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Development of experimental HEMA-free three-step adhesive system

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ABSTRACT

Objective: To evaluate the influence of Bis-EMA 30 on the resin-to-dentin microtensile bond strength (μTBS) and structural reliability of the experimental three-step etch-and-rinse adhesive systems.

Methods: Five experimental primers containing different dimethacrylate monomer concentrations (0, 10, 20, 40, 60 wt% of the Bis-EMA 30, P0.P60) added to acid monomer and solvents (ethanol/water), and a resin bond (Bis-GMA/TEGDMA, 50/50 wt%) were formulated. The adhesive system Scotchbond™ MultiPurpose (SBMP, 3M ESPE) was tested as commercial reference. Sixty bovine incisors were randomly separated into six groups, and their superficial coronal dentin was exposed. After acid etching and rinsing, the excess water was removed from the surface with absorbent paper. Each experimental primer was actively applied (30 s), followed by a mild air stream (10 s). The experimental adhesive resin was applied and light activated for 20 s. Resin composite restorations were incrementally built up. The restored teeth were stored in distilled water at 37 °C for 24 h, and then sectioned to obtain sticks with a cross-sectional area of approximately 0.5 mm^2, after which 24 specimens per group were subjected to the μTBS test. Data (MPa) were analyzed by One-way ANOVA, Tukey test ($\alpha = 0.05$) and Weibull analysis.

Results: The P40 group showed μTBS means similar to those of the control (SBMP), whereas both had statistically higher values when compared with the other groups ($p < 0.001$). Moreover, P40 showed higher structural reliability, represented by the high Weibull modulus and characteristic strength values. The lowest μTBS was observed in the P0, P10 and P20 groups, which also had low structural reliability.

Significance: Bis-EMA 30 is a promising monomer to be considered as a substitute for HEMA in adhesive system compositions.

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1. Introduction

Methacrylate-based filling materials are widely used for restorative procedures in dentistry. To achieve adequate sealing and bond strength to wet dentin, these materials contain hydrophilic compounds that penetrate around the naked collagen fibrils to hybridize the demineralized superficial dentin. The 2-hydroxyethyl methacrylate (HEMA) is a

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hydrophilic monomer often present in resin dental materials, such as resin-modified glass ionomer cements, adhesive systems and resin luting cements. HEMA is added in amounts varying between 35 and 55% in commercially available adhesive systems.[1] HEMA is extensively used in adhesive compositions due to its low molecular weight, acting as a co-solvent, helping to mix hydrophobic and hydrophilic ingredients into a single homogeneous blend, and for the excellent infiltration capacity into the demineralized dentin surface, leading to an increase in bond strengths.[2–4] However, HEMA could diffuse through dentinal tubules,[5] promoting an induction of pulp apoptotic cell death, which might be an important mechanism for the generation and persistence of hypersensitivity reactions in patients.[6] Furthermore, HEMA is a common sensitizer among dentists and dental technicians, and is capable of penetrating through conventional gloves while handling adhesives[7] so that it may lead to the development of contact dermatitis.[8]

From a chemical analysis, HEMA is a functional monomer with only one polymerizable group. In contrast to dimethacrylate monomers that have two polymerizable groups forming cross-linked polymers, HEMA is not able to form cross-linking and when present in a resinous blend, it only links in linear space positions during polymerization process. The behavior of the hydroxyl group at the extremity of the molecule is too hydrophilic, even after the polymerization.[9] Thus, the outcome is a polymer more prone to hydrolysis in the oral environment, with a potential decrease in mechanical properties of dental materials.[9,10]

Recently a HEMA-free one-step self-etch adhesive system was introduced on the market (G-Bond, GC Corporation, Tokyo, Japan). Although, some studies have shown that the one-step self-etch adhesives present satisfactory immediate bond strengths,[11,12] other authors have reported that enamel and dentin bond strengths are quite low, with easy phase separation and reduction of bonding effectiveness over time, mainly due to the fast chemical degradation of the hybrid layer.[13–15] In another recent report, Mine et al.[16] evaluated a three-step etch-and-rinse adhesive system in which HEMA and TEGDMA were replaced by a hydrophilic ethoxylated bisphenol A diglycidyl dimethacrylate (cmf Adhesive System Saremco, St. Gallen, Switzerland). Although three-step etch-and-rinse adhesives are considered the ''gold standard'', this new system showed low immediate bond strength to dentin. Nevertheless, in this study the chain extender length of the ethoxylated bisphenol A diglycidyl dimethacrylate used was not mentioned[16] and it can present variable chain extender lengths or ethylene oxide units that influence the polymer network behavior.[17]

