Porous polylactide particles regulated by phase separation

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ABSTRACT

Porous poly(L-lactide) (PLLA) particles was produced through the phase separation process of PLLA/o-dichlorobenzene and diethylphthalate systems. The turbid system was obtained from a homogeneous solution of PLLA/o-dichlorobenzene. Spherulites were formed during the phase separation process, and most of the solvent was bound in the spherulites. The cluster radius of the solvent bound in the spherulites was a few tens nm. The solvent was extracted by immersing in methanol, and then the particles were obtained. The nanopores were formed after the solvent was extracted. The particle size was regulated from 100 µm to 700 µm, depending on the quenching temperature. The particles have a macroporous structure, with a mesh size of a few µm. The quenching temperature has a strong effect on the porous morphology, which is essentially regulated by the crystallization of PLLA. As a result, it was shown that the porous PLLA particles consist not only of macropores measuring a few µm, but also of nanopores measuring a few tens nm. For the PLLA/diethylphthalate system, the porous particles were obtained by the same procedure. However the particle size was much smaller than that formed by an o-dichlorobenzene solution.

KEYWORDS: polylactide, porous particles, phase separation

INTRODUCTION

Recently, polylactide (PLA) has received a great deal of attention as a renewable polymer. PLA is an aliphatic thermoplastic polyester produced from renewable resources with excellent physical properties comparable to polyolefines such as polypropylene. Therefore, it is expected to reduce the impact on the environment. The hydrolytic degradability of PLA has been studied for non-enzymatic [1-8] and enzymatic processes [1, 2, 9-11]. Porous biodegradable polymers have an attraction for use in drug delivery systems, implants for the regeneration of damaged tissues, and so on. Jerome *et al*. have reported the preparation of macroporous PLA foams by thermally induced phase separation [12-14]. The microcellular foams were prepared by freeze-drying PLA solution in 1, 4-dioxane. Liquid-liquid phase separation for semicrystalline polymers such as PLA enables the system to be stabilized by a three-dimensional polymer network. The macroporous morphology after extracting the solvent tends to take isotropic foams.

In our research group, the bound solvent in the gel as well as the molecular structure at the cross-linking point has been investigated for polystyrene, [15-17] polypropylene, [18-21] and PLLA [22] by means of infrared and solid-state high-resolution ^{13}C NMR spectroscopy and thermal analysis. Our current interest, in particular, centers on the bound state of solvent trapped in a crystalline polymer gel. There are three kinds of solvents in the gel: free, freezable bound, and non-freezable. The free and freezable bound solvents provide freezing and melting enthalpies, whereas the non-freezable solvent has no melting enthalpy. Two pieces of important information can be obtained by a thermal analysis of the solvent in the gel. One is the melting enthalpy, which provides the weight fraction of the three states of solvent; and the

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other is the melting temperature, which has a relation with the cluster size of the solvent. Ishikiriyama *et al.* reported the relation between the pore radius of silica gel and the temperature depression of ice from the melting temperature of pure solvent T_m^o [23, 24]. The melting temperature of freezable bound solvent in the gel becomes lower depending on the gelation condition. Ishikiriyama *et al.*'s analytical procedure was applied to determine the cluster radius of solvent in the gel. In the case of PLLA/o-dichlorobenzene in which the solution grown crystal is constructed and the solvent is bound in the crystal, the cluster radius of solvent changed from 14.6 nm for 20 wt% to 6.8 nm for 50 wt% [22]. After extracting the solvent, a porous structure is expected in the PLLA matrix. The cluster size of solvent plays an important role in regulating the porous structure.

Most of the previous investigations on PLLA were concerned with the porous membrane. In this paper, we aim to create a porous PLLA particle through a phase separation process. The relation of the morphology and the pore size of PLLA particles will be reported as a function of quenching temperature.

EXPERIMENTAL

The PLLA used in the experiment was supplied by Purac Co. Ltd. The L-content and M_w are 99.8% and 2.0×10^5, respectively. Porous samples were prepared as follows. PLA and o-dichlorobenzene or diethylphthalate were placed in an ampoule, degassed in vacuo and sealed. The solution was homogeneously dissolved at 170°C, and quenched in a thermostat and kept at the desired temperature for 24 h. The white turbid sample was immersed in methanol, and dried in vacuo for several days in order to extract the solvent. The diameter of the particles was determined by more than 20 particles.

