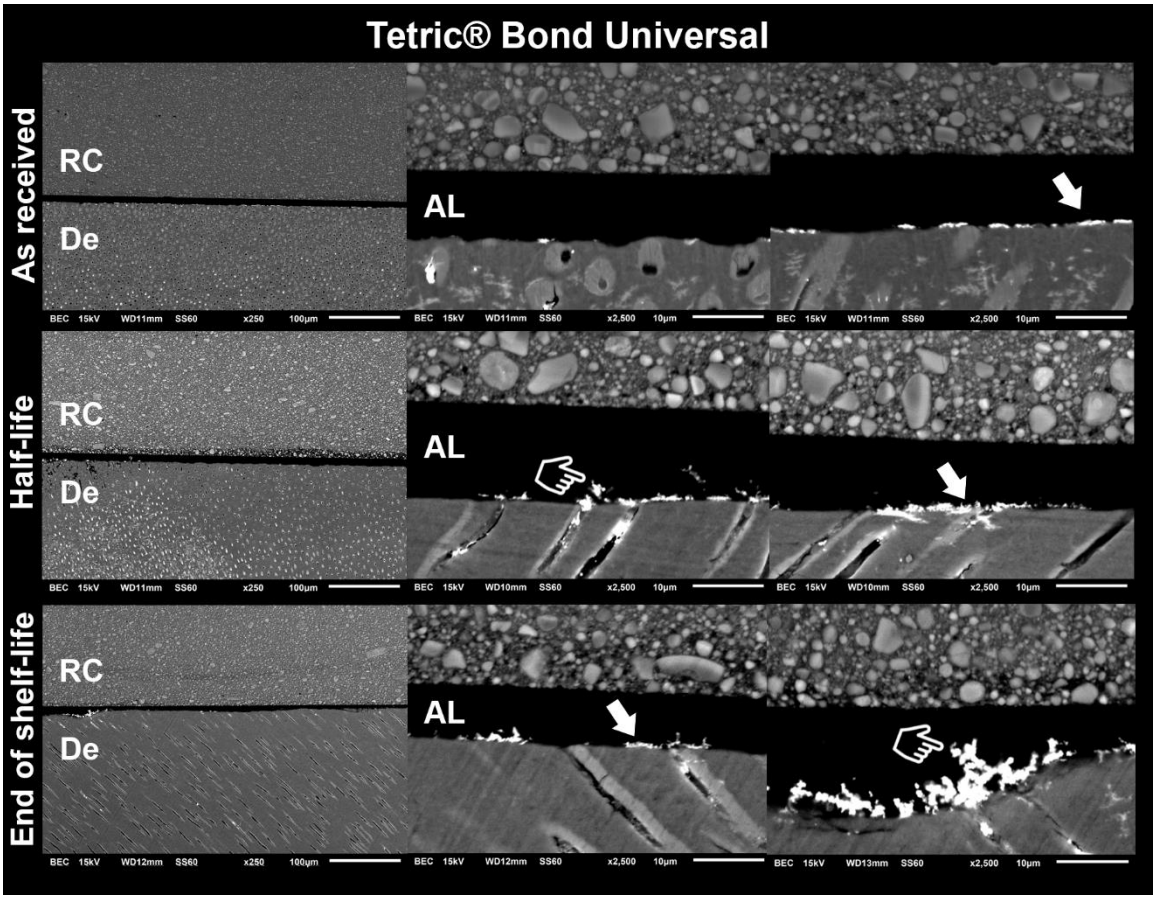

Figure S2. Representative backscatter SEM images of the resin-dentin adhesive interfaces of TBU. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage). Pointers suggesting “water trees”

