

Review of methyl methacrylate (MMA)/tributylborane (TBB)-initiated resin adhesive to dentin

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This review, focusing mainly on research related to methyl methacrylate/tributylborane (MMA/TBB) resin, presents the early history of dentin bonding and MMA/TBB adhesive resin, followed by characteristics of resin bonding to dentin. Bond strengths of MMA/TBB adhesive resin to different adherends were discussed and compared with other bonding systems. Factors affecting bond strength (such as conditioners, primers, and medicaments used for dental treatment), bonding mechanism, and polymerization characteristics of MMA/TBB resin were also discussed. This review further reveals the unique adhesion features between MMA/TBB resin and dentin: in addition to monomer diffusion into the demineralized dentin surface, graft polymerization of MMA onto dentin collagen and interfacial initiation of polymerization at the resin-dentin interface provide the key bonding mechanisms.

Keywords: Dentin bonding, Polymerization, Tributylborane

EARLY HISTORY OF DENTIN BONDING AND EVOLUTION OF MMA/TBB ADHESIVE RESIN

Early history of dentin bonding

Attempts to develop an adhesive system which bonds acrylic resins to the tooth structure started in the early 1950s. In 1949, an adhesive system capable of bonding acrylic resin to the tooth structure was invented by Hagger; it was composed of glycerophosphoric acid dimethacrylate (GPDM) and sulfonic acid as the catalyst. In his patent, shear bond strengths of acrylic resin to porcelain, ivory, gold, steel, aluminum, and glass were presented, but not that of bonding to teeth. In the original first Swiss patent (No. 278946) Hagger applied for in July 21, 1949, titled “Method of Bonding Surface” (Verfahren zum Verkleben Flächen), no bonding to teeth was mentioned. In 1950, patent applications filed with other European countries, including the UK, Germany, and France, bonding to teeth was mentioned. In British patent specification No. 687299, titled “Unsaturated Esters”, applied for on July 17, 1950 and published on February 11, 1953, the following statement was included: This invention relates to unsaturated esters which are polymerizable liquid organic adhesives and particularly to such esters suitable for bonding a self-setting cast filling of synthetic resin to a tooth cavity. However, this statement was not found in the Swiss patent published on February 16, 1952. Therefore, to be exact, dental bonding technology began in 1950 when Hagger proposed using an acidic monomer to achieve bonding to teeth. The bonding agent thus developed was marketed as Sevriton Cavity Seal[®] (Amalgamated Dental Co.). It contained 10% GPDM and methacrylic acid, and 80% methyl methacrylate (MMA), and used in conjunction with a chemically cured resin, Sevriton[®] (Amalgamated Dental Co.), in restorative dentistry¹⁾.

In 1952, Buonocore *et al.*²⁾ used a qualitative screening test to evaluate the adhesive capability of many of the then-available dental acrylic resins to dentin. The results indicated that, with one exception, acrylic resins had very little or no adhesion to wet dentin surfaces. One material which produced better adhesion was Sevriton[®] filling resin. Based on these preliminary test results, Buonocore *et al.*²⁾ prepared an experimental adhesive mixture consisting of Sevriton Cavity Seal[®], MMA monomer and polymer, and Sevriton[®] catalyst and measured its adhesive strength to wet dentin surfaces. Initial bond strength and that after 3 months of water immersion were 28 kgf/cm² and 15 kgf/cm² respectively. A thin layer of adhesive material remained bonded to the dentin, and a marked alteration occurred in the staining reactions of the dentin layers adjacent to the adhesive.

At the same time in 1952, histological studies performed by Kramer and McLean³⁾ showed alterations in a narrow staining zone of about 3 μm thickness in the dentin layers adjacent to the adhesive. They thus proposed that the adhesive produced a molecular attachment between the resin and dentin. In 1958, a histological study of the bond area between an adhesive resin and dentin by Buonocore and Quigley⁴⁾ also revealed a zone of altered staining characteristics in the dentin, which was 3- to 10-μm wide. They suggested that bond formation was due to physical penetration of the adhesive material into dentin, a chemical interaction of adhesive constituents with dentin organic matter, or both.

The altered staining zone was an intermediate layer that was formed after a GPDM-containing adhesive of about pH 2.5 penetrated dentin. This zone could be referred to as a resin-dentin interdiffusion zone⁵⁾ formed by a “self-etching” bonding agent. Therefore,

it could be said that a self-etching bonding agent or primer and impregnation of resin into dentin were already recognized in the 1950s. Today, GPDM is one of the key self-etching adhesive monomers in commercial bonding systems. The works of Hagger and Buonocore may have ushered in a new era in tooth bonding, but their ideas lay dormant for a long period. If the clinical trial of the Sevricon® system were successful at that time, the results would have been different. However, clinical results of the resin were very poor. Pulp reaction to experimental fillings of the resin with or without the adhesive were similar, and the material caused an acute inflammatory reaction when placed in moderately deep unlined cavities⁶.

Resin bonding to enamel was demonstrated by Buonocore⁷ in 1955 and was achieved by acid etching of the enamel. While minor changes continue to be made, the enamel bonding technique has not changed significantly since then and its benefits have been well acknowledged by many dentists.

In contrast to enamel bonding, many generations of dentin bonding systems have been developed, with better products emerging in each new generation. However, the recent modifications of dentin bonding systems have not represented fundamental or essential improvements, but merely made the bonding process more convenient and less technique-sensitive. While appealing to clinicians, the performance of these more recent bonding systems seemed to be inferior when compared with that of earlier generations. Thus, bonding to dentin remains a challenge that requires improvement.

Many current dentin adhesive systems contain acidic adhesive monomers. The bonding mechanism is primarily provided by the formation of a hybrid layer, a transitional layer that is neither resin nor dentin but a hybrid of the two. In 1982, Nakabayashi *et al.*⁸ proposed that the hybrid layer was formed by penetration of monomer which contained both hydrophilic and hydrophobic groups into the etched dentin, followed by *in situ* polymerization which then resulted in resin impregnation. The hybrid layer was formed in intertubular and peritubular dentin, and regarded as a molecular-level mixture of collagen and resin polymers⁹.