Thermal analysis was performed using a Rigaku TAS 200 differential scanning calorimeter. The samples were scanned at a heating rate of 5°C/min under a nitrogen flow. A polarized microscopic measurement was taken at room temperature using an Olympus BX51TF. Scanning electron microscopy (SEM) was performed using a JSM-5200 (JEOL) operating at an acceleration voltage

of 20 kV. Prior to observation, the samples were coated with a thin layer of gold by vacuum deposition.

RESULTS AND DISCUSSION

Formation of spherulite by phase separation process

For the PLLA/o-dichlorobenzene solution, the system quickly turned turbid during the phase separation process. This is a different result from that for the translucent gel that we reported previously [15-21]. First, we measure the polarized optical microscopic photograph of the 40 wt% formed at 60°C as shown in Fig. 1(a). Typical Maltese crosses were observed, corresponding to the formation of spherulites. The diameter of the spherulites was as large as 700 µm. The photograph without cross Nicol in Fig. 1(b) shows a sphere-shaped particle. These particles are identical to the size of the spherulite, so that each particle is constructed by spherulite. In our previous report, it was proposed that gelation such as iPP/o-dichlorobenzene system accompanies the
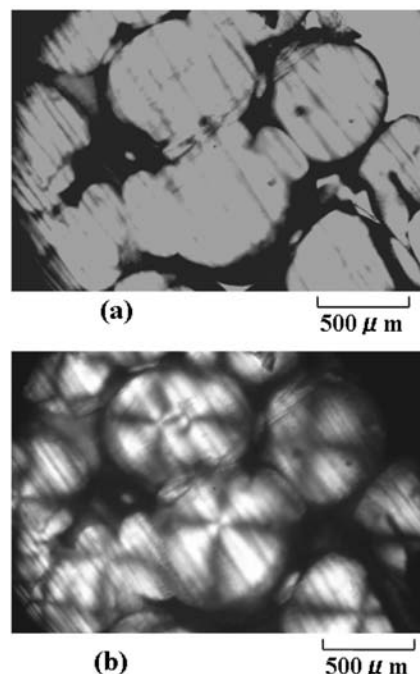

Fig. 1. Optical micrographs of 40 wt% PLLA/o-dichlorobenzene quenched at 60°C with (a) and without (b) cross Nicole.

formation of spherulite, and the solvent is bound in the spherulite. Therefore, the solvent is bound in the PLLA particles. The melting behavior of the solvent provides important information on the aggregation of the solvent. Two melting peaks were observed for o-dichlorobenzene in the iPP gel. One is due to the free solvent that is located among the spherulites, and the other corresponds to the freezable bound solvent that is located in the noncrystalline region among lamellae in the spherulite. Therefore, we carried out a differential scanning calorimeter (DSC) measurement for the PLLA/o-dichlorobenzene system. Fig. 2(a) shows the melting process of o-dichlorobenzene in the PLLA turbid system. There are two endothermic peaks: one corresponds to the melting temperature of pure solvent, and the other is observed at lower temperature than T_m^o. These solvents can be assumed to be free and freezable bound solvents, respectively. Judging from the large melting enthalpy for the low melting peak, most of the solvent is in the spherulites. As the free solvent is located among spherulites or on the surface of spherulites as suggested in our previous report, [20-22] DSC measurement was carried out after evaporating the solvent by holding it at room temperature for 1 h. Fig. 2(b) shows the DSC chart of partially dried sample. As expected, the high melting peak has almost disappeared, whereas the low melting peak remained unchanged. This indicates that the solvent with a low melting temperature is bound as a freezable bound solvent in the spherulite. The melting temperature of freezable bound solvent is often observed at a lower temperature than T_m^o. This temperature depression has a close relation with the cluster size of solvent in the system. Ishikiriyama et al. investigated the temperature depression of ice in various pore sizes of silica gel and obtained the relation between pore radius and temperature depression [23, 24]. Along with their procedure, we estimate the relation for o-dichlorobenzene as follows.

