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ORIGINAL CONTRIBUTION

# Preparation of biodegradable microspheres by anionic dispersion polymerization with PLA copolymeric dispersion stabilizer

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**Abstract** We prepared poly(D,L-lactide) (PLA) microspheres by anionic dispersion polymerization of D,L-lactide. The polymerization was carried out in xylene/heptane (1:2 in *v*/*v*) mixture solution at 368 K for 9 h, with poly(dodecyl methacrylate)-*co*-poly[α-methacryloxyethoxy-poly(L-lactide)] (PDMA-*co*-P(MA-PLLA)) synthesized in this study, as a dispersion stabilizer. The number-averaged diameter and diameter distribution (coefficient of variation) of obtained PLA microspheres ranged from 180 to 800 nm and 14–40%, respectively, depending on the preparation condition. Furthermore, the time courses of monomer conversion, particle diameter, and particle number were investigated to clarify the formation mechanism of microspheres with PDMA-*co*-P(MA-PLLA) as a dispersion stabilizer. From this experiment, we found that the aggregation of primary particles occurred in anionic dispersion polymerization, and the particle diameter of obtained PLA microspheres decreased with increasing PDMA-*co*-P(MA-PLLA) concentration. In conclusion, we clarified that PDMA-*co*-P(MA-PLLA) effectively contributed to the stability of primary particles.

**Keywords** Polylactide microspheres · Anionic dispersion polymerization · Dispersion stabilizer · Diameter control · Microsphere formation

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## Introduction

In recent years, polymeric microspheres and nanospheres have been remarkably interesting because it may be possible to achieve precise control of the particle diameter, morphology, structure, and functionality of the particle surfaces. They have been utilized in commercial liquid products such as paints, inks, and adhesives.

On the other hand, poly(D,L-lactide) (PLA) is attracting much attention as a new polymeric material made from renewable resources such as plants, animals, and microbes called biomass. In addition, PLA is a biodegradable and biocompatible polymer with high mechanical strength [1, 2]. Techniques for preparing PLA microspheres are mainly classified into three approaches. The first is the solvent-evaporation technique, in which volatile organic solvent should be removed after the formation of an emulsion [3, 4]. The second is a spray-drying technique such as the RESS (rapid expansion of supercritical solution) process, in which supercritical carbon dioxide is used as a solvent [5, 6]. However, these preparation techniques have drawbacks such as multi-step preparation and polydispersity of particle diameter. We need a technique in which polymer synthesis and particle formation proceed simultaneously as an effective process for preparing PLA microspheres.

Anionic dispersion polymerization is a promising way to prepare polymeric microspheres with a narrow diameter distribution and only a simple procedure is needed. Poly(trioxane)-*co*-poly(dioxolane) microspheres and poly(glycolide)-*b*-poly(ε-caprolactone) nanoparticles were prepared by ring-opening anionic dispersion polymerization [7, 8]. Recently, Slomkowski et al. published several papers on the preparation of PLA microspheres with a narrow diameter distribution by ring-opening anionic dispersion

polymerization of L-(or D,L)-lactide [9–22]. They investigated the critical concentration of micellization (ccm), which is an important parameter for colloid particles to be stabilized in 1,4-dioxane and heptane (1:4 in *v*/*v*) mixture solution as a reaction medium, and conducted the polymerization at a lower concentration than its ccm. They explained that the cause of the narrow diameter distribution of obtained microspheres is fast nucleation and the absence of particle aggregation [14].

It seems difficult to avoid aggregation of swollen primary particles due to the good solubility of PLA in 1,4-dioxane. On the other hand, El-Aaser et al. reported that the aggregation of primary particles proceeded during anionic dispersion polymerization of styrene [23, 24]. However, experimental results for the aggregation of primary particles are still lacking. Therefore, the objectives that still remain include identifying the formation mechanism of microsphere for anionic dispersion polymerization.

Our paramount objective is to prepare fairly dispersed spherical PLA microspheres with well-controlled diameters. To achieve this, the first point of our strategy in this study was the selection of the solvent used in anionic dispersion polymerization from the viewpoint of the solubility of polymer formed and vapor pressure at the polymerization temperature. Second, a dispersion stabilizer of comb-like polymer should have the potential to both adsorb strongly on precipitated primary particles and disperse them in the medium against aggregation. Therefore, in this study, poly (dodecyl methacrylate)-*co*-poly[α-methacryloxyethoxy-poly(L-lactide)] (PDMA-*co*-P(MA-PLLA)) was synthesized as a dispersion stabilizer and anionic dispersion polymerization of D,L-lactide was conducted in the presence of PDMA-*co*-P(MA-PLLA). In this paper, we describe the experimental results concerning the effect of the dispersion stabilizer both on the diameters of prepared PLA microspheres and on the formation process of PLA microspheres in anionic dispersion polymerization.