Evidences of the estrogenicity of bisphenol A has raised concern about bisphenol A (BPA) contamination in some monomers used in dental industry.[18] Since bisphenol A glycidyl methacrylate (Bis-GMA) is a common resin that carries trace amounts of BPA, the gradual increase in the content of Bis-GMA alternatives, such as like urethane dimethacrylates and higher ethoxylated Bis-EMAs[17,19] appears to be a further trend in development and reformulation of methacrylate-based dental materials. Therefore, the aim of this study was to test the null hypothesis that different ethoxylated bisphenol A diglycidyl dimethacrylate concentrations (Bis-EMA 30), with 30 ethylene oxide units, will not affect the microtensile bond strength and structural reliability of an experimental three-step etch-and-rinse HEMA-free adhesive system applied on dentin.

2. Materials and methods

2.1. *Experimental HEMA-free adhesive system formulations*

The experimental primers evaluated in the study were formulated through an intensive mixture of the components described in Table 1. The resin bond was formulated by mixing the monomers 2,2-bis[4-(2-hydroxy-3-methacryloyloxypropyl)phenyl]-propane (Bis-GMA) and triethyleneglycol dimethacrylate (TEGDMA) (Esstech Inc., Essington, PA, USA), in a 50/50 wt.% ratio. To make the material light-polymerizable, a binary light-curing system constituted by 0.4 wt.% of camphoroquinone (CQ, Esstech) and 0.8 wt.% of ethyl 4-dimethylaminebenzoate (EDMAB, Fluka, Milwalkee, WI, USA) were dissolved in the mixture. Ethoxylated bisphenol A diglycidyl dimethacrylate with 30 ethylene oxide units (Bis-EMA 30), of which the fundamental properties were presented in a previous study, was purchased from Esstech (Esstech Inc., Essington, PA, USA).[17] GDMA-P, is an equimolar mixture of glycerol dimethacrylate dihydrogen phosphate and glycerol tetramethacrylate hydrogen phosphate, produced according to a previous investigation.[20] The reagents were used as received, without further purification.

2.2. *Specimen preparation*

Forty-eight extracted bovine incisors were used in this study. After pulp and periodontal tissue removal, the teeth were stored frozen at −4 °C for less than 3 months. The teeth were randomly allocated into six groups, with one group assigned to each primer evaluated or to commercial reference group treated with Adper, Scotchbond MultiPurpose (Batch No. 6BB, 3M ESPE, St. Paul, MN, USA – SBMP). The buccal enamel was removed with a model trimmer to form a flat superficial, coronal dentin surface. The exposed dentin surface was wet polished with 600-grit silicon carbide paper to create a standardized smear layer.

Table 1 – Composition of the experimental primers.

Primers (groups)	Composition (wt%)			
	Bis-EMA 30	Ethanol	Water	GDMA-P
P0	0	45	45	10
P10	10	40	40	10
P20	20	30	30	10
P40	40	25	25	10
P60	60	15	15	10

Bis-EMA 30, ethoxylated bisphenol A diglycidyl ether dimethacrylate with 30 ethylene oxide units; GDMA-P, is an equimolar mixture of glycerol dimethacrylate dihydrogen phosphate and glycerol tetramethacrylate hydrogen phosphate.

The prepared dentin surfaces were conditioned with Scotchbond Etchant, a phosphoric acid gel 35% (3M ESPE, St. Paul, MN, USA – SBMP), for 15 s and after abundant rinsing, the excess water was removed from the dentine surface with a piece of absorbent paper. Each experimental *primer* was vigorously applied for 20 s using a micro-brush, and gently air-dried for 10 s. One coat of resin bond was applied and light activated for 20 s using a Light Emitting Diode light-curing unit (Radii SDI, Bayswater, Victoria, Australia). The irradiance was measured with a digital power meter (Ophir Optronics, Danvers, MA, USA) and was 1400 mW/cm^2. SBMP was used according the manufacturer's instructions. After the acid treatment, the SBMP *primer* was applied for 20 s using a micro-brush, and gently air-dried for 10 s. One coat of resin bond was applied and light activated for 20 s. After adhesive light-activation, two increments of resin composite (Charisma C2, Heraeus Kulzer, Germany) were placed, completely covering the dentin surface and light-cured for 20 s each. The specimens were stored in distilled water at 37 °C for 24 h. The specimens were sectioned in two directions perpendicular to the bonded interface using a water cooled diamond saw at low-speed (Isomet 1000, Buehler Ltd, Lake Bluff, IL), producing beams with a cross-sectional surface area within a range 0.5–0.7 mm^2 for microtensile bond testing.

