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# Use of (meth)acrylamides as alternative monomers in dental adhesive systems

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## ABSTRACT

Objectives: Methacrylamides are proposed as components for dental adhesive systems with enhanced resistance to hydrolytic and enzymatic degradation. The specific objective of this study was to evaluate the polymerization kinetics, water sorption and solubility, pH-derived degradation and microtensile bond strength of various monofunctional acrylamides and meth(acrylamides) when copolymerized with dimethacrylates. Methods: Base monomers were added at 60 wt%, and included either BisGMA or UDMA. Monofunctional monomers were added at 40 wt%, including one (meth)acrylate as the control, two secondary methacrylamides and two tertiary acrylamides. DMPA (0.2 wt%) and DPI-PF6 (0.4 wt%)/BHT (0.1 wt%) were added as initiators/inhibitor. Polymerization kinetics wwere followed with near-IR spectroscopy in real time. Water sorption (WS) and solubility (SL) were measured following ISO 4049. Monomer degradation at different pH levels was assessed with $^1$H NMR. Microtensile bond strength (MTBS) was assessed in caries-free human third molars 48 h and 3 weeks after restorations were placed using solvated BisGMA-based adhesives (40 vol% ethanol). Data were analyzed with one-way ANOVA/Tukey's test ($\alpha = 0.05$). Results: As expected, rate of polymerization and final degree of conversion (DC) were higher for the acryl versions of each monomer, and decreased with increasing steric hindrance around the vinyl group for each molecule. In general, UDMA copolymerizations were more rapid and extensive than for BisGMA, but this was dependent upon the specific monofunctional monomer added. WS/SL were in general higher for the (meth)acrylamides compared to the (meth)acrylates, except for the tertiary acrylamide, which showed the lowest values. One of the secondary methacrylamides was significantly more stable than the methacrylate control, but the alpha substitutions decreased stability to degradation in acid pH. MTBS in general was higher for the (meth)acrylates. While for all materials the MTBS values at 3 weeks decreased in relation to the 24 h results, the tertiary acrylamide showed no reduction in bond strength. Significance: This study highlights the importance of considering steric and electronic factors when designing monomers for applications where rapid polymerizations are needed, especially when co-polymerizations with other base monomers are required to balance mechanical properties, as is the case with dental adhesives. The results of this investigation will be used to design fully formulated adhesives to be tested in clinically-relevant conditions.

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## 1. Introduction

Methacrylates are widely used in dentistry to create bonding between dental substrate and restorative material. The combination of hydrophilic monomers, such as 2-hydroxyethyl methacrylate (HEMA), with mainly hydrophobic dimethacrylate monomers allowed for the hybridization of the collagen on the dentin substrate [1], as well as co-polymerization with the restorative composite material [2]. However, the incorporation of high concentrations of hydrophilic and/or ionic monomers increases water sorption of the system [3,4], and the adhesive interfaces behave as permeable membranes [5]. In the presence of water, the ester linkage of the methacrylate backbone may undergo hydrolytic cleavage, yielding methacrylic acid and alcohol-bearing residues. In conjunction with the degradation of the collagen, this causes the bonding to progressively degrade over time due to the action of water and enzymes [6].

Acrylamides and methacrylamides, with more stable amide bonds, have been postulated as alternative monomers for the design of more hydrolytically stable adhesive systems [7,8] with the rationale of increasing the longevity of the bonded interface. These monomers have been used in at least one commercial product for a number of years, with conflicting results, especially in clinical trials, with some studies showing similar clinical performance compared to methacrylate controls and others showing worse performance [9,10]. Less than ideal results may be a function of the somewhat increased water sorption for some methacrylamides [11], as well as to their potential lower reactivity [12], which has been reported specifically for tertiary methacrylamides [13]. In fact, in depth, systematic analyses of the reaction kinetics of tertiary methacrylamides in co-polymerizations with monomers leading to the formation of glassy networks are lacking. In addition, past concerns over the cytotoxicity of acrylamides have precluded their use in biological applications, but more recently, non-cytotoxic alternatives have been reported [14]. These factors justify the current use of (meth)acrylamides in commercial preparations in combination with other monomers.

Even for pure methacrylates, a mixture of monomers is typically employed to harness the advantages of each individual compound. For example, the basic composition of fifth generation adhesives contains a relatively viscous crosslinking base monomer, such as BisGMA, which is added to improve both the reactivity and the mechanical properties of the adhesive layer. A low-viscosity, hydrophilic co-monomer, such as HEMA is added to decrease the viscosity and improve spreading, but mainly to allow diffusion into the dentin substrate [7,15]. This implies that all compounds need to be miscible with each other, as well as with the solvent of choice, as this affects both the interaction with the substrate and the reaction kinetics. In addition, the copolymerization of the monomers included in the mixture also needs to be considered. For example, it is well known that acrylates present much higher reactivity than their methacrylate counterparts, resulting in the formation of two independently polymerizing networks [16]. In summary, monomer reactivity and copolymerization ability are critical screening tools for monomer selection and adhesive design. Previous studies have tested the compatibility and co-polymerization of (meth)acrylamides with other commonly used monomers in dental adhesive applications [8,17], with reported improvements in bond strength [8,18,19]. Others have demonstrated lower reactivity of certain methacrylamides [15].

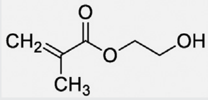
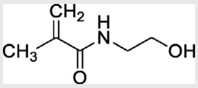
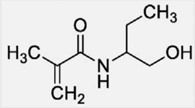
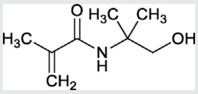
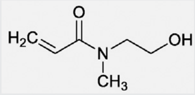
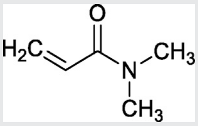
Since the presence of water in the hybrid layer is inevitable, several strategies have been proposed to improve the resistance of the adhesive layer to degradation. One attempt has been the elimination or reduction of the ester groups on the polymeric network, such as with the use of (meth)acrylamide-based adhesives systems. The presence of a nitrogen atom in amides, as compared to the oxygen atom in acrylates, leads to steric and electronic effects that reduce the susceptibility to hydrolysis. Nitrogen is less electronegative than oxygen, which makes it more likely to donate non-bonded electrons to the carbonyl carbon, shortening and strengthening the bond, ultimately decreasing the susceptibility to nucleophilic attack [20]. Tertiary methacrylamides present significant lower reactivity, while tertiary acrylamides and secondary methacrylamides present similar or higher reactivity compared to methacrylates [21]. The substitution of an alpha hydrogen atom (next to the carbonyl group) by a methyl group is expected to impart greater hydrophobicity and hydrolytic stability. Therefore, the objective of this study was to evaluate two tertiary acrylamides and two secondary alpha-substituted methacrylamides, copolymerized with BisGMA and UDMA, for dental adhesives formulations with potentially improved hydrolytic stability. The experimental materials were tested for mechanical properties, water sorption/solubility and dentin bond strength. The tested hypothesis was that compared to conventional methacrylate-based systems, (meth)acrylamide-based dental adhesives would: 1. present comparable properties; and 2. produce higher and more stable microtensile bond strengths.