Evolution of MMA/TBB adhesive resin and its subsequent development

The barrier to effective dentin bonding lies in the complex composition of dentin which consists of organic materials (mainly collagen) and water. This problem was overcome by a sophisticated bonding system developed by Masuhara *et al.*^{10,11} in 1963, in which bonding of MMA-based resin to wet dentin was achieved without the acidic adhesive monomers used in many commercial dental bonding systems. This resin has features completely different from the existing bonding systems. Using a tributylborane (TBB) initiator, the resin bonds to collagen through covalent bonds and forms a hybrid layer in the presence of water. Bonding of the resin can

also be explained through a mechanism involving graft polymerization of MMA onto collagen and interfacial initiation of polymerization at the wet dentin interface.

In 1982, although Nakabayashi *et al.*⁸ stressed the ability of 4-methacryloxyethyl trimellitate anhydride (4-META)¹² monomer to penetrate dentin and form a hybrid layer, the role of TBB was not emphasized. In 1964, Masuhara *et al.*¹³ observed that a thin layer of resin insoluble in xylene remained attached to the dentin surface, a phenomenon now referred to as the chemical bonding of resin to the organic components of dentin. However, the hybrid layer was defined as a form of mechanical adhesion in that resin polymers become entangled with collagen fibrils rather than by means of chemical bonding⁹.

A successful clinical trial of the MMA/TBB resin was reported in 1968. In unlined cavities of vital teeth filled with F1 material [MMA/TBB filling resin equivalent to Palakav® (Firma Kulzer)], pulpal inflammation and pulp damage were minimal after a follow-up period of 9–12 months^{14,15}.

MMA/TBB filling resin first appeared at an international dental show in 1968 as Palakav® and was placed on the market in Germany in 1971. However, it was withdrawn in 1974 because the physical properties of the MMA-based resin were inferior as a filling material when compared with bisphenol A-glycidyl methacrylate (Bis-GMA)-based composite resins available at that time. In Japan, MMA/TBB resin was first marketed as Orthomite® (Mochida Pharmaceutical Co. Ltd., Tokyo, Japan) in 1971 for direct bonding of brackets¹⁶ in orthodontics. In 1982, the resin was marketed under the name, Orthomite Super-Bond® (Sun Medical Co. Ltd., Moriyama, Japan), and then as Super-Bond C&B® (Sun Medical Co. Ltd., Moriyama, Japan) in 1983.

A self-curing adhesive resin (4-META/MMA-TBB resin¹⁷) consisting of 4-META, MMA, poly(methyl methacrylate) (PMMA), and TBB, commercially known as Super-Bond C&B®, Amalgambond® Plus (Parkell Inc., Edgewood, NY, USA), or C&B Metabond® Quick Cement System (Parkell Inc., Edgewood, NY, USA)¹⁸, has been widely used for bonding post cores, inlays, amalgams, crowns, or fixed partial dentures on abutment teeth. These products have had clinical success since 1982 and are popular and reliable bonding resins. This long history indicates the reliability of the MMA-TBB resin, in marked contrast to many other bonding systems that have undergone multiple revisions.

Past review articles have not mentioned the work done by Masuhara *et al.* in the area of dental bonding^{1,19,22}, with one exception²³. This was because the articles were published in Japanese and German during the 1960s. Moreover, MMA/TBB resin has been available in Japan almost exclusively since the introduction of the commercial product, resulting in scarce information about this product outside Japan. Masuhara's original work made a significant contribution to dentin bonding technology, which should be shared internationally. This report reviews the features of MMA/TBB resin

used for dental treatments, such as dentin bonding, bonding mechanism, and resin polymerization. The TBB catalyst used in Super-Bond C&B® is actually partially oxidized TBB (TBB-O) consisting mainly of butoxydibutylborane²⁴. For convenience and simplicity, the term “TBB” is used in this article but it includes TBB-O.

BONDING CHARACTERISTICS OF MMA/TBB ADHESIVE RESIN TO DENTIN

Bond strength between dentin and metal alloy or acrylic materials

Bond strength is one of the most useful and universal parameters in adhesive bonding evaluations. The 24-h bond strength values between 4-META/MMA-TBB resin and dentin conditioned with an aqueous solution containing 10% citric acid and 3% FeCl₃ (10-3) are listed in Table 1. Factors typically known to influence bond strength include adherend material, bonded area, and type of bond strength testing. Values of Groups 1–4 ranged between 12.2 and 18.1 MPa, suggesting the presence of other factors' influences other than those described above^{8,25-27}. When 10-3 conditioner was used in conjunction with 4-META/MMA-TBB resin (10-3/4-META/MMA-TBB system), bonding effectiveness might be hindered by technique sensitivity.

Comparison of adherend materials between Groups 1–4 and Group 5, and between Group 7 and Group 8, indicated that adhesive bonding of metal to dentin was weaker than that of acrylic material to dentin^{8,25-30}. Tensile testing using dumbbell-shaped specimens revealed that conditioning with 10-3 conditioner for 30 s resulted in significantly lower bond strength than conditioning for 10 s only^{31,32}. Bovine dentin (Group 1)

and human dentin (Group 7) exhibited similar bond strengths^{8,29}. Although the adherend materials were different, bond strengths evaluated with conventional tensile testing^{29,30} (Groups 7 and 8) were relatively low compared with data obtained with tensile testing using dumbbell-shaped specimens³² (Group 9), microtensile bond testing³³ (Group 10) according to a report³⁴, and shear bond testing³⁵ (Group 11). Therefore, bond strength values cannot be directly compared when experimental designs are different.

Comparison with other bonding systems

Comparisons between 10-3/4-META/MMA-TBB system (Super-Bond C&B) and seven other commercially available bonding systems are listed in Table 2. Super-Bond C&B and Multibond (Tokuyama Dental Corp., Tokyo, Japan) were unfilled luting agents, while the other luting agents were resin composite luting agents. Imperva Dual (Shofu Inc., Kyoto, Japan) and All-Bond 2 (Bisco Inc., Itasca, IL, USA) employed a two-step surface treatment which entails etching and priming, while Bistite II (Tokuyama Dental Corp. Tokyo, Japan), Panavia 21 (Kuraray Noritake Dental Inc., Tokyo, Japan), Panavia F2.0 (Kuraray Noritake Dental Inc., Tokyo, Japan), Linkmax (GC Corp., Tokyo, Japan), and Multibond were self-etching primer systems. Except for the adherend materials and dentin bonding systems, the same experimental methods (bovine dentin, ø5-mm bonding area, storage of bonded specimens in 37°C water for 24 h, and conventional tensile testing)^{26,28,29,36} were used for the comparisons.

