Design of Poly(trimethylene carbonate) with Hydrophilic Polymer Chain and its Aggregation Property

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Poly(trimethylene carbonate) (PTMC) shows biodegradability and is currently being utilized in medical devices. In this study, poly(ethylene glycol) monomethyl ether (mPEG) was incorporated into the terminating end of a PTMC molecule. mPEG, which has a hydrophilic segment, was selected as the initiator. Two kinds of mPEG with average molecular weight 5000 g/mol and 350 g/mol was used.

The resulting polymer spontaneously aggregated in the organic solvent. The aggregations were quite stable for 2 months at room temperature. The composition, the hydrophilic and hydrophobic segment, was dominant factor to regulate the stability of polymer aggregation. The time to reach complete dissociation was variable, and the stability of the polymer aggregation was more than 1 month. The difference in its stability would depend on its circulation in our body for 2 months because of the difference in its degree of polymerization and composition. Moreover, the drug loading property using the resulting aggregations was examined using Basic Blue17, which is an organic dye and is used as a model substance. We have found that the organic dye was successfully loaded into the aggregations.

Key words: poly(trimethylene carbonate), poly(ethylene glycol), ring-opening polymerization, aggregation, encapsulation

1. INTRODUCTION
Poly(trimethylene carbonate) (PTMC) is used as a biological adaptation material, and it is a remarkable polymer material, and its popularity has increased over the years. PTMC is a promising material for use in drug delivery systems; however, presently, it is being used as the material for suture string used in surgeries. As for TMC, it is reported that the ring-opening polymerization by the organometallic [1], organic [2,3], and enzyme catalysts [4]. In this study, PTMC has been obtained from TMC using this characteristic because it would be ring-opening polymerization.

Moreover, poly(ethylene glycol) monomethyl ether (mPEG), which has low toxicity and is known to the living body as an initiator for PTMC creation, has been used. It has already been reported that the mPEG-PTMC polymer selectively adsorbs hydrophobic model drugs by making it to the membrane [1]. Also, mPEG-PTMC was found to achieve a fine reflexive interface. The mPEG chain spontaneously enriched the outermost surface of the membrane [5].

The aggregation is created using these PTMCs in the solvent. It is thought that the mPEG-PTMC polymer assumes the shape shown in Fig. 1 when it gets aggregated because of its amphiphilic nature. Such an aggregation maintains a very steady character in the solution. In addition, if the drug can be incorporated in the aggregation as shown in Fig. 1, it can possibly be used as a material in the drug delivery system.

2. MATERIALS AND METHOD
2.1 Materials
Trimethylene carbonate (TMC) was purchased from Boehringer Ingelheim. Poly(ethylene glycol) monomethyl ether at 350 g/mol (mPEG350, Alfa Aesar) and poly(ethylene glycol) monomethyl ether at 5,000 g/mol (mPEG5000, Fluka) were used for the
polymerizations. 1,8-Diazabicyclo[5,4,0]7-undecene (DBU) (Kanto Chemicals Co., Inc., Tokyo, Japan) was used as the organic catalyst. Benzoic acid (Wako Pure Chemical Industries, Osaka, Japan) was used for terminating the reaction.

2.2 Instrumentation

$^1$H-NMR spectra were recorded using a VARIAN500 (Varian Technologies Japan Limited) with CDCl$_3$ as a solvent. $^1$H-NMR chemical shifts (ppm) were recorded downfield from 0.00 ppm using tetramethylsilane (TMS) as the internal standard. Gel permeation chromatography (GPC) measurements were performed on a Shodex KF-804 (SHOWA DENKO K.K., Tokyo, Japan). N,N-dimethyl formamide (DMF) with 10 mmol/L lithium chloride was used as an eluent. The flow rate was 1.0 mL/min, and a universal calibration with polystyrene standards (Shodex KF-804) was performed. UV-Vis spectra were recorded using a U-2001 (Hitachi, Tokyo, Japan) spectrophotometer.

2.3 Synthesis of PTMC

Poly(trimethylene carbonate) (PTMC) with a hydrophilic segment was synthesized by ring-opening polymerization. mPEG350 or mPEG5000 was used as the initiator. First, an initiator and catalyst were dissolved in methylene chloride. TMC was dissolved in methylene chloride and these solutions were mixed. The polymerization was carried out under a nitrogen atmosphere at room temperature for 24 h. The reaction was terminated by addition of benzoic acid. The polymerization degree was demonstrated by comparing the segment of starting compound to the PTMC group. We were able to confirm the following peaks by $^1$H-NMR (ppm): 2.05 ppm and 4.25 ppm (mPEG segment on PTMC).

