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Review

A review of our development of dental adhesives — Effects of radical polymerization initiators and adhesive monomers on adhesion

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This paper reviews the development of dental adhesives by collating information of related studies from original scientific papers, reviews, and patent literatures. Through our development, novel radical polymerization initiators, adhesive monomers, and microcapsules were synthesized, and their effects on adhesion were investigated. It was found that 5-monosubstituted barbituric acid (5-MSBA)-containing ternary initiators in conjunction with adhesive monomers contributed to effective adhesion with good polymerization reactivity. Several kinds of novel adhesive monomers bearing carboxyl group, phosphonic acid group or sulfur-containing group were synthesized, and investigated their multi-purpose bonding functions. It was suggested that the flexible methylene chain in the structure of adhesive monomers played a pivotal role in their enhanced bonding durability. It was found that the combination of acidic monomers with sulfur-containing monomer markedly improved adhesion to enamel, dentin, porcelain, alumina, zirconia, non-precious metals and precious metals. A new poly(methyl methacrylate) (PMMA)-type adhesive resin comprising microencapsulated polymerization initiators was also found to exhibit both good formulation stability and excellent adhesive property.

Keywords: Dental adhesive resin, Radical polymerization initiator, Adhesive monomer

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INTRODUCTION

The field of adhesive dentistry has made a remarkable progress over the past decade. A large part of this success is attributed to the major advances in a bonding technology[1]. It can be manifested that the two creative works have opened new vistas in this field. In 1955, Dr. Michael Buonocore[2] first demonstrated the bonding of acrylic resin to etched enamel, and so-called acid-etching technique is ubiquitous in today's dental clinics. In 1963, Dr. Eiichi Masuhara[3] first developed a revolutionary dental adhesive using tri-*n*-butyl borane (TBB) as an initiator. Both creative works[2,3] triggered the extensive research on the bonding to dental hard tissues.

In the development of dental adhesives, the perennial ultimate goal is to achieve strong, durable adhesion to dental hard tissues, and dental alloys and ceramics. In the search of an advanced bonding technology to fulfill this goal, our research strategy has focused on the dual effects of radical polymerization initiators and adhesive monomers on adhesion.

A fundamental problem with dental acrylic resins on adhesion is attributable to volume shrinkage arisen from an internal stress developed during polymerization. Masuhara *et al*.[3] were the first to suggest that a polymerization initiator which circumvents polymerization shrinkage holds the key to the adhesion problem of dental resins on dental hard tissues. Most notably, Masuhara highlighted that TBB initiator or tri-*n*-butylborane oxide (TBBO) initiator reacted violently with water, and that hydrophobic methyl methacrylate (MMA) resin initiated by TBB could withstand the higher polymerization shrinkage attacking the bonding interface and remain bonded to moist ground ivory[3,4]. Indeed, the findings from Masuhara's work[3] brought cheer to many researchers that TBB or TBBO enabled strong adhesion without the use of non-polymerization shrinkage monomers.

Apart from TBBO initiator system, in redox polymerization initiator of benzoyl peroxide (BPO) with aromatic tertiary amines, the amines (electron acceptor) react with acidic adhesive monomers (electron donor) to form a yellowish charge transfer complex (CT complex)[5-7], ultimately resulting in degraded polymerization and insufficient adhesion. To circumvent the compromised adhesion caused by the formation of CT complexes, we have thus invented three kinds of radical polymerization initiators[8-10], as well as investigated the effects on adhesion and polymerization reactivity of an adhesive resin which used a ternary initiator system comprising 5-monosubstituted barbituric acid (5-MSBA)[7].

Nakabayashi[11] was the first to report that a radical polymerizable monomer bearing both hydrophobic and hydrophilic moieties intramolecularly (*i.e.*, adhesive monomer) could exhibit effective adhesion to dentin. Owing to their ability to interact chemically with dental hard tissues[12-14] and hence yield superior bonding effectiveness, adhesive monomers have unquestionably become a prime focus in the design and development of dental adhesives. Therefore, numerous studies have synthesized originally designed adhesive monomers, and evaluated their bonding abilities.

On the molecular structure of adhesive monomers, it typically contains carboxylic acid group (-COOH) or its anhydride group, phosphoric acid group [-O-P(=O)$(OH)_2$], or phosphonic acid group [-P(=O)$(OH)_2$].

As for sulfur-containing adhesive monomers, they were developed for the purpose of adhesion to precious metals and their alloys. For multi-purpose adhesion to a multitude of dental substrates (namely, dental hard tissues, dental alloys and porcelains), we developed several kinds of novel adhesive monomers having carboxylic acid group[15-17], phosphonic acid group[18,19] or sulfur-containing group[20] through our research studies.

The behavior of microencapsulated polymerization initiators in dental adhesives is unknown. Our recent study[21] thus investigated the effects of newly synthesized microencapsulated polymerization initiators on the bonding performance and formulation stability of a novel, multi-purpose, poly(methyl methacrylate) (PMMA)-type adhesive resin, together with multi-purpose primers.

Although a number of dental adhesives are already commercially utilized, little review on their development has been reported. The aim of this review paper, therefore, was to discuss our studies on the development of dental adhesives in the following aspects: (1) Effect of radical polymerization initiators on adhesion; (2) Effect of 5-MSBA-containing radical polymerizable initiators on adhesion; (3) Synthesis of adhesive monomers and their effects on adhesion; (4) New PMMA-type adhesive resin comprising microencapsulated initiators for multi-purpose bonding, together with related studies in this field by collating information from original scientific papers, reviews, and patent literatures.

EFFECT OF RADICAL POLYMERIZATION INITIATORS ON ADHESION

Fundamental problem: Polymerization shrinkage of dental resin monomers

Serious consequences encountered in postoperative restorations, that is, pulpal irritation and secondary caries, are believed to be caused by the invasion (microleakage) of bacteria into interfacial gaps formed along the margins of restorations, according to an *in vivo* histological study by Brännström and Nyborg[22].

With dental acrylic resins, their fundamental adhesion problem lies with volume shrinkage, a consequence that arises from internal stress developed during polymerization. Polymerization shrinkage of resin-based restorations is one of the main causes of postoperative sensitivity, and that it is associated with marginal gap formation and crack initiation in teeth with restoration, thereby leading to microleakage and potential restoration failure[23,24].

Based on the general principle of adhesion that is "good wettability and good hardening", our research strategy has focused on the dual effects of radical polymerization initiators (to make good hardening) and adhesive monomers (to form good wettability) on adhesion.

Water-reactive TBB initiator enables MMA resin to bond to moist adherend

The first success on development of TBB-initiated dental adhesive was achieved by Masuhara *et al.*[3] in 1963. He remarked keenly a polymerization initiator TBB which reacted violently with water, and found that hydrophobic MMA resin initiated by TBB could adhere to moist ground ivory[3,4]. TBB-initiated MMA resin was designed to facilitate chemical adhesion to collagen[25], thereby enabling it to bond to moist dentin despite the polymerization shrinkage attacking the bonding interface. It is noteworthy that although MMA monomer has 21 vol% polymerization shrinkage[26], the water-reactive TBB initiator enabled hydrophobic MMA resin to bond strongly to the moist dentin without the use of non-polymerization shrinkage monomers.

Nakabayashi *et al.*[27] reported that an addition of 4-methacryloyloxyethyltrimellitic anhydride (4-META) to MMA/TBBO resin (*i.e.*, 4-META-MMA/TBBO resin) resulted in strong adhesion to dentin when the latter was pretreated with 10-3 solution (10% citric acid + 3% ferric chloride). It was suggested that the effective bonding performance of 4-META-MMA/TBBO resin to etched dentin was due to a twofold reason: TBBO initiation at the resin-moist dentin interface, as well as interaction of 4-META with the dentin substrate without any adverse interference from the TBBO initiator.

