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Synthesis of imidazolium-containing mono-methacrylates as polymerizable antibacterial agents for acrylic bone cements

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ABSTRACT

With the aim to prepare antibacterial acrylic bone cements, a series of imidazolium-containg mono-methacrylates with N-alkyl chain length varied from 10 to 18 (MEIM-x) were synthesized as polymerizable antibacterial agents through a two-step reaction. The structures of the monomers were confirmed by ^{1}H NMR. Methyl methacrylate in the liquid compoent of cements was partially replaced by MEIM-x to prepare bone cements with 5 wt% of MEIM-x. Properties of prepared cements like antibacterial activity, doughing time, curing parameters including maximum temperature (T_{max}) and setting time (t_{set}), flexual strength (FS) and modulus (FM), compressive strength (CS) and fluid uptake (FU) in Ringer's solution were investigated. Acrylic bone cement without any MEIM-x was used as control. Compared with the control cement, MEIM-x-containing cements had shorter doughing time, lower T_{max}, same or longer t_{set}, and higher FU. Though MEIM-x could endow cements with strong antibacterial activity, it could reduce mechanical properties of bone cements. Therefore, further study should be taken to optimize the content of MEIM-x in cement which could supply sufficient antibacterial activity and maintain mechanical performance.

1. Introduction

Post-surgical infection is one of the most serious complications in orthopedic implant surgery (Alp et al., 2016; Van et al., 2001). The overall infection rate of total joint arthroplasty varies from 0.5% to 6% according to different reports (Blom et al., 2003; Darwiche et al., 2010; Wang et al., 2013). The infection would not only prolong the hospitalization but also bring out revision surgery in some cases while causing severe physical and emotional pain to a patient. As an indispensable bone repair material, acrylic bone cement with antibacterial effect is highly desirable for infection prevention and treatment. Therefore, antibacterial modification of acrylic bone cement has never ceased since people realized the seriousness of infection in implant surgery. The antibiotics were firstly incorporated into acrylic bone cements in 1970s(Gehrke et al., 2013).

Up to now, antibiotic-loaded bone cements have been used extensively for prevention and treatment of the infection. However, it was reported to have several disadvantages in using antibiotics, such as reduced mechanical properties (Paz et al., 2015), short duration of antimicrobial effect (Anagnostakos and Kelm, 2009), and non-negligible risk of developing the antibiotic-resistant strain (Miola et al., 2013). Moreover, the release characteristics of antibiotics were considered not to be indicated for infection prevention (Jiranek et al., 2006). Silver-containing agents were considered to be the preferred alternative for antibiotics because of their broad antimicrobial spectrum and high antimicrobial efficiency. However, some studies showed that silver-impregnated bone cements could induce neuropathy in some cases due to silver accumulation (Sudmann et al., 1994; Vik et al., 1985).

For this reason, many efforts have been directed at using the antibacterial quaternary ammonium salts (QAS, includes quaternary derivatives of N-containing heterocyclics) due to their metabolizability and low-toxicity. Benzalkonium chloride (Mathey et al., 2009), cetyl pyridinium chloride (Mathey et al., 2009), quaternary ammonium polyethyleneimine nanoparticles (Beyth et al., 2014) and quaternarized chitosan (Peng et al., 2010; Tan et al., 2013, 2014) have been reported to be incorporated into acrylic bone cements for antibacterial modification. All of these organic additives could be leached out from the cements since there was no covalent binding between the additives and the polymeric network. As a result, the reduction of the antibacterial activity and mechanical properties of bone cements were hardly to be avoided.

In order to immobilize the QAS structure into polymeric network, some polymerizable QAS compounds that combined both QAS groups and methacrylate in one molecule were studied. Deb et al. (2008), Punyani et al. (2007) and Abid et al. (2015) synthesized two kinds of

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dimethacrylates with the structure of quaternary ammonium iodide and incorporated them into acrylic bone cements in 2007 and 2015, respectively. However, both of these two monomers caused a significant delay in curing process (Deb et al., 2008) and the mechanical properties of cured cements decreased significantly when the contents of monomers were high enough to obtain sufficient antibacterial effect (Abid et al., 2015; Deb et al., 2008). In our point of view, those results might be brought out by the reductivity of iodine ion. Iodine ion was able to react with and consume the initiator benzoperoxide (BPO), thus it inhibited the polymerzation process and impaired the mechanical properties. Changing the iodine ion into bromide or chloride ion with lower reductivity could be a solution.

In this study, a series of methacrylates containing the structure of imidazolium bromide with different N-alkyl chain length were synthesized and incorporated into acrylic bone cements as antibacterial agents. An imidazolium structure was used because it was reported that imidazolium salt (ImS) had an impressive antibacterial effect and had the potential to be used in biomaterials (Anderson and Long, 2010). The variations in the handling and curing characteristics, physicochemical properties and antibacterial activity of bone cements as a function of N-alkyl chain length were studied.