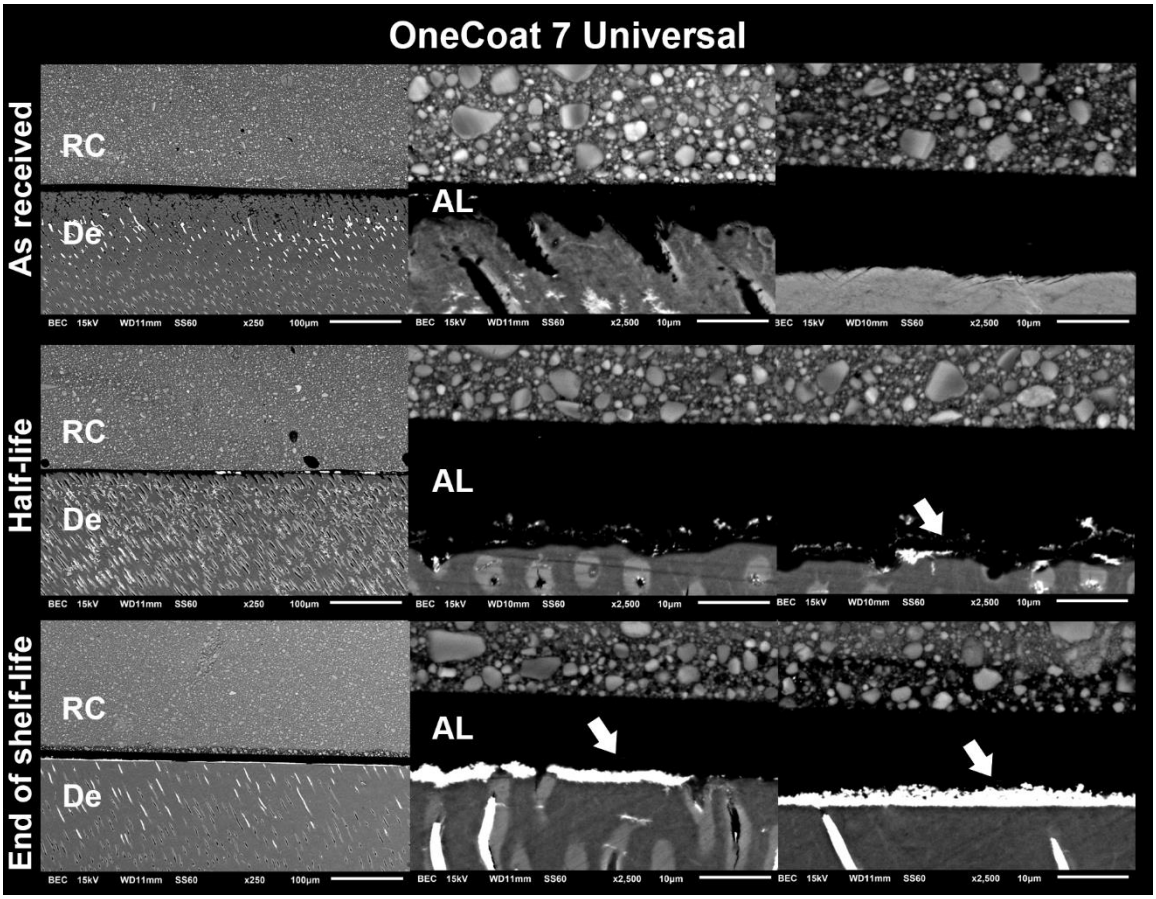

Figure S3. Representative backscatter SEM images of the resin-dentin adhesive interfaces of OCU. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage).

