

Porous Biodegradable Polyesters. I. Preparation of Porous Poly(L-lactide) Films by Extraction of Poly(ethylene oxide) from Their Blends

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ABSTRACT: Porous poly(L-lactide) (PLLA) films were prepared by water extraction of poly(ethylene oxide) (PEO) from solution-cast PLLA and PEO blend films. The dependence of blend ratio and molecular weight of PEO on the porosity and pore size of films was investigated by gravimetry and scanning electron microscopy. The film porosity and extracted weight ratio were in good agreement with the expected for porous films prepared using PEO of low molecular weight ($M_w = 1 \times 10^3$), but shifted to lower values than expected when high molecular weight PEO ($M_w = 1 \times 10^5$) was utilized. The maximum pore size was larger for porous films prepared from PEO having higher molecular weight, when compared at the same blending ratio of PLLA and PEO before water extraction. Differential scanning calorimetry of as-cast PLLA and PEO blend films revealed that PLLA and PEO were phase-separated at least after solvent evaporation. On the other hand, comparison of blend films before and after extraction suggested that a small amount of PEO was trapped in the amorphous region between PLLA crystallites even after water extraction and hindered PLLA crystallization during solvent evaporation. © 2000 John Wiley & Sons, Inc. *J Appl Polym Sci* 75: 629–637, 2000

Key words: polylactide; poly(lactic acid); poly(ethylene oxide); polymer blends; porous biodegradable polymers

INTRODUCTION

Porous poly(lactide) (PLA) has been studied for application as biodegradable scaffolds, because they promote tissue healing by encouraging cell ingrowth into them if they have an appropriate pore size and porosity.^{1,2} Lam et al. reported that

porous poly(L-lactide) (PLLA) underwent slower hydrolysis *in vitro* than nonporous PLLA because of enhanced diffusion of low-molecular-weight oligomers that act as catalyst of hydrolysis.³ Several methods have been proposed to prepare the porous PLA, for instance, by removal of inorganic salts or organic low-molecular-weight compounds from mixtures of PLA and additives.^{1,2} Porous PLA can also be prepared by utilizing other polymers, if they have solvents different from those for PLA. Thomson et al. prepared porous PLA

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with different pore sizes using water-soluble gelatin particles having different sizes.² In this case, the pore size depended on the initial gelatin particle size before blending because it remained unvaried during blending in organic solvents.

Blending of PLLA with poly(ethylene oxide) (PEO), which is soluble in water as well as in organic solvents such as methylene chloride and chloroform, has been studied mostly on the miscibility and crystallization behavior of blends from the two crystalline polymers.^{4–8} Younes and Cohn demonstrated that PLLA and PEO were partially miscible in solution-cast blends but did not strongly disturb crystallization of the other constituent polymer during solvent evaporation performed rapidly within 24 h when either of PLLA and PEO was a minor component.⁴ Nakafuku and Sakoda also reported that PLLA and PEO were miscible in the melt state and produced an equimolar blend by cooling from the melt, the PEO-rich phase being trapped in the PLLA spherulites.⁵ Also, PLLA and PEO were reported to be miscible in the amorphous phase and their blends were found to become more flexible with the increasing amount of PEO when they were prepared by precipitating the mixed polymer solution into a nonsolvent.⁸ The crystalline size, crystallinity, and spherulitic morphology strongly depended on the blending ratio and molecular weight of the constituent polymers.^{4–8}

The present work aims at preparing porous PLLA films having different pore sizes and porosities by means of direct solution blending of PLLA with PEO in the presence of a co-solvent of the two polymers, followed by water extraction of PEO from the blends after solvent evaporation. To obtain PLLA films of various pore sizes and porosities PLLA and PEO of different molecular weights were blended at different polymer ratios. To prepare porous PLLA films, PLLA and PEO are required to yield phase separation into PLLA-rich and PEO-rich phase with a large size. For this purpose, the solvent-casting method was selected, because some solvents are known to induce phase separation between the two polymers even if they are partially miscible in the melt or amorphous state.⁹ In addition, solvent evaporation was allowed to proceed extremely slowly to form a PEO-rich phase of a large domain, in marked contrast with the procedure reported for preparation of solution-cast blend films from PLLA and PEO.^{4–7}

EXPERIMENTAL

Materials

Two blend films of about 10 and 50 μm thick were prepared by casting 1g/dL mixed solution of PLLA (Polysciences, INC., $M_w = 3 \times 10^5$) and PEO [Aldrich, $M_w = 1 \times 10^5$ and 1×10^3 , abbreviated PEO(H) and PEO(L), respectively] with different blend ratios, followed by slow solvent evaporation at room temperature for about one week as reported in our previous work.^{10–13} The period of time for the solvent evaporation was kept longer than that reported by Younes and Cohn⁴ (24 h) to complete phase-separation between the two polymers during solvent evaporation.^{12,13} The cast films were dried in vacuo for another 1 week and stored at room temperature for at least 1 month to reach the equilibrium state before physical measurements and microscopic observation. Blends from the pair of PLLA and PEO(H) and of PLLA and PEO(L) will be abbreviated as PLLA-PEO(H) and PLLA-PEO(L), respectively. Extraction of PEO from the films was performed in distilled water at room temperature for one week and then dried. The water for extraction was exchanged every day.

