Review Article

The Penetration Depth of Resin Infiltration Into Enamel: A Systematic Review

Dayang Fadzlina Abang Ibrahim[1], Annapurny Venkiteswaran[1], Noren Nor Hasmun[2]

[1]Centre of Paediatric Dentistry and Orthodontics Studies, Faculty of Dentistry, Universiti Teknologi MARA, Selangor, Malaysia, [2]Department of Oral Science, Faculty of Dentistry, University of Otago, Dunedin, New Zealand

Abstract

Aims and Objectives: Studies on resin infiltration and its penetration capability are becoming the focus of emerging dentistry. The depth of resin penetration could be a key determining factor in creating a diffusion barrier and in the success of infiltration. The aim of this review article was to evaluate the penetration depth of commercially available resin infiltration in early caries lesions and to identify factors that influence the penetration capability of resin infiltration. **Materials and Methods:** A literature search was performed in four databases (PubMed, Science Direct, Scopus, and Web of Science) and manual searching from 2009 to December 2022. Eligibility criteria included *in vitro* studies pertaining to factors affecting the penetration depth of resin infiltration into the enamel. The risk of bias assessment was done by using checklist for reporting *in vitro* studies (CRIS). **Results:** The initial search resulted in a total of 297 studies. Twenty-nine were assessed for eligibility, and 23 were selected in the qualitative synthesis. According to the CRIS guidelines, all of the studies were classified as moderate risk of bias. The penetration of resin infiltration is influenced by the enamel surface treatment with hydrochloric acid, formulations containing triethylene glycol dimethacrylate (TEGDMA), the addition of ethanol, penetration time, duration of penetration time, saliva contamination, caries activity, and type of tooth. The hypermineralized surface layer needs to be removed for better resin perfusion. **Conclusion:** The key to optimal resin infiltration depends on the enamel surface treatment with hydrochloric acid and application technique, infiltration duration, formulation of TEGDMA and ethanol in the resin composition, as well as the type and caries activity of involved teeth. Resin infiltration has superior penetrability compared to fissure sealant, casein phosphopeptide-amorphous calcium phosphate nanocomplexes, flowable composite, adhesive and fluoride varnish. Resin penetration depth may be a critical factor in forming a diffusion barrier and the effectiveness of infiltration in halting the progression of caries.

Keywords: *Adhesive, etching, ethanol, hydrochloric acid, penetration depth, resin infiltration*

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Introduction

An early caries lesion can be defined as a primary lesion that has not reached the stage of an established lesion with cavitation.[1] A variety of treatment modalities have been proposed for the management of early caries lesions which include preventive measures such as good oral hygiene care, remineralization using fluoride or casein phosphopeptide amorphous calcium phosphate (CPP-ACP),[1] fissure sealant and resin infiltration.[1,2] However, remineralization therapy is usually

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Address for correspondence: Dr. Dayang Fadzlina Abang Ibrahim, Centre of Paediatric Dentistry and Orthodontics Studies, Faculty of Dentistry, Universiti Teknologi MARA, 47000 Sungai Buloh, Selangor, Malaysia.
E-mail: dayangfadzlina3@gmail.com

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esthetically unacceptable to most of the patients, and its effectiveness greatly relies on the patient's compliance.[3] Resin infiltration is a new microinvasive technique that was introduced in 2009 and marketed under the name ICON (DMG, Hamburg, Germany), which consists of resin infiltrant, 15% hydrochloric acid (HCL), and ethanol. A recent meta-analysis showed that resin infiltration is prospective for halting the progression of non-cavitated caries lesions. Therefore, resin infiltration is advocated as a viable noninvasive therapy option that can be used in addition to non-invasive and invasive treatments.[4] The low-viscosity resin infiltrant tends to inhibit enamel pores that serve as diffusion channels for acids and dissolved minerals to permeate the demineralized lesion.[4] In addition to inhibiting caries, resin infiltration can conceal early caries lesions and enamel opacity.[5] Although the refractive index of the infiltrant (1.52) is near to that of enamel/apatite (1.62), as opposed to the refractive indices of water (1.33) and air (1.00), light scattering decreases with infiltration penetration.[5,6] When microporosities in enamel lesions are filled with resin, they lose their whitish discoloration and resemble the color of healthy enamel.[6,7] This novel technique has been proven to fill, reinforce, and stabilize demineralized enamel and preserve the integrity of the tooth.[4,6,7] Thus, the parameters used to evaluate the success of resin infiltration include caries arresting potential,[5] increased microhardness of enamel and improved esthetic outcomes.[6,7]

Microfilled infiltrant resins (MFIRs) had been introduced to improve the mechanical properties of resin infiltration by adding filler particles to the low-viscosity resin matrix.[8] MFIRs combine the infiltrating properties of infiltrants with the consistency of flowable composite resins. Studies showed similar penetration of MFIRs into artificial non-cavitated enamel lesions and cavitated natural occlusal lesions like commercially available resin infiltration.[9] Apart from that, the incorporation of the phosphoric acid 2-hydroxyethyl methacrylate ester (PAM) monomer into the resin infiltration would allow the material to bind with the lesion as well as possibly eliminate the etch-and-rinse steps.[10] It was believed that the addition of PAM in the resin infiltration formulation will increase the viscosity and pH of this material and allows superior penetrability.[10]

The penetration of resin infiltration into the intercrystalline spaces of enamel is driven by capillary forces which are determined by its penetration coefficient (PC).[7,11] According to the "Washburn equation," the infiltrant must have a low-viscosity and a low-contact angle in order to completely penetrate porous enamel.[11] The higher the PC of a liquid, the faster it penetrates into a given porous solid.[12] The penetration depth of the resin infiltration into the demineralized enamel reflects the ability of the infiltrant to fill up the pores and obliterate the caries progression.[11,12] Hence, depth of resin penetration could be a key determining factor for the creation of a diffusion barrier and the success of infiltration in halting the caries progression.[12]