To date, the combination of TBBO with 4-META in MMA resin is already well investigated to the effect that 4-META-MMA/TBBO resin has been commercially marketed as a revolutionary dental adhesive resin, Super-Bond C&B (Sun Medical Co. Ltd., Shiga, Japan), in Japan.

Indeed, with regard to adhesion to moist dentin, water-reactive TBB and TBBO have achieved unequivocal success in delivering outstanding bonding performance. Nonetheless, it must be pointed out that the TBB initiator system has an inherently inflammable

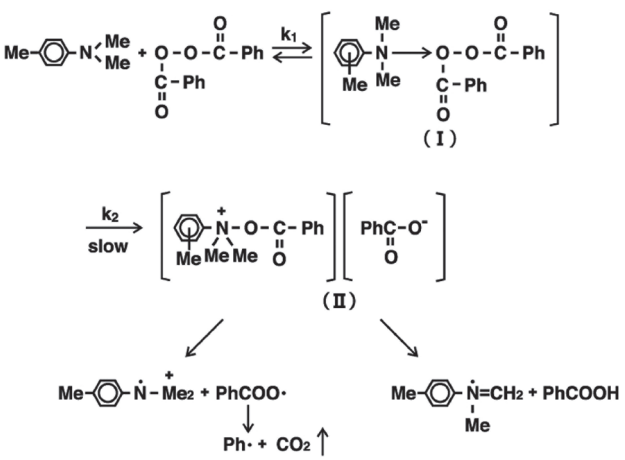


Fig. 1 Mechanism of redox polymerization initiated by the reaction of BPO with aromatic tertiary amine[28].

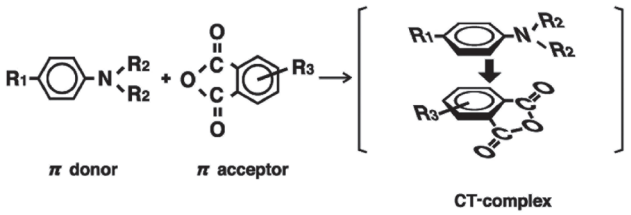


Fig. 2 Formation of charge transfer complex (CT complex) between aromatic acid anhydride and aromatic tertiary amine[7].

nature and its application has been limited to exclusive use with MMA since it was developed. However, the silver lining to this limitation is that it has since spurred many researchers to seek and explore for more stable polymerization initiators with active initiation like TBBO.

BPO-aromatic tertiary amine redox initiators and their problems

With chemically cured and dual-cured resin composites and adhesive resins, the polymerization initiator commonly employed is the redox initiator system of BPO with aromatic tertiary amines, such as *N*,*N*-dihydroxyethyl-*p*-toluidine (DEPT). Figure 1 shows the mechanism of redox polymerization initiated by the reaction of BPO with an aromatic tertiary amine[28]. It is known that a reaction product (I) soon comes to equilibrium, and (I) decomposes slowly to form a tetraammonium salt (II) — a step known as the rate-determining step, and free radical species are generated (Fig. 1)[28].

However, BPO-amine redox initiator system has some inherent disadvantages. First, the hardened material has an unacceptable color change attributable to the reaction products of BPO with tertiary amines because of exposure to ultraviolet light or heat. Besides, there is the concern about reduced mechanical strength[28]. Aromatic tertiary amines (electron acceptors) react with an acidic group (electron donor) of adhesive monomers to form a yellowish charge transfer complex (CT complex)[5-7] (Fig. 2), which then interferes with polymerization and adhesion, thereby compromising the mechanical properties of the adhesive resin.

Effects of BPO-DEPT-p-TSNa type initiator on adhesion and curing time

Although acidic adhesive monomers are potentially capable of interacting chemically with the dentin substrate[12-14], their bonding effectiveness is considerably compromised by the formation of CT complexes[5-7] when BPO-aromatic tertiary amine initiators are used. Regarding this problem, Yamauchi[29] proposed using BPO-aromatic tertiary amine-*p*-toluenesulfinic acid sodium salt (*p*-TSNa) with a phosphate monomer [*i.e.*, 2-methacryloyloxyethyl phenyl hydrogen phosphate (phenyl-P)] to provide good adhesion to dentin.

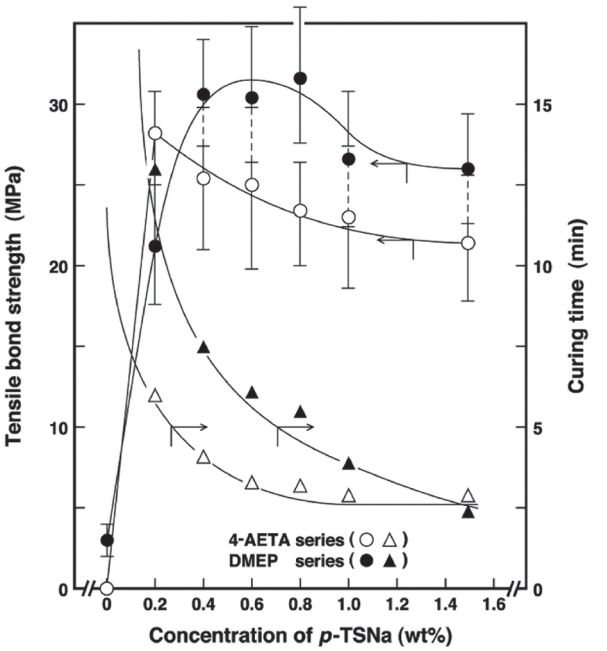


Fig. 3 Effects of *p*-toluenesulfinate sodium salt (*p*-TSNa) concentration in BPO-DEPT-*p*-TSNa type polymerization initiator system on adhesion to Ni-Cr alloy and curing time[7]. 4-AETA: 4-acryloyloxyethyl trimellitate anhydride; DMEP: dimethacryloyloxyethyl hydrogen phosphate.

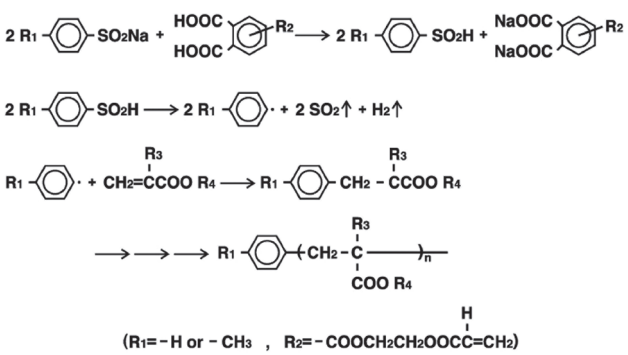


Fig. 4 Mechanism of radical polymerization initiated by the reaction of aromatic sulfinic acid sodium salt with aromatic carboxylic acid[7].

Our previous study[7] investigated the effects of *p*-TSNa concentration in ternary BPO-DEPT-*p*-TSNa type initiator on adhesion to Ni-Cr alloy when used with 4-acryloyloxyethyl trimellitic acid (4-AET) and dimethacryloyloxyethyl hydrogen phosphate (DMEP). Results of tensile bond strength and curing time in Fig. 3 affirmatively endorsed the report by Yamauchi[29], in that the addition of *p*-TSNa to BPO-DEPT-*p*-TSNa initiator system resulted in significantly higher bond strength with higher polymerization reactivity (shortened curing time) than that of BPO-DEPT

initiator system (0 wt% *p*-TSNa) ($p<0.01$)[7].