2.3. μTBS evaluation and fracture analysis

The ends of the prepared beams were covered and individually fixed to a custom-made testing jig using a cyanoacrylate glue (Super Bonder Gel, Loctite, Diadema, SP, Brazil) and tested in a mechanical testing machine (DL-500, Emic, São José dos Pinhais, Brazil) under tension at a crosshead speed of 1 mm/min until failure. Microtensile bond strengths (μTBS) were calculated and expressed in MPa. The premature failures were recorded but were not included in the statistical analysis. The half of each specimen corresponding to dentin was removed from the device and was examined with an optical microscope at a magnification of 100× and 500×. The failure patterns were classified as: on the adhesive interface, cohesive in adhesive resin, cohesive in dentin or mixed.

2.4. Statistical analysis

Microtensile bond strength data (MPa) were analyzed by one-way ANOVA and Tukey's test, at a 0.05 level of significance.

The structural reliability of the adhesives; that is the association of the two main parameters (Weibull modulus and characteristic strength), was determined using the Weibull analysis, based on the μTBS data, according to the following equation:

$$P_f = 1 - \exp[(-\sigma/\sigma_0)^m]$$

where P_f is the probability of failure, defined by the relation $P_f = K/(N + 1)$, K is the rank of the strength from the least to the greatest, N is the total number of specimens in the sample, σ is the maximum strength, m is the Weibull modulus (shape parameter) and σ_0 is the characteristic strength (scale parameter – $\sigma_{63.2\%}$). These parameters and the 5% probability of failure ($\sigma_{0.05}$) were obtained using software designed to perform the Weibull analysis from the fracture data (Minitab 13.1, Minitab Inc., State College, PA, USA).

Table 2 – Microtensile bond strength (μTBS) in MPa ($n = 30$), standard derivation (SD) and number of premature failures (*).

P0	P10	P20	P40	P60	SBMP
19.68^C	24.58^C	27.51^C	56.81^A	41.03^B	57.30^A
(8.32)	(6.05)	(8.69)	(9.90)	(9.96)	(15.67)
8*	5*	6*	0*	0*	0*

Means followed by different letters represent statistically significant differences between groups ($p < 0.001$).

3. Results

The microtensile bond strength means, standard deviations and premature failures are shown in Table 2. Analysis of variance showed that primer composition was a significant factor for bond strength, influenced by dimethacrylate surfactant monomer concentration of the experimental HEMA-free primers ($p < 0.001$). Tukey's test revealed that in the experimental groups, a statistically higher μTBS was found in P40 ($p < 0.001$), which was also similar to that of the commercial reference (SBMP). Lower amounts of Bis-EMA 30, 0–20 wt% (P0, P10 and P20), resulted in significantly lower μTBS than that of P60.

The distribution of failure patterns is shown in Fig. 2. Analysis of the surfaces fractured after the μTBS test showed a similar failure pattern between P40 and SBMP with predominance of mixed failures and lower rates of adhesive failures. Experimental primers with a lower Bis-EMA 30 concentration (P0, P10 and P20) resulted in an increase in adhesive failure rates. Moreover, in these groups premature failures occurred during handling of specimens for the μTBS test (Table 2).

The Weibull modulus (m) and standard error (SE), 95% confidence interval for m, characteristic strength (σ_0) and standard error (SE), 95% confidence interval to σ_0, coefficient of correlation (r), predicted failure level of 5% ($\sigma_{0.05}$) in MPa and standard error (SE) are summarized in Table 3. P40 and SBMP presented high m and σ_0 indicating higher structural reliability of the bond interface. Furthermore, the predicted failure level of 5% showed higher μTBS means than those groups with lower Bis-EMA 30 concentrations. The decrease in the percentage of Bis-EMA 30 in the primers (P20, P10 and P0) affected both m and σ_0, indicating a wider scattering of the results, and consequently, a lower structural reliability of the bond interface. Intermediate values for m, σ_0 and $\sigma_{0.05}$ were observed with P60.

4. Discussion

Methacrylate monomers are the main compounds of the contemporary dental adhesives. Basically, these monomers can be classified into two categories according the molecular structure and functionality. The functional monomers commonly have one specific chemical group and another polymerizable group, which after curing will form linear polymers.

Table 3 – Weibull modulus (m) and standard error (SE), 95% confidence interval to m, characteristic strength (σ_0) and standard error (SE), 95% confidence interval to σ_0, coefficient of correlation (r), predicted failure level at 5% ($\sigma_{0.05}$) in MPa and standard error (SE).

