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Compositional design and optimization of dentin adhesive with neutralization capability

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ABSTRACT

Objectives: The objective of this work was to investigate the polymerization behavior, neutralization capability, and mechanical properties of dentin adhesive formulations with the addition of the tertiary amine co-monomer, 2-*N*-morpholinoethyl methacrylate (MEMA).
Methods: A co-monomer mixture based on HEMA/BisGMA (45/55, w/w) was used as a control adhesive. Compared with the control formulation, the MEMA-containing adhesive formulations were characterized comprehensively with regard to water miscibility of liquid resin, water sorption and solubility of cured polymer, real-time photopolymerization kinetics, dynamic mechanical analysis (DMA), and modulated differential scanning calorimetry (MDSC). The neutralization capacity was characterized by monitoring the pH shift of 1 mM lactic acid (LA) solution, in which the adhesive polymers were soaked.
Results: With increasing MEMA concentrations, experimental copolymers showed higher water sorption, lower glass transition temperature and lower crosslinking density compared to the control. The pH values of LA solution gradually increased from 3.5 to about 6.0–6.5 after 90 days. With the increase in crosslinking density of the copolymers, the neutralization rate was depressed. The optimal MEMA concentration was between 20 and 40 wt%.
Conclusions: As compared to the control, the results indicated that the MEMA-functionalized copolymer showed neutralization capability. The crosslinking density of the copolymer networks influenced the neutralization rate.

1. Introduction

Resin-based composite is rapidly becoming the most popular material for direct restorative dentistry. In 2006, nearly 121 million resin-based composite restorations were placed [1]. Clinical results suggest that these restorations fail at 5.7 years (NIDCR Strategic Plan 2009–13) and the patients at highest risk for decay, including children, are particularly vulnerable to composite failure [2]. The primary reason for failure is recurrent decay [3] and nearly 80–90% of recurrent decay is located at the gingival margin of Class II and V restorations [4]. At the gingival margin, the dentin adhesive is the primary barrier between the oral environment and the repaired tooth.

The structure of polymethacrylate-based dentin adhesives suggests a general mechanism for their chemical and enzymatic degradation in oral fluids. In the oral environment, water penetrates the resin; water infiltration promotes the chemical hydrolysis of ester bonds in methacrylate materials. This reaction is expected to be relatively slow at the neutral pH typical in saliva, but excursions in pH caused by foods or cariogenic bacteria may lead to transient acid or base catalysis. Over years of exposure to salivary fluids, local domains of the polymethacrylate networks are degraded. Esterases infiltrate these degraded domains and accelerate ester bond hydrolysis [5,6]. In general, the ester bonds within the polymethacrylate-based network are vulnerable to two forms of hydrolytic attack: (1) chemical hydrolysis catalyzed by acids or bases and (2) enzymatic hydrolysis catalyzed by salivary enzymes, particularly esterases [7]. Establishing and maintaining the integrity of the adhesive and the adhesive/dentin (a/d) bond has been a critical roadblock to durable composite restorations [8].

Streptococcus mutans is a microorganism and a major causative agent of dental decay [9]. Adhesion of *S. mutans* to the a/d interface creates a biofilm and produces lactic acid (LA). The LA damages the adjacent tooth surface by demineralization. Although numerous monomers have been investigated [10–16], the lack of dentin adhesives that are both effective and durable continues to be a major problem in restorative dentistry. Different strategies have

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been developed to enhance the hydrolytic stability of dentin adhesive resins. These strategies include changing the monomer structure with an emphasis on increasing the hydrophobicity of the monomers by introducing urethane groups [17–19], branched methacrylate linkages [20], or ethoxylated BisGMA (BisEMA) [21]. The extent and rate of water uptake are depressed temporarily, but most of the materials still reach saturation within 7–60 day [22]. A second strategy involves enhancing the conversion of the monomer in the hybrid layer and is done by improving the compatibility between photoinitiator and hydrophilic phase. However, due to the gel effect and vitrification phenomena of polymer matrices occurring early in the initial light-irradiation, the degree of conversion (DC) of C=C double bonds cannot reach 100% [23,24]. A third strategy involves adding effective inhibitors (such as zinc or zinc-chelators) of dentine matrix metalloproteinases (MMPs) to enhance the stability of collagen and resin-infiltrated dentine [25]. The limitations associated with these strategies have fueled the ongoing efforts to identify new approaches for achieving a durable, integrated bond at the a/d interface.