## Experimental

### Materials

D,L- and L-lactide were purchased from PURAC biochem (Holland) and purified by recrystallization from toluene. 2-hydroxyethyl methacrylate (HEMA) and dodecyl methacrylate (DMA) purchased from Wako Pure Chemical Industries were purified by distillation under reduced pressure. Toluene, xylene, and heptane (dehydrated-grade) were purchased from Wako Pure Chemical Industries and were treated with 4 Å molecular sieves to remove dissolved water. Other reagents were purchased from Wako Pure Chemical Industries and used as received.

### Measurements

Gel permeation chromatography (HLC 8120, Tosoh, GPC) measurement was performed on the basis of the polystyrene standards with tetrahydrofuran as an eluent to determine the number-averaged molecular weight and polydispersity index of synthesized polymer. $^1$H NMR (AL300 SC-NMR JEOL) measurement was conducted using $CDCl_3$ as a solvent and TMS (1% in *v*/*v*) as an internal standard to determine the chemical structure and composition of synthesized polymer. Scanning electron microscopic observation (S-4700, Hitachi, SEM) was performed at 1 kV to determine the morphology and diameter of prepared PLA microspheres. The conversion of D,L-lactide was measured at a detector wavelength of 216 nm by high-performance liquid chromatography (LC-6A, Shimazu, HPLC) using a mixture solution of methanol and water (1:49 in *v*/*v*) as an eluent.

### Synthesis

#### *MA-PLLA*

MA-PLLA-A was synthesized by ring-opening polymerization of L-lactide using HEMA as an initiator in the presence of stannous 2-ethylhexanoate as a catalyst [25, 26]. The synthesis recipe of MA-PLLA is summarized in Table 1. L-lactide, HEMA, and a toluene solution of stannous 2-ethylhexanoate were placed into an ampoule, which was sealed under reduced pressure and immersed in an oil bath at 403 K. The polymerization was conducted for 9 h. After cooling, the reaction mixture was dissolved in chloroform and excess hexane was added. After the precipitated polymer was recovered and was washed with 2-propanol, subsequent drying under reduced pressure at 313 K was conducted.

### Copolymerization

#### *PDMA-co-P(MA-PLLA)*

The polymerization recipe is listed in Table 2. MA-PLLA, DMA, and dehydrated toluene as a solvent were placed into a round-bottom reactor. After nitrogen was admitted to

**Table 1** Recipe of ingredients for synthesis of MA-PLLA

| Function | Chemical name | MA-PLLA-A (mmol) | MA-PLLA-B (mmol) |
|---|---|---|---|
| Monomer | L-lactide | 66.15 | 65.60 |
| Initiator | HEMA | 3.53 | 4.15 |
| Catalyst | 2-ethylhexanoate | $2.47 \times 10^{-3}$ | $2.47 \times 10^{-3}$ |

Yield of the polymer: MA-PLLA-A: 63%; MA-PLLA-B: 60%

**Table 2** Recipe of ingredients for synthesis of PDMA-*co*-P(MA-PLLA)

| Function | Chemical name | PDMA-*co*-(MA-PLLA)-A (mmol) | PDMA-*co*-(MA-PLLA)-B (mmol) |
|---|---|---|---|
| Monomer | DMA | 5.01 | 10.74 |
| Macromonomer | MA-PLLA | 0.2 (type A) | 0.43 (type B) |
| Initiator | BPO | 0.94 | 0.16 |
| Solvent | Toluene | 6 (ml) | 12 (ml) |

remove dissolved oxygen, the reactor was immersed in an oil bath at 358 K. Dehydrated toluene dissolving benzoyl peroxide (BPO) was added to initiate the polymerization. The polymerization was conducted for 3 h. After cooling, the reaction mixture was poured into excess methanol. The precipitate was recovered and added to a mixture solution of 1,4-dioxane and heptane (1:4 in *v*/*v*) to remove the remaining MA-PLLA. After the purification, the obtained polymer was dried under reduced pressure at 313 K.