It is found that the existence of the hypermineralized superficial pseudointact surface layer of enamel caries will form a barrier that hampers the capillary action of the resin penetration.[13] Thus, removal or perforation of the surface layer has been considered pivotal for successful of treatment using resin infiltration.[13] Different types of acids have been used for etching dental enamel such as phosphoric acid (H_3PO_4), HCL, polyacrylic acid and maleic acid.[14] It has been reported that HCL 15% gel erodes surface layers more effectively than 37% H_3PO_4 and etching with HCL 15% gel for 120 s is recommended prior to placement of resin infiltration on natural enamel lesions.[12]

This systematic review aimed to (1) compare the penetration depth of commercially available resin infiltration into early caries lesions with fissure sealants, fluoride varnish, adhesive agents and flowable composite, and (2) identify factors that influence the penetration capability of resin infiltration into early caries lesions.

Materials and Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.[15] The research questions were "What is the penetration depth of resin infiltration into early caries lesions and what factors influence the penetration capability of resin infiltration into early caries lesions?" PRISMA 2020 guideline was adhered to for the literature search of this review. The PICOS strategy used to select the inclusion criteria and search strategy is described here: Population (P): human or bovine teeth with sound enamel or lesion confined to enamel; Intervention (I): treated with resin infiltration technique; Comparison (C): surface treatment on enamel, other material (adhesive, fluoride, fissure sealant), technique and teeth and structure; Outcome (O): penetration depth of resin and the factor that influences the penetration depth of resin infiltration into enamel; Study design (S): *in vitro*. The inclusion criteria were as follows: *In vitro* studies that assess the penetration depth of resin infiltration on enamel. The exclusion criteria were as follows: unpublished articles, randomized controlled trials, case reports, review articles, book chapters, dissertations and guidelines. A literature search was done using four search engines namely, PubMed, Scopus, Science Direct and Web of Science were searched between January 2009 and December 2022. Two authors (DFA and NNH) independently and systematically searched each database using the Medical Subject Heading (MeSH) to identify the descriptors. Additionally, the Boolean search was performed in each database using the search term ("Resin Infiltration" OR "ICON Resin Infiltration" OR "Commercially Available Infiltrant" OR "Microinvasive Dentistry" OR "Minimally Invasive Dentistry" OR "Caries Infiltration") AND ("Control" OR "Fluorides" OR "Sodium Fluoride" OR "Fissure Sealant" OR "Sealing" OR "CPP-ACP" OR "Casein Phosphopeptide-Amorphous Calcium Phosphate" OR "Colloidal Silica" OR "Adhesive System") AND ("penetration depth" OR "penetration coefficient" OR "perfusion") AND ("white spot lesion" OR "demineralized enamel lesion" OR "early enamel lesion"). A manual search was conducted using the references list of selected articles to identify other potential sources, and additional studies were added. This review looks at the research pertaining to the penetration depth of resin infiltration and the factors that influence its penetration depth on demineralized enamel lesions.

Study selection and extraction

Study selection and article extraction were conducted using the PRISMA by two independent researchers (DFA and NNH). First, titles and abstracts were screened to identify preselected studies, whereas those that were not eligible were excluded. The full articles were retrieved if the titles/abstracts of the studies did not contain adequate information to support the decision for inclusion and exclusion. Second, the full texts of all included studies were evaluated based on the same eligibility criteria. Any disagreements were resolved until consensus was reached. Then, the data were independently extracted by the two reviewers including author, publication year and geographic location; tooth type/group/number group(s); demineralization method; tools to measure the penetration depth, mean of penetration depth ± SD/penetration area (%) and findings.

Risk of bias

In accordance with the CRIS guidelines (checklist for reporting *in vitro* studies)[16] for *in vitro* studies, the following variables were analyzed for quality assessment: (1) sample preparation and handling; (2) allocation sequence and randomization process; (3) evaluator blinding status, and (4) statistical analysis.[16] Two evaluators (DFA and AV) independently assessed the methodological quality and risk of bias of each included study. Studies with information on all variables were deemed to be of high quality, those with information on two to three variables were deemed to be of moderate quality, and those with information on one variable or none were deemed to be of low quality.

Results

Study selection

A flow diagram of the search strategy is presented in Figure 1. The initial search from the electronic database search resulted in a total of 297 studies. After excluding 120 duplicate studies, 177 articles were included in the abstract analysis phase. Then, 29 articles remained for full-text screening, of which 6 studies were excluded as they did not conform to PICO. Finally, 23 studies met the eligibility criteria. No systematic review or meta-analysis of this subject area was found. All included articles were conducted in Egypt,[17-19] Korea,[20] USA,[18,21] Saudi Arabia,[22] India,[23-26] Germany,[8,21,27-29] Chile,[30] Brazil,[10,11,31,32] Romania,[33] and Switzerland.[26]

Study characteristics

The descriptive results and recorded parameters of each study were presented in [Table 1]. All the reviewed articles were *in vitro*, describing a total of 1836 teeth. In 23 studies, 8 studies used natural enamel lesions,[8,20,21,27-29,33,34] 15 studies created artificial WSLs,[10,17-19,22-26,30-32,35-37] and 3 studies used bovine enamel.[10,32,35] To measure the penetration depth, most of the articles used confocal laser scanning microscopies (CLSM) (18 studies),[8,10,17,18,20-22,25,27-29,31-37] followed by polarized light microscopy (one study),[23] scanning electron microscopy (SEM) (one study),[30] stereomicroscope (two studies)[19,26] and optical profilometer (one study).[24] Adhesive,[18,19,30,32,36] fissure sealant,[22-24,32] flowable composite resin,[8,33] fluoride,[33] CPP-ACP,[19] MFIR[8] and colloid silica[25] were the materials investigated and compared with resin infiltration. In most studies, the artificial WSL was produced by a demineralizing solution,[10,19,22-26,31,35] followed by phosphoric acid,[17,18] pH cycling,[10] HCL,[32] acetate buffer,[37] deionized water[36] or lactic acid.[30] All the studies used HCL as a pretreatment technique for resin infiltration. The factors that contribute to the penetration depth of resin infiltration were surface treatment of enamel,[17,20,21,27,31] penetration time,[28,29] saliva contamination,[35] comparison with the other dental materials,[8,18,19,22-25,30,32,33,36] TEGDMA based formulation,[10,37] permanent vs primary teeth[26] and the caries activity.[34]