The 10-3/4-META/MMA-TBB system exhibited relatively high bond strength, with acrylic material tending to have higher bond strength than metal alloys. Two explanations could be offered for these

Table 1 Bond strengths of 4-META/MMA-TBB resin to dentin conditioned with an aqueous solution containing 10% citric acid and 3% FeCl₃ (10-3)^{8,25-33,35}.

Group No.	Dentin	Adherend material	10-3 (s)	Bonded area (mm)	Type of bond testing	Mean±SD (MPa)	Ref.
1	Bovine	Acryl	30	ø5	Conventional tensile	18.1±3.2	8
2	Bovine	Acryl	30	ø5	Conventional tensile	17.8±3.8	27
3	Bovine	Acryl	30	ø5	Conventional tensile	15.9±3.5	26
4	Bovine	Acryl	30	ø5	Conventional tensile	12.2±1.6	25
5	Bovine	Metal alloy	30	ø5	Conventional tensile	10.4±2.2	28
6	Bovine	PMMA	30	3.0×2.0	Dumbbell tensile	16.2±5.4	31
7	Human	Acryl	30	ø5	Conventional tensile	17.9±4.1	29
8	Human	Metal alloy	10	ø5	Conventional tensile	10.5±1.7	30
9	Human	PMMA	10	7.0×2.0	Dumbbell tensile	23.9±5.5	32
10	Human	Resin composite	10	0.9×0.9	Microtensile	23.9±8.2	33
11	Human	Acryl	30	ø2	Shear	26.6±6.7	35

Table 2 Tensile bond strengths of commercially available bonding systems to dentin^{26,28,29,36}.

Dentin bonding systems	Adherend material	Bonded area (mm)	Type of bond testing	Mean±SD (MPa)	Ref.
10-3/4-META/MMA-TBB ^a	Acryl	ø5	Conventional tensile	15.9±3.5	26
Imperva Dual ^b	Acryl	ø5	Conventional tensile	8.9±2.5	26
Bistite II ^c	Acryl	ø5	Conventional tensile	4.5±1.5	26
Panavia 21 ^d	Acryl	ø5	Conventional tensile	5.4±1.7	26
All-Bond 2 ^e	Acryl	ø5	Conventional tensile	5.4±4.3	29
10-3/4-META/MMA-TBB ^a	Metal alloy	ø5	Conventional tensile	10.4±2.2	28
Panavia F2.0 ^f	Metal alloy	ø5	Conventional tensile	6.1±2.7	36
Linkmax ^g	Metal alloy	ø5	Conventional tensile	5.7±0.6	36
Multibond ^h	Metal alloy	ø5	Conventional tensile	5.6±1.2	36
All-Bond 2 ^e	Metal alloy	ø5	Conventional tensile	3.5±0.9	28

^a The specimens were conditioned with a solution containing 10% citric acid and 3% ferric chloride for 30 s, and then bonded with 4-META/MMA-TBB resin (Super-Bond C&B, Sun Medical Co. Ltd., Moriyama, Japan).

^b Shofu Inc., Kyoto, Japan

^c Tokuyama Dental Corp., Tokyo, Japan

^d Kuraray Noritake Dental Inc., Tokyo, Japan

^e Bisco Inc., Itasca, IL, U.S.A.

^f Kuraray Noritake Dental Inc., Tokyo, Japan

^g GC Corp., Tokyo, Japan

^h Tokuyama Dental Corp., Tokyo, Japan

results. First, the acrylic adherend material reduced stress concentration at the bonded interface during tensile testing but the metal alloy did not. Second, the metal alloy reduced reaction heat created by radical polymerization because of high thermal conductivity. In any case, clinicians should be aware of the characteristics of 10-3/4-META/MMA-TBB system when bonding metal restorations to dentin.

Effect of conditioners

1. Effects of various types of conditioners

The use of acids to demineralize and remove smear layers from the tooth surface also demineralizes the underlying intact dentin⁹. Buonocore *et al.*² reported that surface treatment of dentin with hydrochloric acid did not improve the adhesive bonding of a self-curing resin. Phosphoric acid etching was also examined using a scanning electron microscope^{37,38}. On using acidic solutions to remove dentin smear layers, Bowen³⁹ reported that mildly acidic isotonic solutions with pKa values between 3.8 and 2.5 resulted in substantial smear layer removal. When dentin was etched with citric acid (pKa₁=3.1, pKa₂=4.8, pKa₃=6.4) or phosphoric acid (pKa₁=2.1, pKa₂=7.2, pKa₃=12.7) alone, low bond strengths of 4-META/MMA-TBB resin were yielded; however, bond strength was significantly improved when ferric chloride was added to citric acid⁴⁰. The recommended dentin pretreatment before bonding with 4-META/MMA-TBB resin was 10-3 conditioner

containing 10% citric acid and 3% ferric chloride⁸).

Kojima *et al.*⁴¹ compared the effects of eight types of conditioners consisting of citric acid and a metal chloride—such as chromium, manganese, ferric, nickel, cupric, zinc, or tin—on bonding, and revealed that cupric chloride was as effective as ferric chloride. Akimoto *et al.*⁴² also reported that pretreatment with a solution containing citric acid and copper fluoride or ferric fluoride was as effective as those containing ferric chloride.

A solution of 3% cupric chloride and 10% phosphoric acid was reportedly optimal for simultaneous treatment of dentin and enamel⁴³. A dentin conditioner containing 3% ferric chloride, 5% citric acid, and 10% phosphoric acid was examined as an alternative to the 10-3 conditioner⁴⁴. An experimental dentin conditioner containing 10% ascorbic acid and 5% ferric chloride was also found to induce higher resin-dentin bond strength when compared with the 10-3 conditioner⁴⁵.

2. Role of ferric chloride in dentin conditioners

On the bonding efficacy of MMA/TBB resin to dentin, one explanation was that TBB initiated polymerization at the bonded interface in the presence of water¹³. The presence of water and oxygen in amounts less than 500 ppm in MMA promoted MMA polymerization²⁴. However, this mechanism does not always explain the high bond strength, which was significantly improved when dentin surface was treated with a conditioner

containing citric acid and ferric chloride rather than one containing citric acid alone⁴⁰.