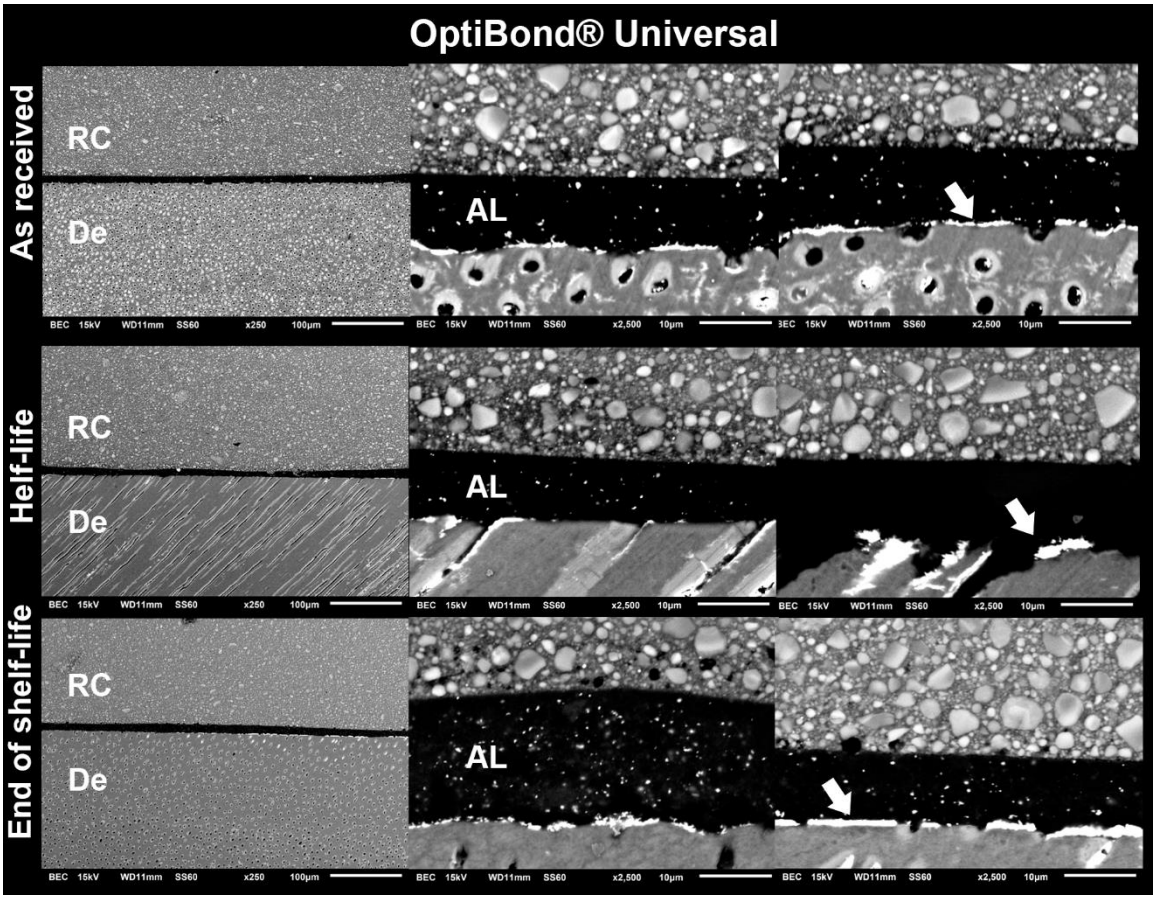

Figure S4. Representative backscatter SEM images of the resin-dentin adhesive interfaces of OBU. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage).