## 2. Materials and methods

### 2.1. Formulation of experimental adhesives

Experimental adhesive resins were formulated with 60 wt% BisGMA (Bisphenol A glycidyl dimethacrylate) or UDMA (urethane dimethacrylate) purchased from ESSTECH (Essington, Pennsylvania, USA), and 40 wt% of one of the monofunctional monomers listed in Table 1 (synthetic procedures and characterization of the monomers, including $^1$H NMR spectra and logP calculations obtained with ChemDraw software are detailed in Supplementary Appendix). In all formulations, the photoinitiator system was composed of 0.2 wt% of the alpha-cleavage type, single component DMPA (2,2-dimethoxy-2-phenylacetophenone) and 0.4 wt% DPI-PF6 (diphenyliodonium hexafluorophosphate). This initiator composition was determined in a pilot study as providing the best compromise between adequate reactivity and high final conversion for the monomers tested. 0.1 wt% Butylated hydroxytoluene (BHT) was added to each formulation as an inhibitor for shelf life. 40 vol% ethanol was added only for the materials to be used for microtensile bond strength tests.

**Table 1 – Monofunctional monomers comprising 40 wt% of the adhesive formulation. Monomer acronyms, IUPAC names, classification, chemical structure and molecular weight are depicted for commercial products (marked with *), as well as newly synthesized compounds.**

| Monomer | Classification | Chemical Structure | Molecular weight (MW) | Log P |
|---|---|---|---|---|
| HEMA * 2-hydroxyethyl methacrylate | Methacrylate |  | 130.14 | 0.50 |
| HEMAM * N-hydroxyethyl methacrylamide | Secondary methacrylamide |  | 129.15 | −0.21 |
| 2EM N-(1-hydroxybutan-2-yl)methacrylamide | Secondary α-substitututed methacrylamide |  | 157.11 | 0.25 |
| 2dMM N-(1-hydroxy-2-methylpropan-2-yl)methacrylamide | Secondary α-substituted methacrylamide |  | 157.21 | 0.30 |
| HEM N-(2-hydroxyethyl)-N-methylacrylamide | Tertiary acrylamide |  | 129.07 | −0.32 |
| DMAM * N,N-dimethylacrylamide | Tertiary acrylamide |  | 99.13 | 0.20 |

### 2.2. *Polymerization kinetics*

Disk samples (10 mm diameter, 0.8 mm thick) sandwiched between glass slides were placed in the chamber of an infrared spectrometer (Nicolet 6700, ThermoScientific, USA) and irradiated with a mercury arc lamp (Acticure, EXFO Acticure 4000 UV Cure; Mississauga, Canada) filtered to 320–500 nm for 300 s, delivering 630 mW/cm$^2$ directly to the specimen. Spectra were collected in real-time during photoactivation, with 2 scans per spectrum at 4 cm$^{-1}$ resolution. The degree of conversion was calculated based on the area of the vinyl overtone in near-IR at 6165 cm$^{-1}$ for methacrylates and around 6130 cm$^{-1}$ for (meth)acrylamides. Clear, distinct separation of the peaks was only possible for one group (BisGMA-HEMMA), whereas in the other groups the peaks were more severely convoluted. For BisGMA-HEMMA, the conversion of each peak was calculated as previously described [22,23]. The rate of polymerization was calculated as the first derivative of the conversion vs. time curve [24].

### 2.3. *Water sorption and solubility*

The same samples used in the polymerization kinetics were tested for water sorption and solubility, according to Ref. [25]. Briefly, the mass of the disks was determined before (m1) and after immersion in distilled water for one week (m2). The disks were then stored in a desiccator until the mass stabilized (m3), which took around one week. Water sorption (WS) and solubility (SL) were calculated using the following equations:

$$WS = \left(\frac{m2 - m1}{V}\right)$$

$$SL = \left(\frac{m3 - m1}{V}\right)$$

where V is the volume of the specimen.

### 2.4. *Microtensile bond strength*

Recently extracted caries-free human third molars (n = 6) had the cusps removed to expose a flat dentin surface. This study was approved by the Oregon Health & Science University IRB (#IRB00012056). The dentin surface was etched with 35% phosphoric acid (3M ESPE, St. Paul, MN, USA) for 15 s, rinsed and blotted dry. The adhesive materials were applied in two consecutive coats, photoactivated for 20 s. For this test only, Adper Single Bond (3M-ESPE) was included as a commercial control. A block of composite (Filtek Supreme, A2, 3M-ESPE) was built in 2 increments with 2 mm thickness, photoactivated for 20 s each at 700 mW/cm$^2$ (Demi Plus, Dentsply-Sirona, Milford, DE, USA). The tip of the light guide (8 mm in diameter) was positioned 1 mm away from the composite, and the irradiance was checked daily at the same distance using a clinical grade radiometer (Demetron LED radiometer, Kerr Co., Orange, CA, USA). The restored teeth were stored for 24 h in distilled water, then sectioned to produce 1 × 1 mm$^2$ sticks. The sticks were then stored for an additional 24 h or 3 weeks in distilled water at 37 °C, and then tested in tension (0.5 mm/min) until failure to determine microtensile bond strength using a custom-made jig (Odeme equipamentos, Luzerna, SC, Brazil) attached to a universal testing machine (Criterion, MTS, Eden Prairie, MN, USA). Selected groups were also tested after storing the sticks for 6 months in distilled water at 37 °C.