A scanning electron microscopy study suggested that in the absence of ferric chloride, denaturation of dentin collagen occurred during acid etching⁴⁶. An atomic force microscopy study showed that ferric chloride prevented the collapse of demineralized matrix^{9,47}. The proposed mechanism was that ferric ions prevented the dissolution of dentin polyelectrolytes, suppressed the collapse of demineralized dentin matrix, and permitted the monomer mixture to diffuse into conditioned dentin⁴⁸⁻⁵⁰. However, this mechanism was refuted by Marshall *et al.*⁵¹ and Saeki *et al.*⁵². Based on atomic force microscopy studies, they reported that the 10-3 conditioner did not stabilize the collagen network against collapse upon drying^{51,52}.

Another explanation was that the polymerization of MMA/TBB resin became accelerated in areas with optimum concentration of ferric ions²⁵. A low concentration of ferric chloride or cupric chloride

accelerated TBB-initiated polymerization of MMA in the early stages⁵³. While MMA was being polymerized by TBB in the presence of collagen powder, a collagen sheet, or decalcified dentin sheet, polymerization would become accelerated if these components were treated with a ferric chloride/citric acid solution of a suitable concentration⁵⁴⁻⁵⁶. It was suggested that ferric ions functioned as a promoter or inhibitor of polymerization, depending on the concentration⁵⁵. Based on these results, it was hypothesized^{54,56} that ferric ions adsorbed on dentin collagen accelerated the polymerization of MMA in cooperation with TBB. Rapid polymerization at the resin-dentin interface was thus advantageous for improving bond strength.

When an adequate concentration of ferric chloride was applied to dentin treated with citric acid, phosphoric acid, or ethylenediaminetetraacetic acid (EDTA), bond strength was favorably increased as it did with 10-3 conditioner (Table 3)²⁵. Such effects of post-treatment with ferric chloride cannot be explained by the

Table 3 Effects of posttreatment with ferric chloride on tensile bond strength between acrylic rod and dentin bonded with 4-META/MMA-TBB resin²⁵.

Pretreatment ^a		Concentration of FeCl ₃ (%) ^b	Bond strength
Solution	Time (s)		Mean±SD (MPa) ^c
10% citric acid/3% FeCl ₃	30	(Washed)	12.2±1.6
10% citric acid/3% FeCl ₃	30	(Washed)	10.3±3.2 ^d
10% citric acid	60	1.0	2.1±0.4
10% citric acid	60	0.3	3.2±2.1
10% citric acid	60	0.1	9.5±1.2
10% citric acid	30	0.075	14.2±3.0
10% citric acid	60	0.075	10.0±2.5
10% citric acid	60	0.05	9.2±2.0
10% citric acid	60	0.025	8.2±1.5
10% citric acid	60	0.01	5.8±2.2
10% citric acid	30	0	2.2±0.6
10% citric acid	60	0	2.6±0.7
40% phosphoric acid	10	0.075	9.6±3.6
40% phosphoric acid	10	0	2.4±0.9
40% phosphoric acid	30	0.075	7.1±2.5
40% phosphoric acid	30	0	1.4±0.6
15%EDTA	60	0.075	10.3±4.6
15%EDTA	60	0	2.0±0.9

^aWashed and dried after pretreatment.

^bThe washed specimens were brushed with the aqueous solutions of FeCl₃ and dried after 30 s.

^cVertical lines join values that were not significantly different at the $p>0.01$ level.

^dMMA-TBB resin without 4-META

mechanism that ferric chloride suppressed denaturation of dentin collagen during the demineralization process with acid. While EDTA did not denature dentin collagen, no increase in bond strength occurred upon conditioning with EDTA alone in the absence of ferric chloride⁵⁷.

When dentin was pre-treated with 10-3 conditioner for only 1 s, the bond strength obtained (13.5±2.1 MPa) was comparable to that of 30-s pre-treatment (12.3±6.0 MPa)⁵⁸. Mizunuma⁵⁹ reported that while 10% citric acid denatured dentin collagen, denaturation was not observed in collagen treated with 10-3 conditioner for 30–360 s. With only the mechanism that ferric ions suppressed the collapse of demineralized dentin matrix or prevented dentin collagen denaturation, 1-s pre-treatment time might be too short for ferric ions in 10-3 conditioner to take effective action.

Effect of primers

1. Primers containing metal ions

In multistep bonding systems, an acidic conditioner is first applied to the dentin surface. After the surface is rinsed with water and gently blown with air, the primer is applied. Results showed that posttreatment with ferric chloride on acid-etched dentin improved adhesion as well as the 10-3 conditioner did²⁵.

When dentin was etched with phosphoric acid, primed, and bonded with MMA/TBB resin, primers containing cupric chloride, ferric chloride, ferrous chloride, or iron (II) perchloride produced superior bond strength when compared with primers containing aluminum, cerium, cobalt, nickel, magnesium, tin, or

zinc chloride (Table 4)⁶⁰⁻⁶².

Cupric chloride and ferric chloride at optimal concentrations accelerated the polymerization of MMA/TBB resin in the early stages⁵³. Bond strength produced with a dentin conditioner containing 10% phosphoric acid and cupric chloride was comparable to that produced with 10-3 conditioner, presumably by promoting interfacial initiation of polymerization⁶³. In addition, when a primer containing copper salts of sulfate, methacrylate, methacryloxyethyl phthalate, or methacryloxyethyl succinate was applied to dentin after phosphoric acid etching, bond strength was comparable to that obtained using 10-3 conditioner⁶⁴. This can be explained by the ability of cupric ions to crosslink collagenous or non-collagenous proteins, thereby stabilizing the structure of interfibrillar spaces that are necessary for monomer permeation during bonding⁹. An alternative explanation is that copper salts function as a crosslinking agent in conjunction with their role as polymerization promoter at the resin-dentin interface⁶⁴.

In self-etching bonding systems, the primer liquid is applied and then blown with air without etching. Studies of these systems revealed that addition of ferric chloride or iron (II) perchloride into a self-etching primer improved the bond strength between MMA/TBB resin and primed dentin^{36,65}. Self-etching systems have minimal risk of drying or causing the collapse of demineralized dentin. Therefore, explaining the role of ferric chloride and iron (II) perchloride solely by the mechanism of monomer diffusion into dentin substrates seems untenable.