Figure 4 shows the mechanism of polymerization initiated by the reaction of aromatic sulfinic acid sodium salts with aromatic carboxylic acids[7]. The sodium salt rapidly reacts with the acidic group to form a sodium salt of the acidic monomer before CT complex is formed, hence producing a phenyl radical which initiates a radical polymerization (Fig. 4)[7]. Therefore, the adverse effect of BPO-DEPT redox polymerization derived from the formation of CT-complex[5-7] is averted by the action of *p*-TSNa as a co-initiator in ternary BPO-DEPT-*p*-TSNa-type initiator system[7,29].

C-H active initiation of 5-MSBA and thiobarbituric acids (TBAD) as amine-free initiators

To circumvent the adverse effects of BPO-tertiary amine initiator on color and reactivity, Bredereck *et al.*[30] proposed using amine-free initiators to obtain polymers with good color stability and good mechanical strength, by means of 5-monosubstituted barbituric acid (5-MSBA) with chlorine ion (Cl^-) and cupric cation (Cu^{2+}).

Figure 5 shows the mechanism of the radical polymerization of 5-MSBA with Cl^- and Cu^{2+} being triggered by C-H active initiator. Thus, C-H active initiation can be triggered by auto-oxidation of C-H at the 5-position of barbituric acid ring to form a peroxide of -C-O-O-H in the presence of a base[7,30].

In seeking an initiator system that can perform like TBB or TBBO, Kadoma and Imai[31] proposed using thiobarbituric acid derivative (TBAD)/copper acetylacetonate (CuAcAc) as a cold polymerization initiator and TBAD/camphorquinone (CQ), methyl-substituted TBAD/CQ and 5-(4-vinyl-benzyl)-2-thiobarbituric acid (VTBA)/CQ as a visible-light curing initiator. Further, the effect of barbituric acid derivative/cupric chloride ($CuCl_2$) as initiator system on adhesion to dentin was investigated[32-35]. On bonding to dentin, the bond strength obtained with the barbituric acid/$CuCl_2$ initiator system under optimal conditions (approximately 11 MPa) was comparable to that of TBB-initiated MMA resin (reportedly 9.3–11.0 MPa)[34,35]. A new cold polymerization initiator system of barbituric acid derivatives/CuAcAc/organic peroxides/*N*-pyrrolidine acetamide or 1-isobutyl-2-methyl-imidazol was more recently invented[36].

EFFECT OF 5-MSBA-CONTAINING RADICAL POLYMERIZATION INITIATORS ON ADHESION

Invention of three kinds of radical polymerization initiator systems

In the course of our development of dental adhesives, three kinds of radical polymerization initiator systems comprising 5-monosubstituted barbituric acid (5-MSBA), aromatic sulfinate amide (ASA), and *tert*-butyl peroxymaleic acid (*t*-BPMA) were invented[8-10].

The effects of adhesive resins comprising these novel radical polymerization initiator systems on adhesion and curing were investigated. Three kinds of

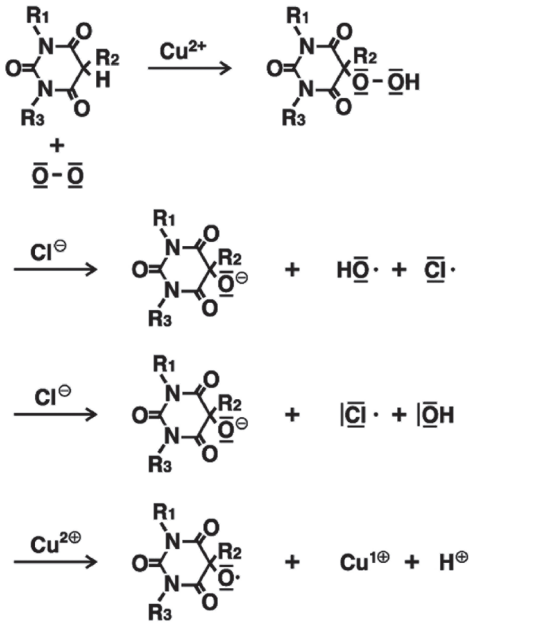
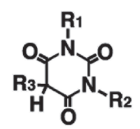


Fig. 5 Mechanism of the radical polymerization of 5-monosubstituted barbituric acid (5-MSBA) with chlorine ion (Cl^-) and cupric cation (Cu^{2+}) triggered by C-H active initiator[7].



General formula of 5-MSBA

Abbr.	R_1	R_2	R_3	mp (℃)
BBA	-H	-H	$-(CH_2)_3CH_3$	200-210
CEBA		-H	$-CH_2CH_3$	115.0-117.5
BPBA	$-CH_2$ 	-H		156.5-159.0

Fig. 6 Structural formulas of 5-monosubstituted barbituric acids (5-MSBA) synthesized[7], where BBA: 5-butylbarbituric acid, CEBA: 1-cyclohexyl-5-ethylbarbituric acid, BPBA: 1-benzyl-5-phenylbarbituric acid.

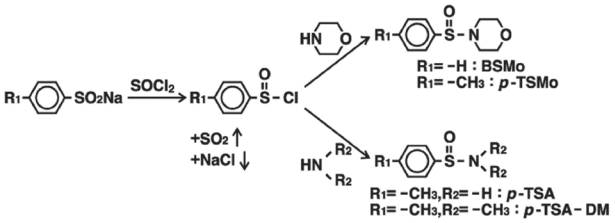


Fig. 7 Schema of the syntheses of aromatic sulfinate amides (ASA)[7], where BSMo: benzenesulfinate morphoride, *p*-TSMo: *p*-toluenesulfinate morphoride, *p*-TSA: *p*-toluenesulfinate amide, *p*-TSA-DM: *N*,*N*-dimethyl-*p*-toluenesulfinate amide.

5-MSBA initiators [namely, 5-butylbarbituric acid (BBA), 1-cycrohexyl-5-ethylbarbituric acid (CEBA), and 1-benzyl-5-phenylbarbituric acid (BPBA)] (Fig. 6) and four kinds of ASA initiators [namely, *p*-toluenesulfinate morphoride (*p*-TSMo), benzenesulfinate morphoride (BSMo), *p*-toluenesulfinate amide (*p*-TSA), and *N*,*N*-dimethyl-*p*-toluenesulfinate amide (*p*-TSA-DM)] (Fig. 7) were synthesized[7]. For the adhesive resins, experimental, chemically cured composite-type or PMMA/MMA-type adhesive resins consisting of powder and liquid components were prepared. These experimental adhesive resins were then used in conjunction with 5-MSBA-containing polymerization initiators, 4-AET and 4-acryloyloxyethyl trimellitic anhydride (4-AETA), dimethacryloyloxyethyl isophorone diurethane (IPDI-HEMA), urethane trimethacrylate (IPDI-HEMA-GDMA), and silanized silica fillers, and their bonding abilities were evaluated[7].

Effects of 5-MSBA-ASA-t-BPMA-type initiator systems on adhesion and curing time

Figure 8 shows the effects of ASA (*i.e.*, BSMo, *p*-TSMo) concentration in 5-MSBA-ASA-*t*-BPMA-type initiator system on tensile bond strength to sandblasted Ni-Cr alloy and curing time[7]. In Fig. 8, it is apparent that tensile bond strength and curing time were affected by the presence of BSMo or *p*-TSMo. Maximum tensile bond strengths attained were 48.7 MPa for 1.5 wt% BSMo and 52.3 MPa for 1.0 wt% *p*-TSMo.

Figure 9 illustrates the effects of *t*-BPMA concentration in 5-MSBA-ASA-*t*-BPMA-type initiator system on tensile bond strength to Ni-Cr alloy and curing time. Similarly, it is apparent from Fig. 9 that tensile bond strength to sandblasted Ni-Cr alloy and curing time were affected by the presence of *t*-BPMA. By increasing the content of *t*-BPMA, tensile bond strength was also increased. The optimum concentration range of *t*-BPMA in 5-MSBA-ASA-*t*-BPMA-type initiator system was found to be 0.5–2.0 wt%.