Microscopic Observation

Morphology of films with the thickness of 10 μm was observed with a Zeiss polarizing microscope and a JEOL field emission scanning electron microscopy (SEM) (JEOL JSM6300F). SEM specimens were coated with a thin layer of gold to 10–20 nm by a BLAZER sputter-coater SCD050.

Measurements

The extracted weight ratio (EWR) of blend films after water extraction was calculated using the following equation:

$$\text{EWR (wt\%)} = 100 \times (W_{\text{before}} - W_{\text{after}}) / W_{\text{before}} \quad (1)$$

where W_{before} and W_{after} are weights of dried blend films before and after extraction with water. EWR can be considered as an index of porosity.

Melting temperature (T_m) and enthalpies of fusion, crystallization, and glass transition (ΔH_m , ΔH_c , and ΔH_g , respectively) of films with the thickness of 50 μm (sample weight of about 10 mg) were evaluated with a Perkin-Elmer DSC7 at a heating rate of 10°C/min in nitrogen. Overall

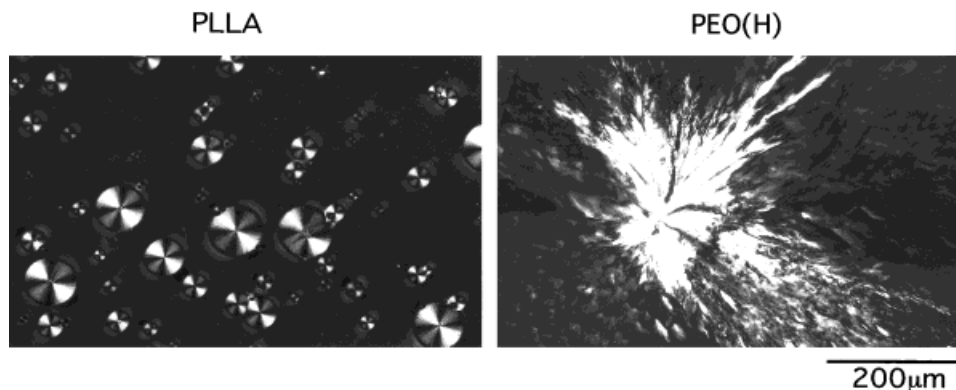


Figure 1 Polarizing optical micrographs of as-cast films of nonblended PLLA and PEO(H).

enthalpies of fusion and crystallization of PLLA and PEO ($\Delta H_{m+c, PLLA}$ and $\Delta H_{m, PEO}$, respectively) of the blend films, which are indexes of crystallinity, were calculated by the following equation using the PLLA content before extraction $X_{PLLA}(w/w) = PLLA/(PEO + PLLA)$ in dried blend films:

$$\Delta H_{m+c, PLLA} \text{ (J/g of PLLA)} \\ = (\Delta H_{m, PLLA} + \Delta H_{c, PLLA})/X_{PLLA} \quad (2)$$

$$\Delta H_{m, PEO} \text{ (J/g of PEO)} \\ = (\Delta H_t - \Delta H_{g, PLLA} \cdot X_{PLLA})/(1 - X_{PLLA}) \quad (3)$$

where $\Delta H_{m, PLLA}$, $\Delta H_{c, PLLA}$, and $\Delta H_{g, PLLA}$ are ΔH_m , ΔH_c , and ΔH_g of PLLA, respectively, and ΔH_t is the enthalpy of overall transition around $T_{m, PEO}$ including $\Delta H_{m, PEO}$ and $\Delta H_{g, PLLA}$. By definition, $\Delta H_{m, PLLA}$ (around 180°C), $\Delta H_{c, PLLA}$ (around 110°C), and ΔH_t (between 20 and 80°C) are positive, negative, and positive, respectively. For calculation of eq. (3), $\Delta H_{g, PLLA}$ of blends was assumed to be equal to that of nonblended PLLA (6 J/g of PLLA).

For extracted dried films, the following equation holds:

$$\Delta H_{m+c, PLLA} \text{ (J/g of PLLA)} \\ = (\Delta H_{m, PLLA} + \Delta H_{c, PLLA})/X_{PLLA, after} \quad (4)$$

where $X_{PLLA, after}$ is the PLLA content after water extraction, defined as

$$X_{PLLA, after} \text{ (w/w)} = X_{PLLA}/(1 - EWR/100) \quad (5)$$

Here we assumed that the water-extracted PEO did not contain any PLLA.

RESULTS AND DISCUSSION

Before Extraction

Blend Morphology

Figure 1 shows the polarizing micrographs of as-cast films of nonblended PLLA ($X_{PLLA} = 1$) and PEO(H) ($X_{PLLA} = 0$). Evidently, normal spherulitic structure is observed for both the nonblended films. Large spherulites of mm order were formed, but any nonblended film samples could not be obtained from low-molecular-weight PEO(L) (photo not shown).