Table 4 Effects of posttreatment with metal chlorides on tensile bond strength between metal rods and dentin bonded with 4-META/MMA-TBB resin^{60,61}.

Etching ^a	Metal chloride in primer ^b		Bond strength	
	Type	Concentration (mol g ⁻¹)	Mean±SD (MPa)	Ref.
10% phosphoric acid	No primer	—	2.9±2.4	61
10% phosphoric acid	Aq. HEMA	—	6.1±1.4	61
10% phosphoric acid	MgCl ₂	2.0×10 ⁻⁵	5.8±5.6	61
10% phosphoric acid	SnCl ₂	2.0×10 ⁻⁵	6.6±2.1	61
10% phosphoric acid	NiCl ₂	2.0×10 ⁻⁶	6.9±3.7	61
10% phosphoric acid	AlCl ₃	2.0×10 ⁻⁶	6.6±2.0	61
10% phosphoric acid	CeCl ₃	2.0×10 ⁻⁵	7.6±2.6	61
10% phosphoric acid	CoCl ₂	2.0×10 ⁻⁶	8.4±2.9	61
10% phosphoric acid	ZnCl ₂	2.0×10 ⁻⁵	9.0±2.1	61
10% phosphoric acid	FeCl ₃	2.0×10 ⁻⁵	15.6±2.3	61
10% phosphoric acid	CuCl ₂	2.0×10 ⁻⁶	19.0±7.2	61
10% phosphoric acid	FeCl ₂	5.0×10 ⁻⁵	22.6±2.5	60

^aWashed and dried after etching for 30 s.

^bAqueous primer contained 35% 2-hydroxyethyl methacrylate with and without a metal chloride.

2. Primers containing heme protein derivatives

Not only ferric chloride but also oxidoreductases with interchangeable Fe^{3+} and Fe^{2+} were effective in improving the bond strength to dentin. The cytochrome protein is a carrier in the mitochondrial electron transport chain, and it is composed of ferroprotoporphyrin (heme) and a specific protein. Cytochrome c is a heme derivative which has a peptide consisting of 104 amino acids⁶⁶, while microperoxidase (MP-11) has a peptide consisting of 11 amino acids, porphyrin, and iron⁶⁷. The structure is equivalent to the heme portion of cytochrome c. The use of a primer containing cytochrome c or MP-11 significantly improved the bond strength of MMA/TBB resin to dentin etched with phosphoric acid^{35,68-70}. Maximum bond strengths were obtained when dentin was primed with both HEMA and a heme protein derivative (Table 5).

Addition of cytochrome c or MP-11 to MMA/TBB resin significantly shortened the polymerization time^{69,70}. Although ferric chloride can act as a polymerization promoter or inhibitor, depending on its concentration⁵⁵, the heme protein derivative did not function as a polymerization inhibitor over a wide concentration

range^{69,70}.

2-hydroxyethyl methacrylate (HEMA) re-expands the collapsed collagen fibrils and facilitates monomer diffusion into the demineralized dentin surface⁷¹. Although further study is needed to confirm the bonding mechanism, it appeared that the strong bonding obtained with heme protein derivative-containing primer was due to HEMA-promoted diffusion of monomers into the demineralized dentin surface and accelerated polymerization at the resin-dentin interface brought about by the primer^{35,68-70}. Once initiation occurs at the resin-dentin interface, resin polymerization proceeds outward from the interface area. Interfacial initiation of polymerization not only contributes to reducing polymerization contraction stress, but also reinforces the resin-dentin interface area—including the resin-dentin interdiffusion zone, to improve bond strength.

Influence of medicaments used for dental treatment

1. Glutaraldehyde and root canal treatment agents

Glutaraldehyde application following EDTA or phosphoric acid treatment improved the bond strength

Table 5 Effects of heme protein derivative-containing primers on tensile bond strength between metal rods and bovine dentin bonded with 4-META/MMA-TBB resin^{69,70}.

Etching ^a	Components of aqueous primer			Bond strength	
	HEMA ^b (wt%)	Heme protein derivative	($\mu\text{mol g}^{-1}$)	Mean \pm SD (MPa)	Ref.
10% phosphoric acid	0	—	0	2.8 \pm 2.0	69
10% phosphoric acid	0	Cytochrome c	0.01	2.6 \pm 2.7	69
10% phosphoric acid	0	Cytochrome c	0.1	5.2 \pm 3.3	69
10% phosphoric acid	0	Cytochrome c	1	7.5 \pm 0.6	69
10% phosphoric acid	35	—	0	4.2 \pm 2.0	69
10% phosphoric acid	35	Cytochrome c	0.01	4.1 \pm 2.4	69
10% phosphoric acid	35	Cytochrome c	0.1	21.3 \pm 5.9	69
10% phosphoric acid	35	Cytochrome c	1	18.3 \pm 5.8	69
10% phosphoric acid	0	—	0	1.4 \pm 0.4	70
10% phosphoric acid	0	MP-11 ^c	0.01	16.3 \pm 7.1	70
10% phosphoric acid	0	MP-11	0.1	16.5 \pm 4.1	70
10% phosphoric acid	0	MP-11	1	19.7 \pm 7.2	70
10% phosphoric acid	35	—	0	5.3 \pm 0.8	70
10% phosphoric acid	35	MP-11	0.01	17.0 \pm 10.9	70
10% phosphoric acid	35	MP-11	0.1	22.7 \pm 6.7	70
10% phosphoric acid	35	MP-11	1.0	29.0 \pm 4.8	70

^aWashed and dried after etching for 30 s.

^bHEMA: 2-hydroxyethyl methacrylate.

^cMP-11: microperoxidase having 11 amino acids.

of MMA/TBB resin to dentin^{72,73}). It was suggested that glutaraldehyde crosslinked collagen and suppressed the denaturation of dentin collagen which typically accompanied acid etching⁷²). Another suggested mechanism was that glutaraldehyde promoted the graft polymerization of MMA onto dentin collagen⁷⁴). Although 10% or 25% glutaraldehyde reduced bond strength, 5% glutaraldehyde produced a positive effect for the 10-3/4-META/MMA-TBB bonding system^{27,72}). A desensitizer containing 5% glutaraldehyde and 36% HEMA was beneficial for the MMA-TBB bonding system^{29,75}).