The effect of 5-MSBA [*i.e.*, 1-cyclohexyl-5-ethylbarbituric acid (CEBA)] in 5-MSBA-ASA-*t*-BPMA-type initiator system on adhesion was also investigated. The combination of CEBA with ASA exhibited high tensile bond strength to Ni-Cr alloy, and the optimum concentrations of CEBA which yielded high bond strength values were found to be 0.75 wt% CEBA for 52 MPa (with BSMo) and 1.0 wt% CEBA for 50.9 MPa (with *p*-TSMo)[7]. Upon comparison of these results, it was thus found that 5-MSBA-containing ternary initiator systems (Figs. 8 and 9) exhibited significantly higher bond strength than BPO-DEPT-*p*-TSNa initiator system (Fig. 3) on adhesion to Ni-Cr alloy ($p<0.01$).

For ASA, such as *p*-TSMo, it can be synthesized by the reaction between an amide compound and an aromatic sulfinate sodium salt such as *p*-TSNa (Fig. 7). It should be highlighted that while *p*-TSNa is insoluble in hydrophobic resins, *p*-TSMo is soluble in the resins, which is definitely a preferred difference and an advantage for hydrophobic adhesive resin formulations[18].

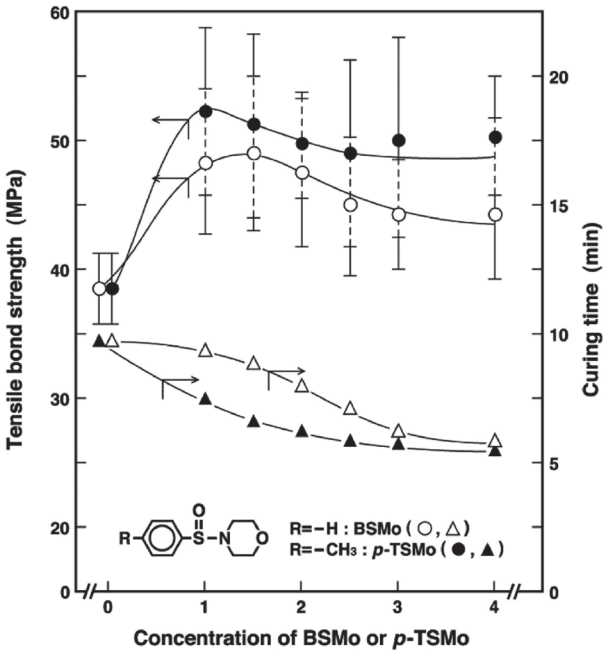


Fig. 8 Effects of aromatic sulfinate amide (ASA) concentration in 5-MSBA-ASA-*t*-BPMA-type polymerization initiator system on adhesion to Ni-Cr alloy and curing time[7].

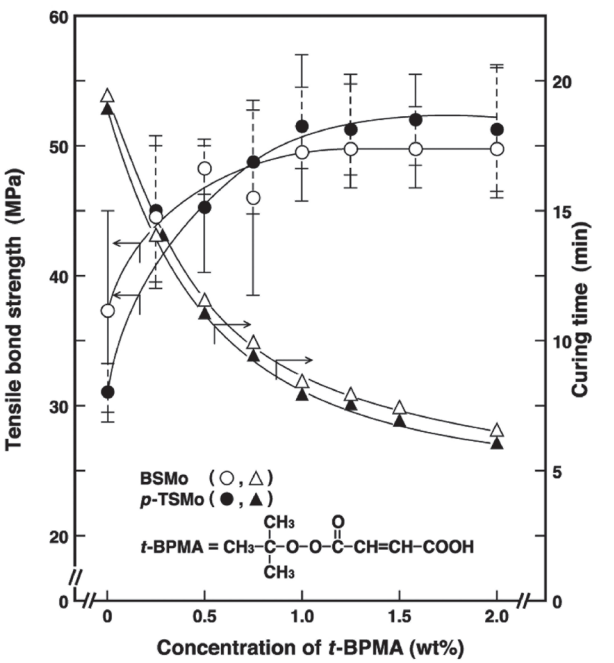


Fig. 9 Effects of *tert*-butylperoxymaleic acid (*t*-BPMA) concentration in 5-MSBA-ASA-*t*-BPMA-type polymerization initiator system on adhesion to Ni-Cr alloy and curing time[7].

On the other hand, since the *p*-toluenesulfonic acid (Fig. 4) derived from *p*-TSNa is strongly hygroscopic nature, it was anticipated that the bonding layer, which comprised the reaction products of BPO-DEPT-*p*-TSNa-type initiator system, might deteriorate over time upon exposure to water.

Effect of 5-MSBA-BPO-DEPT-type initiator system on adhesion

A new 5-MSBA-BPO-DEPT-type initiator system, when used in conjunction with 4-AETA, also exhibited both good polymerization activity and effective adhesion to sandblasted Ni-Cr alloy[7]. In this initiator system, *p*-TSNa in BPO-DEPT-*p*-TSNa-type initiator system[29] was replaced with 5-MSBA as a co-initiator. Moreover, it was found that use of 5-MSBA-BPO-DEPT initiator system resulted in significantly higher bond strength ($p<0.01$) than BPO-DEPT-*p*-TSNa initiator system.

Another advantage of 5-MSBA lies in its active initiation ability, which means that only a low concentration of amine is required. Therefore, although 5-MSBA-BPO-DEPT-type initiator system contained tertiary amine (DEPT), the formation of CT complex between acidic adhesive monomers and DEPT was kept to a minimum. Consequently, the co-initiator 5-MSBA in 5-MSBA-containing initiator system brought about twofold benefits: active polymerization reactivity and enabling adhesive resins to effective adhesion[7].

To date, details of the polymerization initiation mechanism of 5-MSBA-containing ternary initiator systems [*i.e.*, 5-MSBA-BPO-DEPT, 5-MSBA-ASA-*t*-BPMA] remained unclear. Nonetheless, the initiating behavior of 5-MSBA could be triggered by the C-H active initiation mechanism illustrated in Fig. 5. Based on the above findings, it is thus concluded that 5-MSBA-containing ternary initiator systems, when used in conjunction with adhesive monomers, can bestow adhesive resins with good adhesion without the use of non-polymerization shrinkage monomers[7].

SYNTHESIS OF ADHESIVE MONOMERS AND THEIR EFFECTS ON ADHESION

Synthesis of trimellitic acid-type adhesive monomers

An outstanding characteristic of adhesive monomers (adhesion-promoting monomers) is their ability to chemically interact with the tooth surface[12-14], thereby numerous researchers have tirelessly challenged to develop advanced adhesive monomers by means of synthetic organic chemistry. In terms of molecular structure, they typically include the carboxylic acid group (-COOH) or its anhydride group, phosphoric acid group [-O-P(=O)$(OH)_2$], or phosphonic acid group [-P(=O)$(OH)_2$].