### Preparation of PLA microspheres

D,L-lactide (0.5 g, 3.47 mmol) was added into 17 ml of a mixture solution of dehydrated xylene and heptane (1:2 in *v*/*v*) dissolved PDMA-*co*-P(MA-PLLA). In this study, the concentration of dispersion stabilizer ranged from 0.01 to 0.2 g. The solution was stirred at 120 rpm with a magnetic stirrer. Three milliliter of a mixture solution of dehydrated xylene and heptane (1:2 in *v*/*v*) dissolving stannous 2-ethylhexanoate (0.0475 g, 0.12 mmol) as a catalyst and lauryl alcohol (0.011 g, 0.06 mmol) as an initiator was prepared. The solution was added with a syringe and polymerization was conducted at 368 K for 9 h. After polymerization, the reaction mixture was poured into excess cold heptane. The solution was centrifuged for 5 min at 9,000 rpm, and recovered microspheres were redispersed into excess heptane. The solution was filtered to recover the prepared microspheres.

To investigate the polymerization mechanism, we measured the effect of dispersion stabilizer, time courses of monomer conversion, number-averaged diameter, diameter distribution of microspheres, and particle number. In this run, the total volume was 40 ml and the concentrations of ingredients were the same as mentioned above. The number of particles was calculated by the following expression:

$$N_{\text{particle}} = \frac{600x}{\rho(\text{dp})^3\pi}$$

where $N_{\text{particle}}$, $x$, $\rho$, and dp denote particle number, amount of reacted monomer, PLA density, and number-averaged diameter of microspheres, respectively.

## Results and discussion

### Synthesis of PDMA-co-P(MA-PLLA) copolymers

The synthetic scheme of PDMA-*co*-P(MA-PLLA) is shown in Fig. 1. The first step is MA-PLLA synthesis by ring-opening polymerization of L-lactide using HEMA as an initiator. Subsequently, synthesized MA-PLLA was copolymerized with DMA by free radical polymerization using benzoyl peroxide (BPO) as an initiator to obtain PDMA-*co*-P(MA-PLLA). The synthesized MA-PLLA and PDMA-*co*-P