$$R = \frac{0.356\Delta T + 82.9}{\Delta T} \qquad (1)$$

where R and ΔT denote pore radius and temperature shift from T_m^o, respectively [22]. This relation was applied to the low temperature shift
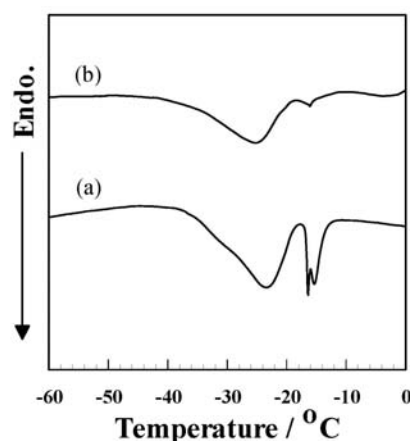

Fig. 2. Melting behavior of o-dichlorobenzene in PLLA/o-dichlorobenzene formed by quenching at 0°C from a homogeneous solution of 160°C (a), and after partially evaporating the solvent (b).

of o-dichlorobenzene in the PLLA system. The cluster radius is estimated to be 11.4 nm for the particle formed from 40 wt% solution at 60°C. The cluster size of the solvent is in the non-crystalline region among lamellae in the spherulite. After partially drying, the low melting temperature moved to a lower temperature. This corresponds to the cluster radius becoming smaller from 11.4 to 9.4 nm.

Porous PLLA particle from o-dichlorobenzene solution

In order to isolate the particles, the white turbid solution was immersed in methanol. In addition to dispersing the particles in methanol, this process has the advantage in that the o-dichlorobenzene in the PLLA particles was exchanged by the methanol. This makes it easy to extract the solvent from the PLLA particles. After extracting the solvent from the 10 wt% turbid solution, the measurements were performed. The SEM photographs were shown in relation to the quenching temperature in Fig. 3. The particle size became larger along with an increase in quenching temperature. In Fig. 4, the average diameter of these particles was plotted against the quenching temperature. When the sample was quenched at 0°C, the average diameter of a particle was about 100 µm, whereas for the particle formed at 60°C, it was as large as 700 µm. In other words, a faster quenching resulted in a decrease in
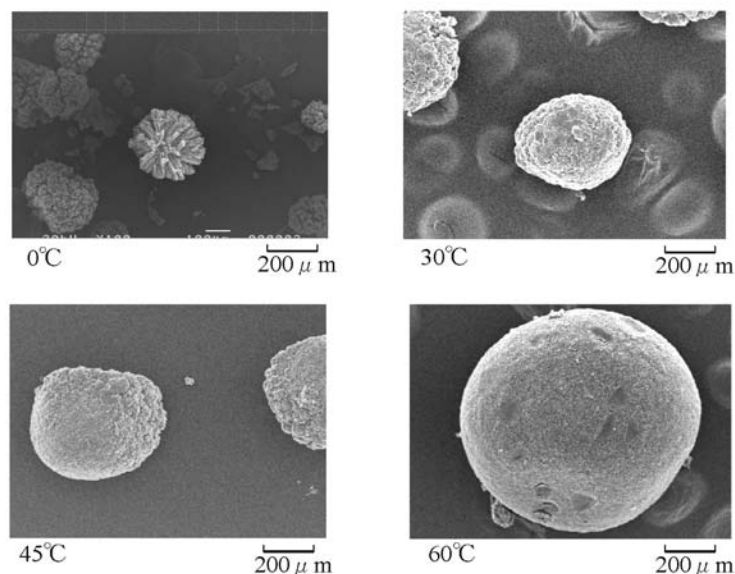
Fig. 3. SEM photographs of PLLA particles as a function of quenching temperature. The turbid solutions were formed by a 10 wt% PLLA/o-dichlorobenzene system.
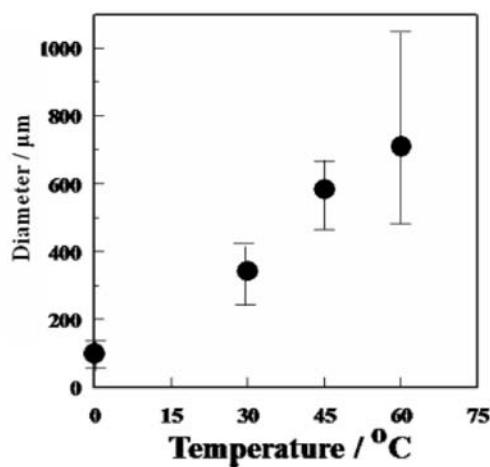

