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New Silyl-Functionalized BisGMA Provides Autonomous Strengthening without Leaching for Dental Adhesives

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Abstract

Resin-based composite has overtaken dental amalgam as the most popular material for direct restorative dentistry. In spite of this popularity the clinical lifetime of composite restorations is threatened by recurrent decay. Degradation of the adhesive leads to gaps at the composite/tooth interface—bacteria, bacterial by-products and fluids infiltrate the gaps leading to recurrent decay and composite restoration failure. The durability of resin-dentin bonds is a major problem. We address this problem by synthesizing silyl-functionalized BisGMA (e.g., silyl-BisGMA), formulating dental adhesives with the new monomer and determining the physicochemical properties and leaching characteristics of the silyl-BisGMA adhesives. Silyl-BisGMA was synthesized by stoichiometric amounts of BisGMA and 3-isocyanatopropyl trimethoxysilane (IPTMS). The control adhesive was a mixture based on HEMA/BisGMA (45/55, w/w). In the experimental formulations, BisGMA was partially or completely replaced by silyl-BisGMA. Water miscibility, polymerization behavior (Fourier transform infrared spectroscopy, FTIR), thermal property (modulated differential scanning calorimetry, MDSC), mechanical properties in dry and wet conditions (dynamic mechanical analysis, DMA), and leached species (HPLC) were investigated. Data from all tests were submitted to appropriate statistical analysis ($\alpha = 0.05$). Silyl-BisGMA-containing adhesives exhibited comparable water miscibility, lower viscosities, and significantly improved degree of conversion of C=C bond as compared to the control. After 4 weeks aqueous aging, the glass transition temperature and rubbery moduli of the experimental copolymers were significantly greater than the control ($p < 0.05$). HPLC results indicated a substantial reduction of leached HEMA (up to 99 wt%) and BisGMA (up to 90 wt%). By introducing silyl-functional group, the new BisGMA derivative exhibited potential as a monomer that can lead to dental adhesives with improved mechanical properties and reduced leaching under conditions relevant to the oral environment.

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Graphical abstract

Keywords

BisGMA; Self-strengthening; Polymerization Kinetic; Dental Adhesive; Dynamic Mechanical Analysis; Elution

1. Introduction

It is widely agreed that resin-based composite has overtaken dental amalgam as the most popular material for direct restorative dentistry. Indeed, the popularity of composite continues to grow in spite of differences in durability, e.g. the failure rate of composite restorations can be 3 to 3.5 times greater than dental amalgam [1]. The primary reason for restoration failure is recurrent decay and results from clinical studies suggest that 80–90% of recurrent caries are located at the gingival margin of class II and V composite restorations [2].

The viscous composite is not attached directly to the tooth instead an adhesive is used to bond the hydrophobic composite to the tooth. At the gingival margin, the adhesive and the bond that it forms between the composite and tooth may be the first defense against enzymes, acids, bacteria and other substances that can undermine the composite restoration. The adhesive is a mixture of hydrophilic and hydrophobic monomers. The monomers are critical to the formation of a crosslinked matrix that is designed to provide chemical and physical stability at the composite/adhesive/dentin interface [3–11]. Because of its high esthetic quality and superior mechanical strength, bisphenol A-glycerolate dimethacrylate (BisGMA) is a popular crosslinking monomer used in dental adhesives and resin composites [12–15].

The main drawback of BisGMA is related to its high viscosity, attributed to the hydrogen bonding between the hydroxyl groups in the monomer [16]. To overcome this disadvantage, a mono-methacrylate monomer with low viscosity and hydrophilic characteristics (water-miscible), 2-hydroxyethyl methacrylate (HEMA) [11, 17, 18], and low-viscosity crosslinkers, such as triethyleneglycol dimethacrylate (TEGDMA), diurethane dimethacrylate (UDMA), or glycerol dimethacrylate (GDMA), have been introduced [19–23]. The developed adhesive formulations showed a relatively low viscosity, improved degree of conversion [19, 20, 24], and higher tensile strength [19]. The increased water sorption and decreased mechanical strength of the formulations produced with these low-viscosity crosslinkers have inhibited their use as replacements for BisGMA [19, 22, 25, 26]. Another attractive strategy is related to BisGMA derivatives through chemical modification of hydroxyl groups with different functional groups to obtain alkoxy, alkyl urethane, silylated, carboxyl-functionalized, and fluorinated derivatives [27–35]. With the substitution

of hydroxyl groups, the viscosities of BisGMA derivatives are reduced significantly as compared to BisGMA. However, due to the long hydrocarbon chain ($n=2-8$) and lack of functionality, the mechanical properties, e.g. flexural strength, were compromised [27, 28].