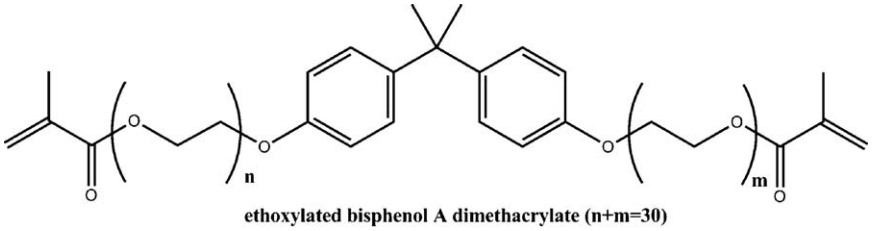
	m (SE)	95% CI	σ_0 (SE)	95% CI	r	$\sigma_{0.05}$ (SE)
P0	2.73 (0.4)	2.0–3.7	21.93 (1.7)	18.8–25.7	0.965	7.37 (1.6)
P10	4.80 (0.7)	3.6–6.4	26.76 (1.2)	24.5–29.2	0.979	14.41 (1.7)
P20	3.90 (0.5)	3.1–5.0	30.25 (1.7)	27.1–33.8	0.975	14.12 (1.8)
P40	6.74 (1.0)	5.0–9.0	60.74 (2.0)	57.0–64.7	0.983	39.09 (3.2)
P60	4.99 (0.7)	3.7–6.7	44.52 (1.9)	40.9–48.5	0.965	24.56 (2.7)
SBMP	4.11 (0.8)	2.8–5.9	62.95 (3.3)	56.8–69.7	0.972	30.58 (4.8)

The 2-hydroxyethyl methacrylate (HEMA) is a small functional monomer[9] which, although it is excellent adhesion-promoting monomer,[21,22] is capable of diffusing rapidly through non-sclerotic dentin at cytotoxic concentrations[23] causing *in vivo* inflammatory pulp reactions.[24,25] Moreover, in uncured state, HEMA quickly absorbs water from dentin compromising the degree conversion.[26] Consequently a poor quality polymer network with weak mechanical properties will be formed.[27]

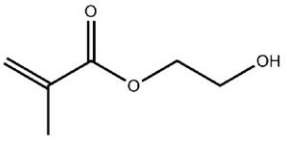
The ethoxylated bisphenol A diglycidyl dimethacrylates (Bis-EMAs) like Bis-GMA, TEGDMA and UDMA, are cross-linking monomers that are characterized by the presence of at least two polymerizable groups (vinyl groups or –C═C–).[28] Dimethacrylates present some advantages when compared with the mono-methacrylate monomers, since they form densely cross-linked polymers,[29] providing the polymer with mechanical strength,[30,31] and reducing the susceptibility to hydrolysis in aqueous solutions.[10] However, as a consequence of their hydrophobic behavior, they have low penetrability into wet demineralized dentin. The Bis-EMA 30 molecule presents two long chain extenders of ethylene oxide units (Fig. 1), which produce a bi-polar behavior,[32] and this monomer acts as a surface active agent or ''surfactant'' that is dependent on the polar/nonpolar unit ratio (i.e. oxyethylene/aliphatic and aromatic C–C bonds). When increasing the polar unit ratio, a higher hydrophilicity can be expected.[17]

The null hypothesis tested was rejected since the P40 group (containing 40 wt% of Bis-EMA 30) produced the highest μTBS in dentin and was statistically similar to the commercial SBMP (Table 2). This fact can be explained by the surfactant action of Bis-EMA 30, and by the most adequate monomer/solvent ratio. The presence of the surfactants in adhesive system formulations might reduce the phase-separation reaction by the formation of micelles at low water concentrations,[32–34] acting with a hybridization agent in the collagen fibrils.[33] The findings of the present study are in agreement with Venz and Dickens[35] who observed a considerable increase in μTBS when low concentrations of surfactant monomer were added to experimental dentin adhesives. In addition, no premature failures and no adhesive failures were observed in Group P40 (Table 2 and Fig. 2, respectively). This result could be related to the more homogeneous and strong hybrid layer formed, with a higher hydrophobic dimethacrylate concentration among the collagens fibrils,[33] making the adhesive-dentin interface more resistant to degradation.