In contrast to the nonblended films, blends of PLLA-PEO(H) and PLLA-PEO(L) gave the complicated morphologies, depending on X_{PLLA} as shown in Figures 2 and 3. When X_{PLLA} decreased to 0.8, disordered PLLA spherulites were noticed, whereas spherulitic morphology was not observed for films of X_{PLLA} between 0.2 and 0.6, except for PLLA-PEO(H) with $X_{PLLA} = 0.2$, where small particles of PLLA-rich phase were dispersed in the PEO(H) spherulites. This was different from the blends crystallized by slow temperature decrease, where PLLA crystallized to form spherulites even at the blend ratio of 50/50 in precedence of PEO crystallization.⁵ This complicated morphology in the blend films was very similar to that observed for phase-separated solution-cast blends from two crystalline polyesters, PLLA and poly(ϵ -caprolactone),¹³ implying that PLLA and PEO were also phase separated after solvent evaporation.

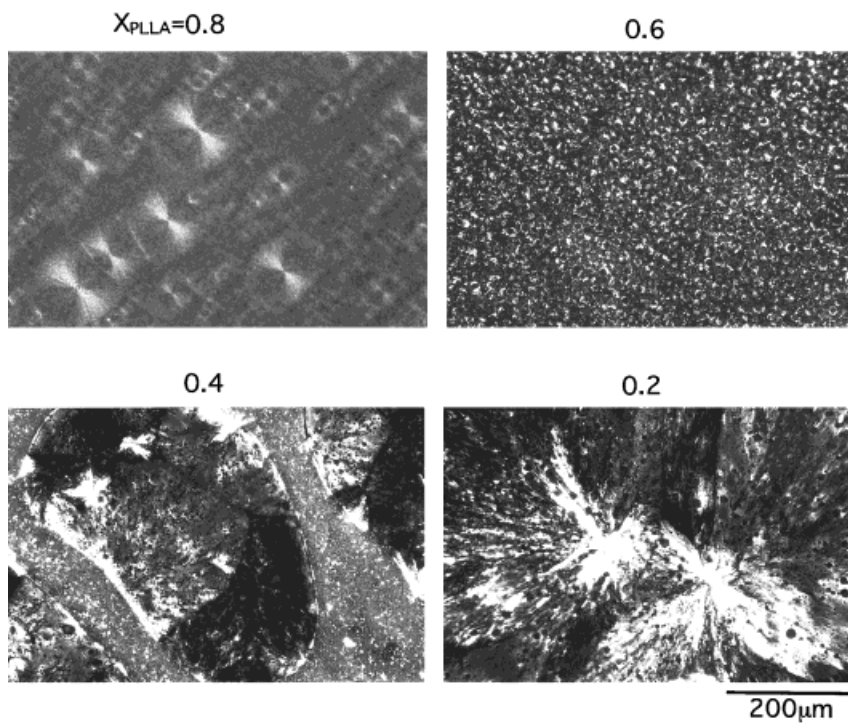


Figure 2 Polarizing optical micrographs of as-cast blend films of PLLA-PEO(H) with different X_{PLLA} .

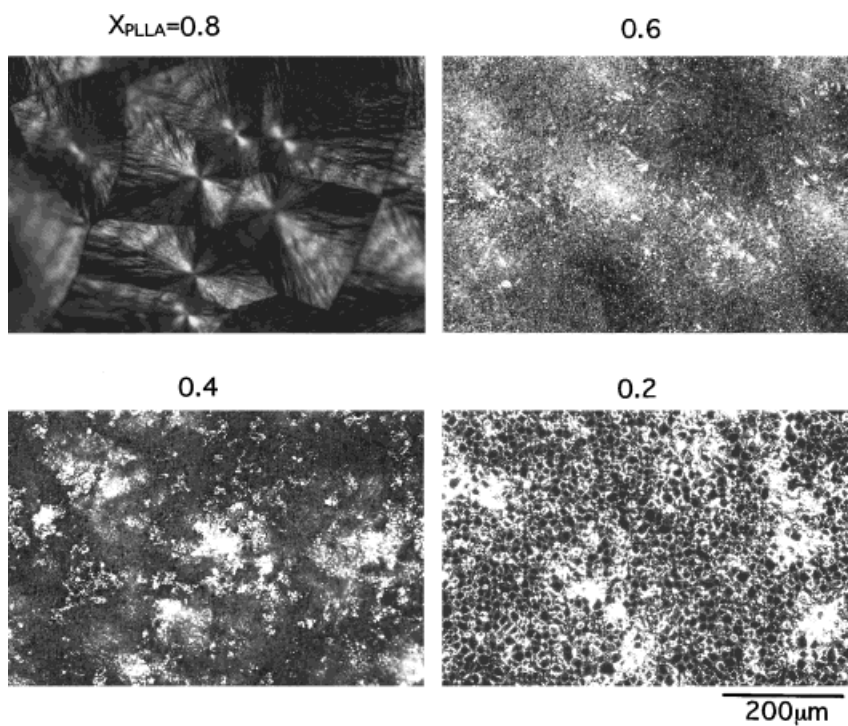


Figure 3 Polarizing optical micrographs of as-cast blend films of PLLA-PEO(L) with different X_{PLLA} .