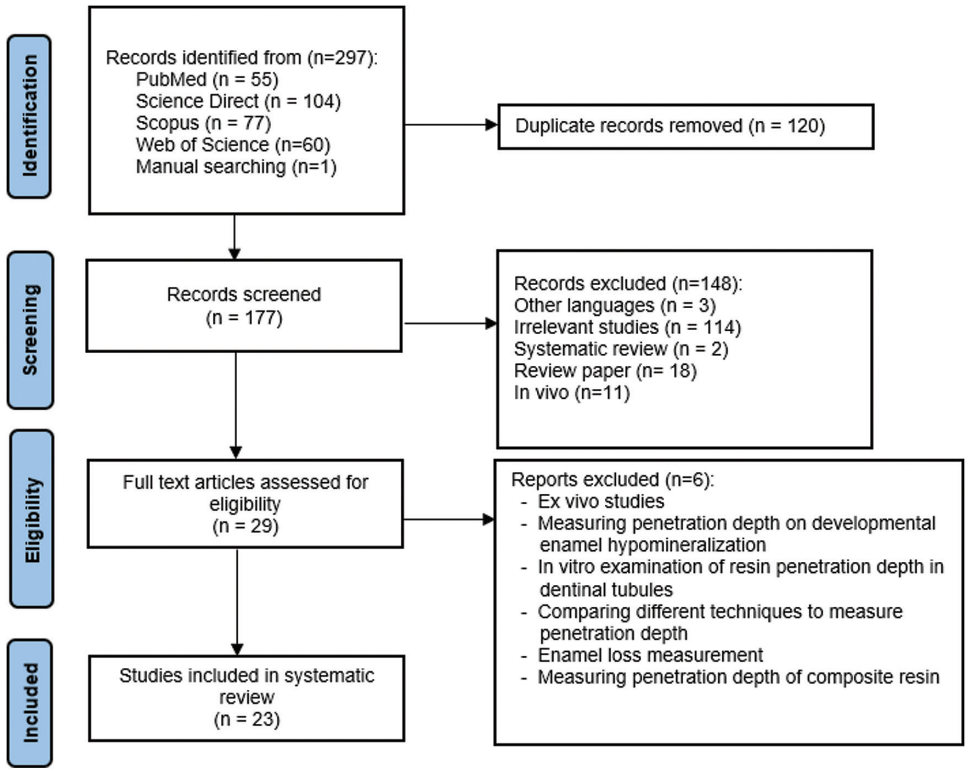

Figure 1: PRISMA diagram for research strategy

Methodological quality of the included studies

Risk of bias and quality assessment of *in vitro* studies were conducted in accordance with CRIS guidelines[22] [Table 2], and all studies showed a moderate risk of bias.

Discussion

Overall, the present review shows that infiltrative resins penetrate enamel porosity more deeply than fissure sealants, fluoride varnish, CPP-ACP, adhesive agents or flowable composite. The application of HCL and surface treatment on enamel, duration of resin infiltrant application, type of tooth and caries activity, formulation of TEGDMA and ethanol content in resin infiltration were the factors that influenced resin penetration. Also, this wide variation of penetration depth may be attributed to the fact differences in demineralization protocol and different tools to measure the penetration depth.

There were five studies that specifically looked at the technique that enhance the penetration of resin.[17,20,21,27,31] All studies concur that before a demineralized enamel can be infiltrated, it must be etched with 15% HCL to remove the hypermineralized pseudointact surface layer of enamel.[17,20,21,27,31] This effect was caused by the increased surface area and complete filling of the pores within the teeth during etching, as well as the destruction of the prismatic layer of the enamel that increases the efficiency of resin infiltration penetration.[17,27,31] Interestingly, studies have shown that etching efficacy depends on the type of acidic monomer used, the application method and the duration of the infiltrant being applied to the lesions.[17,27,31] For the acidic monomer, it was found that the usage of 15% HCL for 120 s efficiently eliminates the hypermineralized layer of enamel up to 36.70 ± 7.62 µm.[17,31] Conversely, 37% phosphoric acid had the highest penetration ability of resin compared with HCL although HCL removed the more hypermineralized layer of enamel.[27] The lower demineralization caused by phosphoric acid may be attributable to two primary factors: (1) less caustic effects when compared to HCL, with a lower ability to remove the mineralized structure in depth, and (2) selective action over the enamel prisms, resulting in variation in the patterns of the conditional surfaces.[27] However, the combination of HCL and phosphoric acid as a pretreatment enamel surface treatment results in superior resin penetrability than HCL alone.[31]

Lopez *et al.*[31] found that the ultrasonic application of etchant showed the highest penetration depth compared to the different experimental protocols, such as manual or sonic application or manual brush. This was due to the surface vibration produced following the ultrasonic procedure which increased penetration speed, facilitates the resin infiltration impregnation

Table 1: Summaries of studies regarding the penetration depth of resin infiltration