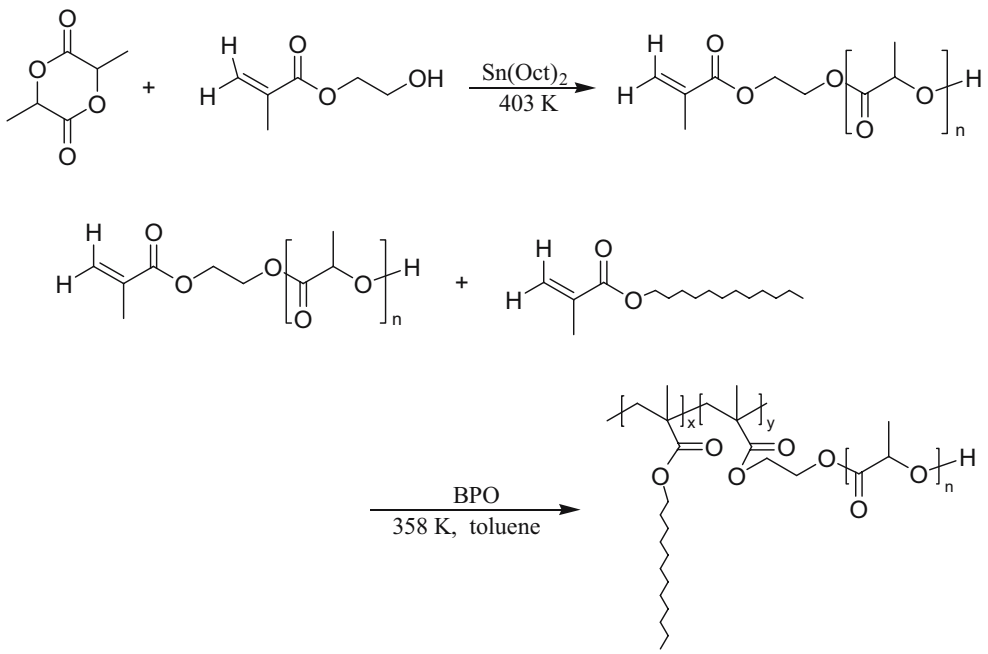


**Fig. 1** Synthetic route of PDMA-*co*-P(MA-PLLA)

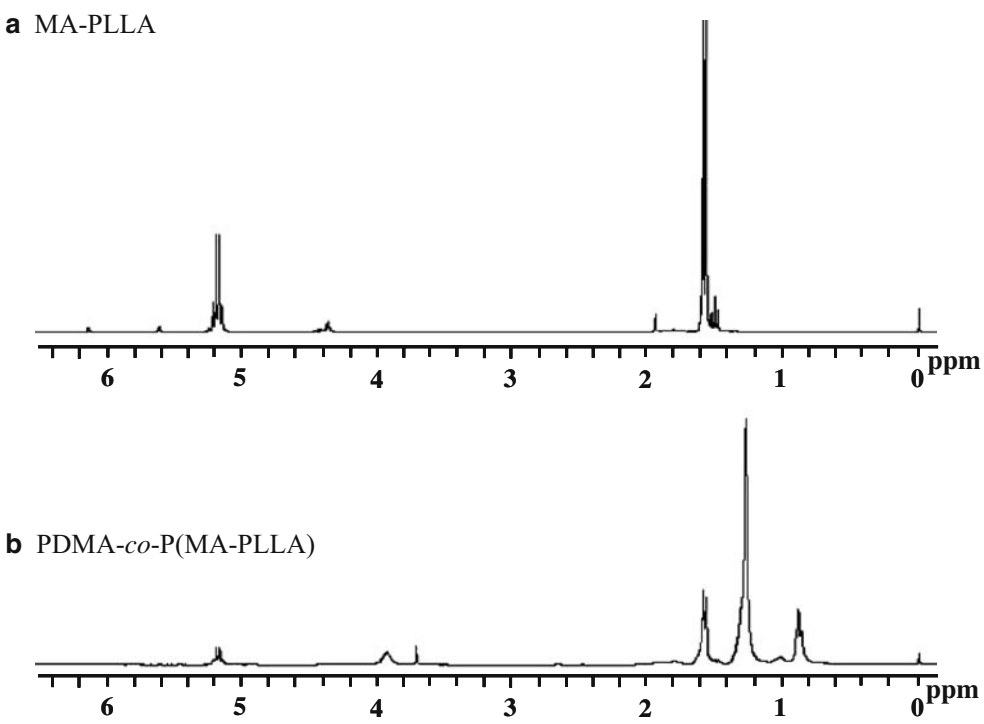


**Fig. 2** $^1$H NMR spectra for PDMA-*co*-P(MA-PLLA) synthesis. **a** MA-PLLA, **b** PDMA-*co*-P(MA-PLLA)

(MA-PLLA) were identified by $^1$H NMR. The $^1$H NMR spectra for the synthesis of PDMA-*co*-P(MA-PLLA) are shown in Fig. 2. The $^1$H NMR spectrum of PDMA-*co*-P (MA-PDLLA) had peaks in the range of 1.5–1.7 ppm ($CH_3$ for the PLA unit) and 5.1–5.3 ppm (CH for the PLA unit) and around 3.9 ppm ($OCH_2$ for the DMA unit). Furthermore, peaks at 5.6 and 6.2 ppm (double bond for the MA-PLLA) were not detected in the $^1$H NMR spectrum (Fig. 2b). Therefore, PDMA-*co*-P(MA-PLLA) was finally identified.

It is well-known that the molecular structure of dispersion stabilizer affects the adsorption property of dispersion stabilizers on precipitated primary particles and that the adsorption becomes an important step in the formation of PLA microspheres. Therefore, in this study, we synthesized PDMA-*co*-P(MA-PLLA) having different molecular structures such as the molecular weights of copolymer and MA-PLLA. The characteristic parameters of two synthesized types of PDMA-*co*-P(MA-PLLA) are shown in Table 3. MA-PLLA content in PDMA-*co*-P(MA-PLLA), $CF_g$, was calculated by $^1$H NMR using the integration ratios corresponding to around 3.9 ppm ($OCH_2$ for the DMA unit) and 5.1–5.3 ppm (CH for the PLA unit) [27]. It was defined by the following equation:

$$S_{\mathrm{MA-PLLA}} = \frac{A_{\mathrm{MA-PLLA}}}{\mathrm{PD}}$$
$$S_{\mathrm{DMA}} = \frac{A_{\mathrm{DMA}}}{2}$$
$$CF_g = \frac{S_{\mathrm{MA-PLLA}}}{(S_{\mathrm{DMA}} + S_{\mathrm{MA-PLLA}})} \cdot 100$$

where $A_{\mathrm{MA\text{-}PLLA}}$, $A_{\mathrm{DMA}}$, and PD denote the peak areas of CH for the PLA in MA-PLLA and $OCH_2$ for the DMA unit