Buffers are used to control the pH of a solution in biological and chemical applications. Monomers that have basic functional groups have the potential to mitigate acidic excursions in pH. 2-(dimethylamino)ethyl methacrylate (DMAEMA) is a basic monomer (pK_a 8.2) [26] and its polymer (poly(2-(dimethylamino)ethyl methacrylate, PDMAEMA) is a weak polybase, which is water-soluble both at neutral pH and in acidic media due to protonation of the tertiary amine groups. PDMAEMA is a polybase that has a critical pH point around 7, which is close to the physiological pH [27]. However, DMAEMA has been shown to be unstable in basic solution by nuclear magnetic resonance (NMR) and can be completely hydrolyzed into methacrylic acid and dimethylaminoethanol, as shown in our previous work [28]. 2-*N*-morpholinoethyl methacrylate (MEMA) is another basic monomer with a pK_a 6.2 and is able to neutralize LA more effectively than DMAEMA [26]. Because the pK_a of MEMA is lower than DMAEMA, it begins buffering and raising the pH of the solution under more acidic conditions. PDMAEMA and poly(2-*N*-morpholinoethyl methacrylate)-based copolymers showed low toxicity when used as a controlled drug-delivery system [29–31].

As reported, the neutralization and physicochemical properties were measured based on tertiary amine monomers, linear polymers or low crosslinking density polymers (hydrogel) [26–28,30,31]. The neutralization behavior of amine-containing dentin adhesive copolymer has not been investigated systematically and the composition-structure-properties relationship of this kind of functionalized adhesive has not been studied before. In this work, MEMA is used as one of the co-monomers in dentin adhesives and the neutralization capacity was studied with the goal of determining its potential to reduce LA-induced demineralization without compromising the other properties required for dentin adhesives. MEMA was chosen as a neutralizing co-monomer because of its nearly neutral pK_a and good biocompatibility. The present study tests the hypothesis that: (i) the tertiary amine group built-in to the dentin adhesive copolymer network can neutralize LA in wet conditions, and (ii) the high crosslinking density of the network structure does not retard the neutralization capacity of the copolymers.

2. Materials and methods

2.1. Materials

2,2-Bis[4-(2-hydroxy-3-methacryloxypropoxy) phenyl]propane (BisGMA), 2-hydroxyethyl methacrylate (HEMA), and 2-*N*-morpholinoethyl methacrylate (MEMA) were obtained from Sigma–Aldrich (St. Louis, MO) and used as received without further purification as monomers in dentin adhesives. Camphoroquinone (CQ), ethyl-4-(dimethylamino) benzoate (EDMAB), diphenyliodonium hexafluorophosphate (DPIHP), and L(+)-lactic acid (LA) were obtained from Sigma–Aldrich (St. Louis, MO). All other chemicals were reagent grade and used without further purification.

2.2. Preparation of adhesive formulations

HEMA/BisGMA (45/55, w/w) was used as the control (C0) [10]. The experimental adhesive formulations consisting of HEMA, BisGMA, and MEMA are listed in Table 1. CQ (0.5 wt%), EDMAB (0.5 wt%), and DPIHP (0.5 wt%) were used as a three-component photoinitiator system, [32,33] with respect to the total amount of monomers. Mixtures of monomers/photoinitiators are prepared in a brown glass vial under amber light. The preparation of adhesive formulations has been reported Previously [16].

2.3. Water miscibility of adhesive formulations

The water miscibility of adhesive formulations has been reported [34]. About 0.5 g of each neat resin was weighed into a brown vial, and water was added in increments of ~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). Then 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.

2.4. Determination of log P

The log *P* values (ratio of solubility in octanol to solubility in water) for each of the monomers and the model adhesive formulations were predicted using ChemBioDraw Ultra 12.0 (Cambridge Soft from PerkinElmer) [34]. The log *P* value for each adhesive formulation was determined using the mole fraction-average of individual monomer values as seen in the following equation:

$$\log P_{\text{mol avg.}} = x_{\text{HEMA}}\log P_{\text{HEMA}} + x_{\text{BisGMA}}\log P_{\text{BisGMA}} + x_{\text{MEMA}}\log P_{\text{MEMA}} \quad (1)$$

Table 1
Control and experimental formulations and polymerization kinetic data.

Run	HEMA/%	BisGMA/%	MEMA/%	DC (%)	$R_p^{max}/[M] \times 100$ (1/s)
C0	45	55	/	64.8 (0.2)	21.2 (0.6)
HBM-40-40-20	40	40	20	71.8[a] (0.8)	17.8[a] (0.1)
HBM-40-30-30	40	30	30	74.1[a] (0.5)	14.6[a] (1.3)
HBM-40-25-35	40	25	35	72.7[a] (1.0)	9.3[a] (1.2)
HBM-40-20-40	40	20	40	66.1 (0.9)	4.6[a] (0.2)
HBM-40-15-45	40	15	45	54.5[a] (0.4)	3.3[a] (0.4)
HBM-40-10-50	40	10	50	34.5[a] (0.8)	2.8[a] (0.1)
HBM-40-5-55	40	5	55	20.9[a] (0.5)	2.7[a] (0.1)

[a] Significantly ($p < 0.05$) different from the control (C0). The value in the () is the standard deviation.

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