

Biodegradable and Biocompatible Crosslinked Film with Trimethylene Carbonate Bearing Oligo(ethylene glycol)

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Three crosslinked films with different ratios of hydrophilic and hydrophobic monomers were prepared using trimethylene carbonate backbone with ester free structure. Oligo(ethylene glycol) (OEG) was selected as hydrophilic moieties due to the high mobility, hydrophilicity and biocompatibility. The obtained crosslinked films were evaluated by thermal properties, mechanical properties, surface properties, and protein adsorption. The results showed soft properties with high biocompatibility, depending on the introduction rate of OEG.

Keywords: Trimethylene carbonate | Oligo(ethylene glycol) | Crosslinking agent

It is known that poly(trimethylene carbonate) (PTMC) can be synthesized via ring-opening polymerization of trimethylene carbonate (TMC).¹ PTMC has been paid much attention because it could be applicable as degradable polymer materials,^{2–5} utilizing their flexibility.⁶ PTMC is decomposed *in vivo*, and it would not cause a pH change since it does not produce any acidic compounds after decomposition. Therefore, it is expected to reduce the possibility of inflammation after degradation. In addition, it is easy to functionalize by introduction of a substituent into the side chain of TMC with a molecular design. Actually, various synthetic routes for TMC derivatives have been developed.^{7–12} As a result, many potential applications have been reported, such as a fluorescent tool to monitor transportation in living cells,¹³ pH-responsive nanoparticles for gene delivery,¹⁴ the charged hydrogel materials for skin treatment,¹⁵ stacked-disk-like self-assembly nanostructures for drug delivery,¹⁶ and surface modification by polymer coating on a substrate.¹⁷

However, most of their PTMC derivatives possess an ester bonds at the side chain for the additional substituent, which could generate the acidic compounds on hydrolysis. As a result, the property of the conventional PTMC that no acidic compound is generated on decomposition has been lost, unfortunately. Therefore, we were motivated to design TMC derivatives as the functional monomers, “ester free”, which will not produce an acidic compound upon decomposition. It has been achieved by introducing a substituent on the side chain of TMC through an ether linkage.⁷ The synthesized ester free PTMC derivative does not produce an acidic compound at the time of decomposition like the conventional PTMC, so its strong feature is that does not cause pH change in the body on hydrolysis.

We have been conducting research on PTMC-MOE3OM which is a PTMC derivative with oligoethylene glycol (OEG) introduced in ester free form in the side chain.⁷ It is known that OEG can suppress protein adsorption from its high mobility and biocompatibility.^{18–21} The surface with OEG also becomes hydrophilic, observed by the gradual change of the contact angles.^{22,23} Previously we have reported that PTMCM-

MOE3OM showed thermal responsiveness with lower critical solution temperature (LSCT) near body temperature.⁷ Thus, it would be expected to be applied to biomaterials. It was interesting that PTMCM-MOE3OM showed different hydrolysis behavior from PTMC. For it is known that decomposition of PTMC is carried out by a lipase, while it is stable in an alkaline solution.²⁴ However, decomposition of PTMCM-MOE3OM is suppressed by OEG introduced into the side chain due to the difficulty of lipase approaching the polymer chain, and decomposition is promoted because OEG coordinates to cation in alkaline solution.²⁵ A series of polymers with OEG in the side chain of TMC consists of viscous liquid polymer and is difficult to handle as a material.⁷ That was the reason why the photo crosslinked polymers by copolymerization with TMC in which coumarin was previously introduced into the side chain²⁶ and nanoparticles using an amphiphilic polymer of a copolymer with poly(lactic acid) have been studied.²⁷

In this study, crosslinked films were synthesized using TMCM-MOE3OM, TMC and 2,2'-bis(trimethylene carbonate-5-yl)-butylether (BTB) as a crosslinking agent in order to overcome the difficulty of handling polymers. Although research on films using TMC has advanced,^{28–31} films using TMCM-MOE3OM have not yet been studied. Therefore, we considered that it is very important to investigate whether TMCM-MOE3OM characteristics are expressed in film. Three kinds of films were synthesized by changing the ratio of TMCM-MOE3OM and TMC, and the change in material properties due to it was confirmed by evaluation of thermal characteristics and mechanical properties. The contact angle and protein adsorption were also evaluated in order to investigate the biocompatibility of the film surface.