2.4 Preparation of polymer aggregation

First, the product was dissolved in methylene chloride. It was dropped into methanol and the resulting solution was subjected to ultrasonic irradiation. As a result, the aggregation was spontaneously formed. In addition, to remove methylene chloride from the resultant solution, the sample was heated using a water bath.

2.5 Characterization of polymer aggregation

The characteristics of the aggregation were examined by addition of Basic Blue17 (BB17) to the solution. The aggregation existed in the solution would encapsulate the BB17 as a model compound. BB17 is an organic dye. Its structure is shown in Fig. 2. The absorbance of this solution was measured using the UV-Vis spectrophotometer.

The stability of the aggregations was analyzed. The transmission of the solution, where the aggregations existed, was measured using the spectrophotometer at 500nm. The wavelength is typically used for transmittance or turbidity measurements.

![Scheme 1](image)

Scheme 1  Synthetic route for mPEG-terminated PTMC.

2.6.3 Preparation of polymer aggregation

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3. RESULTS AND DISCUSSION

3.1 Synthesis of PTMC from mPEG derivatives

The fundamental reaction was the ring-opening polymerization. By using mPEG derivatives, we could synthesize the resulting mPEG-PTMC with a hydrophilic segment in the end group. In the ring-opening polymerization, the hydroxyl group was activated as the initiation point by the catalyst DBU. The activated hydroxyl group was attacked by the TMC. Therefore, the cyclic monomer was ring-opened and got polymerized. Table 1 shows the result of versatile polymerization. Polymerization degree was calculated as the internal standard. Gel permeation chromatography (GPC) measurements were performed on a Shodex KF-804 (SHOWA DENKO K.K., Tokyo, Japan). N,N-dimethyl formamide (DMF) with 10 mmol/L lithium chloride was used as an eluent. The flow rate was 1.0 mL/min, and a universal calibration with polystyrene standards (Shodex KF-804) was performed. UV-Vis spectra were recorded using a U-2001 (Hitachi, Tokyo, Japan) spectrophotometer.

![Table 1](image)

Table 1  Results of mPEG35000 and mPEG350-terminated poly(trimethylene carbonate).

<table>
<thead>
<tr>
<th>Abb.</th>
<th>Feed ratio [mPEG5000]/[I]</th>
<th>Yield (%)</th>
<th>Degree of polymerization$^a$</th>
<th>$M_n/10^3$</th>
<th>$M_w/10^3$</th>
<th>$M_w/M_n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPEG50000-100</td>
<td>100</td>
<td>10.9</td>
<td>92.2±4</td>
<td>9.65</td>
<td>10.0</td>
<td>1.04</td>
</tr>
<tr>
<td>mPEG50000-200</td>
<td>200</td>
<td>58.7</td>
<td>210.5±7</td>
<td>5.79</td>
<td>7.94</td>
<td>1.37</td>
</tr>
<tr>
<td>mPEG50000-300</td>
<td>300</td>
<td>90.1</td>
<td>324.1±8</td>
<td>9.36</td>
<td>11.9</td>
<td>1.28</td>
</tr>
<tr>
<td>mPEG50000-400</td>
<td>400</td>
<td>85.3</td>
<td>403.6±8</td>
<td>12.8</td>
<td>18.8</td>
<td>1.47</td>
</tr>
<tr>
<td>mPEG50000-100</td>
<td>100</td>
<td>52.3</td>
<td>69.4±9</td>
<td>4.86</td>
<td>6.46</td>
<td>1.33</td>
</tr>
<tr>
<td>mPEG50000-200</td>
<td>200</td>
<td>84.3</td>
<td>180.6±6</td>
<td>7.35</td>
<td>9.90</td>
<td>1.35</td>
</tr>
<tr>
<td>mPEG50000-300</td>
<td>300</td>
<td>85.6</td>
<td>243.6±5</td>
<td>12.2</td>
<td>18.6</td>
<td>1.53</td>
</tr>
<tr>
<td>mPEG50000-400</td>
<td>400</td>
<td>85.7</td>
<td>352.5±6</td>
<td>14.3</td>
<td>19.7</td>
<td>1.38</td>
</tr>
</tbody>
</table>

a) Determined by $^1$H-NMR
b) Determined by GPC
3.2 Characterization of polymer aggregation

First, we describe the characteristics of the aggregation achieved by using methanol as the solvent. When the laser beam, which was a conventional laser pointer, was applied to the polymer dispersive solution, the Tyndall phenomenon was observed. Therefore, we could prove that the colloid of the aggregation existed in the solution. When a polymer of mPEG5000-400 was used, the critical concentration at which the aggregation formed was $7.8 \times 10^{-6}$ g/mL.