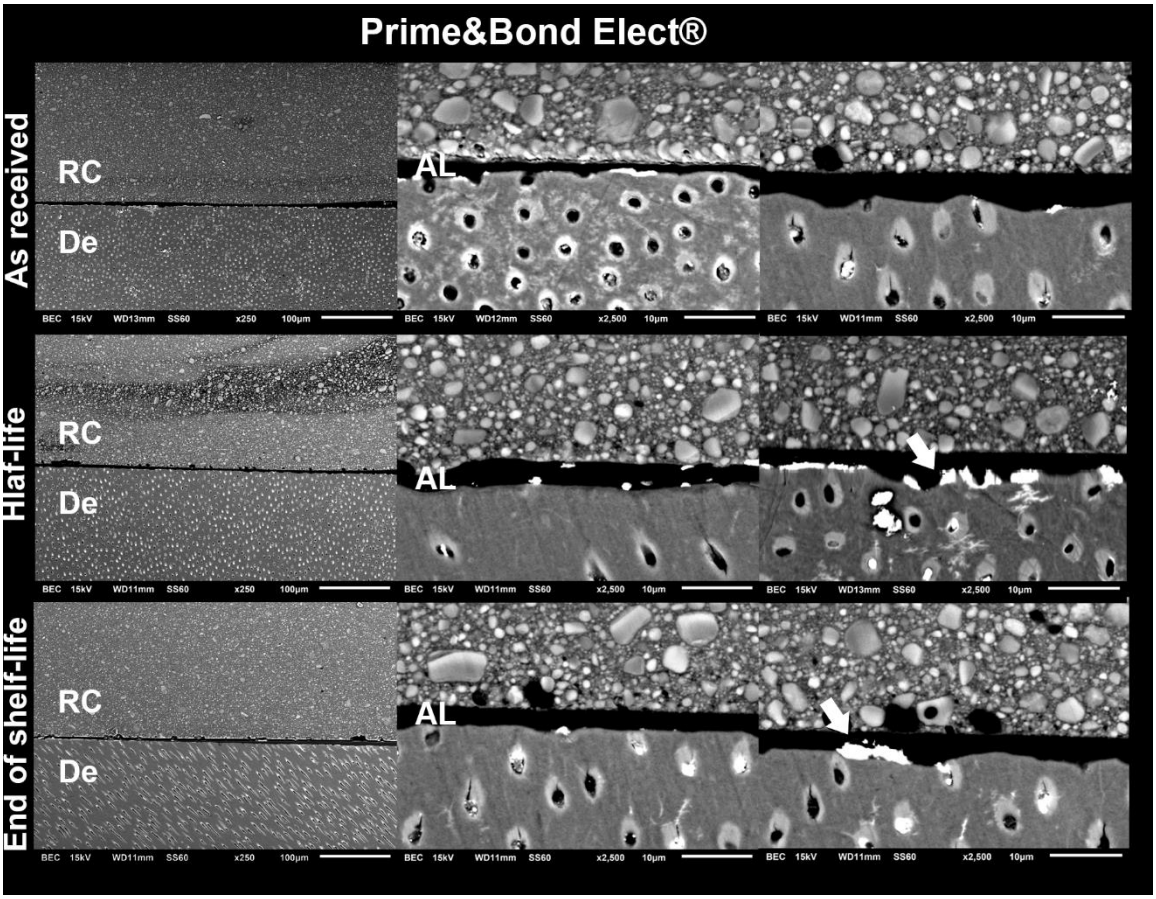

Figure S5. Representative backscatter SEM images of the resin-dentin adhesive interfaces of PBE. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage).