Formaldehyde did not markedly improve dentin bond strength when compared with glutaraldehyde²⁷). As for cresol, eugenol, and phenol camphor, they negatively affected the bond strength of MMA-TBB bonding system to dentin, suggesting polymerization inhibition^{26,76,77}).

2. Sodium hypochlorite

Nikaido *et al.*⁷⁸) reported that sodium hypochlorite weakened the dentin bonding capability of 10-3/4-META/MMA-TBB system. This meant that the chemical reaction between sodium hypochlorite and ferric ion could have inhibited the ability of ferric ions to effect interfacial initiation of polymerization. Similarly, exposure of dentin to oxidants like hydrogen peroxide and carbamide peroxide before bonding decreased the bond strength of 10-3/4-META/MMA-TBB system⁷⁹). In other words, reductants could reverse the undesirable effect of oxidants, like hypochlorite, on dentin bonding. Reductants such as ascorbic acid and sodium thiosulfate were reportedly effective⁷⁹⁻⁸¹). In commercial 10-3/4-META/MMA-TBB sealer for root canal filling (Super-Bond Sealer Accel, Sun Medical Co. Ltd., Moriyama, Japan), aromatic sulfinic salt is used as a reductant. Experimental dentin conditioners which contained ascorbic acid demonstrated efficacy in counteracting the undesirable effect of sodium hypochlorite^{28,30}).

When immersed in water, bond strength of 10-3/4-META/MMA-TBB system to dentin was found to decrease over 2 years⁸²), 3 years⁸³), and 10 years⁸⁴). The hybrid layer degraded, but the overlying hydrophobic resin layer showed little disintegration over 10 years⁸⁴). Thus, durability of the resin requires improvement. In some experiments, surface treatments involving application of ferric chloride onto collagen-depleted dentin showed superior bonding durability compared to 10-3 conditioner⁸⁵⁻⁸⁷).

Bonding mechanism

1. Graft polymerization onto dentin collagen

In 1964, Masuhara *et al.*¹³) observed that a thin layer of resin insoluble in xylene remained attached to the dentin surface, suggesting chemical bonding between resin and the organic components of dentin. From this observation, they inferred that graft polymerization of MMA onto dentin might have taken place. This possibility was examined in a model system using ivory powder, and results showed that polymerization of MMA with TBB in water in the presence of ivory yielded graft polymer composed of ivory and PMMA. In

contrast, polymerization of MMA with a conventional initiator system of benzoyl peroxide (BPO)/dimethyl-*p*-toluidine produced little graft polymer under similar conditions⁸⁸).

Graft polymerization onto various substrates using a MMA/TBB system was studied using natural polypeptides such as collagen, gelatin, silk, wool, and synthetic polypeptides composed of alanine, glycine, leucine, and glutamic acid^{54,55,89-91}). Grafting of MMA occurred most favorably in the presence of water. The degree of grafting depended on the type of polypeptide used, and alanine-rich polypeptides such as collagen and polyalanine produced high grafting yield. In 1990, more sophisticated model experiments using decalcified dentin were reported⁵⁶). In that study⁵⁶), MMA was polymerized by TBB in the presence of bovine dentin slice decalcified with EDTA, freeze-dried, and treated with five types of solutions. The polymerized mass obtained was extracted thoroughly with a Soxhlet extractor to remove free PMMA uncombined with the dentin, giving the graft polymer of PMMA covalently bonded to dentin.

Percentage of grafting, defined as [mass increase before and after polymerization/mass of dentin before polymerization]×100%, varied with treatment solution. Percentages of grafting were 51%, 13%, and 47–101% for water, citric acid, and mixed solutions of citric acid and ferric chloride respectively, indicating that an adequate amount of ferric chloride increased grafting. Therefore, dentin pretreatment with acidic solution containing ferric salt would promote polymerization at the dentin interface as well as grafting onto dentin, both of which favor increasing bond strength at the dentin interface. PMMA grafting onto dentin collagen is illustrated in Fig. 1¹¹).

2. Interfacial initiation of polymerization at the dentin surface

Polymerization of MMA with TBB was accelerated by the cooperative effect of ferric ion and TBB. Rapid polymerization of resin at the resin-dentin interface area was suggested to contribute to adhesive bonding.

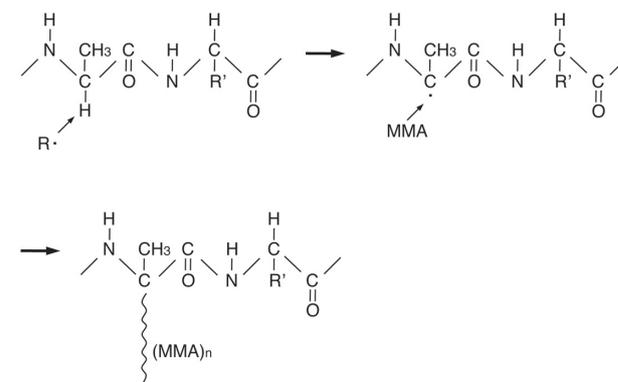


Fig. 1 Schematic illustration of the grafting of PMMA onto dentin collagen¹¹).

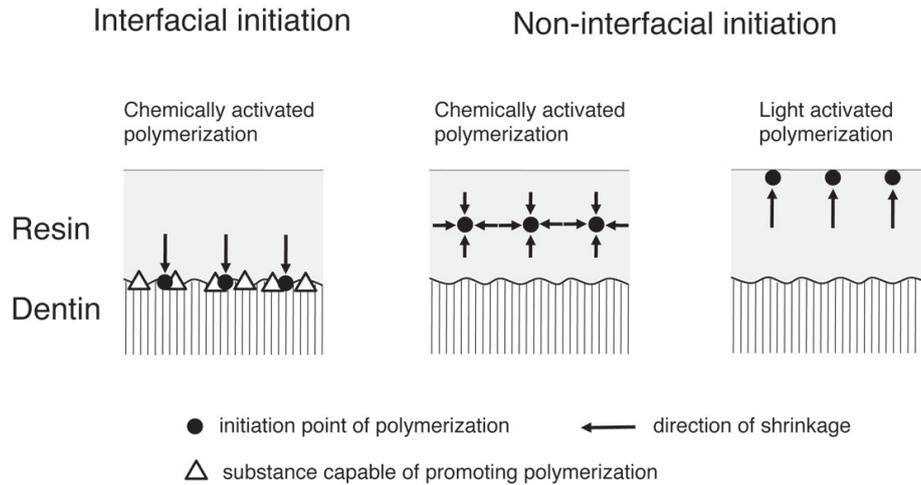


Fig. 2 Comparison of initiation points of polymerization and directions of shrinkage, which accompanies polymerization, in three polymerization systems. Schematic illustrations^{17,25)} were modified.