Author/ year/country	Tooth type/group/ number	WSL creation (pH for hours)	Group(s)	Tools to measure the penetration depth (PD)	Mean of PD ± SD/ Penetration area (%)	Finding(s)
Surface pretreatment						
Lopez *et al.* [31]/ Brazil	Healthy permanent third human molars/48	Demineralizing acid gel, pH=5, 4 weeks	▪H3PO4+ HCL (Manual/ Sonic/Ultrasonic) ▪HCL (Manual/Sonic/ Ultrasonic)	CLSM	Mean PD % HCL ± H_3PO_4 Manual = 34.5 ± 7.7 Sonic= 84.2 ± 8.9 Ultrasonic= 94.1 ± 5.3 HCL Manual= 28.0 ± 9.3 Sonic= 66.8 ± 13.4 Ultrasonic= 84.1 ± 10.1	▪The ultrasonic application showed the highest PD values. ▪H_3PO_4 + HCL presented higher results than HCL.
Abd Alhady and Mohamed[17]/Egypt	Healthy human permanent molar teeth/63	37% $H_3PO_{4,}$ 1 min	▪ICON (surface treatment or without surface treatment) ▪Single Bond Universal (surface treatment or without surface treatment)	CLSM	Mean PD Highest: ICON =7.15 ± 3.551 µm Lowest: Universal = 1.65 ± 0.709 µm	▪ The highest PD was ICON after being subjected to surface treatment and the lowest PD was single bond universal without surface treatment.
Lausch *et al.* [27]/ Germany	Molars and premolars with active, non-cavitated white spot lesions (ICDAS2)/140	Without demineralization	▪G1:Etch + ICON ▪G2:Etch (none brush) + ICON ▪G3:Etch (oscillating brush + ICON ▪G4:Etch (oscillating brush) + ICON (oscillating brush) ▪G5:Etch (flat brush) + ICON ▪G6:Etch (modified toothbrush 120s) + ICON ▪G7:Etch (modified toothbrush 30s) + ICON	Dual fluorescence and CLSM	Mean PD G1:261 µm G2:174 µm G3:503 µm G4:304 µm G5:295 µm G6:844 µm G7:963 µm	▪The use of an abrasive HCL gel in conjunction with a modified brush mostly enhances resin infiltration into fissure caries lesions.
Yim *et al.* [20]/ Korea	Human molars and pre-molars ICDAS 2/70	Without demineralization	▪15% HCL ▪37% H_3PO_4	CLSM	Remove surface layer 15% HCL= 36.70 ± 7.62 µm 37% H_3PO_4= 13.15 ± 2.76 µm 37% H_3PO_{4+} sponge= 22.86 ± 6.74 µm 37% H_3PO_{4+} brush= 35.96 ± 3.45 µm Mean PD % 15% HCL=74 ± 17.58 % 37% H_3PO_4=76 ± 21.51 %	▪Application of 37% H_3PO_4 with a brush for 30 s increased the pore volume of WSL surface layers and the percentage of infiltration areas in comparison to the use of 15% HCl for 120 s.

Table 1: Continued

Author/ year/country	Tooth type/group/ number	WSL creation (pH for hours)	Group(s)	Tools to measure the penetration depth (PD)	Mean of PD ± SD/ Penetration area (%)	Finding(s)
Paris *et al.* [21]/ Germany	Human molars and premolars with ICDAS 02/ 102	Without demineralization	▪Negative control: no further pre-treatment ▪Positive control: 24h air-drying in incubator at 37 °C ▪E1: once application of 100 % ethanol ▪E2: twice application of 100 %ethanol ▪A1: once application of 100 % acetone ▪A2: twice application of 100 % acetone	CLSM	Mean PD≥500 µm NC = 290 µm PC = 687 µm E1= 807 µm E2=628 µm A1= 698 µm A2= 449 µm	▪ The pre-treatment with ethanol or acetone prior to resin infiltration enhanced the penetration of resin into deeper enamel lesions.
Saliva contamination						
Gelani *et al.* [35]/ United States of America	Bovine tooth/252	Demineralization solution, pH 5, 4 weeks	▪G1: ICON ▪G2: ICON + fluoride ▪G3: Saliva contamination + ICON ▪G4: Saliva contamination + ICON + fluoride	CLSM and transversal microradiography	Mean PD G1:112.8 µm G2:103.0 µm G3:110.1 µm G4:106 µm	Saliva contamination decreased the ability of the resin infiltration penetration.
Penetration time						
Paris *et al.* [28]/ Germany	Primary molars showing active ICDAS 2/ 83	Without demineralization	▪0.5 min ▪1min ▪3 min ▪5 min	Dual fluorescence confocal microscopy	Median PD≥400 µm 0.5 min=175 µm 1 min=356 µm 3 min=407 µm 5 min=503 µm	The consistent results of PD were obtained when lesions were treated for at least 3 min of resin infiltration application.
Meyer Lueckel *et al.* [29]/ Germany	Permanent posterior teeth non-cavitated proximal caries lesions/20	Without demineralization	▪0.5 min ▪1min ▪3 min ▪5 min	Dual fluorescence confocal microscopy	Median PD≥500 µm 0.5 min=66 µm 1min= 148 µm 3 min= 537 µm 5 min=615 µm	A 3 min application of resin infiltration is sufficient to achieve almost complete penetration of enamel caries.
Materials						
Edunoori *et al.* [23]/ India	Healthy human premolar/40	Demineralizing solution, pH 4.4, 96 h	▪ICON ▪Clinpro XT varnish	Polarized light microscope	Mean PD ICON = 24.46 µm Clinpro XT varnish = 12.34 µm	▪ICON showed a significantly higher PD and is more effective on remineralization of WSL when compared to Clinpro XT varnish.