Recently, we have developed a self-strengthening strategy to reinforce the dental adhesive by introducing photoacid-catalyzed sol-gel reaction together with the free radical photopolymerization of methacrylate [36, 37]. The results indicated that in wet conditions, the sol-gel reaction is a suitable and novel approach to enhance the mechanical properties of the newly developed dental adhesive copolymers [36]. In response to the limitations noted with BisGMA and its derivatives, a methoxysilyl functionalized BisGMA derivative (silyl-BisGMA) was introduced in this work. Our design was based on the hypothesis that blocking the hydroxyl groups of BisGMA would reduce the viscosity, and the silyl-functional group would offer autonomous strengthening characteristics. The present study tests the hypotheses that: i) blocking hydroxyl group of BisGMA can significantly reduce the resin viscosity, ii) the mechanical properties of dental adhesives can be improved, and iii) the self-strengthening reaction can significantly reduce the leachates. The new monomer was incorporated in dental adhesive formulations and the polymerization behavior, mechanical properties, and leaching characteristics of the formulations were investigated.

2. MATERIALS & METHODS

2.1 Materials

2,2-Bis[4-(2-hydroxy-3-methacryloxypropoxy) phenyl] propane (BisGMA), 2-hydroxyethyl methacrylate (HEMA), camphoroquinone (CQ), ethyl-4-(dimethylamino) benzoate (EDMAB), diphenyliodonium hexafluorophosphate (DPIHP), dibutyltin dilaurate (DBTL), and dichloromethane (DCM) were obtained from Sigma-Aldrich (St. Louis, MO) and used as received without further purification. (3-isocyanatopropyl) trimethoxysilane (IPTMS, 95%) was purchased from Gelest Inc. (Morrisville, PA). Silyl-BisGMA was synthesized in our laboratory and used as a co-monomer. All other chemicals were used as received without further purification.

2.2 Synthesis of silyl-BisGMA

BisGMA was reacted with stoichiometric amounts of IPTMS in dry dichloromethane at 23 ± 2 °C for 3 days. Briefly, to a 250-mL, round bottom flask, fitted with a magnetic stirrer and N_2 -purging, BisGMA (5.12 g, 0.01 mol), DBTL (150 μ L) and DCM (100 mL) were added. Then, IPTMS (4.32g, 0.02 mol), dissolved in 50 mL DCM, was added stepwise over 3 h. The progress of the reaction was monitored by FTIR (Spectrum 400, Perkin-Elmer, Waltham, MA) to observe the disappearance of isocyanate (NCO) at 2264 cm^{-1} (see SI Figure 1). After the reaction was completed, the solvent, DCM, was removed by rotary evaporation under vacuum. The structure of the residual colorless liquid was confirmed using FTIR and ^1H NMR spectroscopies (Bruker AVIIIHD 400 MHz Spectrometer, CDCl_3 as solvent). CDCl_3 as solvent). ^1H NMR (CDCl_3 , δ ppm, see SI Figure 2): 0.64(2H, j), 1.63 (5H, i+g), 1.96 (3H, b), 3.17 (2H, h), 3.56 (9H, k), 4.03–4.35 (5H, c+d+e), 5.61, 6.14 (2H, a), 6.80, 7.13) (4H, f).

2.3 Preparation of adhesive formulations

Neat methacrylate resin made by mixing 45 wt% HEMA and 55 wt% BisGMA was used as the control (HB45) [38]. Three components, e.g., CQ (0.5 wt%), EDMAB (0.5 wt%), and DPIHP (0.5 wt%) were used as the photoinitiator (PIs) system [39–41] with respect to the total amount of monomers. The composition of the neat resin and the experimental resin formulations are listed in Table 1. Mixtures of the monomers/PIs were prepared in brown glass vials under amber light.

2.4 Water miscibility of adhesive formulations

The protocol for determining water miscibility of adhesive formulations has been reported [42, 43]. About 0.5 g of each neat resin was weighed into a brown vial with water added in increments of approximately 0.005 g until the mixture was visually observed to be turbid. The percentage of water in the mixture was noted (w_1). The mixture was then back-titrated using the neat resin until the turbidity disappeared, and the percentage of water in the mixture was noted (w_2). The water miscibility (W_{wm} , %) of the liquid formulation was calculated as the average of w_1 and w_2 . Three specimens of each formulation were measured.

