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Research Paper

Synthesis of antibacterial methacrylate monomer derived from thiazole and its application in dental resin

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ABSTRACT

A non-quaternary ammonium antibacterial methacrylate monomer MEMT derived from thiazole was synthesized and applied into UDMA/TEGDMA dental resin with a series of mass fraction (10 wt%, 20 wt%, and 30 wt%). Double bond conversion, polymerization shrinkage, water sorption, solubility, flexural strength and modulus, and antibacterial activity of MEMT containing resin formulations were investigated with UDMA/TEGDMA as control resin. The results showed that MEMT containing dental resin had higher double bond conversion than control resin. Compared with control polymer, all MEMT containing polymer had comparable or lower polymerization shrinkage, water sorption and solubility, except for the polymer with 30 wt% of MEMT which had higher water sorption and solubility than control polymer. The MEMT had no influence on flexural strength and modulus before water immersion, but all MEMT containing polymers had lower flexural strength and modulus than control polymer after water immersion. The MEMT could endow dental polymer with obvious antibacterial activity by immobilizing MEMT into the polymeric network.

1. Introduction

As a great revolution in dentistry, resin-based dental materials have been widely used in clinic because of their esthetic and easy handling properties. However, compared with other restorative materials, resin-based dental materials have been reported as accumulating more bacteria or plaque in vitro (KKR, 1973, 1976; Tanner et al., 2001, 2003) or in vivo (Tanner et al., 2005; Auschill et al., 2002) due to their lack of antibacterial activity. The service time of resin-based dental materials will be shortened by secondary caries induced by bacteria or plaque accumulation adjacent to the restoration margins.

There are two main approaches to prepare antibacterial resin-based dental materials: one is incorporation of leachable antibacterial agents, such as silver ions (Yamamoto et al., 1996; Melo et al., 2013), zinc ions (Osinaga et al., 2003; Henn et al., 2011), chlorhexidine (Jedrychowski et al., 1983; Leung et al., 2005), and cetylpyridinium (Al-Musallam et al.,

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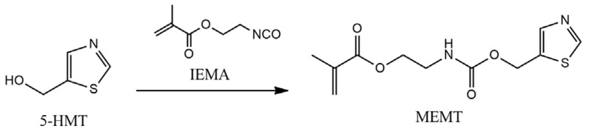

Fig. 1 – Synthesis route of MEMT.

2006), into the materials by physical blending, and the other one is immobilizing antibacterial group into the polymer network through chemical reaction (Imazato et al., 2014).

The concept of "immobilized bactericide" was firstly introduced into dentistry by Imazato in 1990s (Imazato et al., 1994), and a series of polymerizable bactericides were synthesized for dental application from then on (Xiao et al., 2008; Huang et al., 2011; Weng et al., 2011; He et al., 2011, 2014; Antonucci et al., 2012; Xu et al., 2012; Liang et al., 2013, 2014). Usually, the antibacterial functionalities of these polymerizable bactericides are quaternary ammonium salts, which are well known effective antibacterial agents and active against a broad spectrum of micro-organisms. Though the quaternary ammonium methacrylate (QAM) was reported to have no negative influence on mechanical properties (Xiao et al., 2009; He et al., 2012a, 2013a), our previous research found that it would decrease the mechanical properties of dental material when its mass fraction was beyond a certain limit (Liang et al., 2014). In addition, the antibacterial activity of the QAM-containing restoratives could be decreased because of the electrostatic interactions between quaternary ammonium salts and proteins in saliva (Ebi et al., 2001; Imazato et al., 2003). Therefore, it is necessary to explore another bactericide which can be applied into dental materials.

Thiazole ring is a typical heterocyclic ring possessing a wide variety of biological activities, such as antimicrobial (Liaras et al., 2011; El-Wahab et al., 2014; Sharshira and Hamada, 2012), analgesic (Basavaraja et al., 2008), anti-inflammatory (Karabasanagouda et al., 2008), anticonvulsant (Amine et al., 2008), anticancer (Jiang and Gu, 2000; Abbs et al., 2008), and anthelmintic activities (Bhusari et al., 2000). Due to the properties of thiazole ring, we tried to incorporate it into dentistry to see whether it could work as bactericide to endow dental materials with antibacterial activity.

In this study, a methacrylate monomer with thiazole ring was synthesized and added into dental resin system. The hypothesis is that this monomer could endow dental resin with antibacterial activity. The influences of this monomer on double bond conversion, polymerization shrinkage, flexural strength and modulus, water sorption and solubility of dental resin were also investigated.