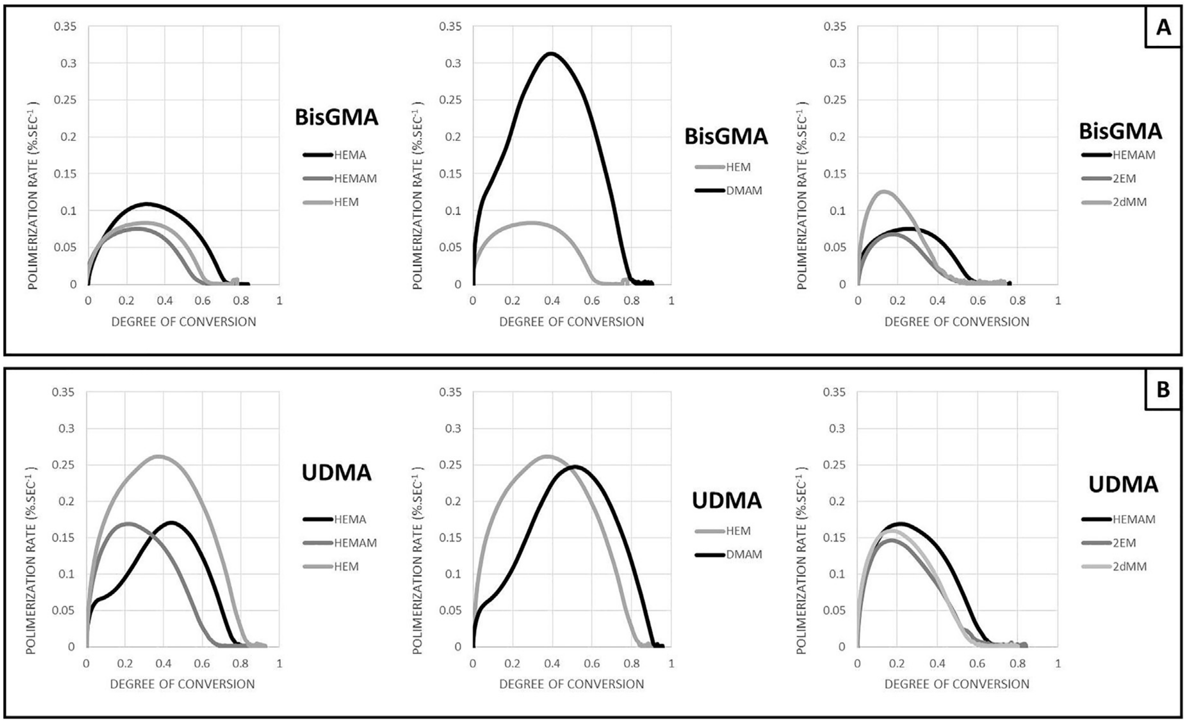


**Fig. 1 – Polymerization rate (% $s^{-1}$) as a function of conversion (%) for non-solvated BisGMA and UDMA-containing adhesives are shown in figures A and B, respectively. Vinyl conversion was followed in real-time as the materials were photocured (630 mW/$cm^2$ for 300 s). (A1 and B1) Comparison of methacrylate, secondary methacrylamide and tertiary acrylamide. (A2 and B2) Comparison of the two tertiary acrylamides. (A3 and B3) Comparison of the secondary methacrylamides.**

### 2.5. *Mechanical properties*

The yield strength (YS) and elastic modulus (E) were analyzed using three-point bending, according to ISO 4049. Twelve rectangular bars (2.0 × 2.0 × 25.0 mm) per group were produced in silicone molds placed between two glass slides. Specimens were polymerized with a single exposure at 630 mW/$cm^2$ using a mercury arc lamp filtered to 320–500 nm (Acticure). The tip of the light guide was positioned 7 cm away from the specimen, creating a spot size large enough to expose the entire bar in one shot, and eliminating heating concerns from the light source. Half of them were stored dry for 24 h, and the other half for 7 days in 20 ml Milli-Q water. Specimens were tested at 0.5 mm/min cross-head speed, with 20 mm between supports. Elastic modulus (GPa) was calculated according to:

$$E = \frac{3LD^3}{2wdh^3}$$

where L is the maximum load (N), D the span between the supports (mm), w the specimen width (mm), h the specimen height (mm), and d the deflection corresponding to L (mm).

Yield strength values (MPa) were obtained for all materials for accurate comparisons of material strength before any plastic deformation occurred. This was achieved by applying a 0.2% offset from the initial elastic region on a stress–strain curve.

### 2.6. *Monomer degradation in low pH environment*

Aqueous solutions with pH values 1, 2, 4, 5 and 7 were prepared using deuterium oxide ($D_2O$, pH 9.8) and adjusted by adding deuterium chloride (20 w/w % in $D_2O$). 1.2 mL of 60 mM solutions of each of the 9 tested monomers were prepared at 5 different pH values (n = 3). The aqueous solutions were stored in capped NMR tubes at 37 °C for 30 days. The pH was measured weekly to ensure that the potential production of acidic by-products (methacrylic acid) did not lead to pH changes. A 45-pulse was used for NMR observation, with accumulation and repetition times of 1000 and 3.8 s, respectively. Detailed procedures and calculations are described in Supplementary Appendix materials.

### 2.7. *Statistical analysis*

After normality and homocedasticiy tests, data were analyzed with one-way ANOVA and Tukey's test ($\alpha = 0.05$).

## 3. Results

Polymerization kinetics (rate of polymerization as a function of conversion) for all experimental materials combined with BisGMA and with UDMA are presented in Fig. 1A and B, respectively. Values of maximum rate of polymerization ($RP_{max}$), degree of conversion at the maximum rate/onset of deceleration (DC at $RP_{max}$, used to estimate the onset of vitrication) and the degree of conversion at 40 s (as an example of the con-