2.5 Real-time conversion and maximum polymerization rate

The degree of conversion (DC) and polymerization behavior were determined by FTIR as reported [43]. Real-time (in-situ) monitoring of the photopolymerization behavior of the adhesive formulations were performed using an infrared spectrometer (Spectrum 400, Perkin-Elmer, Waltham, MA) at a resolution of 4 cm^{-1} . A time-based spectrum collector (Spectrum TimeBase, Perkin-Elmer) was used for continuous and automatic collection of spectra during polymerization. One drop of adhesive resin ($5\mu\text{L}$) was placed on the crystal top plate of an attenuated total reflectance (ATR) accessory (PIKE Technologies Gladi-ATR, Madison, WI) and covered with a mylar film. After 30 IR spectra were collected, the adhesives were light-cured for 40 s at $23\pm 2^\circ\text{C}$ using a commercial visible light lamp (Spectrum® 800, Dentsply, Milford, DE. Intensity is 550 mW/cm^2). Real-time IR spectra were continuously recorded for 600 s after the light irradiation was terminated. Triplicate measurements were carried out for each adhesive formulation. Methacrylic double bond conversion was monitored by the band ratio profile 1637 cm^{-1} ($\text{C}=\text{C}$)/ 1608 cm^{-1} (phenyl). The average of the last 30 values of the time-based spectra is reported as the DC value. The maximum polymerization rate ($R_p^{\max}/[M]$) was determined using the maximum slope of the linear region of the DC vs. time plot [44, 45].

2.6 Preparation of Copolymer specimens

The preparation of polymer beams for mechanical property characterization using dynamic mechanical analysis (DMA) has been reported [41]. The prepared resins were injected into a round glass-tubing mold (Wilma LabGlass, P 1M-1.2M-0-914M, item #:1004-5014, Vineland, NJ) or a Tzero® Hermetic Lid (P/N: 900797.901 TA Instruments Waters LLC, New Castle, DE), covered with a mylar film, then light-cured for 40 s at $23\pm 2^\circ\text{C}$ with a LED light curing unit (LED Curebox, 100 mW/cm^2 irradiance, Proto-tech, Portland, OR). The polymerized samples were stored in the dark at $23\pm 2^\circ\text{C}$ for at least 48 h prior to

testing. The resultant round beam specimens with diameter of 1 mm and length of ~15 mm were used to determine dynamic mechanical properties.

2.7 Modulated differential scanning calorimetry (MDSC) test

Three disc-shaped samples (~4 mm diameter and ~1.2 mm thickness) per each formulation were used for the thermal property study. The thermal behavior of copolymer specimens was measured with a TA instruments model Q200 MDSC (New Castle, DE). The disc specimens (~20 mg) were heated under nitrogen purge 50 mL/min from -20 to 200 °C at 3 °C/min, with a modulation period of 60 s and amplitude of ± 2 °C. The second scan was consistent with the first scan. The T_g values were reported as the temperature of the peaks that represented the inflection points in the heat flow curves.

2.8 Dynamic mechanical analysis (DMA)

The dynamic mechanical analyses of polymethacrylate-based dentin adhesives have been described [37, 44]. DMA tests were performed on round beam specimens using a TA instruments Q800 DMA (TA Instruments, New Castle, USA) with a three-point bending clamp. For the wet test, specimens were aged in water at 37 °C for 1, 2 and 4 weeks, tests were performed using the three-point submersion clamp [41], and three specimens were tested for each formulation. The test temperature was varied from 10 to 75 °C with a ramping rate of 1.5 °C/min. For dry testing, the following testing parameters were used: displacement amplitude of 15 μ m, frequency of 1 Hz, and preload force of 0.01 N [46], and four specimens were tested for each formulation. In addition, temperature was ramped at the rate of 3 °C/min from 20 to 200 °C. To measure the final mechanical properties of the aged specimens (aged in water for 4 weeks) in dry conditions, the hydrated specimens were dried in a vacuum oven in the presence of freshly dried silica gel at 37 °C. The samples were removed every 24 hours to determine the weight. This process was continued until a constant mass was recorded. Then, the mechanical properties were determined using the method described above.