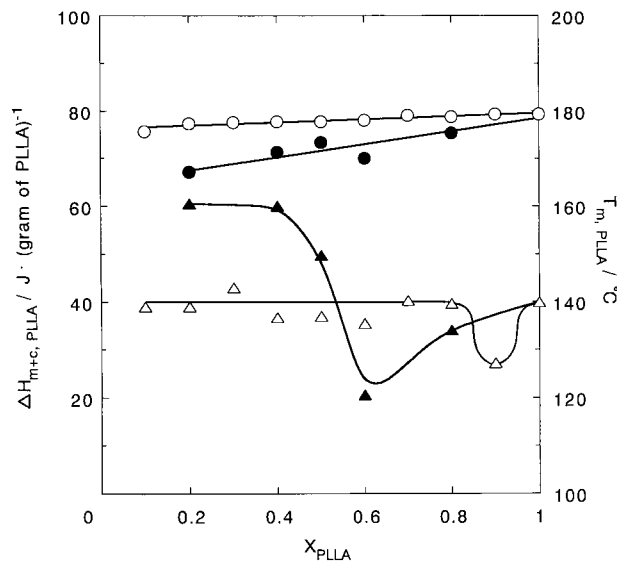


Figure 4 $T_{m, PLLA}$ (○, ●) and $\Delta H_{m+c, PLLA}$ (△, ▲) of as-cast blend films of PLLA-PEO(H) (○, △) and PLLA-PEO(L) (●, ▲) as a function of X_{PLLA} .

Crystallization of PLLA and PEO During Solvent Evaporation

$T_{m, PLLA}$ and $\Delta H_{m+c, PLLA}$, and $T_{m, PEO}$ and $\Delta H_{m, PEO}$ evaluated from differential scanning calorimetry (DSC) measurements are shown in Figures 4 and 5, respectively. Figure 4 shows that $\Delta H_{m+c, PLLA}$ is the same as or higher than that of nonblended PLLA, irrespective of X_{PLLA} , though a decrease of

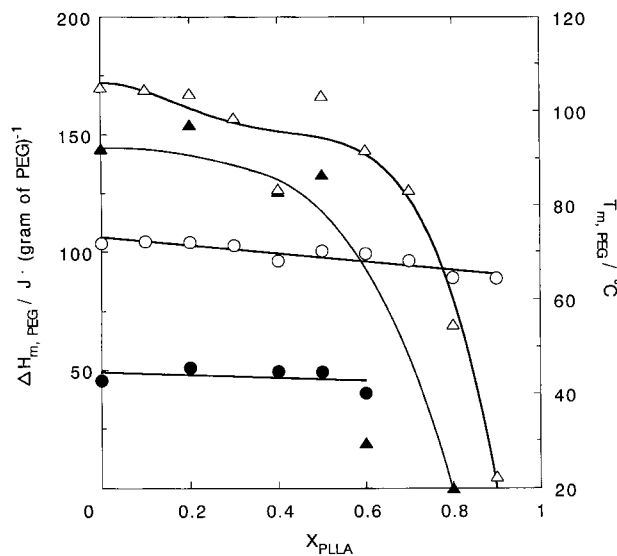


Figure 5 $T_{m, PEO}$ (○, ●) and $\Delta H_{m, PEO}$ (△, ▲) of as-cast blend films of PLLA-PEO(H) (○, △) and PLLA-PEO(L) (●, ▲) as a function of X_{PLLA} .

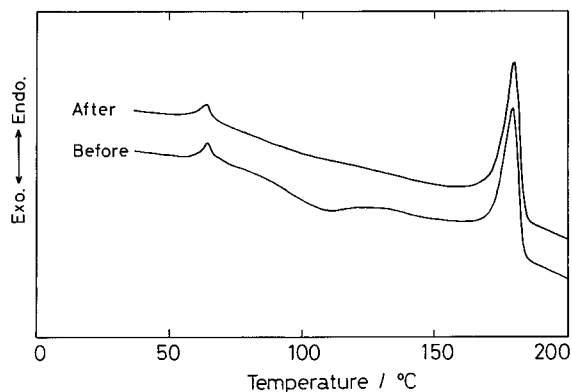


Figure 6 DSC thermograms of PLLA-PEO(H) with $X_{PLLA} = 0.9$ before and after water-extraction.

$\Delta H_{m+c, PLLA}$ was observed for $X_{PLLA} = 0.9$ in PLLA-PEO(H) and $X_{PLLA} = 0.6$ in PLLA-PEO(H). This suggests that PLLA crystallized in precedence of PEO crystallization under phase separation of the two polymers before or during crystallization of PLLA. If PLLA and PEO were kept miscible during solvent evaporation, PLLA could not crystallize when X_{PLLA} decreased below 0.2.