**Table 3** Characteristic parameters of PDMA-*co*-P(MA-PLLA) as dispersion stabilizer

| Sample | Yield[a] (%) | Mw[b] copolymer (g/mol) | Mw /Mn | Mw MA-PLLA (g/mol) | $CF_g$[c] (%) | $N$[d] | $CN_g$[e] number | $f_{\mathrm{MA\text{-}PLLA}}$[f] |
|---|---|---|---|---|---|---|---|---|
| PDMA-*co*-P(MA-PLLA)-A | 79.46 | 37,857 | 2.33 | 3,628 | 3.06 | 31.65 | 3.24 | 0.31 |
| PDMA-*co*-P(MA-PLLA)-B | 71.27 | 52,329 | 2.07 | 2,958 | 3.20 | 30.25 | 4.92 | 0.28 |

MA-PLLA-A: Mw/Mn=1.14; MA-PLLA-B: Mw/Mn=1.15
[a] Yield was determined gravimetrically with respect to the monomer used.
[b] Mw was measured by GPC with standard polystyrene.
[c] MA-PLLA content in PDMA-*co*-P(MA-PLLA)
[d] Number of DMA units per one MA-PLLA
[e] Number of MA-PLLA units per molecule of PDMA-*co*-P(MA-PLLA)
[f] Weight fraction of MA-PLLA in PDMA-*co*-P(MA-PLLA)

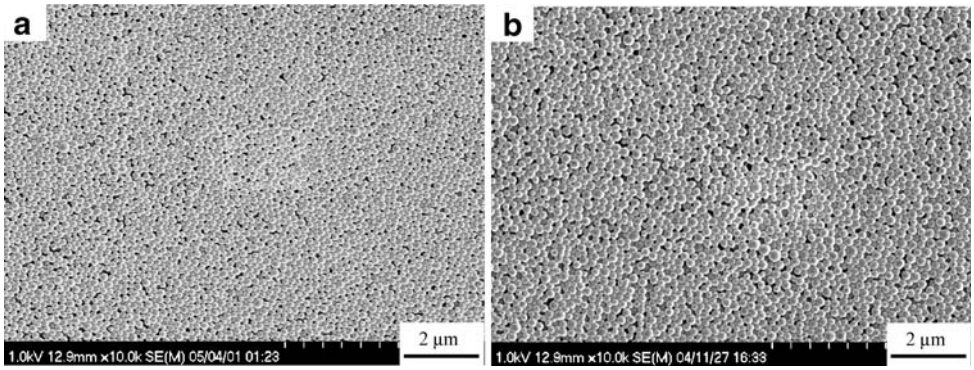


**Fig. 3** SEM images of PLA microspheres with various dispersion stabilizers, [PDMA-*co*-P(MA-PLLA)] = 7.5 g/l. **a** Type A: dp = 180 nm, CV = 14.1%, **b** type B: dp = 220 nm, CV = 18.1%

in $^1$H NMR spectra of PDMA-*co*-P(MA-PLLA) and the polymerization degree of MA-PLLA, respectively. The number of DMA units per MA-PLLA unit, $N$, was defined by

$$N = \frac{S_{\mathrm{DMA}}}{S_{\mathrm{MA-PLLA}}}$$

$CN_g$ expresses the number of MA-PLLA units per molecule of PDMA-*co*-P(MA-PLLA). It was defined by

$$CN_g = \frac{\mathrm{Mw_{copolymer}}}{(\mathrm{Mw_{DMA}} \cdot N + \mathrm{Mw_{MA-PLLA}})}$$

where $\mathrm{Mw_{copolymer}}$, $\mathrm{Mw_{DMA}}$, and $\mathrm{Mw_{MA\text{-}PLLA}}$ denote the weight-averaged molecular weight of DMA-*co*-P(MA-PLLA), DMA, and MA-PLLA, respectively. The weight fraction of MA-PLLA in PDMA-*co*-P(MA-PLLA), $f_{\mathrm{MA\text{-}PLLA}}$, was defined by

$$f_{\mathrm{MA-PLLA}} = \frac{\mathrm{Mw_{MA-PLLA}} \cdot CN_g}{\mathrm{Mw_{copolymer}}}.$$

As shown in this table, the $CF_g$ of synthesized PDMA-*co*-P(MA-PLLA) was found to be ca. 3% and dispersion stabilizer with higher $CF_g$ was not dissolved in the solvent. This low value of $CF_g$ is attributable to the solubility in the solvent used in this study because we aimed to use dispersion stabilizer with high affinity to precipitated PLA particles.