2.9 Leachable study by high performance liquid chromatography (HPLC)

Round disc samples (~4 mm diameter and ~1.2 mm thickness) were used for the leachable study [36, 47]. The polymerized disc was submerged in 1 mL ethanol (200 proof) at 23 ± 2 °C for 1 to 28 days. The storage solutions were collected at various time intervals, i.e. 1, 3, 6, 9, 14, 21, and 28 days, and analyzed for concentration of leachates. Fresh ethanol was added to the disc samples after each collection. The analysis was made using high performance liquid chromatography (HPLC) on a system (Shimadzu® LC-2010C HT, software EZstart, version 7.4 SP2) equipped with a 250 $\times$ 4.6 mm column packed with 5 μ m C-18 silica (Luna®, Phenomenex Inc., Torrance, CA). The mobile phase was acetonitrile/water (70/30, v/v). The system was operated under the following conditions: 0.5 mL/min flow rate, detection at 208 nm, 20 μ L sampling loop, 40 °C. The column was calibrated with known concentrations of the following compounds: BisGMA, HEMA, silyl-BisGMA, at concentrations of 5, 10, 20, 50, 100, 250 and 500 mg/L in ethanol. The calibration curves with the linear fittings of BisGMA (5–250 mg/L, $R^2=0.999$), HEMA (5–500 mg/L, $R^2=0.999$), and silyl-BisGMA (5–500 mg/L, $R^2=0.999$) were used to calculate the concentration of these species in the extracts. The concentration was based on the intensity

of the chromatographic peaks at the corresponding retention times. The HPLC analysis was performed using the extract of three samples from each formulation.

2.10 Statistical analysis

The results (water miscibility, viscosity, degree of conversion measured by FTIR, rubbery moduli and glass transition temperature values obtained from DMA, accumulative concentration of leachates determined by HPLC) were analyzed statistically using one-way analysis of variance (ANOVA) together with Tukey's test at $\alpha = 0.05$ (Microcal Origin Version 8.0, Microcal Software Inc., Northampton, MA) to identify significant differences in the means.

3. RESULTS

The water miscibility and viscosity of the control (HB45) and experimental formulations are shown in Table 1. The W_{wm} of the HB45 is 10.5 ± 0.3 wt%. With increasing silyl-BisGMA concentration from 10, 20, 30, to 55 wt%, the W_{wm} remains similar and is not significantly different from the control ($p < 0.05$). The viscosity of HB45 is 181.8 ± 0.4 cP at 25 ± 0.2 °C. With the increase in silyl-BisGMA concentration from 10, 20, 30, to 55 wt%, the viscosities of the experimental adhesives are 173.9 ± 0.6 , 169.4 ± 1.3 , 162.1 ± 0.6 , and 143.6 ± 1.3 cP, respectively.

Figure 2A shows the real-time photopolymerization behavior of the control and experimental adhesives. The experimental formulations exhibit significantly higher DC than that of the control ($p < 0.05$). The maximum polymerization rates ($R_p^{max}/[M]$) of the experimental formulations were significantly lower than that of the control ($p < 0.05$) when silyl-BisGMA concentration was higher than 30 wt% (see Table 1). Figure 2B and C show the characteristic peaks of FTIR spectra of HS45 formulation before and after visible-light irradiation. The hydrolysis of methoxy group $[-Si-(OCH_3)_3]$ was observed through the disappearance of the symmetric stretch band located at 2840 cm^{-1} . Meanwhile, the intensity of the broad band at 3400 cm^{-1} (hydrogen bonded OH stretching mode) increased gradually. The increasing intensity of the peak located at 1025 cm^{-1} indicated the formation of Si–O–Si bond through condensation reaction.

Figure 3 shows the reversing and nonreversing heat flow signals of the control and experimental polymer specimens. In the first heating cycle, two transitions (~ 52 °C and ~ 118 °C) are observed in the reversing heat flow signal. Meanwhile, with the increase of silyl-BisGMA concentration in formulation, the peak area at about $60\sim 120$ °C in nonreversing heat flow signal decreased. In the secondary heating cycle, just one transition appeared (~ 120 °C), and the T_g values of the experimental specimens are comparable to that of the control (121 °C).

Figure 4 shows the mechanical properties of the control and experimental adhesive copolymers soaked in water at 37 °C for 1, 2, and 4 weeks. With the increase in storage time in water from 1 to 4 weeks, the storage moduli of the experimental copolymers at 37 °C are not significantly different from the control ($p < 0.05$) with the exception of HS45.

Figure 5 shows the mechanical properties of the control and experimental copolymers tested in dry conditions before and after aging in water for 4 weeks. With the increase in silyl-BisGMA concentration from 10 to 55 wt%, the rubbery moduli of nonsoaked experimental specimens were significantly higher than that of the control ($p<0.05$). While the T_g showed a decreasing trend and decreased from $\sim 135^\circ\text{C}$ (HB45) to $\sim 101^\circ\text{C}$ (HS45). After aging in water for 4 weeks and drying, the rubbery moduli and T_g of the experimental copolymers are significantly greater than that of the control ($p<0.05$).