Figure 1 shows the synthetic route of crosslinked film. TMCM-MOE3OM⁷ and BTB³¹ were synthesized, according to the literature. As a result, it was possible to synthesize a film having a carbonate bond in the main chain and OEG chain grafted to the main chain (Figure 1a). As in the photograph, the synthesized film became soft and flexible (Figure 1b). In order to confirm the characteristics of the film, three kinds of films were synthesized by changing the ratio of TMCM-MOE3OM and TMC (Table 1). Herein, a film with a ratio of TMCM-MOE3OM to TMC of 1 to 5 is referred to as L-OEG-film (low; L) (Table 1, Entry 1), 3 to 3 is referred to as M-OEG-film (medium; M) (Table 1, Entry 2), 6 to 0 is referred to as H-OEG-film (high; H) (Table 1, Entry 3). The proportion of crosslinking agent was 14.3% in all films. The yield was 91.0% in L-OEG-Film, 93.4% in M-OEG-Film and 92.5% in H-OEG-Film. As a result, it was confirmed that each monomer was incorporated in the film.

The synthesized films were analyzed by FT-IR (Figure 2). The peak around of 1230 cm⁻¹, which could not be confirmed with the monomer, was the C-O stretching of the ester and it was

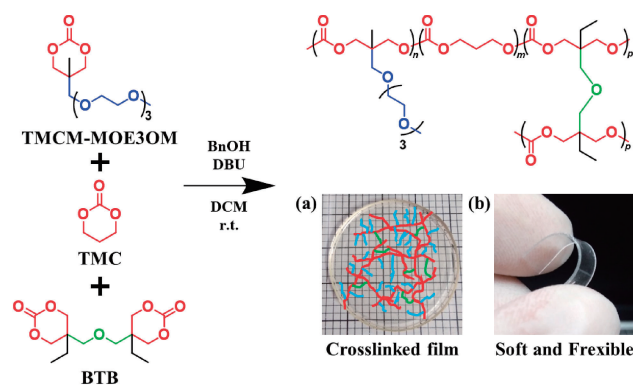


Figure 1. Synthesis of crosslinked film (a) and the photo of M-OEG-film (b).

Table 1. Preparation table of crosslinked film

Entry	Sample	Quantity of monomers (mmol)			BnOH (mmol) ^a	DBU (mmol) ^b	Yield (%)
		TMCM-MOE3OM	TMC	BTB			
1	L-OEG-Film	1.71	8.55	1.71	0.09	0.17	91.0
2	M-OEG-Film	3.42	3.42	1.14	0.06	0.11	93.4
3	H-OEG-Film	3.42	-	0.57	0.03	0.06	92.5

^a Initiator = BnOH. ^b Catalyst = DBU. Solvent = DCM

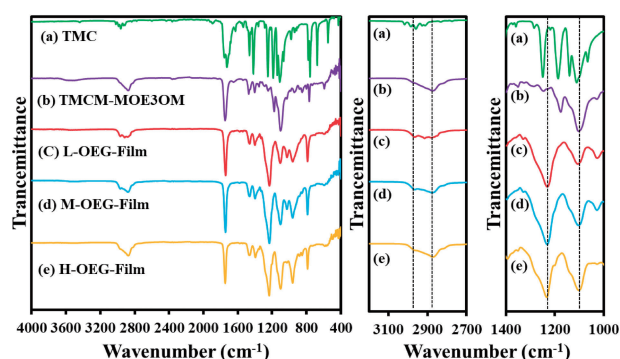


Figure 2. FT-IR spectra of TMC (a), TMCM-MOE3OM (b), L-OEG-Film (c), M-OEG-Film (d) and H-OEG-Film (e).