## Preparation of PLA microspheres

In their previous research, Slomkowski et al. used a mixture solution of 1,4-dioxane and heptane (1:4 in *v*/*v*) as a solvent for dispersion polymerization of D,L-lactide [9, 22]. This solvent had a high vapor pressure at the polymerization temperature (boiling point of 1,4-dioxane=374 K) and was swollen enough to adsorb the monomer into the precipitated primary particles. However, the swollen primary particles could easily form undesired aggregation. Thus, xylene (boiling point=413 K) is a suitable solvent in this reaction system because it has poorer solubility of PLA than 1,4-dioxane. The mixing ratio of xylene to heptane is limited because the solubility of D,L-lactide in xylene and heptane mixture solution is nearly equal to that of PLA. However, D,L-lactide is soluble in the xylene and heptane mixture solution (1:2 or 1:3 in *v*/*v*, 2.5% *w*/*v*), and PLA (Mw=7,700) is insoluble in the solution. Therefore, we selected to xylene and heptane (1:2 in *v*/*v*), which is able to dissolve D,L-lactide more.

Anionic dispersion polymerization of D,L-lactide was carried out with the selected solvent in the absence of

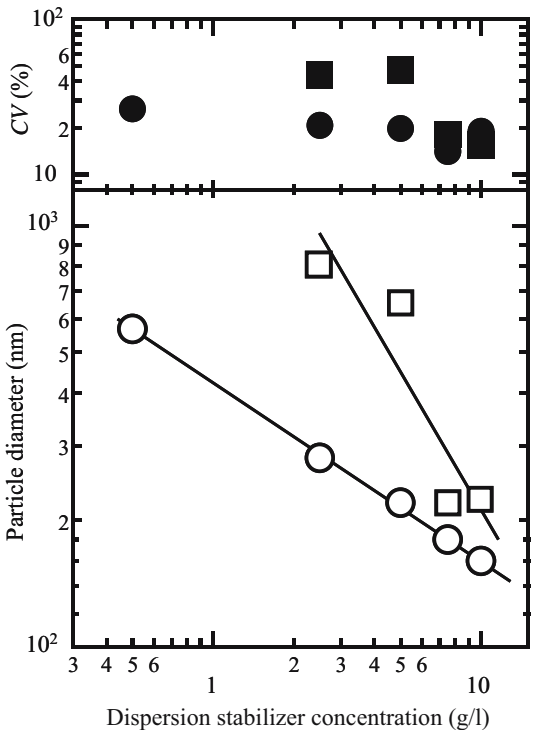


**Fig. 4** Effect of PDMA-*co*-P(MA-PLLA) concentration on number-averaged diameter and diameter distribution of PLA microspheres. *Open circle*: PDMA-*co*-P(MA-PLLA)-A; *open square*: PDMA-*co*-P(MA-PLLA)-B, (*open circle*, *open square*: particle diameters; *filled circle*, *filled square*: CV)