2. Materials and methods

2.1. Materials

N-(2-Hydroxyethyl) imidiazole (HEIM), 2-isocyanatoethyl methacrylate (IEMA), N, N-Dimethyl-p-toluidine (DMPT), methyl methacrylate (MMA), hydroquinone (HQ), dibutyltin dilaurate (DBTDL), 1-bromodecane, 1-bromododecane, 1-bromotetradecane, 1-bromohexadecane, 1-bromooctadecane, and extra dry tetrahydrofuran (THF) were purchased from J & K Scientific Ltd., China. Poly(methyl methacrylate) (Mw ≈ 120,000 by GPC) was a product of Sigma-Aldrich Co., USA. Benzoperoxide (BPO) and zirconium dioxide (ZrO_2) were provided by Shanghai Macklin Biochemical Technology Co., Ltd, China. All of reagents were used directly without further purification except for BPO, which was dried under vacuum at 30 °C for 24 h before being used.

2.2. Synthesis of 1-(2-(((2-(methacryloyloxy)ethyl)carbamoyl)oxy)ethyl)-3-alkyl- imidazolium bromide (MEIM-x)

MEIM-x (x is the number of carbon atoms in N-alkyl chain) was synthesized via a two-step reaction as shown in Fig. 1. 2.24g (0.02 mol) HEIM, several drops of DBTDL, 10 mg HQ and 80 mL THF were added into a flask equipped with refluxing condenser at 45 °C. Under stirring condition, 3.10g (0.02 mol) IEMA was added dropwisely into the solution within 2 h. The reaction was continued until the infrared absorbance peak of the –NCO group (2270 cm^{-1}) disappeared in FTIR (Vector33 Model Fourier Transform Infrared Instrument, Bruker Co., Germany) spectrum of the sample that was taken from the reaction medium. Then, 0.04 mol 1-bromoalkane was added into the medium and the reaction was carried out at 70 °C for 72 h. After that, the solvent was removed by distillation under vacuum and the resulting liquid was washed by diethyl ether and centrifuged to remove the remaining haloalkane, HQ and DBTDL. Finally, the residual diethyl ether was removed by distillation under vacuum to provide a light yellow, semi-transparent, semi-solid paste. The yield was from 70% to 75% according to different 1-bromoalkane. The molecular structures of products were confirmed by ^1H NMR (AVANCE III HD 600 600 MHz NMR spectrometer, Bruker Co., Germany) spectra.

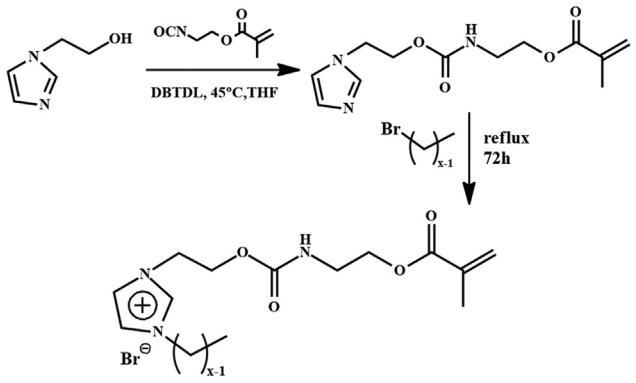

Fig. 1. Synthesis route of MEIM-x.

Table 1
Formulations of experimental bone cements.

Formulations	Solid component (g)			Liquid component (g)			
	PMMA	ZrO_2	BPO	MMA	MEIM-x	DMPT	HQ
Control	55.37	10	1.33	32.58	0	0.67	0.05
MEIM-x-5%	55.37	10	1.33	27.58	5	0.67	0.05

2.3. Preparation of bone cements samples

The PMMA beads were grinded in a high-speed universal grinder (Tianjin Taisite Instrument Co., Ltd, China) and sieved through a 100 mesh screen. The formulation of each bone cement was shown in Table 1. The solid and liquid components were mixed at a mass ratio of 2:1. The samples were prepared by manually stirring two components in a plastic bowl at 23 ± 1 °C until dough shape being formed. When the mixture reached dough state, it was immediately filled into different molds with given dimensions according to specific measurements. After 1 h curing time, cured samples were removed from the molds for further processing.

2.4. Measurement of doughing time and polymerization exotherm

The solid and liquid components of each bone cement were added into a polypropylene bowl at 23 ± 1 °C and the timer was started as soon as two components were contacted to each other. The mixture was stirred and the fresh surface was touched with a finger gloved with an unpowdered non-water-rinsed surgical latex glove (SafeTouch 1144 C, A.R. Medicom Inc. Healthcare (Shanghai) Ltd., China) every 10 s. The time was recorded as doughing time when the latex glove finger could be first cleanly separated from the surface of mixture. The dough was filled into a Teflon mold in accordance to ISO-5833 standards to measure the polymerization exotherm. The temperatures were measured by a negative temperature coefficient thermistor that was fixed in the mold before testing and recorded using a self-made automatic data acquisition device every 0.5 s. The maximum temperature (T_{max}) was read from the curve. The setting time (t_{set}) was defined as the time when the temperature reached the midpoint between the ambient temperature and T_{max}.

2.5. Three-point bending and compression test

The bone cement dough was cured in a steel mold with a dimension of 150 mm × 75 mm × 4 mm to make a bone cement plate. The plate was then cut into 12 specimens at a size of 75 mm × 10 mm × 4 mm for three-point bending test. The test (span = 64 mm) was carried out to evaluate the flexural strength (FS) and modulus (FM) with a universal testing machine (Model Z010, Zwick GmbH & Co., KG, Germany), at a cross-head speed of 5 mm/min. The FS (MPa) and FM (MPa) were then calculated as:

$$FS = \frac{3FL}{2bh^2} \quad (1)$$