A decrease of $\Delta H_{m+c, PLLA}$ at $X_{PLLA} = 0.9$ for PLLA-PEO(H) and $X_{PLLA} = 0.6$ for PLLA-PEO(L) must be due to imperfect crystallization of PLLA during solvent evaporation. Probably, relatively

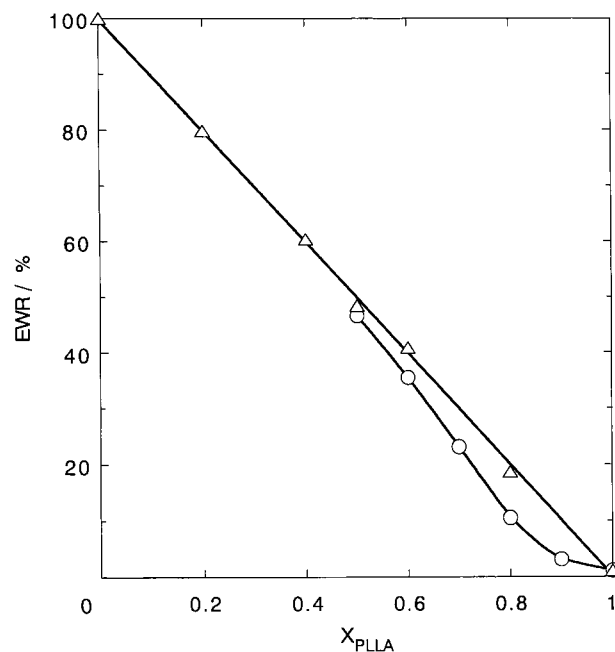


Figure 7 EWR of water-extracted, dried blend films of PLLA-PEO(H) (○) and PLLA-PEO(L) (△) as a function of X_{PLLA} .

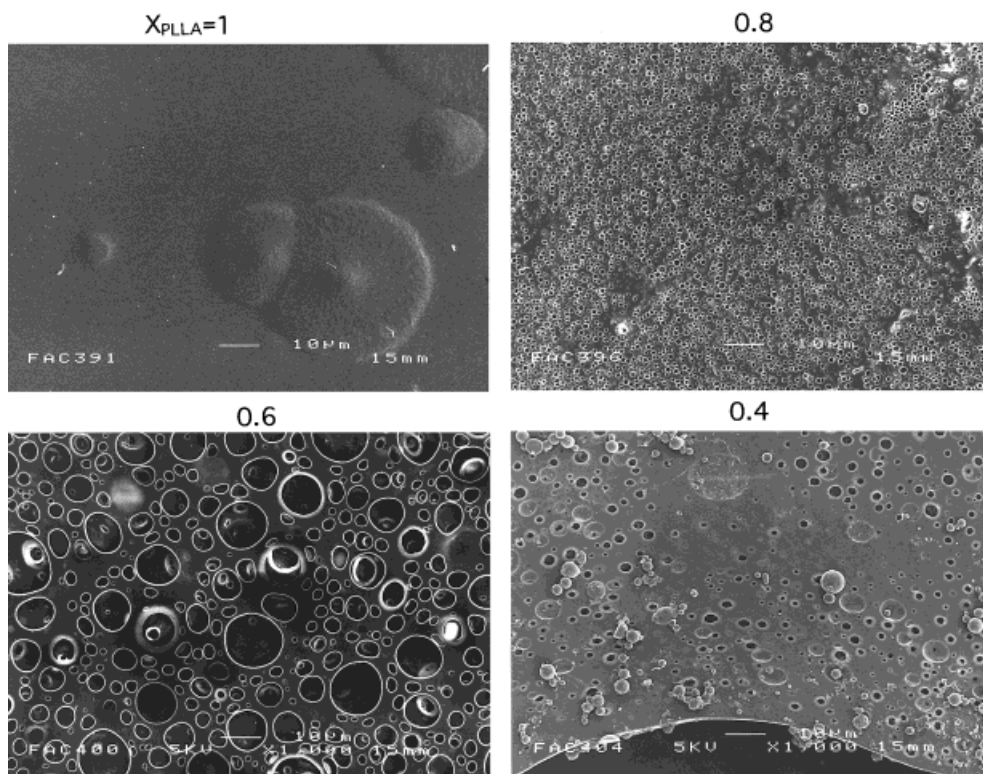


Figure 8 SEM micrographs of water-extracted, dried blend films of PLLA-PEO(H) with different X_{PLLA} .