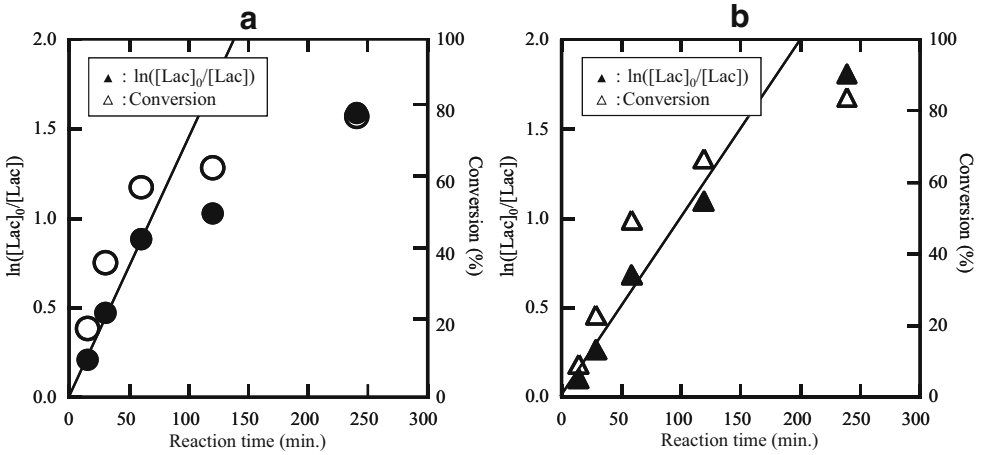


**Fig. 5** Kinetics of the dispersion polymerization of D, L-lactide, [PDMA-*co*-P(MA-PLLA)-B] =10 g/l (**a**) and 1 g/l (**b**)

dispersion stabilizer. As a result, PLA microspheres were not obtained and only products with undefined shapes were observed after dispersion polymerization. And so, we focused on the dispersion stabilizer with hydrophobic groups because xylene and heptane mixture solution was a highly hydrophobic solvent. For this purpose, a good candidate is alkyl methacrylate with hydrophobic groups. Therefore, anionic dispersion polymerization of D,L-lactide was carried out with PDMA (Mw=35,000) as a dispersion stabilizer. However, discrete spherical microspheres were not prepared.

The preparation of spherical microspheres is thought to require a dispersion stabilizer with a PLA segment that interacts with stronger primary particles. The PLA segment in the dispersion stabilizer physically adsorbs on the surface of the precipitated primary particles and the PDMA segment has high solubility in the solvent. Therefore, we synthesized PDMA-*co*-P(MA-PLLA) and used it in dispersion polymerization as a dispersion stabilizer. Figure 3 shows SEM images of the products obtained by anionic dispersion polymerization of D,L-lactide with two types of PDMA-*co*-P(MA-PLLA). Spherical PLA microspheres with a smooth surface were obtained and they were found to have a satisfactorily narrower diameter distribution. The number-averaged diameters were different between the two types of PDMA-*co*-P(MA-PLLA). Therefore, these results suggested that an adequate dispersion stabilizer is necessary to prepare PLA microspheres and that their number-averaged diameter is influenced by the molecular structure of PDMA-*co*-P(MA-PLLA).

Figure 4 shows the effect of PDMA-*co*-P(MA-PLLA) concentration on the number-averaged diameter and diameter distribution of obtained PLA microspheres. In the case of polymerization in the presence of PDMA-*co*-P(MA-PLLA)-B (concentration=0.5 g/l), PLA microspheres were not obtained and only undefined-shaped products and agglomerates were observed after dispersion polymerization. As shown in this figure, the number-averaged diameter of obtained microspheres decreased in proportional to the dispersion stabilizer concentration, and the number-averaged diameter was controlled in the range between 180 and 800 nm. Therefore, it was clarified that PDMA-*co*-P(MA-

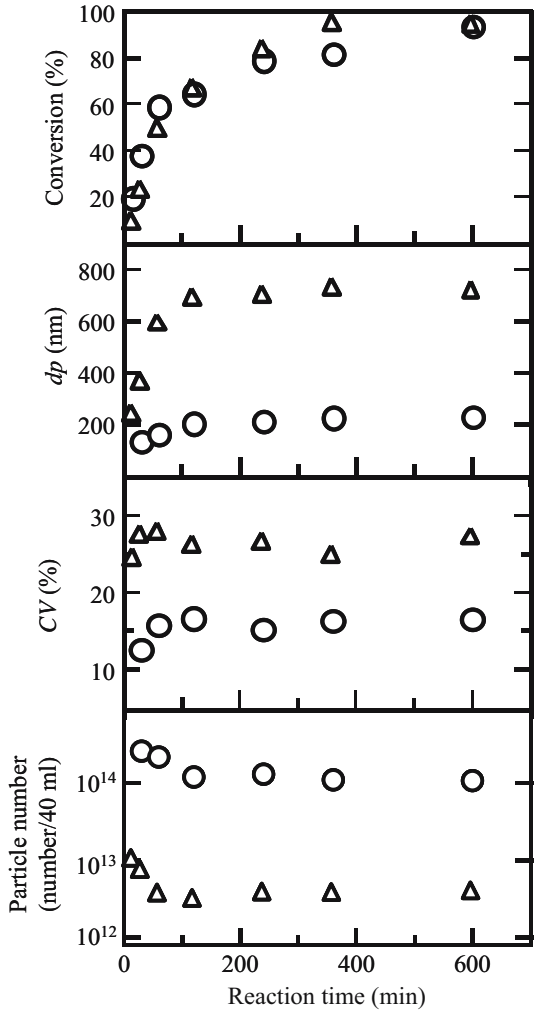


**Fig. 6** Dependence of number-averaged diameter and diameter distribution of microspheres, monomer conversion, and particle number on polymerization times, [PDMA-*co*-P(MA-PLLA)-B] = 10 g/l (*open circle*) and 1 g/l (*open triangle*)