Figure 6 shows the results of cumulative monomers released from the control and experimental copolymers as a function of incubation time in ethanol at $23\pm 2^\circ\text{C}$. With the increase of silyl-BisGMA concentration from 0, 10, 20, 30, and 45 wt% in the formulations, the cumulative release of HEMA decreased from 875, 318, 64, 25, to $7.6\text{ }\mu\text{g/mL}$, and the percentage of leached HEMA based on the total HEMA used in the corresponding adhesive formulation decreased from 9.3, 3.4, 0.7, 0.3, to 0.1 wt%. The cumulative release of BisGMA decreased from 467, 142, 56 to $20\text{ }\mu\text{g/mL}$, and the percentage of leached BisGMA decreased slightly from 4.1, 1.5, 0.7, to 0.4 wt%. There is no BisGMA detected in the leachates from the HS45 copolymer. There is no silyl-BisGMA detected in the leachates from the experimental copolymers.

4. DISCUSSION

4.1 Synthesis of Silyl-BisGMA

In this study, a new BisGMA derivative that substituted methoxysilyl groups for hydroxyl groups was synthesized. Silyl-BisGMA was synthesized based on the stoichiometry of isocyanate with hydroxyl group of BisGMA. From the FTIR spectra (see SI Figure 1) it can be observed that the hydroxyl groups (3470 cm^{-1}) have been completely substituted by the formed urethane substitute (3370 cm^{-1}). Since the synthesized silyl-BisGMA is colorless, it is postulated that it could be used in dental composites to replace BisGMA without affecting the esthetics.

The physicochemical and mechanical properties of dental adhesives formulated with this new monomer were determined. The viscosities of the experimental formulations decreased according to the increase of silyl-BisGMA concentration (see SI Figure 3). With the increase of silyl-BisGMA content from 0, 10, 20, 30, to 55 wt%, the viscosities decreased from 181.8 ± 0.4 (for control, HB45), 173.9 ± 0.6 , 169.4 ± 1.3 , 162.1 ± 0.6 , to 143.6 ± 1.3 cP. It has been reported that the viscosities of BisGMA derivatives were significantly lower than BisGMA and these differences were attributed to the plasticizer effect of alkyl pendant substituents and the weaker intermolecular hydrogen bonding of urethane substitutes compared to the stronger hydrogen bonding interactions of the OH group in BisGMA molecules [27, 28]. The low viscosities of silyl-BisGMA-containing resin compared to the control are attributed to the flexible silyl substituent and the weak intermolecular hydrogen bonding of the urethane groups [28]. Therefore, the hypothesis (i) blocking hydroxyl group of BisGMA can significantly reduce the resin viscosity, was accepted.

4.2 Polymerization behavior

The polymerization behavior (conversion and reactivity) of dental adhesives play an important role in determining the quality of the adhesive/dentin (a/d) hybrid layer. The conversion of C=C double bond in the multifunctional methacrylate monomers is rarely complete due to the limited mobility of propagating free radical species in the crosslinked networks [24, 48]. The unpolymerized components, such as HEMA, BisGMA, and oligomers, tend to leach in the oral environment, which leads to cytotoxicity concerns [49, 50]. In our previous work, real-time FTIR has been used to monitor the conversion of C=C double bond and the progress of hydrolysis-condensation reactions initiated by the visible-light induced photoacid [36, 37]. With the increase of silyl-BisGMA concentration, the DC of C=C bond increased significantly from about $64.6 \pm 0.3\%$ (HB45) to $78.7 \pm 0.5\%$ (HS45). These differences were attributed to the decreased C=C bond molar concentration in the experimental formulations (see SI Table 1), and the reduced viscosity (Table 1). With the replacement of BisGMA by silyl-BisGMA, the less viscous formulations contributed to an improvement in the conversion of C=C bond. The reduced viscosity may also facilitate infiltration of the prepared dentin substrate leading to an improvement in the a/d hybrid layer [4].

To clearly show the variation of different functional groups before and after light irradiation, HS45 formulation was characterized spectroscopically to show the free radical polymerization and photoacid-induced sol-gel reactions. The free radical polymerization was monitored by the band ratio profile of 1637 cm^{-1} (C=C)/ 1608 cm^{-1} (phenyl). At 10 minutes after light irradiation ceased, the intensity of C=C bond decreased significantly and the intensity of phenyl group did not change. Even after post-curing 18 h at $23 \pm 2\text{ }^{\circ}\text{C}$, the DC of C=C bond is very similar to that recorded at 10 min (Figure 2C). This result indicated that the C=C double bond was polymerized efficiently during visible-light irradiation, and the post-curing free radical polymerization was very limited in the highly crosslinked network. At the same time, FTIR peak located at 2840 cm^{-1} was the first indication of hydrolysis reaction of methoxysilyl group, and the evolution of the OH stretching (around 3400 cm^{-1}) intensity may give insight into the formed silanol group after irradiation. When the storage time is 18 h, the intensity of methoxy peak decreased and OH peak at around 3400 cm^{-1} increased. Meanwhile, the intensity of the peak located at 1025 cm^{-1} increased with time, which is attributed to the formation of Si–O–Si bond by condensation reaction between silanol groups.