**Table 2 – Average (SD) of maximum rate of polymerization (Rp max) (% s$^{-1}$), degree of conversion at Rp$_{max}$ (DC at Rp$_{max}$) and degree of conversion at 40 s (%) for BisGMA and UDMA mixed at 60 wt% with the different mono-functional monomers. Values followed by the same upper case letter within the same column are statistically similar.**

| | BisGMA | | | UDMA | | |
|---|---|---|---|---|---|---|
| | Rp$_{max}$ | DC at Rp$_{max}$ | DC at 40 s | Rp$_{max}$ | DC at Rp$_{max}$ | DC at 40 s |
| HEMA | 10.9(0.6)B | 29.8(1.9)BC | 67.7(2.7)B | 17.1(0.1)B | 44.7(1.0)B | 75.3(1.2)B |
| HEMAM | 6.9(0.9)C | 26.1(0.2)C | 47.3(6.9)D | 16.9(0.2)B | 22.7(0.9)D | 65.4(1.5)C |
| HEM | 8.3(1.4)C | 29.6(0.6)BC | 60.3(0.7)C | 26.2(0.5)A | 36.5(2.3)C | 84.2(1.9)A |
| DMAM | 31.3(0.6)A | 39.1(2.9)A | 81.3(0.8)A | 24.6(2.0)A | 54.0(0.9)A | 91.0(1.5)A |
| 2dMM | 12.4(0.6)B | 14.5(3.0)D | 45.3(0.6)D | 15.9(0.2)B | 18.6(1.6)DE | 57.0(1.0)D |
| 2EM | 6.8(0.1) C | 18.5(0.7)D | 41.3(0.7)D | 14.7(0.6)B | 16.5(2.7)E | 58.4(1.6)CD |
| p | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

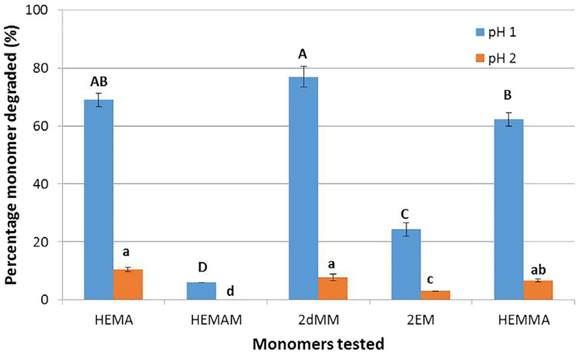


**Fig. 4 – Percentage of remaining monomer after hydrolytic degradation at pH 1 and 2, as determined by the $^1$H NMR experiments (described in detail in Supplementary Appendix). Different uppercase letters indicated statistical difference among neat monomers incubated at pH 1 and different lowercase letters indicated statistical difference among neat monomers incubated at pH 2 ($p \leq 0.001$). Note: the tertiary methacrylamide (HEMMA) was tested instead of the tertiary acrylamide (HEM). DMAM was not tested.**

version at clinically-relevant exposure times) are presented in Table 2. In general and as expected, the acryl versions of the monomers presented higher polymerization rates and conversions compared to the methacryl versions of the monomers. UDMA-containing mixtures also presented higher rates and conversion values compared to the BisGMA counterparts.

Results for water sorption and solubility are shown in Fig. 2. For UDMA mixtures, in terms of water sorption, DMAM showed the highest results (224.7 μg/mm$^3$), followed by HEM > HEMA = 2dMM = 2EM (203.5, 102.8, 102.7, and 102.7 μg/mm$^3$, respectively). DMAM showed the highest solubility in both co-polymerizations (UDMA = 44.3 and BisGMA 52.3 μg/mm$^3$). The most solubility resistant monomers were HEMA, HEM and 2dMM. BisGMA co-polymerizations showed similar trend for water sorption results in comparison to UDMA mixtures (DMAM > HEMA > 2EM = 2dMM), except HEM that showed the lowest results (38.7 μg/mm$^3$).

Results for microtensile bond strength are shown in Fig. 3. Immediate μTBS results showed that highest values for BisGMA copolymerizations (HEMA = 33.2, DMAM = 26.0, 2dMM = 25.6, and 2EM = 25.1 MPa) (exception for HEM), and 2EM-U (26.0 MPa). After 3 weeks, DMAM-B, 2dMM-B, and 2EM-B showed the highest results (28.2, 31.0 and 30.0 MPa, respectively), and HEM-U, DMAM-U and 2dMM-U the lowest ones (16.5, 18.1, and 18.5 MPa, respectively). In 6 months, 2dMM-B presented the highest value (27.39 MPa) and HEMA-U the lowest one (12.5 MPa). In general, BiGMA mixtures had slightly better performance than UDMA copolymerizations. In terms of storage time, both methacrylate experimental controls showed significant bond strength reduction after 3 weeks (HEMA-B) or 6 months (HEMA-U). Among the methacrylamides and acrylamides, only 2EM-U presented some reduction over time (6 months); all other versions maintained constant bond strength, even after 6 months.

Results for mechanical properties are shown in Table 3. For UDMA mixtures, HEM, DMAM and 2dMM showed the highest yield strength results (125.5, 100.9, and 100.8 MPa, respectively). After 7 days water storage, 2EM and 2dMM showed the highest values (64.8 and 51.0 MPa, respectively), and HEM the lowest ones (11.84 MPa). The mechanical properties were reduced for all groups after water storage, with the least amount of reduction for 2EM (23.4%) and HEM being the most affected (reduction of 90.4%). For BisGMA mixtures, the highest values of dry yield strength were obtained when HEMA was used as the monofunctional monomer, statistically similar to all others, except for HEM, which showed roughly 50% lower YS compared to the HEMA group. After wet storage, this trend was maintained, with percent reductions in YS ranging from 51 (HEMA) to 64% (HEM). Except for HEMA formulations, there was no statistically significant difference between BisGMA and UDMA mixtures under dry storage ($p < 0.001$). However, under wet conditions, in general, BisGMA mixtures showed higher results ($p < 0.001$). In relation to the modulus, UDMA mixtures followed the same trend describe for the yield strength results for both storage conditions (dry: DMAM (4.37) ≥ 2dMM (4.01) ≥ HEM (3.94) ≥ HEMA (3.46) = 2EM (3.42)–wet: 2dMM (2.50) = 2EM (2.47) > HEMA (2.06) > DMAM (1.34) > HEM (0.48)). For BisGMA, the highest value for dry elastic modulus was obtained by BisGMA/HEMA mixtures, statistically greater than all other groups. The mixtures containing HEM presented statistically lower results than all other groups (except for 2dMM). All combinations were affected by the water storage ($p < 0.001$).