Figure 10 shows the chemical structures of carboxylic acid-type adhesive monomers incorporated in commercially utilized dental adhesives. In particular, adhesive monomers bearing trimellitic acid and its anhydride moiety (trimellitic acid-type adhesive monomers) have been well investigated since a study

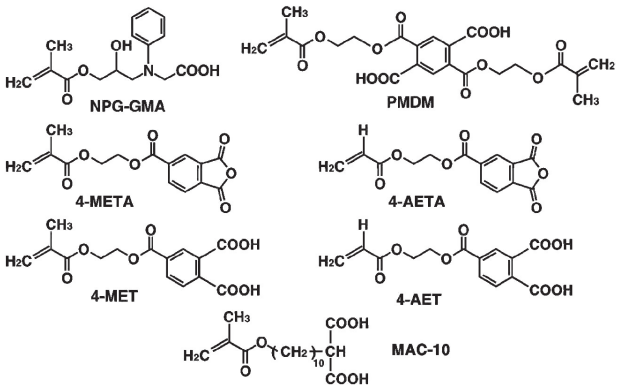


Fig. 10 Chemical structures of commercially utilized carboxylic acid-type adhesive monomers, where NPG-GMA: N-phenylglycine-glycidilmethacrylate, PMDM: an adduct of pyromellitic dianhydride and 2-hydroxyethyl methacrylate, 4-META: 4-methacryloyloxyethyl trimellitic anhydride, 4-AETA: 4-acryloyloxyethyl trimellitic anhydride, 4-MET: 4-methacryloyloxyethyl trimellitic acid, 4-AET: 4-acryloyloxyethyl trimellitic acid, MAC-10: 11-methacryloyloxy-1,1-undecanedicarboxylic acid.

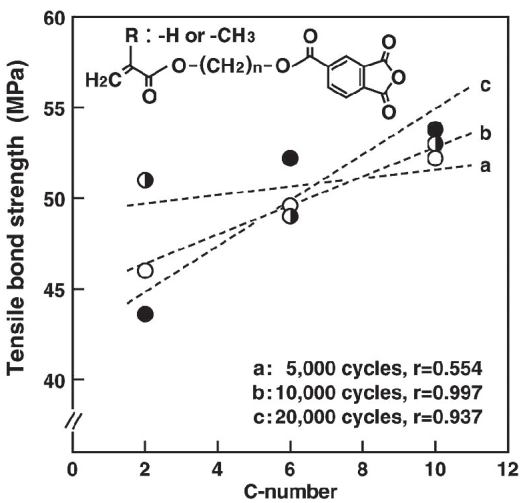


Fig. 11 Correlation between the C-number of -$(CH_2)_n$- in the structure of 4-(meth)acryloyoxyalkyl trimellitic anhydride and tensile bond strength during 5,000–20,000 thermal cycles[17].

by Nakabayashi[11].

In the course of our research and development of dental adhesives, six kinds of trimellitic acid-type adhesive monomers have been synthesized and their bonding abilities were evaluated[15-17]. They were namely 4-AET, 4-AETA, 4-META, 4-methacryloyloxy-*iso*-propyl trimellitic anhydride (4-MPTA), 4-methacryloyloxyhexyl trimellitic anhydride (4-MHTA), and 4-methacryloxydecyl trimellitic anhydride (4-MDTA). In particu-

lar, 4-AET and 4-AETA were employed in the formulations of commercial dental adhesives manufactured and marketed by Shofu Inc. (Kyoto, Japan).

Effect of methylene chain [-(CH$_2$)$_n$-] in adhesive monomers on bonding durability

On adhesion to dentin or Ni-Cr alloy, it has been reported that bond strength achieved with 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) (=C10: 10 carbon atoms in methylene chain) or 6-methacryloyloxyhexyl dihydrogen phosphate (6-MHP) (=C6) was higher than that of 2-methacryloyloxyethyl dihydrogen phosphate (2-MEP) (=C2)[37]. Based on these results, it was thus concluded that the methylene chain as a spacer group in phosphate monomers was necessary for adhesion to both dentin and metal[37].

Our previous study[17] also investigated the effect of the molecular structure of trimellitic anhydride-type adhesive monomers (C2: 4-AETA, C6: 4-MHTA and C10: 4-MDTA) on adhesion. When used in conjunction with 1-benzyl-5-phenylbarbituric acid (BPBA)-BPO-DEPT initiator, the tensile bond strength to Ni-Cr alloy after 20,000 times of thermal cycling was found to be affected by the molecular structure of adhesive monomers[17]. After 10,000–20,000 thermal cycles, bond strength was found to decrease in this order: 4-MDTA (C10) > 4-MHTA (C6) > 4-AETA (C2). Notably, there was high positive correlation between bonding durability and the C-number (C2–C10) of methylene chain [-(CH$_2$)$_n$-] in adhesive monomers (r = 0.937, 20,000 cycles)[17] (Fig. 11).

According to the published studies[17,37], it was further revealed that the flexible methylene chain (C6–C10) of adhesive monomers formed a more stable molecular layer on the surface of adherends, thereby resulting in enhanced bonding durability.

Synthesis of new phosphonic acid monomers

Figure 12 depicts the chemical structures of commercially utilized phosphorus-containing adhesive monomers. Phosphate monomers [R-O-P(=O)(OH)$_2$] have been well investigated, and in particular phenyl-P and 10-MDP[37] have been utilized in the formulations of commercial products manufactured by Kuraray Co. (Osaka, Japan).

Phosphonic acid monomers [R-P(=O)(OH)$_2$], namely *N*-methacryloyl-ω-aminoalkyl phosphonic acid (MωP)[38,39], ethyl 2-[4-(dihydroxyphosphoryl)-2-oxabutyl]acrylate (EAEPA) and 2,4,6-trimethylphenyl 2 - [4 - (dihydroxyphosphoryl) - 2 - oxabutyl] acrylate (MAEPA)[40] were recently developed. In particular, to design single-bottle self-etching adhesives, they have received considerable recent attention because of their superior hydrolytic stability[38-40].

Through our research and development on dental adhesives, seven kinds of novel phosphonic acid monomers[18,19] were synthesized, namely 5-methacryloyloxypentyl 3-phosphonopropionate (5-MPPP), 6-methacryloyloxyhexyl 3-phosphonopropionate (6-MHPP), 6-methacryloyloxyhexyl phosphonoacetate (6-MHPA),

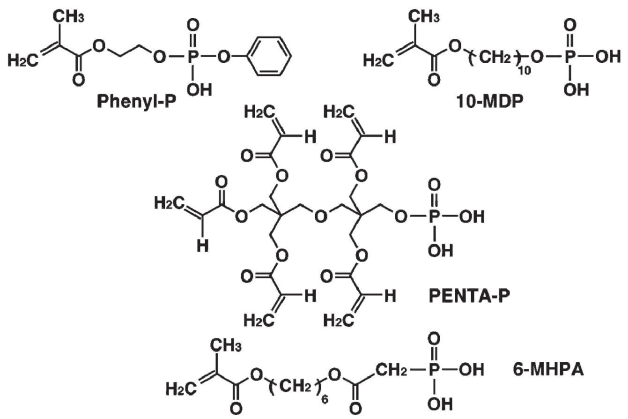


Fig. 12 Chemical structures of phosphorus-containing adhesive monomers utilized in the formulations of commercial dental adhesives, where phenyl-P: 2-methacryloyloxyethyl phenyl hydrogen phosphate, 10-MDP: 10-methacryloyloxydecyl dihydrogen phosphate, PENTA-P: dipentaerythritol pentaacrylate phosphoric acid, and 6-MHPA: 6-methacryloyloxyhexyl phosphonoacetate.

6-acryloyloxyhexyl 3-phosphonopropionate (6-AHPP), 6-acryloyloxyhexyl phosphonoacetate (6-AHPA), 10-methacryloyloxydecyl 3-phosphonopropionate (10-MDPP), and 10-methacryloyloxydecyl phosphonoacetate (10-MDPA). Leveraging on the results of these research studies[18,19], these novel phosphonic acid monomers were subsequently employed in our invention[41].

Figure 13 shows a general schema of the syntheses of four kinds of phosphonic acid monomers [R-P(=O)(OH)$_2$]. During the synthesis process, carboxyethyl phosphonic acid [HOOC-(CH$_2$)$_2$-P(=O)(OH)$_2$] (1) reacted with mono-OH monomers (2) to yield the respective phosphonic acid monomers (3)[18]. For carbon-phosphorus bond [>P(=O)-C] formation, ethyl diethylphosphonate [EtOOC-(CH$_2$)$_2$-P(=O)(OEt)$_2$] (1′) is a valuable synthetic intermediate that can be synthesized from either the ring-opening reaction or the Michaelis-Arbuzov rearrangement[42]. During the transformation in the latter reaction, a tervalent phosphorus [P(III)] is converted into a pentavalent phosphorus [P(V)], which involves the conversion of >P-O-C linkage into >P(=O)-C linkage[42].