Table 1: Continued

Author/ year/country	Tooth type/group/ number	WSL creation (pH for hours)	Group(s)	Tools to measure the penetration depth (PD)	Mean of PD ± SD/ Penetration area (%)	Finding(s)
Mohamed *et al.* [18]/ Egypt	Healthy permanent teeth/60	37% H_3PO_4, 1 min	▪ G1: ICON (15% HCL) ▪ G2:OptiBond (37.5% H_3PO_4) ▪ G3: Bond-1SF (35% H_3PO_4)	CLSM	Mean with conditioning G1: 7.15 ± 3.55 nm G2: 3.63 ± 1.415 nm G3: 1.90 ± 1.064 nm Mean without conditioning G1:3.53 ± 1.547 nm G2:1.65 ± 0.709 nm G3: 0.90 ± 0.588 nm	▪ ICON shows the best PD value in relation to WSL, whereas Bond-1SF shows the worst. ▪ Surface treatment has a positive effect on the PD of the resin based materials.
Theodory *et al.* [36]/ USA	Permanent molar teeth/75	Deionized water lactic acid, pH 4.3, 3 months	▪ G1: ICON ▪ G2: Optiguard ▪ G3: Permaseal ▪ G4: Biscover	CLSM	Mean PD % G1:69.92 ± 9.60 G2:57.04 ± 3.91 G3: 56.25 ± 9.84 G4: 42.02 ± 10.65	The mean PD were significantly higher for ICON, intermediate for Optiguard and Permaseal, and lower for Biscover.
Al Tuwirqi *et al.* [22]/ Saudi Arabia	Healthy premolars/ 60	Demineralized solution,1 to 2 weeks	▪ G1: ICON ▪ G2: Helioseal F	CLSM	Mean PD G1: 104.86 ± 7.63 µm G2: 5.32 ± 3.83 µm	ICON displayed more penetration and less microleakage than Helioseal F in pits and fissures.
Arora *et al.* [24]/India	Healthy premolars/ 120	Demineralized solution, pH 4.5, 4 days	▪ G1: ICON ▪ G2: Embrace ▪ G3: Clinpro ▪ G4: Control (no material)	Optical profilometer	Mean PD G1: 177.71 ± 4.93 µm G2: 104.99 ± 4.69 µm G3: 109.18 ± 5.29 µm G4: 95.76 ± 6.26 µm	ICON showed the maximum PD compared with Embrace and Clinpro.
Askar *et al.* ,[8] Germany	Proximal molars and premolars with ICDAS 2 and ICDAS 5/120	Without demineralization	▪ MFIR ▪ ICON + Flowable composite	CLSM	Median (Q1/Q3) ICDAS 3 ICON = 448 (221/503) µm MFIR = 639 µm (426/771) ICON + Flowable composite = 452 (332/662) µm Median (Q1/Q3) ICDAS 5 ICON = 428 (152/587) µm MFIR = 727 (395/808) µm ICON + Flowable composite = 934 (629/1216) µm	MFIR showed similar penetration into natural lesions as the ICON, but better ability to fill cavitated areas.

Table 1: Continued

Author/ year/country	Tooth type/group/ number	WSL creation (pH for hours)	Group(s)	Tools to measure the penetration depth (PD)	Mean of PD ± SD/ Penetration area (%)	Finding(s)
Mandava *et al.* [25]/ India	Permanent incisor teeth/ 40	Demineralizing solution, 96 h, pH 4.4	▪G1: ICON ▪G2: Colloidal silica infiltrant	CLSM	Mean PD % G1:67.14% G2: 53.54%	The resin PD was shown to be greater compared to colloidal silica.
Rosianu *et al.* [33]/ Romania	Healthy premolars/ 60	Not mention	▪G1: ICON ▪G2: Terric flow ▪G3: Fluorodose	CLSM	Mean PD % G1:111 ± 21 G2:40 ± 29 G3:11 ± 4	ICON significantly has the highest PD in comparison to Terric flow and Fluorodose.
Zamorano *et al.* [30]/ Chile	Healthy premolars and third molars/75	0.1 M lactic acid solution, pH 4.5, 8 weeks.	▪G1: ICON ▪G2: XP-Bond ▪G3: Single Bond 2	SEM	Mean PD G1: 82.67 ± 26.83 μm G2: 58.53 ± 29.34 μm G3: 44.83 ± 32.45 μm	The PD of ICON was significantly higher than the adhesive systems.
Shimaa *et al.* [19]/ Egypt	Healthy premolars/ 49	Demineralizing solution pH 4.4, 4 days	▪G1: ICON ▪G2: CPP-ACP ▪G3: Exite F adhesive ▪G4: Control group	Stereomicroscope at ×80	Mean PD G1:26.32 ± 4.61 μm G2: 19.27 ± 3.21 μm G3:15.47 ± 3.6 μm	ICON significantly has the highest PD in comparison to CPP-ACP and Exite F
Ionta *et al.* [32]/Brazil	Bovine enamel/75	0.01 M HCl, pH 2.3, for 30 s	▪G1: AdheSE ▪G2: Tetric N-Bond ▪G3: Adper Single Bond 2 ▪G4: Helioseal Clear ▪G5: ICON	CLSM	Mean PD Without etching G1: 0.8 ± 0.9 μm G2:0.75 ± 0.75 μm G3: 0.66 ± 0.8 μm G4: 1.78 ± 1.5 G5: 4.66 ± 1.55 μm With etching G1: 1.52 ± 0.57 μm G2: 3.53 ± 1.7 μm G3: 3.34 ± 2.3 μm G4: 6.03 ± 1.4 μm G5: 8.24 ± 4.92 μm	▪Etched enamel resulted in higher PD than non-etched. ▪ICON showed the highest PD in enamel followed by Helioseal. No difference was found among AdheSE, Tetric N-Bond and Single Bond 2.