When increasing the amount of Bis-EMA 30 in the primer (P60 group), a significant reduction in μTBS was obtained (Table 2). Furthermore, there was larger number of adhesive failures (Fig. 2), indicating inadequate dentin hybridization. As opposed to the primer P40, which showed a visual viscosity similar to that of SBMP, the primer P60 was highly viscous during application. Monomers with high molecular weights generally tend to form viscous blends. Moreover, the long ethylene oxide chains form hydrogen bonding (H-bonding)[32] and consequently it is necessary to adapt the monomer/solvent ratio to obtain mixtures sufficiently fluid to impregnate the exposed collagen fibrils. In this case, it is necessary to increase solvent concentration in order to produce less viscous and more hydrophilic formulations.[9,36,37] The lowest μTBS values were obtained with experimental primers



ethoxylated bisphenol A dimethacrylate (n+m=30)



2-hydroxyethyl methacrylate

Fig. 1 – Molecular structures from 2-hidroxyethyl methacrylate (HEMA) and ethoxylated bisphenol A based dimethacrylate with 30 ethylene oxide units (Bis-EMA 30).

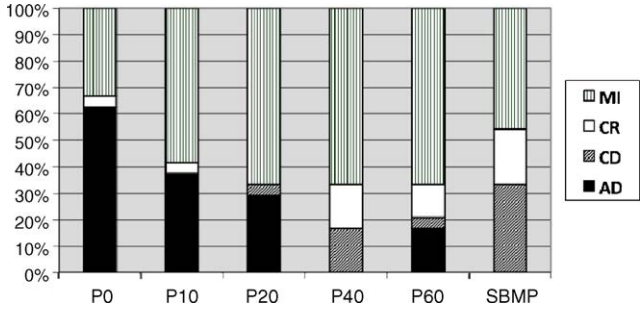


Fig. 2 – Failure distribution observed with optical microscopy at 100× and 500× magnifications. CD: cohesive in dentin; MI: mixed; AD: adhesive interface; CR: cohesive in the adhesive resin.

containing lower amounts of Bis-EMA 30 (Table 2). These results indicate that for P0, P10 and P20 the presence of surfactant was insufficient to achieve satisfactory dentin hybridization. Moreover, premature failures were recorded during the handling of specimens and an increase in adhesive failures was observed after the μTBS test. Probably the reduced bond strength found in groups with reduced monomer concentration could be due to a poor degree of conversion that allowed monomer leaching, leaving behind the formation of voids. It has been suggested that these incompletely infiltrated zones are more susceptible to the appearance of flaws that weaken the bonding layer and reduce the μTBS.[15] It is important to point out that due limitations of the methodology, the μTBS means are related to superficial dentine. Other adhesion variables such as bond strength characterization in deep dentin, with different moisture conditions and using caries affected dentin should be investigated in subsequent studies.

Bond strength data usually present large variability,[38] resulting from the inter-relation of brittle materials with the superficially demineralized dentin. For this reason, a methodological approach that allows evaluation of the structural reliability of the bond interface, such as the Weibull statistics (m and σ_0), should be used to describe the strength variations.[38–40] Weibull parameters also indicate techniques and materials that induce lower variability of results.[39,40] The m indicated the lowest bond reliability for P0 (Table 3), reflecting the influence of the poor hybridization of dentin that created intrinsic flaws at the bond interface.[27] The higher data dispersion observed might be explained by the zones of incomplete adhesive infiltration,[41] and the formation of a heterogeneous hybrid layer.[15] Whereas, P40 presented the highest m and $\sigma_{0.05}$. These findings, associated with a high σ_0 value, as well as the low number of adhesive failures detected, indicate a higher structural reliability of the bond interfaces created with P40, with a similar performance to that observed in the commercial SBMP (Table 3), indicating satisfactory immediate results.

With regard to toxicity and pulp reactions, molecular weight (MW) probably has a remarkable influence on monomer diffusion through non-sclerotic dentin.[5] If the diffusion coefficient is inversely related to molecular weight, the substitution of HEMA (MW = 130 g/mol) by Bis-EMA 30 (MW = 1686 g/mol), would theoretically result in reduction of the adhesive toxicity by a steric impedance.[42] Considering the potential and advantages of Bis-EMA 30, and the lack of information available in literature, further studies, such as cytotoxicity tests and long-term evaluation, are necessary for better understanding of its use as an adhesion promoter in dental adhesives.

5. Conclusions

Within the limits of this investigation, it was concluded that the Bis-EMA 30 is of potential usage in the development of HEMA-free adhesive systems. The experimental primer containing 40 wt% of Bis-EMA 30 presented satisfactory immediate bond strength and structural reliability, demonstrating a performance similar to that of the commercial reference product used.

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