Effect of new phosphonic acid monomers with 5-MSBA-containing initiators on adhesion

On bonding ability, that of the new phosphonic acid monomers was evaluated when used in conjunction with BPBA-BPO-DEPT initiator system[18]. Table 1 presents the tensile bond strengths of experimental composite-type adhesive resins comprising 5-MPPP, 6-MHPP, 6-AHPP, 10-MDPP, phenyl-P, vinylbenzyl phosphonic acid (VBPA), and None (control) to sandblasted Ni-Cr alloy after 0 and 2,000 thermal cycles[18].

It is apparent that acidic adhesive monomers con-

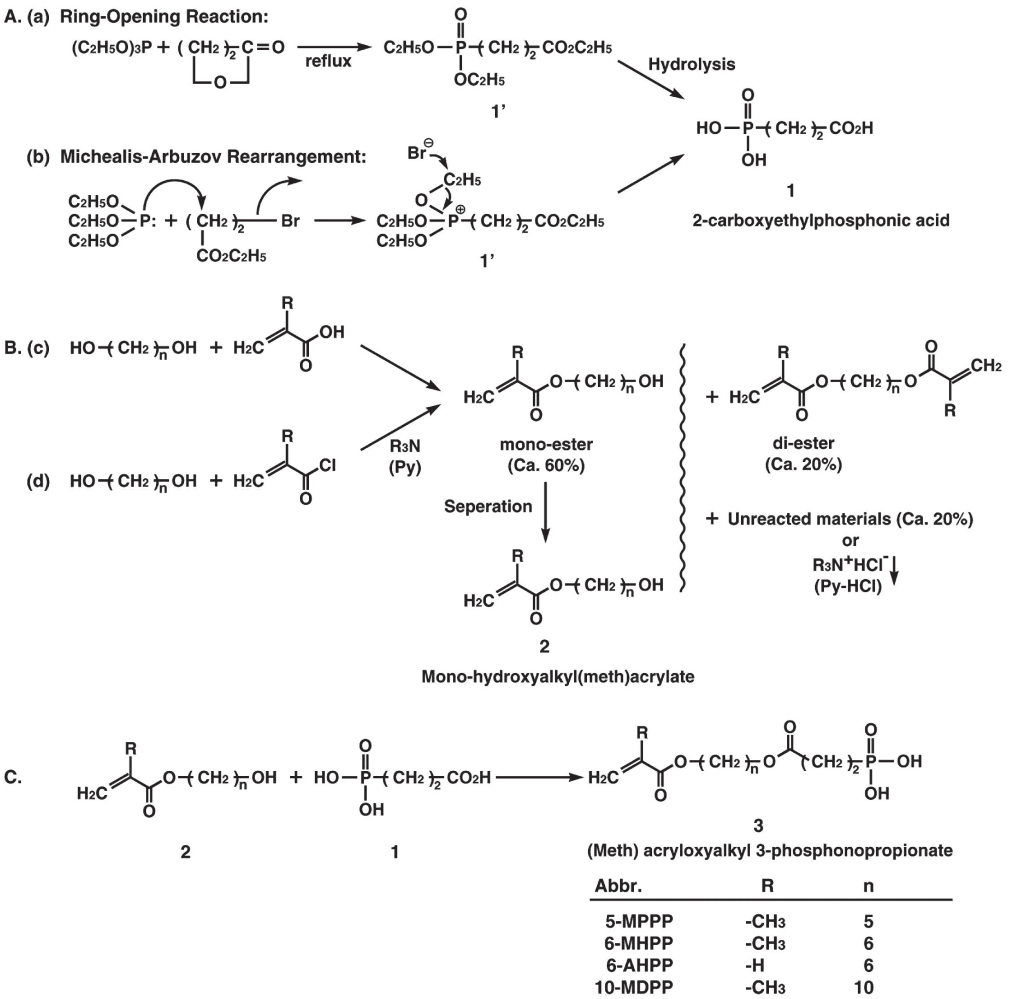


Fig. 13 General schema of the syntheses of four kinds of phosphonic acid monomers [R-P(=O)(OH)$_2$], where novel phosphonic acid monomers (3) were: 5-methacryloyloxypentyl 3-phosphonopropionate (5-MPPP), 6-methacryloyloxyhexyl 3-phosphonopropionate (6-MHPP), 6-acryloyloxyhexyl 3-phosphonopropionate (6-AHPP), and 10-methacryloyloxydecyl 3-phosphonopropionate (10-MDPP)[18].

Table 1 Effects of phosphorus-containing adhesive monomers on tensile bond strengths of experimental composite-type adhesive resins between sandblasted Ni-Cr alloy rod and Ni-Cr alloy plate after 0 and 2000 thermal cycles[18]

Adhesive monomer	Ni-Cr alloy (n=10) *			
	0 cycle †	A/M/C (%) §	2000 cycles †	A/M/C (%) §
5-MPPP	40.8 (9.7)[a]	0/10/90	40.8 (10.2)[a]	0/20/80
6-MHPP	42.8 (10.8)[a]	0/10/90	42.5 (12.5)[a]	0/10/90
6-AHPP	41.9 (9.5)[a]	0/0/100	42.6 (10.7)[a]	0/0/100
10-MDPP	42.4 (11.2)[a]	0/0/100	44.8 (12.0)[a]	0/0/100
Phenyl-P	31.0 (6.4)[b]	0/30/70	31.8 (8.8)[b]	0/40/60
VBPA	30.3 (4.8)[b]	0/40/60	30.2 (4.8)[b]	0/40/60
None	5.2 (1.2)[c]	100/0/0	4.2 (1.4)[c]	100/0/0

*Ni-Cr alloy: Shofu Summalloy Ni (Shofu Inc., Kyoto, Japan) rod cast was sandblasted with aluminum oxide.
† Values are presented as mean value (standard deviation). Values of the same column that are identified with the same superscript letters are not significantly different (p>0.01).
§ Failure modes: percent of Adhesive failure/Mixed failure/Cohesive failure in adhesive.
5-MPPP: 5-methacryloyloxypentyl 3-phosphonopropionate, 6-MHPP: 6-methacryloyloxyhexyl 3-phosphonopropionate, 6-AHPP: 6-acryloyloxyhexyl 3-phosphonopropionate, 10-MDPP: 10-methacryloyloxydecyl 3-phosphonopropionate, Phenyl-P: 2-methacryloxyethyl phenyl hydrogen phosphate, VBPA: 4-vinylbenzyl phosphonic acid.

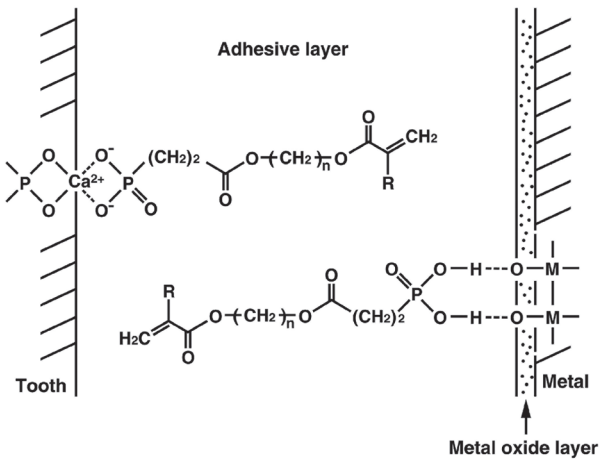


Fig. 14 A schematic illustration of the hypothetical interaction of phosphonic acid moiety of acryloyl- and methacryloyloxy 3-phosphonopropionates with hydroxyapatite or metal[18]. R = -H or -CH_3.

tributed to significant (p<0.01) improvements in bond strength when compared with the control formulation which did not contain any acidic adhesive monomer (Table 1). Further, be it with or without thermal cycling, all the new, experimental phosphonic acid monomers exhibited significantly (p<0.01) higher tensile bond strengths (40.8–44.8 MPa) than both phenyl-P (31.0–31.8 MPa) and VBPA (30.2–30.3 MPa), whereby the latter served as control phosphorus-containing adhesive monomer (Table 1).