confirmed that ring-opening polymerization was occurring (Figure 2c, 2d and 2e). Since the peak around of 1100 cm^{-1} derived from the C-O-C stretching of ether is stronger in the order of L-OEG-film, M-OEG-film and H-OEG-film, it coincides with the content of TMCM-MOE3OM in the film (Figure 2b, 2c, 2d and 2e). From the peaks around 2870 cm^{-1} and 2970 cm^{-1} , when the content of TMCM-MOE3OM increases, the CH_2 stretching peak around 2870 cm^{-1} and the CH_3 stretching peak around 2970 cm^{-1} become stronger. This shows that the ratio of TMCM-MOE3OM in the film agrees with the ratio shown in Table 1.

Thermal characteristics are summarized in Table 2 and Figure 3, including the glass transition temperature (T_g), and the decomposition temperature of 10% weight loss (T_{10}). As a result of examining the thermal properties of the film, the thermal decomposition temperature improved as the content of TMCM-MOE3OM increased. The results imply a difference in molecu-

Table 2. Thermal properties of crosslinked film

Entry	Sample	T_{10} (°C) ^a	T_g (°C) ^b
1	L-OEG-Film	228	-21
2	M-OEG-Film	238	-39
3	H-OEG-Film	265	-48

^a Determined by thermogravimetric analysis (TGA) (10 °C/min). ^b

Determined by differential scanning calorimetry (DSC) in the second heating (10 °C/min).

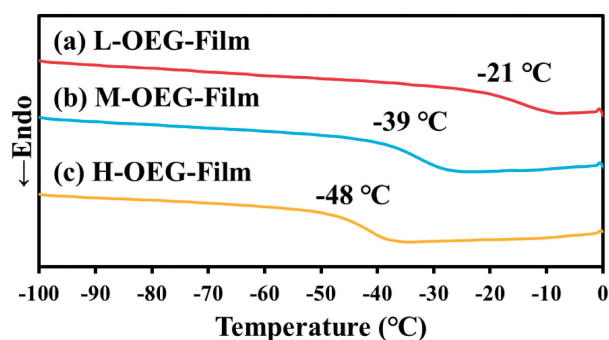


Figure 3. DSC traces of L-OEG-Film (a), M-OEG-Film (b) and H-OEG-Film (c).

Table 3. Mechanical properties of crosslinked film

Entry	Sample	Tensile modulus (MPa)	Strain at break (%)	Stress at break (MPa)
1	L-OEG-Film	3.45 ± 0.07	50.5 ± 11.0	1.22 ± 0.24
2	M-OEG-Film	2.28 ± 0.09	22.5 ± 3.73	0.43 ± 0.05
3	H-OEG-Film	0.78 ± 0.48	22.4 ± 3.59	0.15 ± 0.10

Values are means $\pm$ standard deviation ($n = 3$).

lar weight between TMC and TMCM-MOE3OM. Since the intermolecular force increases as the molecular weight increases, it is considered that T_{10} increased in proportion to the content of TMCM-MOE3OM. Thermal analysis showed that T_{10} was more than 200 °C in all film. This makes it possible to conduct dry heat sterilization allowing it to be used as a medical material.

Figure 3 shows the T_g of the film. According to the literature, T_g of the film using only TMC is reported as -19 °C .²⁸ The T_g values of L-OEG-film, M-OEG-film, and H-OEG-film were -21 °C , -39 °C , and -48 °C , respectively (Figure 3a–3c). This result shows that the T_g decreases in proportion to the content of TMCM-MOE3OM in the film. It would be possibly derived from OEG in the side chain of TMCM-MOE3OM. Decreasing T_g by introducing OEG into the side chain of the polymer is due to high mobility of OEG and inhibits packing of the polymer.³²