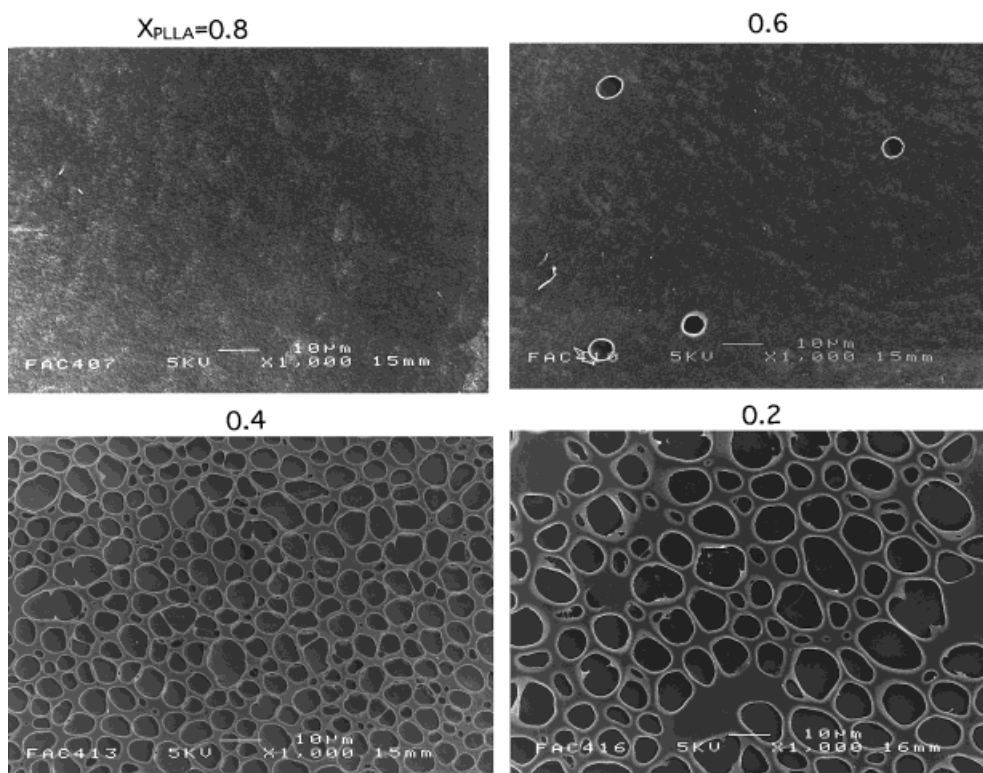


Figure 9 SEM micrographs of water-extracted, dried blend films of PLLA-PEO(L) with different X_{PLLA} .

high miscibility of the two polymers at these specific X_{PLLA} may decrease the nucleus density of PLLA crystallites during solvent evaporation, resulting in imperfect crystallization of PLLA. The imperfect crystallization of PLLA during solvent evaporation is evidenced by DSC thermograms of PLLA-PEO(H) with $X_{\text{PLLA}} = 0.9$ before extraction shown in Figure 6, where cold crystallization occurs around 110°C. Similarly, cold crystallization was observed in DSC heating for PLLA-PEO(L) with $X_{\text{PLLA}} = 0.6$ before extraction (data not shown).

The increased $\Delta H_{m+c, \text{PLLA}}$ for X_{PLLA} below 0.5 in PLLA-PEO(L) may be due to the increased nucleus density of PLLA crystallites in the presence of high concentration of PEO, as reported by Nakafuku for the PLLA and PEO blends crystallized from the melt under high pressure.⁶ $T_{m, \text{PLLA}}$ decreased with a decrease in X_{PLLA} , suggesting that the crystalline thickness of PLLA decreased in the presence of high concentration of PEO, probably due to trapped PEO molecules in the amorphous region between the crystallites of PLLA.⁸ Nakafuku reported that $T_{m, \text{PLLA}}$ was constant, irrespective of X_{PLLA} ,⁶ probably due to imperfect crystallization of PLLA during rapid solvent evaporation and crystallization during DSC measurement.

On the other hand, as evident from Figure 5, PEO(H) and PEO(L) could crystallize in the blends of X_{PLLA} below 0.9 and 0.6, whereas $\Delta H_{m, \text{PEO}}$ of PEO(H) and PEO(L) decreased dramatically for X_{PLLA} above 0.8 and 0.6, respectively. Probably, at high X_{PLLA} , PLLA crystallized prior to PEO crystallization and PEO molecules must have been trapped in the amorphous region between the crystalline lamellas of PLLA. As a result, PEO could not crystallize at high X_{PLLA} . A slight decrease in $T_{m, \text{PEO}}$ with an increase in X_{PLLA} suggests that the crystalline thickness of PEO decreased with the increasing X_{PLLA} .

The dependence of $T_{m, \text{PLLA}}$, $T_{m, \text{PEO}}$, and $\Delta H_{m, \text{PEO}}$ on X_{PLLA} is mostly in agreement with that of solution-cast blends from PLLA and PEO reported by Younes and Cohn.⁴ However, our investigation shows that the maximum X_{PLLA} below which PEO could crystallize depended on the molecular weight of PEO and that nucleation of PLLA crystallites was strongly hindered at a specific X_{PLLA} of PLLA-PEO blends, probably due to high interaction between the two polymers. It is well known that the interaction parameter between the two polymers depends on the blend ratio of the constituent polymers and the solvent.⁸

After Extraction

Film Porosity

EWR of water-extracted, dried blend films is plotted in Figure 7 as a function of X_{PLLA} . EWR of PLLA-PEO(L) with X_{PLLA} between 0.2 and 0.8 is in good agreement with that expected under the assumption that all the PEO molecules were completely extracted with water from the blend films. Complete extraction of PEO with water and porous PLLA film formation without any X_{PLLA} dependence means that both the PEO(L)-rich phase and PLLA-rich phase formed the continuous phase in all PLLA-PEO(L) blends.

