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Short communication

Contrast effect on hydrolysis of poly(trimethylene carbonate) depending on accelerated species due to the hydrophilic oligo(ethylene glycol) units at side groups

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ABSTRACT

Poly(trimethylene carbonate) (PTMC) is a biodegradable polymer which doesn't generate any acidic organic compounds after hydrolysis, leading to good biocompatible properties and biomedical application. Poly(TMCM-MOE3OM) and poly(TMCE-MOE4OM), bearing oligo ethylene glycol (OEG) at the side chain of PTMC, were selected to investigate *in vitro* accelerating hydrolysis behaviors at pH = 7.4 in a phosphate-buffered solution (PBS) through the use of Lipase and NaOHaq. Their degradation behaviors were in contrast to that of PTMC, resulting in the fast degradation in NaOHaq. and the slow degradation by Lipase. The contrast in results of degradations are due to the side chain of hydrophilic OEG which should interact with degradation species.

1. Introduction

Trimethylene carbonate (TMC) is a cyclic carbonate composed of a six-membered ring, and poly(trimethylene carbonate) (PTMC) [1–3] is obtained by ring-opening polymerization. PTMC has good biocompatibility and novel PTMC derivatives [4] or applications of PTMC have been reported using the organic catalyst system [5]. In particular, the thermosensitive copolymers with poly(ethylene glycol) (PEG) [6–9] and PTMC derivatives modified by carboxylic acid ester [10] and amide [11] were reported as biocompatible applications. For example, the stimuli-responsive gel [12], the surface control [13], magnetic polymersome [14], enzymatically degradable microspheres [15], and detachable moiety introduction by sulfide [16] have been reported. However, the strategy of copolymerization or chemical modification of the polymer side chain have a lack of physical uniformity, although a lot of researches create various functional PTMC derivatives.

We previously reported the synthesis and property of poly(TMCM-MOE3OM) introducing oligo ethylene glycol (OEG) which have thermosensitive property to the side chain [17–19]. It is well known that OEG shows thermosensitive behavior in aqueous media [20,21] so we introduced into the side chain of PTMC. The homopolymer showed a sharp phase transition at 33 °C around body temperature. From this result, we think that the polymer can be applied to implant medical materials bearing contractile function due to its thermosensitive property.

On the other hand, TMC is known as a biodegradable polymer [22], and there are many reports regarding the related degradation behaviors, such as surface degradation of poly(D,L-lactide-*co*-1-methyl-1,3-trimethylene carbonate) [23], copolymers of trimethylene carbonate with ε-caprolactone [24], copolymers of L-lactide with cyclic carbonate [25], and PTMC decomposition is reported to be accelerated by using lipase, while it is stable under the acid and base conditions [26].

It is well known that the degradation of PTMC is accelerated by lipase [18,26], in spite of the low effect of acceleration under acid and base conditions [6]. It is also known that degradation of PLLA film is accelerated by proteinase K [27]. The degradation behaviors of the copolymer of poly[(L-lactide)-*co*-trimethylene carbonate] (Poly(TMC-*block*-LLA)) have been reported and mentioned for their possible application as a stent coating material for long-term drug

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release [28]. Since TMC moiety of poly(TMC-*block*-LLA) delayed degradation rate, we previously employed a strategy where TMC moieties were segregated on the film surface, by introducing a hydrophilic methoxyethoxyl group into only TMC moieties [18,19]. This resulted in the further delaying effect of hydrolysis, revealed by the degradation experiments with proteinase K or lipase. In our previous studies, however, the degradation behaviors were controlled by the components of TMC and LLA, and it was not actually clear that there was an effect on the hydrophilic side chain.

In this study, we investigated *in vitro* the degradation behavior of poly(TMCM-MOE3OM) and poly(TMCE-MOE4OM), using lipase and NaOHaq at 37 °C at 7.4 pH in a phosphate-buffered solution (PBS). The cloud points of homopolymers, poly(TMCM-MOE3OM) and poly(TMCE-MOE4OM), are 33 °C and 37 °C at around body temperature, which makes them suitable for biomedical applications.

2. Experimental section

2.1. Polymerization

Polymerization of TMC derivatives were achieved by the literature [5,17]. Typical polymerization procedure was described for TMCE-MOE4OM. In the three-necked flask, 0.5 g of TMCE-MOE4OM (2.45 mmol) was dissolved in about 5 mL of anhydrous CH_2Cl_2 with CaH_2 to stir for overnight. Using a cannula with glass filter to remove CaH_2, the monomer solution was transferred to the other flask with three way cock and the solvent CH_2Cl_2 was evaporated under reduced pressure. Then, the required amount of anhydrous CH_2Cl_2 under nitrogen atmosphere was introduced. Into the monomer solution, 0.6 mL of benzyl alcohol (0.049 mmol) solution in CH_2Cl_2 as initiator and 0.6 mL of DBU (0.049 mmol) solution in CH_2Cl_2 as catalyst was added to start the polymerization at room temperature for 8 h. The reaction was stop by adding small portion of acetic acid, then the reaction mixture was poured into a large amount of hexane/2-propanol (9/1, v/v). The product was recovered by decantation and centrifugation and dried under vacuum (73% yield).