The advantages of rapid interfacial initiation of polymerization on adhesive bonding are illustrated in Fig. 2²⁵⁾ and explained as follows.

In conventional initiator systems for chemically activated polymerization, such as BPO/amine, polymerization shrinkage generally begins within the resin, and then progresses from the bonded interface to the center, leading to contraction gap formation. In contrast, initiation of polymerization at the resin-dentin interface directs polymerization shrinkage toward the bonded interface. In light-activated polymerization, light irradiating the resin surface initiates polymerization at the surface. Therefore, polymerization shrinkage is directed from the bonded interface to the external surface, leading to contraction gap formation too. Even when TBB was used, interfacial initiation of polymerization was difficult without ferric ions at the resin-dentin interface. The absence of ferric ions resulted in non-interfacial initiation and decreased bond strength. On the other hand, excess ferric ions negatively affected polymerization at the bonded interface and bond strength. It is therefore essential that an optimal amount of ferric ions is present. To control and ensure that an optimal concentration of ferric ions remains on the dentin surface, the ferric chloride conditioner must be properly rinsed off with water.

FT-Raman spectroscopy was used to verify the occurrence of accelerated polymerization at the resin-dentin interface⁹²⁾. Percentage of residual MMA in the resin sample was determined using Raman spectrum signals at 1,726 cm^{-1} and 1,640 cm^{-1} , which originated from the carbonyl group of methacrylate and the double bond of MMA respectively. Residual MMA on dentin after treatment with 10% citric acid and 3% ferric chloride was $3.5 \pm 0.8\%$, which was significantly less than that on dentin treated with 10% citric acid

alone ($5.5 \pm 0.9\%$). These results indicated that MMA polymerization was accelerated on the dentin surface treated with conditioner containing ferric chloride, and that the resin apart from the bonded interface polymerized relatively slowly. Results also suggested that ferric chloride adsorbed onto dentin promoted MMA polymerization in cooperation with TBB. When a BPO/amine initiator was used to polymerize resin on dentin treated with 10% phosphoric acid, residual MMA was $10.0 \pm 2.0\%$ and no polymerization acceleration occurred.

POLYMERIZATION CHARACTERISTICS OF MMA/TBB RESIN

Comparison of TBB with other polymerization initiators
MMA and PMMA powder was polymerized using a chemically activated initiator (benzoyl peroxide with N,N-dimethyl-*p*-toluidine, BPO/DMPT), light-activated initiator (camphorquinone with N,N-dimethylaminoethyl methacrylate, CQ/DMAEMA), or TBB. Amount of residual monomer and molecular weight (Mw) were determined for each polymerization system (Table 6)^{93,94)}. When TBB was used, the amount of residual monomer decreased significantly with time from 8.15% (30 min) to 0.48% (4 weeks). For BPO/DMPT, the residual monomer level decreased from 8.39% (30 min) to 3.54% (4 weeks), and the rate of decrease after 24 h was less than that before 24 h. In the CQ/DMAEMA system, decrease was minimal: from 9.19% (30 min) to 6.79% (4 weeks).

The Mw values of polymers polymerized by TBB tended to decrease with time. Those polymerized by BPO/DMPT showed some degree of variation, while those polymerized by CQ/DMAEMA showed minimal change. The features of TBB initiator system were quite different from those of BPO/DMPT and CQ/DMAEMA initiator systems, in that the amount of residual

Table 6 Effects of initiator type and polymerization time on residual monomer and molecular weight (Mw) of polymerized PMMA/MMA resin^{93,94}.

Initiator	Polymerization time			
	30 min	24 h	1 week	4 week
Residual MMA monomer (%)				
8% TBB	8.15	1.96	0.84	0.48
BPO/DMPT ^a	8.39	4.50	3.67	3.54
CQ/DMAEMA ^c	9.19	7.99	7.28	6.79
Molecular weight (Mw) ($\times 10^3$)				
8% TBB	351	351	306	247
BPO/DMPT	297	235	255	282
CQ/DMAEMA	267	233	224	231

^a1% benzoyl peroxide (BPO) in PMMA powder/1% N,N-dimethyl-*p*-toluidine (DMPT) in MMA

^b0.5% camphorquinone (CQ) and 0.5% N,N-dimethylaminoethyl methacrylate (DMAEMA) in MMA

Molecular weight of PMMA powder used: 239×10^3

Powder/liquid ratio=2:1 in mass

monomer and Mw decreased during post-polymerization in the long term.

Combinations of TBB and other polymerization initiators

Amount of residual monomer and Mw of resins polymerized by combinations of TBB, BPO/DMPT, and CQ/DMAEMA were monitored over time (Table 7)⁹⁵. No marked differences in residual monomer amount were found among the three combinations at 30 min. At 24 h and beyond, the two initiator systems combined with TBB showed less residual monomer compared to CQ/DMAEMA+BPO/DMPT. For the combinations of CQ/DMAEMA and TBB or BPO/DMPT, residual monomer amount significantly decreased up to 24 h. For BPO/DMPT+TBB, residual monomer amount decreased significantly for up to 1 week. An additive effect was observed between TBB and CQ/DMAEMA as well as between TBB and BPO/DMPT, but not between CQ/DMAEMA and BPO/DMPT.

The BPO/DMPT+TBB system produced polymers of larger Mw values compared to those produced by CQ/DMAEMA+TBB and CQ/DMAEMA+BPO/DMPT. Comparison of Mw at 30 min and 4 weeks indicated that the three systems using TBB (TBB with CQ/DMAEMA or BPO/DMPT and TBB alone) experienced substantial decreases in residual monomer amount and Mw. In contrast, CQ/DMAEMA+BPO/DMPT and CQ/DMAEMA alone experienced no significant differences during the same period. The additive effect of TBB was also reported in a chemically activated barbituric acid initiator system⁹².