Neat monomer degradation results are shown in Fig. 4. No degradation was observed at pH 4, 5 or 7 after 30 days incubation for any of the monomers tested. At pH 1 and 2, the degree of degradation for each monomer increased with time. HEMAM showed one order of magnitude greater stability than HEMA at pH = 1, with 6.0 (0)% degradation compared to 69.0

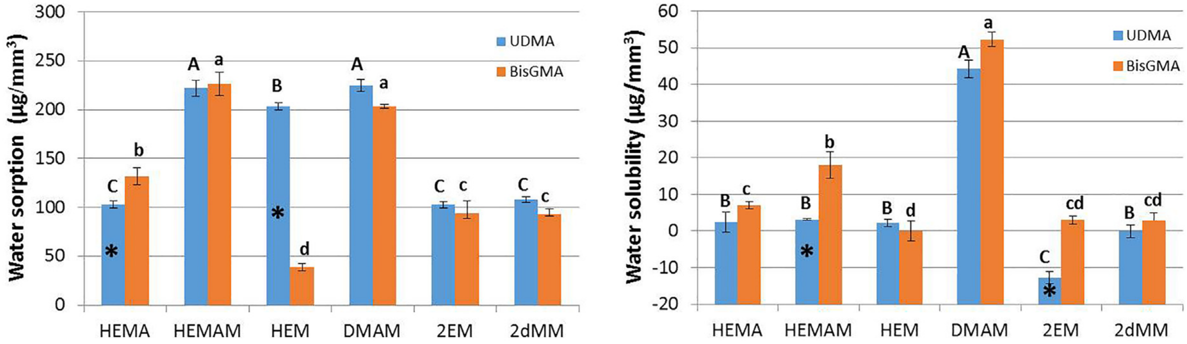


Fig. 2 – Water sorption and Solubility results for all tested copolymerizations. Different uppercase letters indicate statistically significant differences among the monofunctional monomers copolymerized with BisGMA ($p \leq 0.05$). Different lowercase letters indicate statistically significant differences among the monofunctional monomers copolymerized with UDMA copolymerizations ($p \leq 0.001$). Significant differences between BisGMA and UDMA within the same monofunctional monomer are indicated by asterisks ($p < 0.05$).

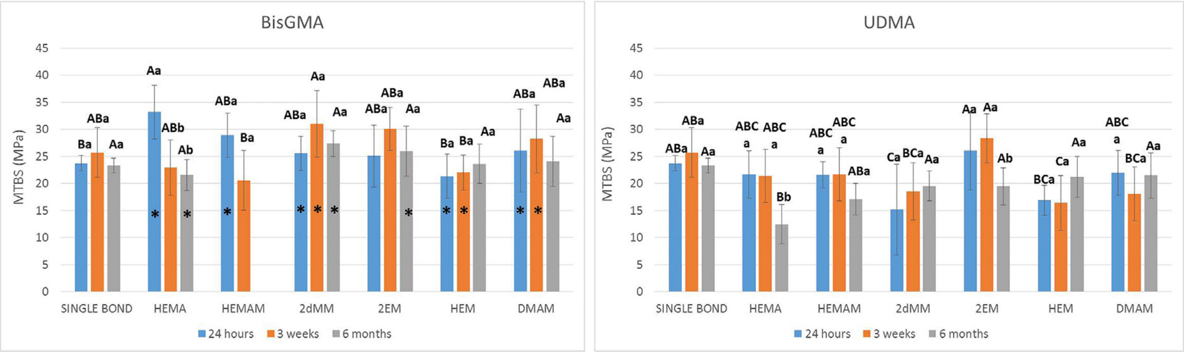


Fig. 3 – dentin micro-tensile bond strength (MPa) for control groups and all mono-functional monomers copolymerized with BisGMA and UDMA after 24 h (blue), 3 weeks (orange) and 6 months (grey) water storage. Different uppercase letters indicate statistically significant differences between the groups within the same storage time ($p < 0.05$). Different lowercase letters indicate statistically significance difference between the storage times within the same group. Significant differences between BisGMA and UDMA within the same monofunctional monomer are indicated by asterisks ($p < 0.05$). The BisGMA/HEMAM materials were not tested at 6 months. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3 – Yield Strength (MPa) and elastic modulus (E) for all tested co-polymerizations after 48 h dry and 1 week wet storage. Different uppercase letters indicate statistically significant differences between the monofunctional monomers copolymerized with the same base monomer and under the same storage condition. Different lowercase letters indicate statistically significance differences BisGMA versus UDMA co-polymerizations. Asterisks indicate statistically significant differences within each material between the storage conditions (meaning all materials were statistically affected by water storage). Overall level of significance for statistical analysis: 95% ($\alpha < 5\%$).

| Base | Mono-functional monomer | Yield strength (MPa) | | Reduction (%) | Modulus (GPa) | | Reduction (%) |
|---|---|---|---|---|---|---|---|
| | | Dry | Wet | | Dry | Wet | |
| BisGMA | HEMA | 155.2 (20.7)Aa* | 76.6 (7.3)Aa | 51 | 5.9 (0.2)Aa* | 2.8 (0.3)Aa | 53 |
| | HEM | 77.1 (9.4)Bb* | 27.5 (4.3)Ca | 64 | 2.3 (0.3)Cb* | 1.7 (0.3)Aa | 26 |
| | DMAM | 124.6 (19.8)ABa* | 51.2 (6.4)Ba | 59 | 4.6 (0.2)Ba* | 2.8 (0.4)Aa | 39 |
| | 2EM | 100.9 (19.8)ABa* | 42.0 (3.7)BCa | 58 | 4.0 (0.5)Ba* | 2.58 (0.6)Aa | 35 |
| | 2dMM | 109.4 (6.3)ABa* | 51.3 (5.2)Ba | 53 | 3.6 (0.2)BCa* | 2.22 (0.2)Aa | 38 |
| UDMA | HEMA | 85.3 (6.0)Bb* | 58.9 (8.0)Bb | 31 | 3.46 (0.3)Bb* | 2.06 (0.1)Bb | 40 |
| | HEM | 123.5 (18.2)Aa* | 11.84 (2.37)Db | 91 | 3.94 (0.3)ABa* | 0.48 (0.01)Db | 87 |
| | DMAM | 100.9 (15.2)ABa* | 31.8 (10.8)Cb | 69 | 4.37 (0.5)Aa* | 1.34 (0.2)Cb | 69 |
| | 2EM | 84.6 (12.3)Ba* | 64.8 (8.5)Aa | 23 | 3.42 (0.2)Bb* | 2.47 (0.2)Aa | 28 |
| | 2dMM | 100.8 (21.6)ABa* | 51.0 (6.0)Aa | 49 | 4.01 (0.2)ABa* | 2.50 (0.3)Aa | 38 |