The results of the tensile tests are shown in Table 3 and Figure 4. It was found that the mechanical strengths became low when the content of TMCM-MOE3OM increased. The Young's modulus of the film was $3.45 \pm 0.07\text{ MPa}$ in L-OEG-film (Table 3, Entry 1), $2.28 \pm 0.09\text{ MPa}$ in M-OEG-film (Table 3, Entry 2) and $0.78 \pm 0.48\text{ MPa}$ in H-OEG-film (Table 3, Entry 3). Considering that the BTB content is 14.3% in all the films, it turns out that it was a very soft material. This was attributed to the characteristics of TMCM-MOE3OM. TMCM-

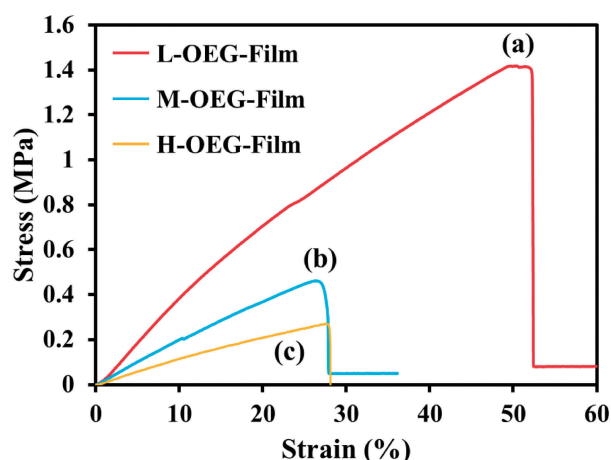


Figure 4. Stress–strain curves for L-OEG-Film (a), M-OEG-Film (b) and H-OEG-Film (c) ($n = 3$).

MOE3OM is a liquid monomer with a low viscosity, and viscosity is not improved even in a high molecular weight substance.⁷ Therefore, it was considered that the film became soft. The elongation at break was $50.5 \pm 11.0\%$ in L-OEG-film (Table 3, Entry 1), $22.5 \pm 3.73\%$ in M-OEG-film (Table 3, Entry 2) and $22.4 \pm 3.59\%$ in H-OEG-film (Table 3, Entry 3). Since the breaking elongation of M-OEG-film and H-OEG-film was hardly changed, it was found that elongation at break becomes constant when TCMC-MOE3OM is incorporated in 43% or more of the whole films. The tensile strengths were 1.22 ± 0.24 MPa in L-OEG-film (Table 3, Entry 1), 0.43 ± 0.05 MPa in M-OEG-film (Table 3, Entry 2) and 0.15 ± 0.10 MPa in H-OEG-film (Table 3, Entry 3). As a result, it was found that the breaking strength decreases in proportion to the content of TCMC-MOE3OM.

In Figure 5, the time-dependent water contact angle was measured. In all films, the contact angle after 60 seconds decreased as compared with after 0 seconds. The reduction rate after 60 seconds is 14.9% in L-OEG-film (Figure 5a), 39.1% in M-OEG-film (Figure 5b) and 45.0% in H-OEG-film (Figure 5c), the contact angle decreases in proportion to the content of TCMC-MOE3OM. This is due to the side chain OEG of TCMC-MOE3OM. OEG is known as a hydrophilic compound and attracts water when the polymer main chain is flexible. As a result, OEG on the film surface segregated due to contact with water droplets, and the film surface changed to hydrophilic with time. Although segregation behavior on the surface of thin film on the substrate coated with polymer has been confirmed,^{22,23} segregation behavior was confirmed similarly in film.

Figure 6 shows the results of the swelling degrees of film and the protein adsorption. L-OEG-film has already been found to be a relatively hydrophobic film from contact angle measurements (Figure 5a). It was conceived that the swelling ratio when penetrated into the albumin solution varied from film to film. Therefore, the swelling ratio was measured (Figure 6A). The swelling ratio was measured under the same conditions as the immersion time in the protein adsorption measurement. The results of swelling ratio were $2.80 \pm 1.13\%$ in L-OEG-film (Figure 6Aa), $5.40 \pm 1.47\%$ in M-OEG-film (Figure 6Ab) and $14.76 \pm 2.84\%$ in H-OEG-film (Figure 6Ac). As a result, it was