Next, the encapsulating characteristic of mPEG5000-400 polymer was examined by adding BB17, which is the drug model of the encapsulation substance. The absorbance of each colloid solution that was added by BB17 is shown in Fig. 3.

![Absorbance of mixture of Basic Blue17 and colloid solution.](image)

The absorbance, which is attributed to the BB17, increased with an increase in polymer concentration. The difference between the absorbance of the solution spectrum when BB17 was added to the aggregation and that of the aggregation spectrum alone is shown in Fig. 4.

![Absorbance of Basic Blue17 at each polymer concentration. Circles show the absorbance of Basic Blue.](image)

Without the aggregation, the absorbance of the solution by BB17 occurred at 0.317 abs. The absorbance decreased to 0.302 abs when the final concentration of the polymer aggregation was $4 \times 10^{-5}$ g/mL. Moreover, the absorbance decreased to 0.204 abs as the final concentration became more than $1 \times 10^{-3}$ g/mL. It is considered that BB17 would be incorporated into the hydrophobic segment during the aggregation. The number of aggregations increased with an increase in the final concentration. Therefore, the amount of BB17 also increased.

Next, the stability of the aggregation was evaluated. The aggregation was prepared from the polymer of mPEG5000-100, mPEG5000-300, and mPEG5000-400, and then the transmittance at 500 nm was measured. This result is shown in Fig. 5.

![Change in transmittance at 500 nm. Stability of aggregation formed in methanol solvent was recorded; symbols indicate mPEG5000-100(○), mPEG5000-200(▲), mPEG5000-400(×).](image)

In the case of mPEG5000-100, the aggregation gradually changed precipitations due to its instability. Also, the precipitation was formed after approximately 144 h. The time taken to reach complete precipitation increased with the repeating unit of PTMC segment. In particular, mPEG5000-400 was very stable at around 1000 h.

In the case of mPEG5000-100, the transmittance of the polymer aggregation was 75, 60, and 100 % at 0, 50, and over 100 hours, respectively. Because transmittance decreased to be stabilized the polymer aggregation at early stage. Moreover, similar trend was observed in mPEG5000-200. However, mPEG5000-400 did not show any change in transmittance at the early stage, because the polymer aggregation was already stabilized.

In addition, Fig. 6 shows the stability of mPEG350-PTMC polymer aggregation.

![Change in transmittance at 500 nm. Stability of aggregation formed in methanol solvent was recorded; symbols indicate mPEG350-100(○), mPEG350-200(▲), mPEG350-400(×).](image)
The aggregation using mPEG350–400 polymer was repeatedly found to stabilize after approximately 300 h at the most. When the mPEG350-PTMC polymer was compared with the mPEG5000-PTMC polymer, the difference of the stability of 1000 h was caused.

It is considered that the effect of entanglement of PTMC segments with each other was dominant for the stability. The longer polymer chain was thought to be excellent aggregation in the solution. Therefore, the time to stabilize the aggregation would be variable in terms of the repeating unit of the PTMC segment.

Next concern of this aggregation would be formed in a water solvent. Now, we have examined and will report in the near future.

4. CONCLUSIONS

We succeeded in the ring-opening polymerization of TMC, where mPEG was used as the initiator. Moreover, we successfully formed the aggregation in an organic solvent using the mPEG-PTMC polymer. It turned out that the aggregation characteristic differed because of the polymer composition. The aggregation with a long PTMC chain was proven to be excellent both in the case of characteristic and stability. From these results, the aggregation voluntarily wrecked at the given period by combining the polymer of a different characteristic. If this property can be achieved, precisely targeted drug will become possible.

Moreover, we have also succeeded in forming the aggregation in a water solvent. This aggregation shows stability that exceeds 1000 h; therefore, future applications of this can be expected.

5. ACKNOWLEDGEMENT

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6. REFERENCES


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