On bonding to unetched ground enamel, it was found that new phosphonic acid monomers also exhibited good adhesion (8.3–11.5 MPa) when used in conjunction with 5-MSBA-containing initiator system[18]. When compared with the results shown in Table 1, it could be seen that the tensile bond strength of newly synthesized phosphonic acid monomers to metal alloy was about 4 times higher than the tensile bond strength to enamel.

Similar to the adverse interactions that occurred between conventional phosphate monomers and dual-cured composites[43], it was anticipated that the newly synthesized phosphonic acid monomers would likewise exhibit low polymerization reactivity as a result of the acid moieties being neutralized by the basic, binary, redox BPO-DEPT initiator system. To circumvent the problem of compromised adhesion caused by CT complex formation[5-7], 5-MSBA-containing initiator systems were employed in adhesive resins so that the phosphonic acid monomers could perform their essential adhesion-promoting functions unimpeded.

Indeed, it was found that apart from markedly reducing the adverse effects on both polymerization and adhesion[5-7], ternary 5-MSBA-containing initiators also increased the cohesive strength of the adhesive layer between the adherends[18]. Therefore, 5-MSBA (*i.e.*, BPBA, CEBA) as a co-initiator imparted outstanding reactivity to the polymerization initiation of adhesive resins, thereby resulting in improved bond strength.

In addition, similar to the chemical interaction of carboxylic acid functional group with hydroxyapatite[12-14], we further speculated that the newly synthesized phosphonic acid monomers, as ligand monomers, would achieve good chemical interaction with both hydroxyapatite on tooth surfaces and metal oxide on metal surfaces *via* the hypothetical mechanism illustrated in Fig. 14.

A NEW PMMA-TYPE ADHESIVE RESIN COMPRISING MICROENCAPSULATED POLYMERIZATION INITIATORS FOR MULTI-PURPOSE BONDING

Effects of microencapsulated BPO and TMBA in PMMA-type adhesive resin on bonding and stability

The behavior of microencapsulated polymerization initiators in dental adhesives is unknown. The effect of newly synthesized microencapsulated (MC) polymerization initiators in PMMA-type adhesive resin on multi-purpose bonding performance and formulation stability was thus investigated[21].

Briefly, BPO and 1,3,5-trimethylbarbituric acid (TMBA) as core materials were microencapsulated within poly(ethyl methacrylate) (PEMA) as a shell polymer to form MC-BPO and MC-TMBA respectively. Adhesive-MC comprising MC-BPO and MC-TMBA and Adhesive-BR comprising non-microencapsulated initiators (*i.e.*, bare BPO and bare TMBA), together with adhesive monomers (*i.e.*, 4-AET and 4-AETA), were thus prepared. In preparation for bonding, enamel and dentin surfaces were treated with ResiCem Primer (Shofu Inc., Kyoto, Japan), while sandblasted SUS rod, titanium, and gold alloy were treated with Metal Link Primer (Shofu Inc., Kyoto, Japan).

Table 2 presents the shear bond strengths of the prepared adhesive resins between sandblasted titanium and unetched ground enamel or dentin treated with or without surface treatment agent[21]. Statistical analysis (ANOVA) indicated that there were no significant differences (p>0.05) between Adhesive-MC and Adhesive-BR in their bond strengths to unetched enamel (15.2–16.6 MPa) with or without surface treatment agent. However, there were significant differences (p<0.05) between the bond strength to ground dentin treated with surface treatment agent and that without surface treatment agent.

Table 3 presents the shear bond strengths of the prepared adhesive resins to gold alloy[21]. The starting shear bond strength of Adhesive-MC at baseline was 42.5 MPa. After 1-month storage at 40°C, the shear bond strength slightly decreased to 73% of its starting strength to 31.0 MPa with no statistically significant difference from the starting shear bond strength (p>0.05). After 2-month storage period at 5°C and 23°C, the shear bond strength of Adhesive-MC maintained at 39.5–41.8 MPa. These results thus confirmed

Table 2 Shear bond strengths of experimental PMMA-type adhesive resins between titanium and unetched ground enamel or unetched ground dentin[21)]

Adherend	Surface treatment agent	Adhesive	Bond strength (MPa)	A/M/C (%)§
Titanium-enamel	No	Adhesive-MC	16.6 (6.5)[a]	20/80/0
Titanium-enamel	No	Adhesive-BR	15.7 (6.5)[a]	20/80/0
Titanium-enamel	Yes	Adhesive-MC	15.2 (4.5)[a]	20/80/0
Titanium-enamel	Yes	Adhesive-BR	15.8 (4.8)[a]	20/80/0
Titanium-dentin	No	Adhesive-MC	4.0 (2.4)[b]	100/0/0
Titanium-dentin	No	Adhesive-BR	3.8 (2.2)[b]	100/0/0
Titanium-dentin	Yes	Adhesive-MC	18.7 (6.1)[a]	20/80/0
Titanium-dentin	Yes	Adhesive-BR	17.5 (5.8)[a]	20/80/0

Note: n=10.
Adhesive-MC: Adhesive resin comprising microencapsulated polymerization initiators.
Adhesive-BR: Adhesive resin comprising bare polymerization initiators.
Surface treatment agent, where Yes: Metal Link Primer for titanium (CP Ti), ResiCem Primer for ground enamel or ground dentin.; No: not treated with these primers.
Values are presented as mean value (standard deviation). Values of the same column that are identified with the same superscript letters are not significantly different (p>0.05).
§ Failure modes (A/M/C): percent of Adhesive failure/Mixed failure/Cohesive failure in adhesive.

Table 3 Shear bond strengths of experimental PMMA-type adhesive resins between SUS rod and gold alloy[21)]

Storage periods of adhesive resins	Adhesive-MC		Adhesive-BR	
	Bond strength (MPa)	A/M/C (%)§	Bond strength (MPa)	A/M/C (%)§
Control*	7.5 (3.5)[c]	100/0/0	7.0 (5.3)[c]	100/0/0
Starting	42.5 (3.7)[a]	0/100/0	39.8 (4.9)[a]	0/100/0
1-month at 5°C	41.0 (8.0)[a]	0/100/0	40.3 (2.8)[a]	0/100/0
2-month at 5°C	41.8 (4.8)[a]	0/100/0	40.1 (2.8)[a]	0/100/0
1-month at 23°C	40.7 (7.8)[a]	0/100/0	43.8 (3.5)[a]	0/100/0
2-month at 23°C	39.5 (8.1)[a]	0/100/0	12.8 (6.4)[b, c]	90/10/0
1-month at 40°C	31.0 (9.8)[a, b]	0/100/0	CNT	CNT
2-month at 40°C	27.2 (7.8)[b]	20/80/0	CNT	CNT

Note: n=10.
Adhesive-MC: Adhesive resin comprising microencapsulated polymerization initiators.
Adhesive-BR: Adhesive resin comprising bare polymerization initiators.
The adhesive surface of SUS rod or gold alloy, except control*, was treated with Metal Link Primer.
Values are presented as mean value (standard deviation). Values of the same column that are identified with the same superscript letters are not significantly different (p>0.05).
CNT: Could not be tested.
§ Failure modes (A/M/C): percent of Adhesive failure/Mixed failure/Cohesive failure in adhesive.

that the microencapsulated polymerization initiators exhibited adequate ability to control polymerization activation when applied to the PMMA-type adhesive resin.