The shift of EWR of PLLA-PEO(H) at X_{PLLA} between 0.6 and 0.9 to lower values from the expected implies that part of PEO could not diffuse out from the blends because the PEO-rich phase was dispersed in the continuous PLLA-rich phase at these X_{PLLA} . EWR for PLLA-PEO(H) with X_{PLLA} below 0.4 was not able to calculate, as film formation after water extraction was incomplete. The PLLA-rich phase might be partially dispersed in the continuous PEO-rich phase for X_{PLLA} below 0.4.

SEM Observation

Figures 8 and 9 show the SEM photographs of the water-extracted, dried films of PLLA-PEO(H) and PLLA-PEO(L), respectively. The micrograph for the PLLA-PEO(H) with $X_{\text{PLLA}} = 0.4$ (Figure 8) was obtained for the imperfect film. Spherulites were noticed for the nonblended PLLA, in agreement with the result of polarizing optical microscopy, but pore was not present even when magnification was increased to 2×10^4 times. In contrast to the nonblended PLLA, pore was formed for the extracted blend films of PLLA-PEO(H) with X_{PLLA} between 0.4 and 0.9. In the case of PLLA-PEO(H) with $X_{\text{PLLA}} = 0.4$, a large pore was noticed at the bottom of the micrograph. On the other hand, many pores were formed all over the PLLA-PEO(L) films, irrespective of X_{PLLA} , indicating that the PLLA-rich phase composed the continuous phase, independent of X_{PLLA} . In the case of PLLA-PEO(L) with $X_{\text{PLLA}} = 0.8$, pores could be observed only at higher magnification (photo not shown).

Pore Size

The maximum pore size evaluated from the SEM photographs is plotted in Figure 10 as a function

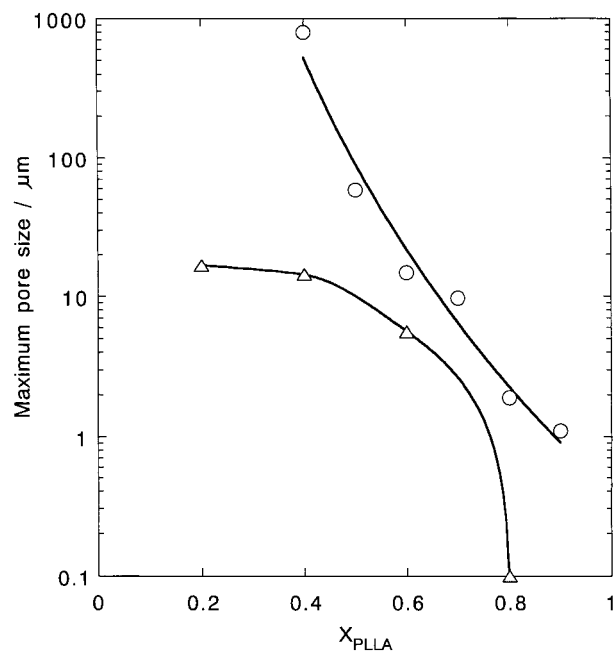


Figure 10 Maximum pore size of water-extracted, dried blend films of PLLA-PEO(H) (\circ) and PLLA-PEO(L) (\triangle) as a function of X_{PLLA} .

of X_{PLLA} . It can be seen that the maximum pore size increased with the decreasing X_{PLLA} , irrespective of the molecular weight of PEO in the blends. The extracted PLLA-PEO(H) films had larger maximum pore sizes than the extracted PLLA-PEO(L) when compared at the same X_{PLLA} . This suggests that the domain size of the PEO-rich phase in as-cast blends became larger when the molecular weight of PEO increased. The maximum pore size of PLLA-PEO(H) increased dramatically at X_{PLLA} below 0.5, whereas that of PLLA-PEO(L) saturated around $20 \mu\text{m}$ at X_{PLLA} below 0.4. Figures 7 and 10 reveal that the porosity and pore size can be controlled by the X_{PLLA} and molecular weight of PEO, and probably also by the rate of solvent evaporation and the type of solvent.

Morphology of Porous Films

PLLA had spherulitic structure for all the blends, irrespective of X_{PLLA} , before drying of the extracted films. Examples of polarizing optical micrographs before drying taken for films in distilled water are given in Figure 10 for water-extracted PLLA-PEO(H) with $X_{\text{PLLA}} = 0.4$ and PLLA-PEO(L) with $X_{\text{PLLA}} = 0.2$. Spherulite for-