Table 1: Continued

Author/ year/country	Tooth type/group/ number	WSL creation (pH for hours)	Group(s)	Tools to measure the penetration depth (PD)	Mean of PD ± SD/ Penetration area (%)	Finding(s)
TEGDMA based formulation						
Wang *et al.* [10]/ Brazil	Bovine enamel/65	Demineralization solution, Remineralization solution, pH cycling, pH=4.7, 7 days	▪ICON + 15% HCL ▪ICON+ 35% H_3PO_4 ▪ICON without acid etching ▪TEGDMA+ 35% H_3PO_4 ▪TEGDMA without acid etching ▪75% TEGDMA +25% PAM (Phosphoric acid 2-hydroxyethyl methacrylate ester) + 35% H_3PO_4 ▪75% TEGDMA +25% PAM without acid etching ▪50% TEGDMA +50% PAM + 35% H_3PO_4 ▪50% TEGDMA +50% PAM without acid etching ▪25% TEGDMA +75% PAM + 35% H_3PO_4 ▪25% TEGDMA +75% PAM without acid etching ▪PAM + 35% H_3PO_4 ▪PAM without acid etching	CLSM	Mean PD Without acid etching (Control) ICON= 42.38 ± 7.43 µm TEGDMA= 34.36 ± 4.71 µm 75% TEGDMA +25% PAM = 37.84 ± 3.26 µm 50% TEGDMA +50% PAM = 33.72 ± 9.74 µm 25% TEGDMA +75% PAM = 29.05 ± 3.91 µm PAM = 36.47 ± 6.11 µm HCL ICON=12.98 ± 1.23 µm H_3PO_4 ICON=41.94 ± 5.73 µm TEGDMA= 55.46 ± 4.25 µm 75% TEGDMA +25% PAM = 30.11 ± 4.14 µm 50% TEGDMA +50% PAM = 25.64 ± 5.23 µm 25% TEGDMA +75% PAM = 33.08 ± 7.90 µm PAM = 34.93 ± 2.56 µm	▪Etching with 15% HCL resulted in the lowest PD. ▪75T-25PAM, 25T-75PAM and PAM presented similar PD to the ICON after 37% H_3PO_4 etching, whereas 75T-25PAM,50T-50PAM and PAM yielded similar PD to the control group when no pre-treatment was conducted. ▪The association between TEGDMA and the acidic monomer PAM seem to be promising, and this combination probably allows proper penetrability without the need to etch the surface of WSL.
Araújo *et al.* [37]/ Brazil	Healthy third human molar/55	0.05 M acetate buffer solution, pH 5.0, at 50% hydroxyapatite saturation, 10 h	▪ICON ▪G1(TEGDMA 100%) ▪G2(TEGDMA 80%, Ethanol 20%) ▪G3(TEGDMA 80%, HEMA 20%) ▪G4(TEGDMA 75%, BisEMA 25%) ▪G5(TEGDMA 60%, BisEMA20%, Ethanol20%) ▪G6(TEGDMA 60%, BisEMA 20%, HEMA 20%) ▪G7(TEGDMA 75%, UDMA25%) ▪G8(TEGDMA 60%, UDMA 20%, Ethanol 20%) ▪G9(TEGDMA 60%, UDMA20%, HEMA 20%)	CLSM	Mean PD ICON=170.6µm G1= 98.2 µm G2 = 97.5 µm G3 = 124.1 µm G4 = 157.9 µm G5 = 120.6 µm G6 = 141.5 µm G7 = 164.8 µm G8 = 120.5 µm G9 = 117.6 µm	The addition of hydrophobic monomers and solvents into TEGDMA blends affected the degree of conversion (DC), elastic modulus (EM) and knoop hardness (KHN). UDMA added to TEGDMA resulted in an increase in DC, EM and KHN.

Table 1: Continued

Author/ year/country	Tooth type/group/ number	WSL creation (pH for hours)	Group(s)	Tools to measure the penetration depth (PD)	Mean of PD ± SD/ Penetration area (%)	Finding(s)
Permanent vs primary tooth						
Aswani *et al.* [26]/ India	Healthy anterior primary and permanent teeth/ 60	Demineralizing solution, pH=4.4, four days	▪ Primary teeth ▪ Permanent teeth	Stereomicroscope at 80 × magnification	Mean PD Primary teeth=32.6 ± 15.72 µm Permanent teeth=24.23 ± 6.85 µm	Resin infiltration penetrated deeper into enamel lesions in primary than permanent teeth.
Caries activity						
Neuhaus *et al.* [34]/ Switzerland	Premolars and molars (ICDAS code 2)/ 104	Without demineralization	▪ 15% HCL ▪ 35% H_3PO_4	CLSM	Median HCL Active lesions =549 µm Inactive lesions =340 µm Median H3PO4 Active lesions=475 µm Inactive lesions =296 µm	▪ In active lesions, no significant difference in the percentage of maximum PD and the percentage of average PD between lesions pretreated with HCL or H_3PO_4. ▪ In inactive lesions, H_3PO_4 pretreatment resulted in significantly lower PD compared to HCL pretreatment.

WSL = white spot lesion, RI = resin infiltration, TEGDMA = triethylene glycol dimethacrylate, UDMA = urethane dimethacrylate, HCL = hydrochloric acid, H_3PO_4 = phosphoric acid, CLSM = confocal laser scanning microscopy, PAM = phosphoric acid 2-hydroxyethyl methacrylate ester, CPP-ACP = casein phosphopeptide-amorphous calcium phosphate, NC = negative control, PC = positive control, PD = penetration depth, PC = penetration coefficient, TMR = transverse microradiography, MFIR = microfilled infiltrant resin, inf = infiltration, nB = none brush, OB = oscillating brush, FB = flat brush, MB = modified toothbrush, DC = degree of conversion, EM = elastic modulus, KHN = knoop hardness, SEM = surface electron microscopy

Table 2: Assessment of the risk of bias and quality for *in vitro* studies (checklist for reporting *in vitro* studies guidelines)