Fig. 4. Diameter of a PLLA particle as a function of quenching temperature. The average diameter was estimated by more than 20 particles.

the average particle size. These processes can be explained by nucleation and crystal growth. Nucleation is promoted more when quenching was carried out at 0°C. A large number of nuclei are simultaneously formed, however, the phase separation is rapidly frozen, preventing the growth of large particles. Therefore the particles are very small, and the size distribution is comparatively small. On the other hand, nucleation at high temperature is very slow. Spherulites nucleated at the early stage allow for a larger particle size, but those at the later stage do not have enough time for the formation of large particles. The time lag of nucleation allows the distribution of a larger particle size.

A porous structure can be seen on the surface of the particles, as seen in the SEM photographs of the surface area shown in Fig. 5. The surface is characterized by a matrix with a sheet-like structure. The spaces between sheets are in the order of a few micrometers and increased along with an increase in quenching temperature. This porous structure can be seen not only on the surface area, but also in the middle of particles. Fig. 6 shows a SEM photograph of the cross section of a particle. All parts of a particle have a porous structure. As described in the previous section, a particle is constructed from a spherulite in which the lamellae radially expand from the center of nucleation. It is possible that the sheet in the particle is constructed by a bundle of lamellae, so the nanoporous structure after extracting o-dichlorobenzene would remain in the bundle of lamellae. Therefore, PLLA particle can be characterized by the nanopore in a bundle of lamellae as well as the micropore of the particle.
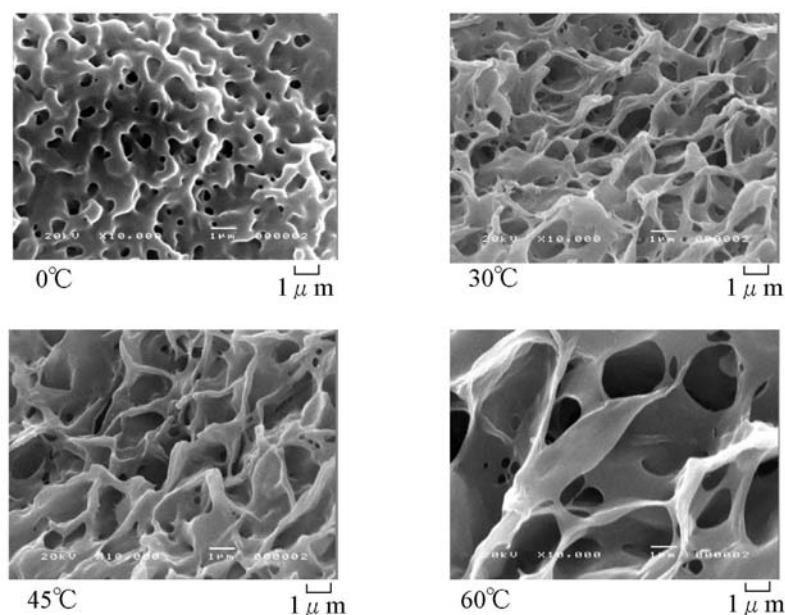
Fig. 5. SEM photographs of the particle surface as a function of quenching temperature.
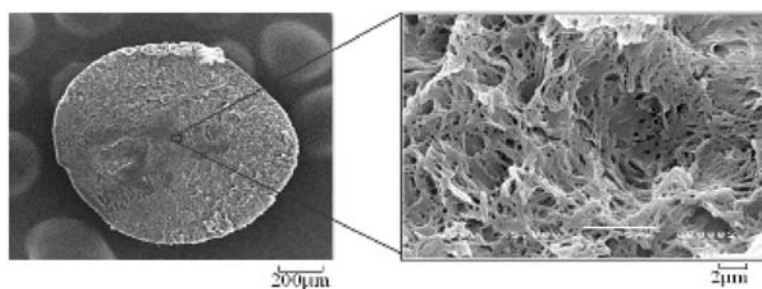

Fig. 6. SEM photograph of the cross section of a PLLA particle.

