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Research Article

Preparation and Drug-Release Kinetics of Porous Poly(L-lactic acid)/Rifampicin Blend Particles

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Porous polymer spheres are promising materials as carriers for controlled drug release. As a new drug-carrier material, blend particles composed of poly(L-lactic acid) (PLLA) and rifampicin were developed using the freeze-drying technique. The blend particles exhibit high porosity with a specific surface area of 10–40 $m^2\,g^{-1}$. Both the size and porosity of the particles depend on the concentration of the original solution and on the method of freezing. With respect to the latter, we used the drop method (pouring the original solution dropwise into liquid nitrogen) and the spray method (freezing a mist of the original solution). The release kinetics of rifampicin from the blend particles into water depends significantly on the morphology of the blend particles. The results show that the release rate can be controlled to a great extent by tuning the size and porosity of the blend particles, both of which are varied by parameters such as the solution concentration and the method of freezing.

1. Introduction

Recently, microspheres and capsules for controlled drug release have been developed by using biodegradable and biocompatible polymers [1–3]. Highly porous polymeric spheres are often used as drug carriers because their high porosity allows for a high efficiency of drug loading and facilitates controllable release [4–7]. As carrier materials, poly(L-lactic acid) (PLLA), a typical biodegradable polymer, and its copolymer poly(lactic-co-glycolic acid) have been frequently studied [8–13]. Porous polymer spheres can be prepared using various techniques, among which freeze-drying from a dilute solution has been demonstrated to be a particularly excellent method [14, 15]. We have investigated the properties of highly porous poly(L-lactic acid) (PLLA) materials prepared using the freeze-drying technique (FDPLLA), which exhibit very high specific surface areas of 10–40 $m^2\,g^{-1}$, and have found that they crystallize at a lower temperature and at a higher crystallization rate than bulk amorphous PLLA [15, 16].

The capability for controlled drug release from FDPLLA has been demonstrated using bovine serum albumin (BSA) as a model drug compound [11]. The immersion of FDPLLA in a BSA aqueous solution results in BSA-loaded FDPLLA via a simple adsorption mechanism, which shows an extremely high efficiency of loading (up to 79 wt% with respect to PLLA). It was also observed that the release kinetics strongly depends on the porosity of FDPLLA, which can be controlled by the concentration of the original solution and the rate of freezing. Such a simple adsorption method allows us to obtain particles containing a large amount of the drug. However, the adsorption tends to occur heterogeneously within the particle because the drug solution cannot penetrate entirely into the very porous PLLA in the adsorption process. The resulted localization of the drug makes it difficult to control the drug-release kinetics.

In this study, we further explored the possibility of using FDPLLA as a drug carrier by developing new PLLA/drug blend particles without using the adsorption method. We used rifampicin ($C_{43}H_{58}N_4O_{12}$, molar mass: 822.95 Da), an antibiotic drug used as an antibacterial and antifungal agent, as the drug compound. We considered rifampicin to be highly suitable for the present study because it is soluble in both 1,4-dioxane and water; the former is a unique solvent that can be used to freeze-dry PLLA. In addition, rifampicin exhibits maximum absorbance at 473 nm, which allowed us to easily measure the concentration of the drug that is released in

water using UV-visible spectroscopy. First, we prepared a solution that was composed of PLLA, rifampicin, and 1,4-dioxane; then, the solution was freeze-dried to obtain blend particles composed of PLLA and rifampicin. The obtained blend material has the following advantages over the BSA-loaded FDPLLA developed in the previous study (simple adsorption method): (1) the blend material is macroscopically homogeneous such that the drug release is expected to be very stable; thus, reproducible release data can be obtained; (2) the amount of drug loading can be easily controlled by the solution content. We investigated the structure and release kinetics of blend materials prepared under different conditions. For comparison, we also executed the release experiments on the PLLA/rifampicin particles prepared by the simple adsorption method.

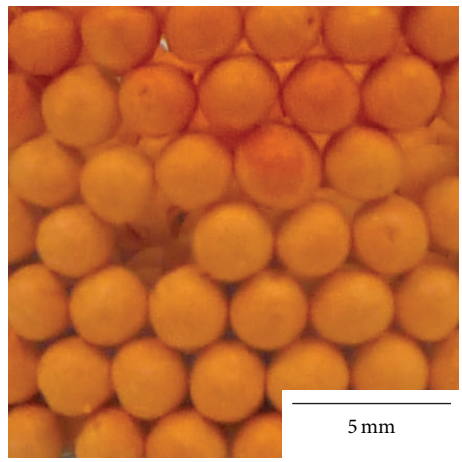

Figure 1: PLLA/rifampicin blend particles prepared by the drop freeze-drying method with C_{PLLA} = 4.9 wt%.

2. Experimental

The PLLA used in this study was supplied by Mitsui Chemicals, Tokyo, Japan. The polymer contained 98% L units, and its molar mass was 210 kDa. Rifampicin was purchased from Tokyo Chemical Industry, Tokyo, Japan, and was used as received. Two solutions containing PLLA/rifampicin/1,4-dioxane in ratios of 2.0/1.0/98 and 5.0/2.5/95 by weight were prepared. The PLLA content of the solution is denoted by C_{PLLA}; therefore, C_{PLLA} = 2.0 wt% for the former solution and C_{PLLA} = 4.9 wt% for the latter solution. The solutions were frozen using two methods: (a) pouring dropwise into liquid nitrogen (drop method) and (b) spraying the solution as a mist into liquid nitrogen (spray method). The frozen materials were kept under vacuum for 24 h to remove the solvent by sublimation, and additional vacuum drying was performed for 24–700 h at room temperature. The diameters of the obtained particles prepared using methods (a) and (b) were 2-3 mm and 10–200 μm, respectively. A typical appearance of the blend particles obtained by method (a) is shown in Figure 1. Drug release was executed in water (pH = 7.0) at 37.0°C. Typically, 4.5 mg of the blend particles was immersed in 50 mL of water. Prior to release, water was permeated into the blend particles under reduced pressure. The procedure was described in detail in our previous paper [11]. This permeation procedure was required to obtain reproducible release data, because PLLA is highly hydrophobic.