Author/year	Sample preparation and handling	Allocation sequence and randomization process	Blinding	Statistical analysis	Risk of bias
Askar *et al.* [8]	Yes	No	No	Yes	Moderate
Wang *et al.* [10]	Yes	No	No	Yes	Moderate
Lopez *et al.* [31]	Yes	No	No	Yes	Moderate
Abd Alhady A and Mohamed [17]	Yes	No	No	Yes	Moderate
Lausch *et al.* [27]	Yes	No	No	Yes	Moderate
Yim *et al.* [20]	Yes	No	No	Yes	Moderate
Paris *et al.* [21]	Yes	No	No	Yes	Moderate
Gelani *et al.* [35]	Yes	No	No	Yes	Moderate
Paris *et al.* [28]	Yes	No	No	Yes	Moderate
Meyer Lueckel *et al.* [29]	Yes	No	No	Yes	Moderate
Edunoori *et al.* [23]	Yes	No	No	Yes	Moderate
Mohamed *et al.* [18]	Yes	No	No	Yes	Moderate
Theodory *et al.* [36]	Yes	No	No	Yes	Moderate
Al Tuwirqi *et al.* [22]	Yes	No	No	Yes	Moderate
Arora *et al.* [24]	Yes	No	No	Yes	Moderate
Mandava *et al.* [25]	Yes	No	No	Yes	Moderate
Zamorano *et al.* [30]	Yes	No	No	Yes	Moderate
Rosianu *et al.* [33]	Yes	No	No	Yes	Moderate
Shimaa *et al.* [19]	Yes	No	No	Yes	Moderate
Ionta *et al.* [32]	Yes	No	No	Yes	Moderate
Araújo *et al.* [37]	Yes	No	No	Yes	Moderate
Aswani *et al.* [26]	Yes	No	No	Yes	Moderate
Neuhaus *et al.* [34]	Yes	No	No	Yes	Moderate

and destroys the microscopic bubbles formed within the resin.[31] Besides that, Yim *et al.* [20] and Lausch *et al.* [27] in their studies evaluated a modified brush and mechanical agitation versus sponge application with abrasive HCL gel slurry prior to resin infiltration placement. When compared to a sponge applicator, brushes are comprised of multiple filaments and have abrasive surfaces that exerted a greater friction force than the sponge applicator, enabling nearly complete resin infiltration.[20,27]

Studies suggested that the penetration depth of resin infiltration into the enamel lesion is time-dependent.[28,29] According to Paris *et al.* and Meyer Lueckel *et al.* , 1-min treatment times resulted in only superficial infiltration, whereas 3- and 5-min application intervals are required to completely obliterate the natural enamel lesion in both primary and permanent teeth.[28,29] Three and five minutes after resin infiltration application, Paris *et al.* found no significant difference in the penetration depth.[28] This is in contrast with Soveral *et al.* that showed that the longer the application duration, the deeper the average penetration.[7]

TEGDMA-based materials show desirable traits for an infiltrant material, including low viscosity, a high degree of conversion and penetration coefficient.[10,37] In contrast, HEMA and UDMA, the main core materials in adhesive, fissure sealant, and composite are polymers composed of multifunctional molecules with a complex structure and high molecular weight, leading to a lower power of penetration depth.[10,37] Thus, these materials are unable to penetrate to the full thickness of the lesion if compared to resin infiltration.[10,37]

The addition of ethanol into TEGDMA was reported to decrease viscosities, surface tensions, and contact angles of all mixtures leading to increased penetration coefficients for all monomer combinations.[21,37] This is supported by Paris *et al.* that revealed that 99% of TEDGMA resin has a penetration coefficient value of 204 cms^{-1}, whereas a mixture of TEDGMA and ethanol increases the penetration coefficient value to 391 cms^{-1} and therefore proved to be effective for greater resin perfusion.[21] Contrary to Aroujo *et al.* , the addition of ethanol to TEGDMA did not result in substantially deeper penetration and homogeneity of resin infiltration.[37] This may be due to the incomplete evaporation of ethanol caused by a higher ethanol concentration, which inhibits the polymerization of resin and thus reduces infiltration efficacy.[37] Thus, the author suggested that solvent-free compounds are typically more suitable for resin infiltration.[26]

Studies on the penetration depth of the resin infiltration showed that penetration was often variable, particularly in the case of natural human teeth and bovine teeth.[22,25,29,36] Three studies used bovine resulted in penetration depth ranging from 8.24 to 112.8 µm.[10,32,35] This was attributed to the variations in the arrangement of prisms, decussations and interprismatic regions between human and bovine teeth as well as differences in pore size, pore distribution and pore volume.[10,15,16,20,27,37] Furthermore, bovine teeth have a greater crystalline diameter and a more homogeneous calcium distribution that enhances resin perfusion,[10,32,35] similar to the findings of Soveral *et al.* [7]

Aswani *et al.* reported that the mean depth of resin penetration was more with enamel lesions of primary teeth (32.6 µm) compared to permanent teeth (24.23 µm).[26] The difference is attributed to structural differences such as less mineralization, more porous and the presence of aprismatic layer in the enamel of the primary teeth in which more diffusion of resin is anticipated in primary compared to permanent teeth.[26]

Neuhaus *et al.* revealed that active lesions may be particularly receptive for infiltration because the surface layer of these lesions is more porous, thinner and rougher than that of inactive lesions.[34] Additionally, active lesions were more frequently presented with pH ≤ 5.5 in the pores of their lesion bodies, which might favor more porous surface lesions if compared to inactive non-cavitated enamel lesions.[34] For a natural human tooth, porosity is dependent on the caries activity and the stage of demineralization.[34] Differing mineral distributions, as well as contamination with organic materials like proteins and carbohydrates within the lesion body of natural lesions, might be responsible for the reduced penetration speed.[35] The deeper areas of the lesion may not be penetrated well by the resin infiltration and appear to be inhomogeneous depending on irregularities of the porous volume of the body of the lesion.[28] This is because extensive lesions are associated with a higher polymerization shrinkage and the consequent appearance of porosities and cracks.[35] The unsatisfactory result is possibly due to air bubbles, firmly bound water and organic matter fill the nanochannels (outlined by hydroxyapatite walls) in dry demineralized lesions and the presence of residual biofilm.[20] Also, Gelani *et al.* reported that lesion contaminated with saliva prior to resin treatment was not homogeneously infiltrated and predisposed the tooth to further acid attack.[35] These inhomogeneities also developed as a consequence of oxygen inhibition or incomplete evaporation of the solvent.[35]