Modulated DSC (MDSC) has been used to determine the thermal properties of polymers and provide information on the degree of crosslinking [51, 52]. Prior to measurement by MDSC, the DC of the control and experimental copolymers was about 65 to 80% (Figure 2A and Table 1). When the disc sample was heated at the transition region ($\sim 50\text{ }^{\circ}\text{C}$), the thermal energy was sufficient to facilitate the curing reaction of the unpolymerized methacrylate monomers which were trapped in the crosslinked network. An exothermic peak was observed from the non-reversing heat flow curve (Figure 3 A2). At temperatures over $120\text{ }^{\circ}\text{C}$, the reaction finally ceased as the system reached full cure. With the increase of silyl-BisGMA concentration in the formulation, the DC of C=C bond increased accordingly (see Table 1), which indicated that the amount of the unconverted C=C bonds was reduced in the

crosslinked network. Therefore, the area of exothermic peak showed a decreasing trend. In Figure 3 A1, the first transition temperature ($\sim 50^{\circ}\text{C}$) could be attributed to the movement of the side-chain under the effect of the plasticizer (unpolymerized components). After the first heating cycle, most of the unpolymerized components have been cured therefore the first transition temperature disappeared in the second cycle test (Figure 3 B1). The second transition temperature was due to the movement of segments of the main chains (T_g), and it only increased about $2\text{--}3^{\circ}\text{C}$ as compared to the first cycle. Due to the heterogeneous characteristic of crosslinked polymethacrylate-based network structures [53, 54], the highly crosslink regions were affected minimally by the post-curing reaction during the heating process, and the further crosslinking reactions mainly occurred in the loosely crosslinked regions.

4.3 Mechanical Properties

With the introduction of silyl-BisGMA in the formulation, FTIR results have shown the spectral features associated with the hydrolysis and condensation reaction of silyl groups. To confirm the autonomous strengthening characteristics of the experimental polymers, dynamic mechanical analysis has been used to monitor the mechanical properties. DMA tests were carried out using both 3-point bending submersion (for wet conditions test) and 3-point bending clamps (for dry conditions test). In dry conditions, DMA tests show the bulk mechanical properties of polymers, while the results obtained in wet conditions are expected to be more representative of the polymer behavior in the oral environment.

In wet conditions, increasing the aging in water from 1, 2, to 4 weeks provided the opportunity to gain insight into the autonomous strengthening characteristics. With the increase in time for aging, the storage moduli at 37°C of the control and experimental samples, with the exception of HS45, were not significantly different ($p < 0.05$) at about $1.7\text{--}1.8\text{ GPa}$. Meanwhile, the T_g values obtained from the derivative storage modulus vs temperature curves (see SI Table 2) increased about $3\text{--}4^{\circ}\text{C}$ for the control and experimental polymers after aging for 4 weeks. When the highly crosslinked polymethacrylate-based matrix was aged in water, the water molecules penetrate the network and the mobility of the backbone is enhanced. The “trapped” free radical species can further initiate the unreacted $\text{C}=\text{C}$ bond, which leads to a slight improvement in the crosslink density of the polymethacrylate-based matrix, and the T_g shifts to higher temperature. In the experimental copolymers, the mobility of the silyl functional groups located at the $\text{C}-\text{C}$ crosslink points as pendant groups was limited, and the FTIR results (Figure 2C) indicated that the silyl functional groups have been hydrolyzed and partially condensed to form $\text{Si}-\text{O}-\text{Si}$ bonds during the storage process. Even though the experimental samples were aged in water, the post sol-gel reaction was limited and more time is required to reach equilibrium. Therefore, the difference (T_g) between the control and experimental copolymers was independent of the aging time (see SI Table 2).

In dry conditions, with the increase in silyl-BisGMA concentration from 10 to 55 wt%, the storage moduli at 37°C and the T_g were significantly lower than that of the control ($p < 0.05$). However, the storage moduli in the rubbery region were significantly greater than that of the control ($p < 0.05$). There are three main reasons: i) relatively weaker hydrogen

bonds of urethane groups in silyl-BisGMA; ii) unreacted silyl side chains and methanol generated from hydrolysis reaction act as plasticizers; iii) number of Si–O–Si or Si–O–C bonds generated from sol-gel reaction increases. Due to the larger molecular weight of silyl-BisGMA as compared to BisGMA, the C=C bond mole concentration in the formulation decreased with an increase in silyl-BisGMA content, which may reduce the crosslinking density of polymethacrylate-based network. However, the photoacids generated from the photoinitiator system catalyze the hydrolysis and condensation reactions of methoxysilyl groups, leading to the formation of Si–O–Si or Si–O–C crosslinking points. Therefore, the increase of the storage modulus in the rubbery region indicated increased crosslink density in the experimental copolymers [53].