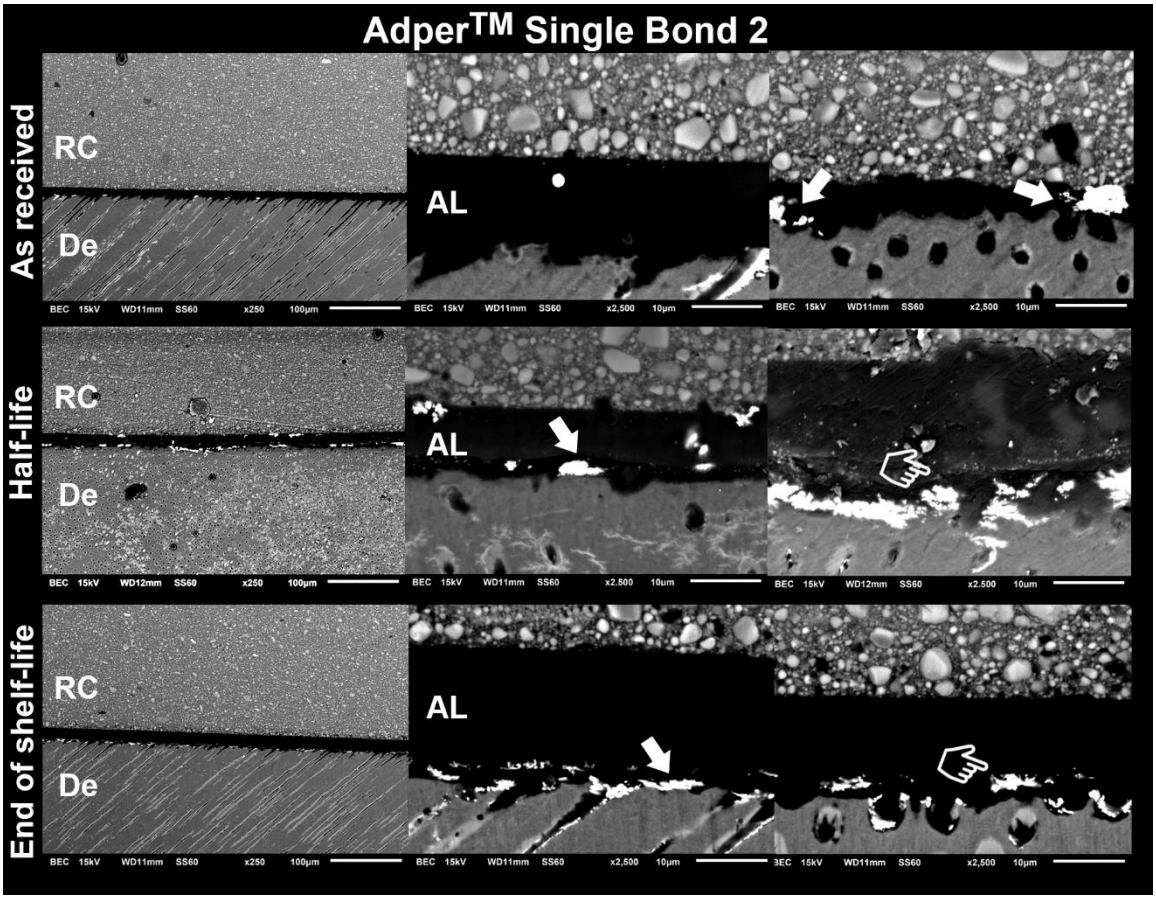

Figure S6. Representative backscatter SEM images of the resin-dentin adhesive interfaces of ASE. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage). Pointers representing “water trees”