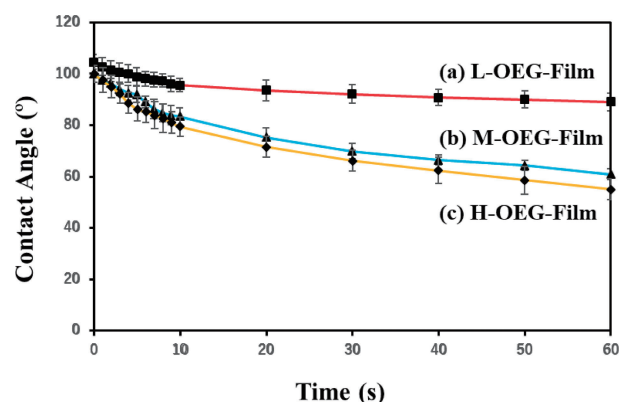


Figure 5. Time-dependent contact angle of water droplet of L-OEG-Film (a), M-OEG-Film (b) and H-OEG-Film (c) at 25 °C ($n = 3$).

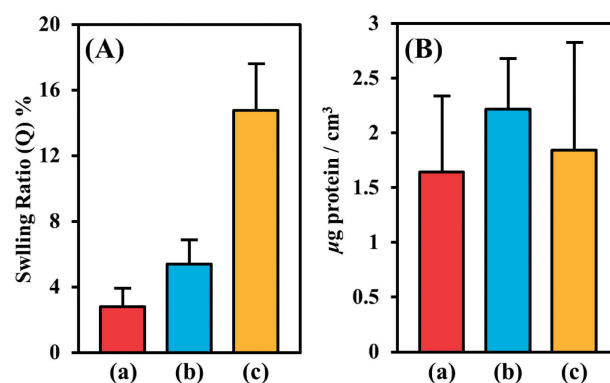


Figure 6. Dynamic swelling studies (A) and albumin adsorption (B) of L-OEG-Film (a), M-OEG-Film (b) and H-OEG-Film (c) of film volume ($n = 5$).

found that the swelling ratio of the film was different, the result of H-OEG-film being most swollen, and the swelling ratio increased in proportion to the content of hydrophilic OEG. The albumin adsorption amount was $1.64 \pm 0.70 \mu\text{g}/\text{cm}^3$ in L-OEG-film (Figure 6Ba), $2.22 \pm 0.47 \mu\text{g}/\text{cm}^3$ in M-OEG-film (Figure 6Bb) and $1.85 \pm 0.99 \mu\text{g}/\text{cm}^3$ in H-OEG-film (Figure 6Bc). L-OEG-film having the lowest adsorption amount was considered to be attributable to the low encounter with albumin because the swelling ratio was the lowest. When comparing M-OEG-film and H-OEG-film, despite the fact that H-OEG-film swells three times as much as M-OEG-film, H-OEG-film resulted in lower albumin adsorption. This clearly derives from the high mobility and biocompatibility of the side chain OEG. Therefore, it was confirmed that the biocompatibility of TCMC-MOE3OM is also demonstrated in the film.

In conclusion, a crosslinked film using TCMC-MOE3OM having OEG in the side chain of TMC was newly synthesized. In all films, T_{10} was above 200 °C and increased according to the introduction rate of OEG. As a result, this makes it possible to conduct dry heat sterilization allowing it to be used as a medical material. Further, in all the films, T_g was less than -20 °C, and it turned out that it was a very soft film. T_g decreased according to the introduction rate of OEG. As a result of the tensile test, the

mechanical properties decreased according to the introduction rate of OEG. This result reflects the soft characteristics of TCMC-MOE3OM as a liquid monomer. In the film as well, the contact angle changed to hydrophilic with time, and OEG segregated on the film surface. The swelling ratio increased in proportion to the introduction rate of OEG. However, no significant difference in albumin adsorption was observed. This suggested the possibility of producing a biocompatible film. Starting with this research, application to drug delivery and application to biomaterials such as artificial blood vessels are expected using films.

Supporting Information is available on <https://doi.org/10.1246/cl.180960>.

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