After aging in water for 4 weeks and drying, the storage moduli of experimental copolymers at 37 °C were comparable to that of the control (Figure 5B), except HS45 (data shown in SI Table 3). The rubbery moduli and T_g of the experimental samples were significantly greater than that of the control ($p < 0.05$). When the samples were aged in water, the “trapped” strong photoacid (Brønsted acid) was efficient at driving the sol-gel reaction in wet conditions. The formed Si–O–Si or Si–O–C bonds by homogeneous or heterogeneous condensation reaction significantly improved the physico-mechanical strength. It was reported that the structural heterogeneity in crosslinked polymers depended strongly on the crosslinking density and the type of crosslinking monomers [53, 55]. In this study, as a multifunctional monomer, silyl-BisGMA has two C=C bonds and six methoxysilyl groups, which could lead to the formation of relatively higher crosslinked and more heterogeneous network after photopolymerization. However, the heterogeneity, as presented by the full-width-at-half-maximum (FWHM) [37] of the aged experimental copolymers, was not significantly different from that of the control ($p < 0.05$), except for HS45 (see SI Table 3). Therefore, with the introduction of silyl-BisGMA in a wide range of concentrations (10–30 wt%), copolymers with higher crosslinking density were obtained without sacrificing the homogeneity. This result is likely due to the relatively slow rate of sol-gel reaction compared to the free radical polymerization [36, 37, 56]. The sol-gel crosslinking reactions continued during aging in wet conditions. As a result, the hypothesis (ii) the mechanical properties of dental adhesives can be improved, was accepted.

A schematic illustration of the network formation in the experimental copolymers before and after visible-light irradiation and following post-curing is presented in Scheme 1. As confirmed by FTIR, the free radical polymerization rate is much faster than the photoacid-catalyzed sol-gel reaction. The increased rubbery moduli following 4-weeks aqueous aging indicated that the “trapped” strong photoacid (Brønsted acid) was efficient at driving the sol-gel reaction which contributed to higher crosslink density in the experimental copolymers.

4.4 Leaching properties

Due to the incomplete conversion of methacrylate monomers in the dental adhesive, there can be irreversible leaching of components into the oral fluids. Leaching of HEMA into the tissues of the oral environment can be particularly concerning [57] since in-vitro investigations report that HEMA can induce apoptosis, produce reactive oxygen species (ROS) and interfere with DNA synthesis [58–62]. In addition, low concentrations of HEMA

can interfere significantly with the expression of type I collagen by gingival fibroblasts [63]. The leachates not only provoke toxicity concerns [22, 49, 64–71] but can also compromise the integrity of the hybrid layer, accelerate the degradation and promote premature failure of the material [4, 72, 73]. In our previous work [36, 37], the concentration of leached HEMA and BisGMA in autonomous strengthening adhesive systems has been reduced significantly, which was attributed to the heterogeneous condensation reaction between the silanol and hydroxyl groups of HEMA/BisGMA. In the present study, with the increase of silyl-BisGMA concentration, the amount of both HEMA and BisGMA that was leached from the copolymer decreased significantly. This may be attributed primarily to the higher DC of C=C bond in the experimental formulations (see Table 1) and the further crosslinking reactions between silanol/silanol or silanol/hydroxyl groups of HEMA/BisGMA. No silyl-BisGMA was detected by HPLC in the experimental copolymers, which indicated that the sol-gel reaction through the silyl functional groups has effectively inhibited leaching of this species. The newly developed silyl functionalized BisGMA derivative offers the opportunity to develop dental adhesives that provide both autonomous strengthening and resistance to leaching. Therefore, the hypothesis (iii) the self-strengthening reaction can significantly reduce the leachates, was accepted.

4.5 Perspectives

Through this work, the silyl-functionalized BisGMA derivative showed great potential to replace BisGMA in dental adhesive formulations. The combination of low viscosity, high vinyl conversion, substantially reduced leachables, and enhanced mechanical properties in wet conditions indicated that the new monomer provides promising characteristics. Meanwhile, it is very likely that the silyl-BisGMA can also be adopted in other dental resin materials, e.g. dental composite, resin-based cement. The unique characteristics of the silyl-BisGMA, including colorless, low viscosity, and self-strengthening capability, could endow the composite with excellent esthetics, good compatibility with the inorganic fillers, and durability [74, 75].

