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Synthesis of new antibacterial quaternary ammonium monomer for incorporation into CaP nanocomposite

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ABSTRACT

Objectives. Composites are the principal material for tooth cavity restorations due to their esthetics and direct-filling capabilities. However, composites accumulate biofilms in vivo, and secondary caries due to biofilm acids is the main cause of restoration failure. The objectives of this study were to: (1) synthesize new antibacterial monomers and (2) develop nanocomposite containing nanoparticles of amorphous calcium phosphate (NACP) and antibacterial monomer.

Methods. Two new antibacterial monomers were synthesized: dimethylaminohexane methacrylate (DMAHM) with a carbon chain length of 6, and dimethylaminododecyl methacrylate (DMADDM) with a chain length of 12. A spray-drying technique was used to make NACP. DMADDM was incorporated into NACP nanocomposite at mass fractions of 0%, 0.75%, 1.5%, 2.25% and 3%. A flexural test was used to measure composite strength and elastic modulus. A dental plaque microcosm biofilm model with human saliva as inoculum was used to measure viability, metabolic activity, and lactic acid production of biofilms on composites.

Results. The new DMAHM was more potent than a previous quaternary ammonium dimethacrylate (QADM). DMADDM was much more strongly antibacterial than DMAHM. The new DMADDM–NACP nanocomposite had strength similar to that of composite control ($p > 0.1$). At 3% DMADDM in the composite, the metabolic activity of adherent biofilms was reduced to 5% of that on composite control. Lactic acid production by biofilms on composite containing 3% DMADDM was reduced to only 1% of that on composite control. Biofilm colony-forming unit (CFU) counts on composite with 3% DMADDM were reduced by 2–3 orders of magnitude.

Significance. New antibacterial monomers were synthesized, and the carbon chain length had a strong effect on antibacterial efficacy. The new DMADDM–NACP nanocomposite possessed

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potent anti-biofilm activity without compromising load-bearing properties, and is promising for antibacterial and remineralizing dental restorations to inhibit secondary caries.

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1. Introduction

Dental caries remains a prevalent problem worldwide [1–3]. The longevity of tooth cavity restorations is limited, with half of all restorations failing in less than 10 years, mainly due to secondary caries and fracture [4–7]. Replacing the failed restorations accounts for 50–70% of all restorations performed [8,9]. This is costly, considering that the annual cost for tooth cavity restorations in the U.S. was approximately $46 billion in 2005 [10]. Furthermore, the need is rapidly increasing as baby boomers enter into retirement, with increases in life expectancy as well as tooth retention in seniors [11]. Due to their esthetics and direct-filling capabilities, resin composites are the principal material for cavity restorations [6,7,12–19]. Improvements in filler particles and matrix polymers have significantly enhanced the composite properties [20–23]. Nonetheless, one major drawback remains: composites tend to accumulate more biofilms/plaques than other restoratives in vivo [24,25]. Acidogenic bacteria such as *Streptococcus mutans* (*S. mutans*) and their biofilms, upon exposure to fermentable carbohydrates, produce acids that lead to caries [26]. Therefore, efforts were made to develop antibacterial resins [27–32]. Quaternary ammonium methacrylates (QAMs) were synthesized with antibacterial activities [33–36]. Indeed, 12-methacryloyloxydodecyl-pyridinium bromide (MDPB) and other antibacterial resins decreased the growth of oral bacteria [32–36].

Calcium phosphate (CaP) biomaterials are important due to their bioactivity, biocompatibility and similarity to the minerals in teeth and bones [37–39]. Resin composites with CaP fillers released Ca and P ions and remineralized tooth lesions [37–39]. However, traditional CaP composites contained CaP particles with sizes of 1–55 μm [37–39], with relatively low mechanical properties that were "inadequate to make these composites acceptable as bulk restoratives" [40]. Furthermore, the CaP resin composites had no antibacterial activity.

Novel nanoparticles of CaP were synthesized and mixed into composites with the release of Ca and P ions [41–43]. Composites with nanoparticles of amorphous calcium phosphate (NACP) neutralized acid attacks, while commercial controls failed to neutralize the acids [44]. Glass filler reinforcement yielded photo-cured NACP nanocomposite with Ca and P ion release comparable to, and mechanical properties 2–3 fold of, traditional CaP composites [45]. In 2 years of water-aging, mechanical properties of NACP nanocomposite matched those of commercial non-remineralizing composite control [46]. NACP nanocomposite reduced secondary caries in enamel in a human in situ study [47], and remineralized tooth lesions in vitro [48]. Recently, NACP were combined with a quaternary ammonium dimethacrylate (QADM) to develop nanocomposite with a combination of remineralizing and antibacterial capabilities [49,50]. In the present study, a new quaternary ammonium monomer, dimethylaminododecyl methacrylate (DMADDM) was synthesized, which had a much greater antibacterial potency than the previously used QADM.

Therefore, the objectives of this study were to synthesize new antibacterial monomer DMADDM, and develop nanocomposite containing NACP for remineralization and DMADDM for potent antibacterial activity for the first time. The following hypotheses were tested: (1) the new antibacterial monomer DMADDM would have lower minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC) than the former QADM; (2) DMADDM could be incorporated into NACP nanocomposite without decreasing the composite mechanical properties; (3) DMADDM–NACP nanocomposite would significantly reduce dental plaque microcosm biofilm growth, metabolic activity, and lactic acid production.

2. Materials and methods

2.1. *Synthesis of new quaternary ammonium methacrylates (QAMs)*

A modified Menschutkin reaction approach was used to synthesize the new QAMs. This method uses a tertiary amine group to react with an organo-halide, as described in previous studies [32,49]. A benefit of this reaction is that the reaction products are generated at virtually quantitative amounts and require minimal purification [32]. In the present study, 2-bromoethyl methacrylate (BEMA) was the organo-halide. N,N-dimethylaminohexane (DMAH) and 1-(dimethylamino)docecane (DMAD) were the two tertiary amines.

The scheme of synthesis of dimethylaminohexane methacrylate (DMAHM) is shown in Fig. 1A. Ten mmoles of DMAH (Tokyo Chemical Industry, Tokyo, Japan), 10 mmol of BEMA (Monomer-Polymer and Dajac Labs, Trevose, PA), and 3 g of ethanol were added to a 20 mL scintillation vial with a magnetic stir bar. The vial was capped and stirred at 70 °C for 24 h. After the reaction was complete, the ethanol solvent was removed via evaporation at room temperature over several days. This yielded DMAHM as a clear liquid.

The scheme of synthesis of dimethylaminododecyl methacrylate (DMADDM) is shown in Fig. 1B. In a 20 mL scintillation vials were added 10 mmol of DMAD (Tokyo Chemical Industry), 10 mmol of BEMA, and 3 g of ethanol. A magnetic stir bar was added, and the vial was capped and stirred at 70 °C for 24 h. After the reaction was complete, the solvent was removed via evaporation. The number of the alkyl chain length units was 6 for DMAHM and 12 for DMADDM (Fig. 1).

To characterize the reaction products, Fourier transform infrared spectroscopy (FTIR, Nicolet 6700, Thermo Scientific, Waltham, MA) was used. FTIR spectra of the starting materials and the viscous products were collected between two KBr windows in the 4000–400 cm^{-1} region with 128 scans at 4 cm^{-1} resolution [32]. Water and CO_2 bands were removed from all spectra by subtraction. ^1H NMR spectra (GSX 270,

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