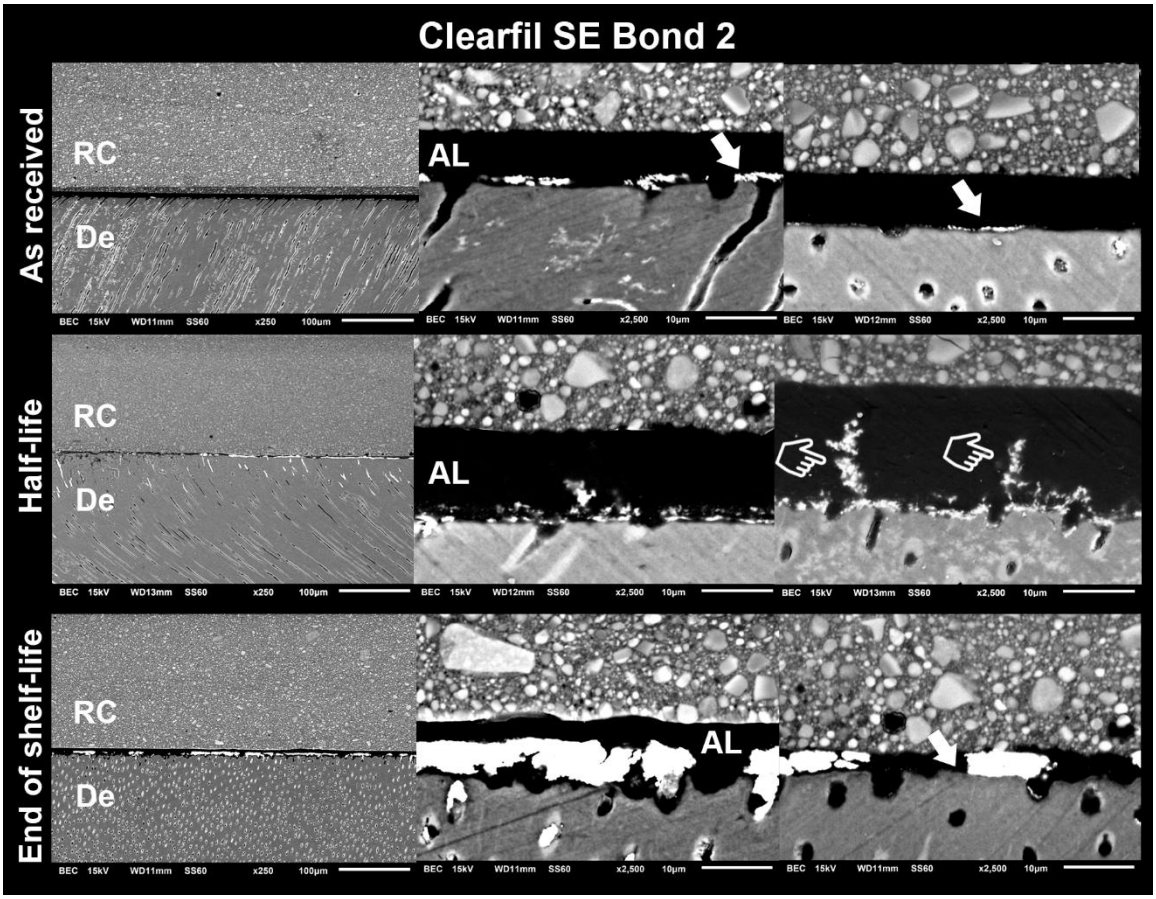

Figure S7. Representative backscatter SEM images of the resin-dentin adhesive interfaces of CSE. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage).