Mechanism of polymerization

Polymerization initiated by basic reactions between trialkylboranes (*i.e.*, trimethylborane⁹⁶, triethylborane⁹⁷,

and tributylborane¹³⁹) and oxygen have been reported. With triethylborane, an ethoxy radical is initially produced and an ethyl radical is subsequently formed through the reaction of ethoxy radical with triethylborane⁹⁸. The initiation mechanism of triethylborane suggests that for TBB, a butoxy radical is initially produced and a butyl radical is subsequently formed through the reaction of butoxy radical with TBB. Polymerization of MMA/TBB resin proceeded for a long period and was accompanied by Mw decrease, suggesting that the polymer radical existed for a long period of time^{93,94,99}.

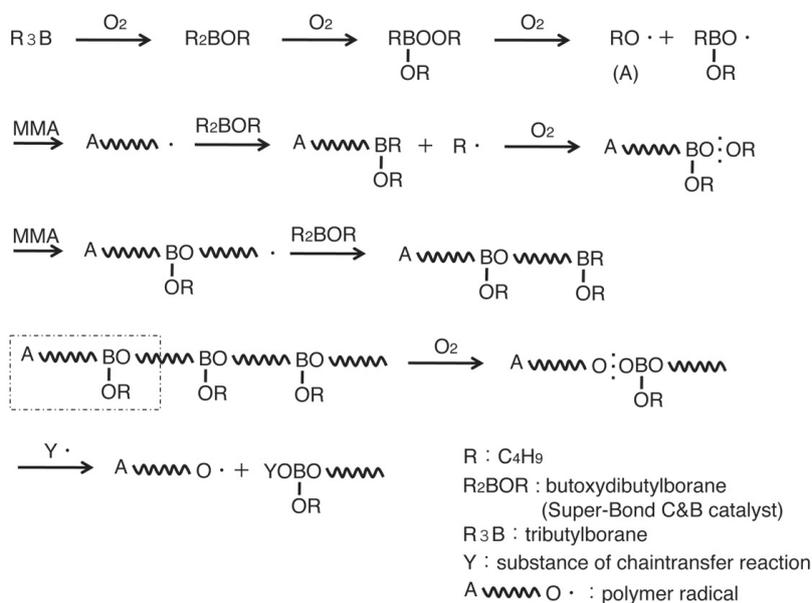
Post-polymerization decrease in Mw can be explained using this mechanism of polymerization (Fig. 3)⁹⁰. Initially, a high-Mw polymer was formed, composed of TBB and PMMA blocks. TBB connecting the PMMA blocks was oxidized by oxygen, generating polymer peroxides. Although these peroxides were usually stable, chain transfer reactions with the polymer radicals could easily occur. When polymer peroxide was cut by a chain transfer reaction, Mw decreased. During these processes, oxygen was gradually consumed, allowing the polymer radicals to remain active for a long period of time.

CONCLUSIONS

1. An adhesive resin, MMA/TBB, effective with wet dentin surfaces, was developed during the 1960s and has been used with clinical success. It has become one of the most reliable dentin bonding systems.
2. Use of dentin conditioner containing 10% citric acid and 3% ferric chloride (10-3) as well as primers containing metal ions such as ferric, ferrous, and cupric, or heme protein derivatives

Table 7 Effects of combined initiators and polymerization time on residual monomer and molecular weight (Mw) of polymerized PMMA/MMA resin^{94,95}.

Initiator	Polymerization time			
	30 min	24 h	1 week	4 week
Residual MMA monomer (%)				
3% TBB	12.86	6.97	5.50	4.83
BPO/DMPT ^a	8.39	4.50	3.67	3.54
CQ/DMAEMA ^c	9.19	7.99	7.28	6.79
BPO/DMPT+TBB ^b	6.40	2.35	1.44	0.83
CQ/DMAEMA+TBB ^d	6.97	3.37	2.53	1.97
CQ/DMAEMA+BPO/DMPT ^e	7.33	6.25	5.46	5.31
Molecular weight (Mw) (×10 ³)				
3% TBB	414	382	345	342
BPO/DMPT	297	235	255	282
CQ/DMAEMA	267	233	224	231
BPO/DMPT+TBB	304	290	263	230
CQ/DMAEMA+TBB	227	234	210	187
CQ/DMAEMA+BPO/DMPT	217	209	206	203

^a1% benzoyl peroxide (BPO) in PMMA powder/1% N,N-dimethyl-*p*-toluidine (DMPT) in MMA^bBPO/DMPT+3% TBB^c0.5% camphorquinone (CQ) and 0.5% N,N-dimethylaminoethyl methacrylate (DMAEMA) in MMA^dCQ/DMAEMA+3% TBB^eCQ/DMAEMA+BPO/DMPTFig. 3 Mechanism of polymerization of MMA/TBB resin⁹⁴.

(cytochrome c and MP-11) improved the bond strength of MMA/TBB resin to dentin.

3. Main mechanisms proposed to explain the role of 10-3 conditioner in 4-META/MMA-TBB resin were: (1) diffusion of monomers into the demineralized dentin surface, (2) graft polymerization of PMMA onto dentin collagen, and (3) rapid initiation of polymerization at the resin-dentin interface.
4. Glutaraldehyde had both positive and negative effects on bond strength depending on its concentration, while sodium hypochlorite, hydrogen peroxide, cresol, eugenol, and phenol camphor reduced the bond strength. However, application of a reducing agent, such as ascorbic acid to sodium hypochlorite-treated dentin, could restore the bond strength.
5. TBB differed from other polymerization initiator systems, such as BPO/DMPT and CQ/DMAEMA, in post-polymerization behavior. Use of TBB led to a lower amount of residual monomer and a gradual decrease in polymerized MMA resin over the long term.
6. Polymerization of resin is never a necessary and sufficient condition for adhesive bonding. Different mechanisms, such as diffusion of monomers into dentin, graft polymerization of resin onto dentin collagen, and interfacial initiation of polymerization, have been suggested to have a cooperative effect in producing reliable bonding of MMA/TBB resin to dentin.

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