PLLA) effectively contributed to the stability of primary particles and the stability of primary particles is influenced by the molecular structure of PDMA-*co*-P(MA-PLLA). Furthermore, the number-averaged diameter of microspheres obtained in this study was one order smaller than that reported by Slomkowski et al. (dp=2.46–4.07 μm) [11]. In general, the difference is caused by a shorter critical precipitated chain length of particulate nucleus because the solubility of PLA in xylene and heptane (1:2 in *v*/*v*) is lower than that in 1,4-dioxane and heptane (1:4 in *v*/*v*).

### Formation mechanism of PLA microspheres

The kinetics of the dispersion polymerization of D,L-lactide under different PDMA-*co*-P(MA-PLLA) concentrations is shown in Fig. 5. The $\ln([Lac]_0/[Lac])$ was directly proportional to the polymerization time. It was found, from this result, that the polymerization proceeded by a living mechanism in this reaction system and that the deviation from linear in the later stage was mainly caused by the decrease in monomer concentration [10, 28].

An experiment was carried out on time courses of monomer conversion, particle diameter, particle diameter distribution, and particle number to clarify the formation mechanism of microspheres with PDMA-*co*-P(MA-PLLA) as a dispersion stabilizer. The obtained results are summarized in Fig. 6. In the initial stage, monomer conversion and particle diameter increased with increasing polymerization time. In contrast, particle number decreased with increasing polymerization time. In particular, from a comparison with the previous study under the same conditions of concentration ratio between monomer and dispersion stabilizer, it is noteworthy that the particle number in this reaction system was about four orders of magnitude higher than that reported by Slomkowski et al. [14]. This result is considered to come from the differences in both the solubility of PLA in the solvent used and the stabilization property of synthesized dispersion stabilizer.

In addition, the change in diameter at lower concentrations of dispersion stabilizer was more significant than at higher concentration of dispersion stabilizer, leading to the preparation of larger spherical microspheres. Therefore, the number-averaged diameter and diameter distribution of obtained PLA microspheres strongly depends on the stability of primary particles, that is, on the adsorption of dispersion stabilizer on the surface of primary particles.

From the results mentioned above, it was clarified that the aggregation of precipitated primary particles occurs in the initial stage of anionic dispersion polymerization and that the dispersion stabilizer synthesized in this study effectively coated the surface of the precipitated primary particles to prevent aggregation. That is, PLA segments in PDMA-*co*-P(MA-PLLA) strongly absorb on primary particles, so PDMA-*co*-P(MA-PLLA) has good potential as a dispersion stabilizer in anionic dispersion polymerization of lactide [9, 11, 12].

## Conclusions

To study anionic dispersion polymerization for the preparation of PLA microspheres from the viewpoint of the stabilization effect of polymeric dispersion stabilizer, we synthesized a comb-like copolymer with a PLA segment, PDMA-*co*-P(MA-PLLA) and conducted anionic dispersion polymerization of D,L-lactide in its presence. As a result, well-dispersed and spherical PLA microspheres were obtained with a narrow diameter distribution. The molecular structure such as the length of the PLA segment significantly affected the number-averaged diameters of obtained PLA microspheres.

Experiments were conducted on the time courses of monomer conversion, particle diameter, and particle number to clarify the formation mechanism of microspheres with PDMA-*co*-P(MA-PLLA) for anionic dispersion polymerization. We found that the aggregation of precipitated primary particles occurred in the initial stage of anionic dispersion polymerization. Furthermore, the dispersion stabilizer synthesized in this study worked well as a dispersion stabilizer to prevent aggregation of precipitated primary particles, providing PLA microspheres with a smaller average diameter.

Remaining topics for further study include elucidating the stabilization mechanism of dispersion stabilizer such as an adsorption of the dispersion stabilizer on precipitated primary particles, to prepare PLA microspheres with precisely controlled diameters.

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