2. Materials and methods

2.1. *Materials*

5-hydroxymethylthiazole (5-HMT), and Camphoroquinone (CQ) were purchased from J&K Scientific Ltd., China. 2-isocyanatoethyl methacrylate (IEMA), and dibutyltin dilaurate (DBTDL) were purchased from Tokyo Chemical Industry Co., Ltd., Japan. 1,6-Bis (methacryloxy-2-ethoxycarbonylamino)-2,4,4-trimethylhexane (UDMA), triethylene glycol dimethacrylate (TEGDMA), and N,N′-dimethyl aminoethyl methacrylate (DMAEMA) were purchased from Sigma-Aldrich Co., USA. All of the reagents were used directly without further purification.

2.2. *Synthesis of 5-(methacryloxy-2-ethoxyaminocarbonyl)methyl-thiazole (MEMT)*

The MEMT was synthesized according to the route shown in Fig. 1. A mixture of 5-HMT (11.5 g, 0.1 mol), IEMA (15.5 g, 0.1 mol), 50 ml acetone, and two droplets of DBTDL was stirred at 45 °C. The reaction was continued until the infrared absorbance peak of the –NCO group (2270 cm^{-1}) disappeared in the FTIR (Vector33 Model Fourier Transform Infrared Instrument, Bruker Co., Germany) spectra of the samples that taken from the reaction medium. After removing the acetone by distillation under vacuum, the product was washed with diethyl ether to remove DBTDL. Then the yellow liquid was dried under vacuum at 35 °C to obtain MEMT with yield of 95%. FTIR: υ (cm^{-1}) 3340, 2955, 1717, 1636, 1167, 1252, 655. ^1H NMR (CDCl3, 400 MHz): δ 8.81, 7.87[2H, $\underline{H}$ in thiazole ring], 6.10[1H, $C\underline{H}_2{=}C(CH_3)$ *trans*], 5.59[1H, $C\underline{H}_2{=}C(CH_3)$ *cis*], 5.31[2H, $–O–C\underline{H}_2$–thiazole], 5.19[1H, $–CH_2–N\underline{H}–C{=}O$], 4.22–4.25[2H, $–O–CH_2–C\underline{H}_2–$], 3.50–3.54[2H, $–O–CH_2–C\underline{H}_2–$], 1.93[3H, $CH_2{=}C(C\underline{H}_3)$].

2.3. *Preparation of resin formulation*

The MEMT was added into UDMA/TEGDMA (50/50, wt/wt) resin system with a series of mass fraction (10 wt%, 20 wt%, 30 wt%), and then 0.7 wt% of CQ and 0.7 wt% of DMAEMA were incorporated into prepared resin systems as photoinitiation system. The UDMA/TEGDMA resin system without MEMT was used as control. Instead of Bis-GMA, UDMA was used in this research because of the estrogenic potential of Bis-GMA.

2.4. *Measurement of double bond conversion*

The degree of double bond conversion (DC) during and after the photoinitiation of polymerization was monitored by Fourier transform infrared spectroscopy (FT-IR) (Vector33, Bruker Co., Germany). Resin sample was coated on KBr Pellets to form a very thin film and the absorbance peak of uncured sample was obtained. Then photopolymerization of sample was carried out by irradiation of a dental light source (Mini LED Curing Lights, $\lambda = 390–510$ nm, $I \approx 1250$ mW cm^{-2}, Satelec Inc., France) at room temperature. Spectra during irradiation process was recorded every 10 s for 1 min. The DC was calculated from the aliphatic $C{=}C$ peak at 1636 cm^{-1} and normalized against the carbonyl $C{=}O$ peak at 1720 cm^{-1} according to formula (1)

$$DC(t)=\frac{(A_{C=C}/A_{C=O})_0-(A_{C=C}/A_{C=O})_t}{(A_{C=C}/A_{C=O})_0} \qquad (1)$$

where $A_{C=C}$ and $A_{C=O}$ are the absorbance peak area of methacrylate $C{=}C$ at 1636 cm^{-1} and carbonyl at 1720 cm^{-1}, respectively; $(A_{C=C}/A_{C=O})_0$ and $(A_{C=C}/A_{C=O})_t$ are the normalized absorbance of functional group at radiation time of 0 and t, respectively; DC(t) is the conversion of methacrylate $C{=}C$ as a function of radiation time.