Moreover, after 2-month storage at 40°C, it was found that Adhesive-MC exhibited sufficient ability to initiate radical polymerization and hence maintained its adhesion to gold alloy when compared to the shear bond strength after 1-month storage at 40°C (p>0.05). In a sharp contrast, the bond strength of Adhesive-BR degraded pronouncedly with markedly delayed polymerization reactivity after storage.

Microcapsule technology is rarely applied in dentistry. Nonetheless, through our investigation on the behavior of microencapsulated initiators in dental adhesives, an invention termed as "A one-liquid medical and dental curable composition"[44)] was achieved. All the findings presented in this paper were gleaned from the research studies that culminated in this invention.

Role of surface treatment agents for multi-purpose bonding

As shown in Table 2, the bond strengths of Adhesive-MC and Adhesive-BR to dentin treated with ResiCem Primer [MC: 18.7 MPa; BR: 17.5 MPa] were significantly higher (about 4.6 times higher) than that to dentin without ResiCem Primer [MC: 4.0 MPa; BR: 3.8 MPa] (p<0.05).

As shown in Table 3, the bond strengths of

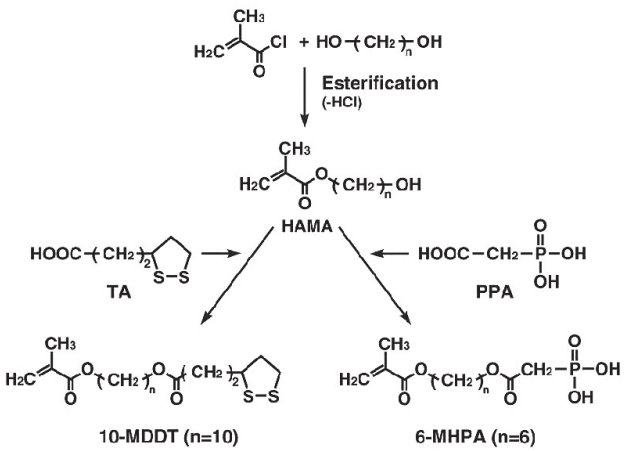


Fig. 15 Schematic illustration of the syntheses of 6-methacryloyloxyhexyl phosphonoacetate (6-MHPA)[19] and 10-methacryloyloxydecyl 6,8-dithioctanoate (10-MDDT)[20]. HAMA: monohydroxyalkyl methacrylate; PPA: phosphonoacetic acid; TA: thioctonic acid.

Adhesive-MC and Adhesive-BR to gold alloy treated with Metal Link Primer [MC: 42.5 MPa; BR: 39.8 MPa] were significantly higher (about 5.7 times higher) than that without the primer treatment [MC 7.5 MPa; BR: 7.0 MPa] ($p<0.05$).

It was apparent that the high bond strengths to dentin were achieved *via* the surface treatment with ResiCem Primer that contained 6-MHPA and 4-AET as acidic adhesive monomers. Similarly, the significantly higher bond strengths to the gold alloy were achieved *via* the surface treatment with Metal Link Primer which contained 6-MHPA[19] and 10-methacryloyloxydecyl 6,8-dithioctanoate (10-MDDT)[20]. It was confirmed that surface treatment with ResiCem Primer and Metal Link Primer improved multi-purpose bonding performance, and that 6-MHPA and 10-MDDT were indeed valuable adhesive monomers for the design of multi-purpose adhesives.

Multi-purpose bonding with both phosphorus-containing and sulfur-containing adhesive monomers

A mandatory requirement of multi-purpose dental adhesive resins is to deliver strong and durable adhesion to a multitude of adherends which may coexist in the oral environment, ranging from dental hard tissues (*i.e.*, enamel and dentin), precious metals (*i.e.*, gold, platinum, and gold alloys), and non-precious metals to porcelains and ceramics (*i.e.*, alumina- and zirconia-based ceramics). As a result, concomitant with the development of multi-purpose adhesive resins, surface treatment agents for ceramics and dental metal prostheses were also developed for the purpose of improving interfacial bonding.

Although acidic adhesive monomers bearing acidic groups (*i.e.*, carboxylic acid, phosphonic acid, and phosphoric acid) adhere strongly to dental hard tissues and non-precious metals, they provide poor adhesion to precious metals such as gold. Conversely, as shown in the studies carried out by Kadoma and Kojima[45,46], sulfur-containing adhesive monomers enhanced the adhesive strength with gold and gold alloys. Chemical adsorption of organic disulfides on gold surfaces and formation of monolayer films by the spontaneous assembly of organic thiols on gold are well investigated in the semiconductor industry[47].

Figure 15 shows a schematic illustration of the syntheses of 6-MHPA[19] and 10-MDDT[20]. During the synthesis processes, monohydroxyalkyl methacrylate (HAMA; alkyl chain: n=6 or 10) reacted with phosphonoacetic acid (PPA) or thioctonic acid (TA) to yield 6-MHPA (n=6) or 10-MDDT (n=10) respectively.

Metal Link Primer contained both 6-MHPA[19] and 10-MDDT[20] (Fig. 15) in its formulation, thereby enabling it to strongly promote the adhesion of adhesive resins to both precious and non-precious metals. Further, a recent work[48] found that AZ Primer (Shofu Inc., Kyoto, Japan) which contained 6-MHPA exhibited strong adhesion to alumina- and zirconia-based all-ceramic prostheses. Together, it is unequivocally shown that 6-MHPA and 10-MDDT are the must-have components in the design of multi-purpose adhesives.

Based on our studies, new 5-MSBA-containing polymerization initiators and newly synthesized adhesive monomers (*i.e.*, trimellitic acid monomers, phosphonic acid monomers, and sulfur-containing monomers) were employed in the formulations of 10 kinds of commercial dental adhesives and primers manufactured by Shofu Inc. (Kyoto, Japan), such as the ResiCem adhesive resin and a single-bottle self-etching adhesive, BeautiBond.

CONCLUSIONS

This paper reviewed our research studies on the development of dental adhesives, using a two-pronged approach that focused on both radical polymerization initiators and adhesive monomers. The key conclusions derived from this review paper are as follows:

1. 5-monosubstituted barbituric acid (5-MSBA)-containing ternary initiator systems [*i.e.*, 5-MSBA-BPO-DEPT, 5-MSBA-ASA-t-BPMA], when used in conjunction with adhesive monomers, bestowed adhesive resins with effective adhesion.
2. On trimellitic acid and trimellitic acid anhydride monomers, six kinds were synthesized through our research and development efforts: 4-AET, 4-AETA, 4-META, 4-MPTA, 4-MHTA, and 4-MDTA. It was suggested that the flexible methylene chain in the molecular structure of these adhesive monomers contributed to their bonding durability.
3. On phosphonic acid monomers [R-P(=O)$(OH)_2$], seven kinds of acryloyl- and methacryloyloxyalkyl phosphonic acids were synthesized: 5-

MPPP, 6-MHPP, 6-MHPA, 6-AHPP, 6-AHPA, 10-MDPP, and 10-MDPA. These novel phosphonic acid monomers strongly adhere to enamel, dentin, alumina- and zirconia-based all-ceramic prostheses and non-precious metals.

4. On sulfur-containing adhesive monomer, 10-methacryloyloxydecyl 6,8-dithioctanoate (10-MDDT) was synthesized, and that it promotes adhesion between adhesive resins and precious metals.

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