2.2. Degradation experiments

10 mg of the polymer and 50 mg lipase were dissolved into 10 mL phosphate buffered saline (PBS), in 20 mL vial, and the cap was sealed by parafilm to set at 37 °C. Each 1 mL was taken for analysis after 1, 3, 6, 7 days, and 2, 4, and 9 weeks. Each aliquot was extracted by CH_2Cl_2/water and organic layer was evaporated to recover the degraded compound mixture. The three samples for each condition were repeated and SEC and ^{1}H NMR were then measured ($n = 3$). Similarly, 0.01 M NaOHaq. was employed for alkali condition. 10 mg of the polymer was dissolved in 10 mL of 0.01 M NaOHaq. in 20 mL vial, and the cap was sealed by parafilm to set at 37 °C. The same analyses were achieved for alkali condition as condition with lipase.

2.3. Measurements

^{1}H NMR spectra were measured by a JEOL JNM-ECX400 system. Attenuated total reflection (ATR) IR spectra were obtained with IR Affinity-1S (SHIMADZU CORPORATION, Japan). The interferograms were co-added 64 times and Fourier-transformed at a resolution of 4 cm^{-1}. The number average molecular weights and their distribution were measured by gel permeation chromatography. ChromNAV system (JASCO Corporation, Japan) using AS-2055 and RI-2031 was employed with PMMA standards at 40 °C. Two commercial columns (TSKgel SuperH3000 and TSKgel GMHXL) were connected in series and tetrahydrofuran was used as an eluent. The mass spectra were measured on a JEOL AccuTOF, JSM-T100LC mass spectrometer for novel monomers. MALDI-TOF/MS was measured with BRUKER auto flex II.

3. Results and discussion

TMCM-MOE3OM and TMCE-MOE4OM for the degradation were synthesized and polymerized according to the literature [17]. The M_n values of poly(TMCM-MOE3OM) and poly(TMCE-MOE4OM) were determined as 11,000 and 4800 by SEC, respectively.

The degradation behaviors of poly(TMCM-MOE3OM) and poly(TMCE-MOE4OM) by lipase were analyzed by the changes of molecular weights with SEC (Fig. 1). The initial values of M_n at 0 day (white circles) were different form those after starting degradation, because of the difference of sample preparation with and without extraction by CH_2Cl_2/water as described in experimental section. The slight increase of M_n over degradation was observed, probably due to the small M_n moiety degradation as same as PTMC degradation under various pH [26]. However, there were almost no changes in their molecular weights in 9 weeks in both cases, although PTMC would degrade as reported [26]. The present results indicate that the side substituents of alkyl and OEG units influenced the degradable behaviors. It is probably because the steric bulkiness of the substituents don't allow lipase a close enough position to the hydrolysis reaction along the polymer main chain.

To add to this, the hydrophilic properties of OEG made it difficult to obtain polymer-lipase interaction, which enabled the dissolving in water.

The cloud point of poly(TMCM-MOE3OM) is 33 °C, so there is complete liquid-liquid phase separation of the polymer and water [17], which is the similar degradation condition as solid-liquid phases of PTMC degradation in the literature [26]. On the other hand, polymer chains partially exist in solution in the case of poly(TMCE-MOE4OM) because its cloud point is 37 °C. The

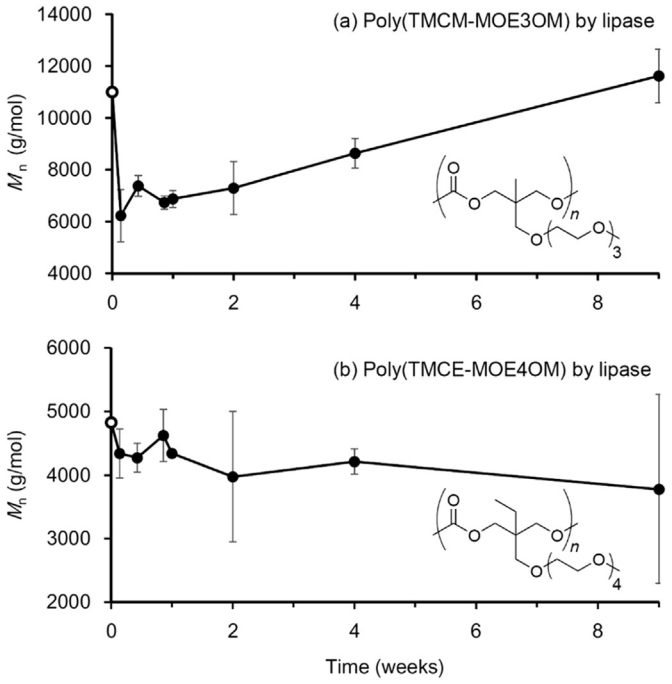

Fig. 1. The M_n changes of poly(TMCM-MOE3OM) (a) and poly(TMCE-MOE4OM) (b) under the condition of degradation by lipase at 37 °C.