This study have compared the penetration of the resin infiltration with different dental materials such as fissure sealant,[22-24,32] adhesive,[18,19,30,32,36] CPP-ACP,[19] fluoride varnish[33] and flowable composite resin.[8,33] Based on this study, the penetration ability of resin infiltration is superior to the other materials.[18,23,30,32,36] Resin infiltration showed that the enamel pores were filled with resin and the surface showed a complete blockage of enamel rods with resin infiltration whereas other materials formed a shallower coating layer and a diffusion barrier just on the surface of the lesions.[18,23,30,32,36] Unlike dental sealants, which sit on the surface of the enamel, the resin infiltration can penetrate the enamel up to 177 µm which showed the highest depth of penetration followed by Embrace, Clinpro, Helioseal, Optiguard, and Permeseal.[22-24,32] This is due to the high viscosity of the HCL gel and the presence of air bubbles within the fissures prevented the HCL gel and infiltrant from reaching the lesion area, especially in the deep fissures, resulting in shallow penetration.[22-24,32] Apart from that, the effect of CPP-ACP localizes the amorphous calcium phosphate onto the tooth surface, which creates a hypersaturation state with respect to tooth mineral and the remineralization process requires several factors such as saliva composition and time of remineralization to give an effective depth of penetration in contrast to the method of resin infiltration.[19] Moreover, urethane dimethacrylate, the resin in ACP, has a higher molecular weight and a higher filler content than resin infiltration, which restricts penetration.[19] Five studies compared the penetration depth of adhesives such as Tetric N Flow, Adhesive SE, Single Bond, Optibond, Biscover, Parmaseal, Optiguard, Single universal, and Exite with the resin infiltration technique, and all concluded that the resin infiltration technique provided greater penetration depth.[18,19,30,32,36] This may be attributable to a layer of adhesive that is nonhomogeneous and partially polymerized due to its solvent (water).[18,19,30,32,36] Also, the adhesive has a greater viscosity than resin infiltration.[18,19,30,32,36]

The results of the included studies indicated that all materials including resin infiltration were not consistently and completely obliterate the demineralized enamel after application and there are heterogenous patterns of material perfusion.[18,19,30,32,36] Furthermore, the penetration of this material is restricted to the enamel structure and it performed poorly in the dentinal lesion, in accordance with Soveral *et al.*'s[7] study. It was hypothesized that the poor penetrability of the resin was due to the histological difference between enamel and dentinal caries lesions.[7,11] Upon demineralization, the dentinal tubules will enlarge, thereby facilitating the discharge of dentinal fluids into the lesion.[18,19,30,32,36] This subsequently prevents the resin from completely penetrating the dentinal lesion.[7] Also, this could be because the quantity and diameter of interprismatic enamel diminish as one descends apically in the dentin, limiting material penetration.[32,37] The unsatisfactory result is possibly due to air bubbles, firmly bound water and organic matter fill the nanochannels (outlined by hydroxyapatite walls) in dry demineralized lesions and the presence of residual biofilm.[32] In addition, the materials that contain ethanol such as resin infiltration and adhesive in their composition resulted in heterogeneous patterns as ethanol evaporates and inhibits the polymerization of resin and thus reduces penetration success.[37] As a result, repeated application (twice) of the resin infiltrant to overcome the problem of polymerization shrinkage and therefore deepen the penetration of the infiltrant.[7]

Variations in penetration depth may result from disparities in measuring instruments. CLSM is a valuable tool that has provided useful data on the extent of resin infiltration as well as some data on histological location.[22,25,32-34,37] The disadvantage of the CLSM method is that the morphology of the caries lesion cannot be investigated and the device is a destructive evaluation method that required tooth sectioned longitudinally into two halves, similar to the stereomicroscope device.[32,34,37] The other limitation of CLSM includes the staining of resins before penetration in enamel can lead to the misinterpretation of ima ges.[8,10,17,18,20-22,25,27-29,31-37] In comparison to SEM, CLSM has the advantage of providing accurate information to determine the adaptation and distribution of resin inside tooth porosity in non-dehydrated samples.[8,10,30,31]

The limitation of this study is that all of the included studies were *in vitro* studies that limits the ability to extrapolate their results to the oral environment. Investigating the function of saliva, curing shrinkage and expansion of resin by intraoral thermal cycling is therefore limited. In most of the studies, artificial demineralization was used to immerse samples in an attempt to replicate the complex dynamic nature of the oral environment, however, the acid demineralization protocol used diminishes its resemblance to the complex enamel-caries microstructure.[10,17,31] In one of the study, the artificial WSL was created using a variety of techniques such as different pH and the duration of the demineralization process resulting in heterogeneous enamel pore formation. For example, using a pH cycle, which is a dynamic process similar to what occurs in the oral cavity, enables an intensive ion exchange and, as a result, a higher demineralization rate compared to other methods.[10] Owing to their accessibility, demineralizing agents were used in the majority of the studies to induce artificial lesions.[10,22,23,31,35]

Conclusion

The key to optimal resin infiltration depends on the enamel surface treatment with HCL and application technique, infiltration duration, formulation of TEGDMA and ethanol in resin composition, as well as the type and caries activity of involved teeth. Resin infiltration has superior penetrability in comparison to fissure sealant, casein phosphopeptide-amorphous calcium phosphate nanocomplexes, flowable composite, adhesive and fluoride varnish. Resin penetration depth may be a critical factor in the formation of a diffusion barrier and the effectiveness of infiltration in halting the progression of caries.

Recommendation for the future research

Future studies shall look for a harmonization of the protocol of teeth selection and towards a consistent study methodology.

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Author contribution

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