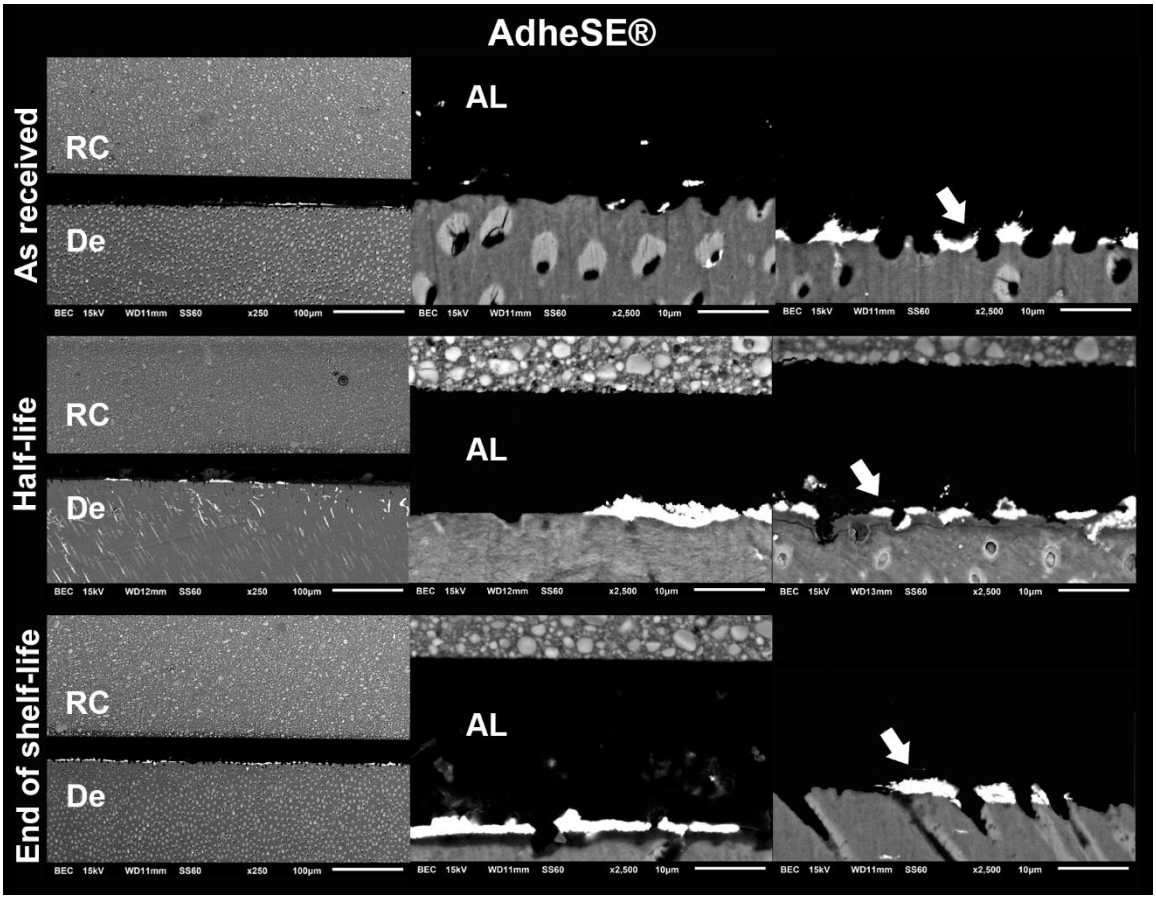

Figure S8. Representative backscatter SEM images of the resin-dentin adhesive interfaces of ASB. RC, Resin composite. De, Dentine. AL, Adhesive Layer. Arrows represent silver staining (nanoleakage).

6 Considerações finais

A evidência *in vitro* sugere que a resistência de união à dentina dos adesivos universais depende do seu pH. O uso de adesivos universais classificados como leves, aplicados na técnica de condicionamento seletivo do esmalte, parece ser a estratégia mais efetiva para lograr uma resistência de união adequada e durável.

Quanto ao desempenho dos adesivos universais em substratos indiretos, a sua capacidade para obter uma resistência adesiva adequada é limitada e depende do substrato ao qual eles são aplicados. Para cerâmicas com alto conteúdo de vidro e ligas metálicas, o uso de um primer específico em uma etapa separada continua sendo o padrão ouro para a cimentação adesiva desses substratos. Por outro lado, o procedimento clínico de cimentação de zircônia e restaurações de resina composta demonstrou ser mais simples e eficiente utilizando um adesivo universal.

Por outro lado, o método de preparação das amostras dos materiais utilizados para os testes de viabilidade celular foi determinante nos resultados. A quantidade de substâncias não regidas e lixiviadas também foram influenciadas pelo método utilizado para o preparo da amostra, dentre estas, parece ser que o sistema fotoiniciador utilizado é um parâmetro a ser considerado no desenvolvimento de novos materiais. Com base nisso, uma atenção especial deve ser dada ao interpretar os resultados de viabilidade celular, já que este é frequentemente usado para determinar a citotoxicidade preliminar de um material.

Finalmente, foi demonstrado que grande parte das propriedades dos adesivos universais testados foram alteradas após o armazenamento progressivo em câmera climática. Segundo o protocolo de simulação do tempo de prateleira utilizado neste estudo, a maioria dos adesivos avaliados teve um prazo de validade superestimado. A simulação do tempo de prateleira deve ser considerada como uma metodologia de rotina durante o processo de desenvolvimento e caracterização de sistemas adesivos universais.