In conclusion, porous PLLA particles were formed in the following process. The phase separation of PLLA provides spherulites including solvent through the thermally induced density fluctuation. The cluster size of the solvent was a few nm. A nanoporous structure was formed after the solvent was extracted. In addition, the macroporous structure is formed by making a bundle of lamellae, and the spaces among the bundles resulted in pores of a micrometer order. Thus, the phase separation process is responsible for the characteristic features of the two kinds of porous morphology.

Porous PLLA particles from diethylphthalate

In this section, a non-halogen solvent such as diethylphthalate was used to make a porous particle. It was confirmed that this system also provided turbid system. Fig. 7 shows SEM photographs of porous particles formed at 0°C from a 10 wt% PLLA/diethyphthalate solution. Similar to the result from the o-dichlorobenzene system, sphere-shaped particles were obtained, however the particle size was about 30 µm, which is much smaller than the 120 µm particles formed by o-dichlorobenzene solution under the same conditions. In the case of diethylphthalate, the density fluctuation of phase separation is small, so that a smaller particle is formed. As for the surface morphology in Fig. 7(b), the small pore and dense matrix of PLLA were seen, which is different from the morphology shown in Fig. 5. Thus, the solvent used has a strong effect on particle size and surface morphology.
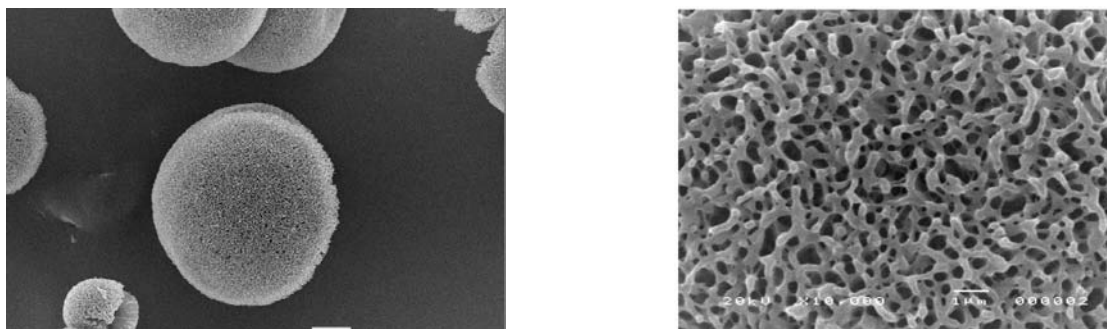
Fig. 7. SEM photographs of a PLLA particle formed from 10 wt% PLLA/diethylphthalate quenched at 0°C.

CONCLUSIONS

Porous PLLA particles were prepared through the phase separation process of PLLA/o-dichlorobenzene and diethyphthalate solutions. A turbid system was formed during the phase separation process for the PLLA/o-dichlorobenzene system. A typical spherulite was observed by polarized optical microscopy. The melting behavior of o-dichlorobenzene in the spherulite showed two endothermic peaks. One was due to the free state, and the other can be assumed to be the freezable bound solvent that was observed at a lower temperature than T_m^o. The former solvent is outside of the particle, and the latter is located inside the particle. The low temperature shift of the freezable bound solvent has a close relation with the cluster size of the solvent. The cluster size for 40 wt% PLLA/o-dichlorobenzene system was as large as 11.4 nm. The o-dichlorobenzene in the particle was excluded by immersion in methanol. A porous structure in the order of nanometers was formed by extracting the solvent. The particle size was between 100 to 700 µm, depending on quenching temperature. A porous structure of a few micrometers was confirmed by SEM measurement. It can be concluded that a PLLA particle has two kinds of porosity: micropores in the order of micrometers to characterize the porous particles, and nanopores in the order of nanometers in the PLLA matrix. Porous particles were also formed by diethylphthalate, however, the particle size was much smaller than that formed by o-dichlorobenzene.

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