5. CONCLUSION

In the present study, silyl-BisGMA was successfully synthesized through reaction of isocyanate with hydroxyl group of BisGMA. Compared to the HEMA/BisGMA adhesive, silyl-BisGMA-containing adhesive formulations showed lower viscosity, higher conversion, and self-strengthening characteristics. Further, it appears that by introducing multifunctional silyl-BisGMA, higher crosslinked networks can be obtained without sacrificing the homogeneity. This approach could be an efficient strategy to synchronously access higher crosslink density and homogenous network structure, which are important to the long-term performance of the crosslinked polymers. Meanwhile, when BisGMA was completely replaced by silyl-BisGMA, the leached amount of HEMA was reduced ~99%, and no silyl-BisGMA was detected by HPLC. Future studies will focus on the durability and biocompatibility of the silyl-BisGMA containing adhesive copolymers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of significance

The low-viscosity adhesive that bonds the composite to the tooth (enamel and dentin) is intended to seal and stabilize the composite/tooth interface, but it degrades leading to a breach at the composite/tooth margin. As the most popular crosslinking monomer in adhesives, Bisphenol A-glycerolate dimethacrylate (BisGMA) has limitations, e.g. susceptible to hydrolysis and concomitant property degradation. A methoxysilyl-functionalized BisGMA derivative (silyl-BisGMA) was introduced in this work to respond to these limitations. Our results indicated that by introducing silyl-BisGMA, higher crosslinked networks were obtained without sacrificing the homogeneity, and the leached amount of HEMA was reduced up to 99%. This novel resin offers potential benefits including prolonging the functional lifetime of dental resin materials.

Figure 1.
Synthesis of silyl-BisGMA

Figure 2.

Real-time conversion of C=C bond of the control and experimental adhesive (A), and FTIR characteristic peaks of HS45 before and after visible-light irradiation, selective spectral ranges of FTIR for (B) hydrogen bond and methoxy group and (C) Si-O-Si bond.

Figure 3. Representative data from Modulated DSC. (A) First cycle and (B) second cycle reversing heat flow and nonreversing heat flow versus temperature of the control and experimental copolymer specimens.

Figure 4.

Representative data from DMA, storage modulus (A1–3) and Tan δ (B1–3) vs. temperature curves of the control and experimental copolymers soaked in water at 37 °C for 1, 2, and 4 weeks.

Figure 5. Representative data from DMA, storage modulus (A and B) and $\tan \delta$ (C and D) vs. temperature curves of the nonsoaked (Top) and soaked (Bottom, soaked in water for 4 weeks and dried again in vacuum oven at 37°C) specimens in dry conditions.

Figure 6. Cumulative monomer release from the control and silyl-BisGMA-containing copolymers as a function of incubation time in ethanol: (A) HEMA and (B) BisGMA. The release of silyl-BisGMA is not detected in any of the silyl-BisGMA-containing copolymers.

Scheme 1.

Proposed polymethacrylate-based matrix network structure and the autonomous self-strengthening process of silyl-BisGMA-containing adhesive. (A) Neat resin (before light irradiation), (B) Formation of polymethacrylate-based network by free radical polymerization (during 40 s visible-light irradiation), (C) Autonomous self-strengthening reactions (post-curing after light irradiation).

Table 1.

Results of Water Miscibility, Viscosity, and Polymerization Kinetics of Adhesive Formulations

Run	HEMA (wt%)	BisGMA (wt%)	silyl-BisGMA (wt%)	W_{wm} (wt%)	Viscosity (cP)	DC ^a (%)	$\frac{R_p^{max}}{[M]} \times 100$ (1/s)
HB45	45	55	/	10.5(0.3)	181.8 (0.4)	64.6 (0.3)	17.4 (1.8)
HBS10	45	45	10	10.2(0.1)	173.9 * (0.6)	67.0 * (0.2)	16.9 (0.8)
HBS20	45	35	20	10.8(0.6)	169.4 * (1.3)	71.9 * (0.1)	14.3 (0.6)
HBS30	45	25	30	10.8(0.4)	162.1 * (0.6)	74.9 * (0.1)	12.6 * (0.3)
HS45	45	/	55	10.8(0.2)	143.6 * (1.3)	78.7 * (0.5)	10.6 * (0.3)

^adegree of conversion of C=C double bond.* Significantly ($p < 0.05$) different from the control (HB45). The value in the () is the standard deviation.