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Apêndices

Apêndice A – Nota da Tese

Avaliação do desempenho e estabilidade de sistemas adesivos universais.

Performance and stability evaluation of universal adhesive systems.

Os adesivos universais foram introduzidos para serem usados em qualquer estratégia de adesão, ainda, segundo o conceito de universal, os fabricantes incluíram na composição deles diferentes monômeros funcionais que melhoram a ligação química a diferentes substratos indiretos. Por outro lado, aspectos como a sua citotoxicidade e tempo de vida útil ainda não foi amplamente estudada. O objetivo da presente tese de Doutorado foi investigar o desempenho químico-mecânico e biológico de diferentes adesivos universais. Os resultados demonstraram que o desempenho adesivo dos adesivos universais depende do substrato ao qual eles são aplicados. Em esmalte e dentina, o uso de adesivos universais classificados como leves, aplicados na técnica de condicionamento seletivo do esmalte, parece ser a estratégia mais efetiva. Em substratos indiretos os adesivos universais podem simplificar o procedimento clínico de cimentação de zircônia e resina composta indireta. A viabilidade celular dos adesivos universais depende amplamente do método de preparação das amostras. Por outro lado, para garantir o seu desempenho máximo, os adesivos universais devem ser usados no primeiro ano de vida útil.

Campo da pesquisa: Odontologia Restauradora; materiais odontológicos.

Candidato: Carlos Enrique Cuevas-Suárez, mestre em *Ciencias Biomédicas y de la Salud* pela *Universidad Autónoma del Estado de Hidalgo.*

Data da defesa e horário: 10/12/2018 9:00 hrs

Local: Auditório do Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas. 5º andar da Faculdade de Odontologia de Pelotas. Rua Gonçalves Chaves, 457.

Membros da banca: Profa. Dra. Fernanda Barbosa Leal. Doutora em Odontologia (Dentística) pela Universidade Federal de Pelotas; Prof. Dr. Rafael Ratto de Moraes. Doutora em Materiais Dentários pela Universidade Estadual de Campinas; Prof. Dr. Neftali Lenin Villarreal Carreño. Doutor em Química pela Universidade Federal de São Carlos; Profa. Dra. Melissa Feres Damian, Doutora em Radiologia Odontológica pela Universidade Estadual de Campinas. Dra. Cristina Pereira Isolan. Doutora em Ofontologia (Materiais Dentários) pela Universidade Federal de Pelotas

Orientador: Prof. Dr. Evandro Piva. Doutor em Materiais Dentários pela Universidade Estadual de Campinas. **Coorientadores:** Profa. Dra. Adriana Fernandes da Silva. Prof. Dr. Cesar Liberato Petzhold

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Apêndice B – Súmula do currículo do candidato

Carlos Enrique Cuevas-Suárez nasceu em 1987, em Pachuca de Soto, Hidalgo, México. Completou o ensino fundamental na *ESTV No. 28 "Cuauhtémoc"* na cidade de Tulancingo, Hidalgo, México. No ano de 2004 ingressou na *Área Académica de Odontología* da *Universidad Autónoma del Estado de Hidalgo (UAEH)*, tendo sido graduado cirugião-dentista em 2010. Em 2010, ingressou no Mestrado em *Ciencias Biomédicas y de la Salud – UAEH*, sob orientação da Profa. Dra. Ana María Herrera-González, onde trabalhou na área de síntese e caracterização de dimetacrilatos. Dissertação defendida e aprovada em 2012. Em 2013 ingressou como Professor Pesquisador Associado na *Área Académica de Odontología – UAEH*. Em 2015 iniciou Doutorado na Universidade Federal de Pelotas (UFPel) na área de Materias Odontológicos sob orientação do Prof. Dr. Evandro Piva. Durante o período 2015/2 – 2018/1 de doutorado foi bolsista do *Programa para el Desarrollo Profesional Docente (PRODEP, México)*, assim como bolsista da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) durante o período 2018/2.

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