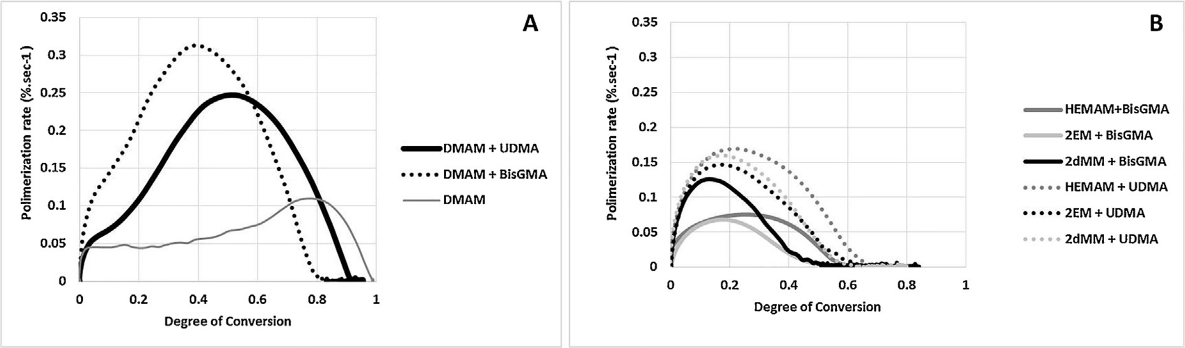


**Fig. 5 – (A) Kinetics polymerization curves of pure DMAM and combined with UDMA and BisGMA. (B) Comparison between UDMA and BisGMA when mixed with the secondary methacrylamides.**

(2.3)% for HEMA. At pH 2, HEMAM did not show any significant amount of degradation products, compared to 10.5 (0.7)% degradation for HEMA. For the alpha-substituted methacrylamides in relation to HEMAM, the degree of degradation of the monomers followed the order: HEMAM < 2EM < 2dMM. The tertiary methacrylamide presented degradation statistically similar to HEMA.

## 4. Discussion

Most commercial adhesive systems are based on ester-containing methacrylate polymers, making them susceptible to hydrolysis and enzymatic degradation [26]. (Meth)acrylamides lack ester bonds and are more hydrolytically stable [27], which makes their use for adhesive applications a logical alternative to overcome intraoral degradation issues. However, for these monomers to be useful in dental applications, a balance must exist between their reactivity and susceptibility to degradation. In this study, this was evaluated in terms of water sorption and solubility and degradation potential as a function of pH, and correlated to the short- to medium-term microtensile bond strength.

BisGMA presents a few limitations as a base monomer, including the potential for BPA contamination (though the risk is low, and many studies have failed to demonstrate its presence from commercial materials containing BisGMA — [28]), the high viscosity, which precludes the inclusion of larger amounts of filler in composites, and the potentially decreased diffusion of adhesive formulations in the dentin tubules [29]. For these reasons, UDMA was also tested as a potential base monomer. When comparing monomers with the same polymerizable functionality, such as HEM and DMAM, both tertiary acrylamides, different polymerization kinetic profiles can be observed for the copolymerizations with BisGMA (Fig. 1A). DMAM had a polymerization rate almost four times greater than HEM (31.2 vs. 8.3%$\cdot$ $s^{-1}$, respectively), as well as higher degree of conversion (90.2% vs. 78.1%, respectively). This dramatic difference can be explained by the much lower initial viscosity of DMAM compared to HEM. BisGMA is a very viscous monomer (1̃400 Pa s) and does not reach conversions much higher than 30% in homopolymerizations, due to early onset of diffusional limitations to propagation [30]. The addition of lower viscosity diluents, such as TEGDMA, has been shown to significantly increase the conversion of BisGMA [31]. In this study, the lower viscosity of DMAM contributed to delaying diffusional limitations (and the onset of autoacceleration/deceleration) to higher degrees of conversion, which increased both the maximum rate of reaction as well as the final conversion in relation to the more viscous HEM mixtures.

However, although the maximum rates of polymerization were similar for HEM and DMAM in copolymerizations with UDMA, their kinetic profiles were markedly different (Fig. 1B), with a two-stage kinetic profile ("shoulder") when DMAM is used (this was also the case in the copolymerization of DMAM with BisGMA and of HEMA with UDMA, discussed later). This kinetic profile, although not conclusive, points to the formation of distinct phases within the material, either via polymerization-induced phase-separation or the formation of interpenetrating polymer networks (IPNs). IPN formation, rather than co-polymerization, is common when monomers with differential reactivity are polymerized together [32]. Since the reactivity of DMAM/HEMA, and monofunctional monomers in general [33], is very low in homopolymerizations, it can be speculated that the first stage in the kinetic profile corresponds to the faster polymerization of UDMA or BisGMA-rich phases, followed by the polymerization of DMAM or HEMA-rich phases [34]. Moreover, when comparing the DMAM copolymerizations with UDMA or BisGMA, the rates are much lower for the former (Fig. 5), likely due to the much greater initial viscosity for BisGMA. This led to much faster autoacceleration for BisGMA, which reached $Rp_{max}$ at lower conversion and much faster deceleration than UDMA. Therefore, the mixture of DMAM/UDMA ultimately reached higher conversion than the DMAM/BisGMA mixture.

It is also possible that the miscibility of the different monomers both prior and during polymerization has influenced the results. All monomers were completely miscible at room temperature, and presented as a single phase before curing. It is possible that the mixture is only metastable, however [35]. As the polymerization proceeds, the polymeric chains increase in length and molecular weight, decreasing the entropy of mixing and reducing the miscibility [32,36,37]. Therefore, the degree of mixing is controlled by the balance between the kinetics and thermodynamics of cure, because large-scale macro-molecular diffusion and subsequent phase-separation are not usually observed after gelation [16,38], with notable exceptions including liquid crystal systems, which are not relevant to the present study [35]. If sufficient cross-linking takes place before substantial diffusion of the components can occur, phase-separation is prevented and a high degree of mixing will be obtained [38,39]. For UDMA + HEMA, the DC at $Rp_{max}$ was much higher (44.7 ± 1.0%), as compared to 29.8 ± 1.9% for BisGMA/HEMA, indicating that the system preserved its mobility to much higher stages in conversion. This could have allowed for the diffusion of monomers in a state of metastability [40,41], leading to the formation of two (or more) types of domains with different compositions [40]. The reactivity difference between the monomers involved in the mixture causes one of them to react faster, thereby forming both highly internally cross-linked and loosely connected microgel particles, and explaining the shoulder present on the kinetics curve [40].