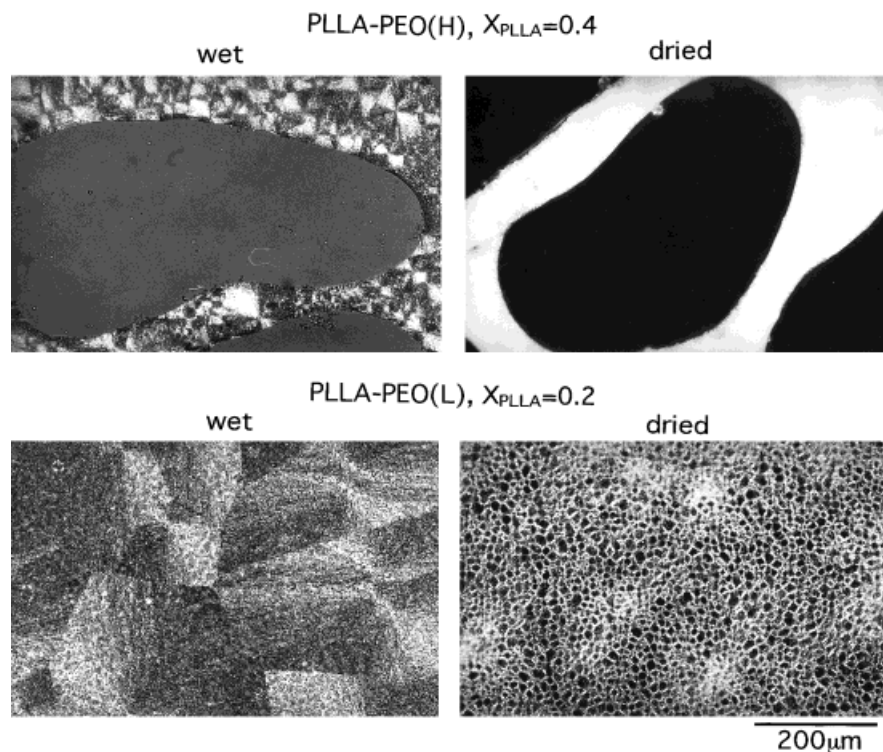


Figure 11 Polarizing optical micrographs of water-extracted wet and dry films of PLLA-PEO(H) with $X_{\text{PLLA}} = 0.4$ and PLLA-PEO(L) with $X_{\text{PLLA}} = 0.2$.

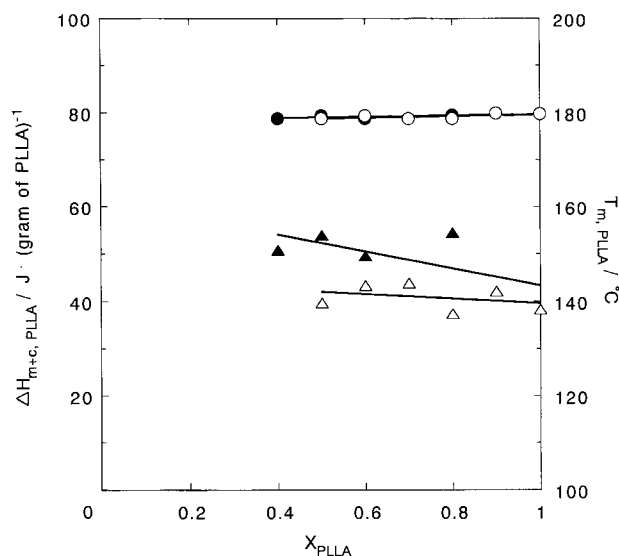


Figure 12 $T_{m, PLLA}$ (○, ●) and $\Delta H_{m+c, PLLA}$ (△, ▲) of extracted, dried blend films of PLLA-PEO(H) (○, △) and PLLA-PEO(L) (●, ▲).

mation confirms the finding obtained by DSC measurements that crystallization of PLLA occurred in the blends prior to that of PEO. The polarizing optical micrographs for the water-extracted films after drying are also given in Figure 10. As is evident, the spherulitic structure present on the extracted wet blends disappeared after drying, except for the nonblended PLLA and PLLA-PEO(L) with $X_{PLLA} = 0.8$ (photo not shown). This may be ascribed to a larger difference in refractive index between air and PLLA than between water and PLLA or deformation of PLLA chains in the amorphous region during drying.

Crystallization of PLLA During Water Extraction

$T_{m, PLLA}$ and $\Delta H_{m, PLLA}$ of water-extracted, dried blend films evaluated from DSC thermograms are plotted in Figure 12 as a function of X_{PLLA} . Both $T_{m, PLLA}$ and $\Delta H_{m, PLLA}$ of water-extracted, dried blends surpassed those of as-cast blends shown in Figure 4. It seems probable that the removal of PEO molecules trapped in the amorphous region between the PLLA crystalline lamellas allowed PLLA chains in the amorphous region to recrystallize. This enhancement in crystallization was

remarkable for PLLA-PEO(H) with $X_{PLLA} = 0.9$ and PLLA-PEO(L) with $X_{PLLA} = 0.6$, where crystallization of PLLA during solvent evaporation was strongly disturbed by the presence of PEO molecules, due to good miscibility of the two polymers.

CONCLUSION

Porous PLLA films could be prepared by water extraction of the PEO component from solution-cast blend films from PLLA and PEO. Their pore size and porosity were controllable by varying the blend ratio of the two polymers and the molecular weight of PEO.

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