In relation to the secondary methacrylamides with α-carbon substitutions, 2dMM showed polymerization rate that was almost twice as high as that of HEMAM (no substitution in the α-carbon) and 2EM (12.3, 7.4, and 6.7%$\cdot$ $s^{-1}$, respectively), although the final degrees of conversion were very similar, at 73.7, 75.9, and 72.6%, respectively. This was unexpected, based on the fact that the presence of two bulky groups in 2dMM had been hypothesized to impose greater steric hindrance compared to the somewhat more flexible ethyl group in 2EM. One possible explanation is the electron-donating nature of alkyl chains, which creates a partial negative charge on the carbon they are attached to [42]. In the case of 2dMM, it is possible that partial charge was twice as strong as in 2EM. Since the amide bond is an even stronger electron-donating group [42,43], those partial charges may have combined to provide separation from the electron-rich vinyl group, further exposing the double bond. In addition, the higher polymerization rate of 2dMM in comparison to the other secondary methacrylamides may be due to the fact that its calculated logP value is much more similar to that of BisGMA (logP: 2dMM = 0.33, 2EM = 0.60, HEMAM = −0.21, BisGMA = 5.09) — Table 1. It can be speculated that this improves miscibility and facilitates copolymerization. In general, the association between the secondary methacrylamides with UDMA led to more reactive mixtures than with BisGMA. Comparing the kinetic results, the final degree of conversion increased between 8 and 14%, and the polymerization rate increased by more than two-fold for HEMAM and 2EM, and 25% for 2dMM when combined with UDMA (Fig. 1B). This was expected due to the difference of reactivity between UDMA and BisGMA [44], as discussed above. Another interesting aspect is that the UDMA combinations followed exactly the same trend indicated by the steric hindrance, with HEMAM being slightly more reactive than 2EM and 2dMM. However, in BisGMA mixtures, the miscibility seems to have played a more crucial role than the steric hindrance [43].

Water uptake leads to deterioration of the mechanical properties due to the increasing free volume as the water swells the polymer and disrupts intermolecular interactions between polymeric chains [45,46]. Amides are known to be more hydrolytically stable than acrylates [47], but they have also been demonstrated to be more hydrophilic [48]. Water uptake in the amides is maximized by the fact that the electron-withdrawing oxygen of the carbonyl group decreases the nitrogen electronic density more markedly than for the oxygen-containing methacrylate, making the former slightly more polar. Interestingly, these same factors increase the resonance stability of the methacrylamide monomer, and make it less prone to hydrolysis compared to methacrylates [21]. In this study, these effects were further compounded by the fact that the mono-functional monomers were co-polymerized with dimethacrylates, which made up for 60 wt% of the overall formulation. Therefore, it was expected that the absolute values for dry and wet mechanical properties would be largely influenced by the dimethacrylate structure.

As far as the stability of the neat monomers, no degradation was observed at pH 4, 5 or 7, even after 30 days of incubation. The lack of degradation of all the monomers at pH 4 and 5, which are still acidic environments, is in agreement with the results of others [49]. At pH 1 and 2, as expected, the degree of degradation for each monomer increased with time. The results for two structurally similar monomers, methacrylamide HEMAM and methacrylate HEMA, agreed with previous reports stating that methacrylamides are more stable to hydrolysis than the analogous methacrylates [49]. This is due to the stronger character of the amide bond due to its inherent double bond component, derived from the electron donation of the nitrogen lone pair into the N—C bond. At pH 2, HEMAM did not show any significant amount of degradation products, which compared favorably to the 10.5 (0.7)% degradation for HEMA. The systematic addition of alkyl groups at the α-carbon to the nitrogen in HEMAM led to secondary methacrylamides 2dMM and 2EM. It was hypothesizes that the addition of electron-donating alkyl chains to the alpha-carbon on the methacrylamides would contribute to the stabilization of the amide bond. However, there is a clear increase of the degree of degradation as the steric bulkiness at the α-carbon increased, thus leading to a rejection of this hypothesis. These results indicate that the steric demand imparted by the substituents at that position creates strain in the amide bond, weakening it.

For BisGMA, the (meth)acrylamides had similar percent reduction in yield strength (YS) compared to the methacrylate control (HEMA). The reduction in YS values was 51% for HEMA and varied between 53–59% for the remainder groups. HEM, the tertiary acrylamide containing a terminal hydroxyl group, showed a much greater reduction in yield strength, of 64%. The reduction in modulus for the BisGMA groups was actually greater for HEMA (53%) as compared to the (meth)acrylamide groups (35–39%). Regardless, the YS and E values after storage in water were statistically similar for all groups. Interestingly, contrary to what was expected, the water sorption and solubility results did not seem to correlate with the drop in mechanical properties for the BisGMA groups. For example, DMAM had the highest WS/SL values, and yet the drop in mechanical properties was similar or less than its counterparts with much lower WS/SL values. This points to the complexity of structure-property relationships in polymer networks. At least two factors need to be considered: the partition coefficient (log P) and final degree of conversion (Table 1). Among the monofunctional monomers tested, DMAM is the second most hydrophilic (log P = 0.2), and the one with the smallest molecular weight. This only partially explains why its WS was the highest. However, if the partition coefficient was the only or most important factor, then HEM (log P = −0.32) should have presented the highest WS, and at least for BisGMA co-polymerizations, the opposite was observed. This was possibly related to the formation of IPNs, as already explained, which, under certain conditions, can be more prone to solvation [50]. This allied with the low log P value, helps explain the high WS observed. For UDMA-based materials, the correlation between WS/SL and mechanical properties is clearer. The materials with the greatest WS were also the ones to present the highest percent reductions in both YS and E. For DMAM, the drop in YS/E after water storage was 70%, while for HEM, the reduction was 91 and 99% for YS and E, respectively. DMAM still had the statistically highest WS/SL, likely also explained by the formation of interpenetrating networks [50].

It is noteworthy that in co-polymerizations with HEMA, BisGMA (log P = 5.09) presented higher WS/SL than UDMA (log P = 3.64), in spite of BisGMA's higher log P and therefore, greater hydrophobic character [46,51]. Again, this is explained based on the much greater conversion value achieved in the co-polymerization with UDMA. Finally, the secondary methacrylamides with substitution on the α-carbon (2dMM and 2EM) were the most stable compounds, with either base monomer, both in terms of WS/SL (among the lowest values achieved) and of percent mechanical property reduction (according to values calculated in Table 2). This was expected based on their relatively higher log P values (0.33 and 0.25, respectively), and also on the conversion values, which indicate co-polymerization with the base monomers. This is significant in light of the bond strength results discussed in the following paragraphs.

In terms of immediate μTBS results, formulations containing BisGMA as the base monomer presented slightly higher values compared to UDMA-based ones, in general, though the differences were not statistically significant for all groups. This is in general agreement with the mechanical properties, as already discussed. Within BisGMA groups, except for HEM formulation, all materials showed similar results ($p > 0.05$) at 48 h. The lowest values for HEM were not completely unexpected, due to the sharp decrease in yield strength after water storage (64%) and the initially much lower modulus (60% lower than HEMA-containing materials) shown by this tertiary acrylamide. After 3 weeks and 6 months water storage, the MTBS values presented by all groups were statistically similar to the methacrylate control (HEMA). The reduction in MTBS for the HEMA containing material was about 30%, observed at 3 weeks storage and maintained at 6 months. For all other groups, no reduction in MTBS was observed. For the UDMA-based formulations, at 48 h and 3 weeks all experimental materials were statistically similar to the control, and no drop in bond strength was observed for any of the groups. After 6 months storage, all (meth)acrylamide-containing formulations had statistically higher MTBS values than the methacrylate control. While the methacrylate presented a drop of roughly 40% in MTBS after 6 months, no drop was observed for the (meth)acrylamide-containing formulations. In summary, two interesting findings need to be highlighted: 1. within a given base monomer, the (meth)acrylamides led to more stable bonds after 6 months; 2. when (meth)acrylamides were used as the monofunctional monomer, the base monomer did not affect bond strengths. This indicates that the use of these novel monomers can lead to more stable bonds, and may allow for the use of BisGMA-free formulations.

One explanation for the unstable bonding presented by the methacrylates and the consistent performance of the acrylamides and methacrylamides is based on the different enzymatic and hydrolytic degradation susceptibilities shown by these compounds, as already discussed. The fact that methacrylates are based on ester bonding makes these compounds highly prone to hydrolysis [46]. It has been well established that pendant and unreacted methacrylate monomers, in the presence of water, are hydrolyzed to produce alcohol and methacrylic acid intermediates after storage in distilled water. It is also possible for methacrylamides to undergo hydrolysis under specific conditions, but the substitution of the ester group with an amide significantly decreases this susceptibility, since this functional group is more resistant to nucleophilic attack due to resonance stabilization and the donating of non-bonded electrons from the nitrogen to the carbonyl carbon. This delocalization reduces the carbonyl carbon electrophilicity and, consequently, reduces its susceptibility to nucleophilic attack [20]. Since the oxygen in the methacrylates is more electronegative than nitrogen, this atom is less likely to donate its non-bonded electrons to the adjacent carbonyl, which results in a lower degree of resonance delocalization through the ester carbonyl than in the amide carbonyl, and makes ester carbonyl carbons more electrophilic than amide carbonyl carbons. In summary, amides undergo hydrolysis but at a slower rate than esters, which may partially explain the stable μTBS results even after a long-term storage [20].

In this study, to further improve the stability of methacrylamides, the monomers were designed to take advantage of potential steric mechanisms to curtail the hydrolysis process. Bulk substitutions were added to the carbon alpha to the carbonyl in an attempt to reduce the hydrolysis rate [20], which, allied to the other factors related to log P already discussed, may have contributed to the greater bonding strength performance of the alpha-substituted monomers 2EM and 2dMM compared to the two acrylamides. In the dentin, however, other than the presence of water, the hydrolysis may be enhanced by the presence of enzymes. At least for salivary enzymes such as cholesterol esterase and pseudocholesterol esterase, the direct hydrolysis of methacrylates has been convincingly demonstrated [46,52]. The two monomers with the best microtensile bond strength performance (as defined by maintenance of the bond strengths value after 6 months storage) were subjected to incubation in water or in the presence of cholinesterase as neat compounds, and the percent intact monomer remaining was quantified with HPLC. The results show that under aqueous conditions, HEMA showed 8% of degradation, while 2EM and 2dMM presented virtually no degradation. Under enzymatic conditions the difference between the methacrylate and the alpha-substituted secondary methacrylamides was even more marked, with HEMA showing 52% of degraded monomers, compared to 22 and 8% for 2EM and 2dMM, respectively. In both tested conditions the methacrylamides were significantly more stable than the methacrylate, which may help explain the μTBS results, in spite of the significant drop in mechanical properties observed for those networks.

These results highlight the fact that the bonding strength is not only a product of the materials mechanical properties, but is highly dependent on the quality of the interaction between the adhesive layer and the dental substrate, complicated by temperature and chemical challenges by acids and enzymes. Several studies have shown that amides can form hydrogen-bonded interactions with the carboxylic acids of the side-chain of aspartic and/or glutamic acids in the macromolecule of the dentinal collagen [21,48]. This occurs due to the presence of a triple helix structure associated with a hydrogen bond between the >C=O of the proline residue and the >NH of the glycine residue on the dentinal collagen [49,53,54]. These hydrogen bonds between the amides and the collagen fibrils would translate to stronger and more stable bond strength, besides potentially working as metalloproteinase (MMP) inhibitors [55].

## 5. Conclusion

In conclusion, the results of the present study indicate that the alpha-substituted secondary methacrylamides led to more stable bonds after 6 months, which was true regardless of the base monomer (BisGMA or UDMA). Steric hindrance influenced the polymerization kinetics of the monomer mixtures. However, copolymerization is a complex reaction affected by many additional factors, such as initial viscosity, partition coefficient, intermolecular interactions, and reactivity. Overall, UDMA copolymerizations were faster and progressed to a greater extent than BisGMA. These novel monomers may be a viable alternative for dental adhesives, including BisGMA-free formulations.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dental.2019.02.012.

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