The amount of rifampicin released in water was monitored by measuring the absorbance at 473 nm, where the maximum absorbance of rifampicin in water is observed. The molar extinction coefficient at this wavelength was estimated to be 15,900 M^{-1} cm^{-1}. A Hitachi U-3900H UV spectrometer was used for monitoring, and release profiles of rifampicin with respect to time were obtained.

For comparison, we also prepared rifampicin-loaded particles by a simple adsorption method [11]: pure PLLA was freeze-dried from a 1,4-dioxane solution (C_{PLLA} = 2.0, 5.0, and 8.0 wt%) by the drop method. The average diameter of the obtained porous PLLA particles was 2.3 mm, which was nearly independent of C_{PLLA}. The particles were immersed in a 0.20 wt% aqueous rifampicin solution by the permeation method under reduced pressure as was performed at the beginning of the release experiment (see above). The particles were dried under vacuum for 24 h. The rifampicin contents in the obtained particles were 6.2, 5.6, and 0.4 wt% for C_{PLLA} = 2.0, 5.0, and 8.0 wt%, respectively. These rifampicin contents are lower than those obtained for the blend particles (33.3 wt%), which is partially due to the low concentration of the rifampicin aqueous solution; a higher concentration could not be achieved because of the low solubility of rifampicin. Drug-release experiments were performed using these rifampicin-adsorbed PLLAs under the same conditions used to test the blend materials.

The morphology of the particles was examined using a Hitachi S-2600H scanning electron microscope (SEM). In order to observe the interior of the particles, the surface part was peeled away using adhesive tape. The specific surface area σ was evaluated by the Brunauer-Emmett-Teller (BET) adsorption isotherm of krypton. The volume fraction of voids (void fraction) r_v for the larger particles (drop method) was evaluated from the mass and apparent size of the particles. For the density of amorphous PLLA, we used the value of 1.248 g cm^{-3} reported in the literature [17]. Wide-angle X-ray scattering (WAXS) measurements were performed using a Rigaku RINT2100 diffractometer with a CuKα radiation source (0.154 nm).

3. Results and Discussion

3.1. Morphology. The obtained PLLA/rifampicin blend particles exhibited a high porosity similar to that obtained by the freeze-dried particles of pure PLLA [15]. Figure 2 shows SEM micrographs of the larger particles that were prepared by the drop method. For the particles with C_{PLLA} = 2.0 wt%, both the surface and interior were observed to be highly porous. On the other hand, the surfaces of the particles with C_{PLLA} = 4.9 wt% were not highly porous, exhibiting only very small holes; however, their interiors were still highly porous. The porous morphology observed for the particle interiors was composed of fine membranes, the thickness of which was

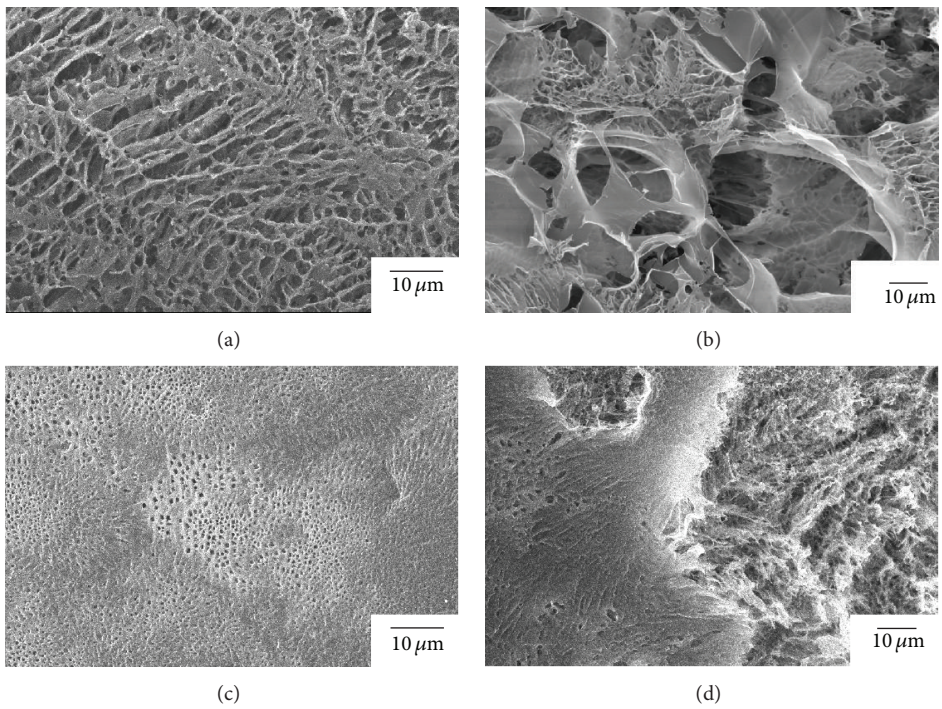

Figure 2: SEM images of the surface and interior of PLLA/rifampicin blend particles prepared by the drop freeze-drying method. (a) C_{PLLA} = 2.0 wt%, surface, (b) C_{PLLA} = 2.0 wt%, interior, (c) C_{PLLA} = 4.9 wt%, surface, and (d) C_{PLLA} = 4.9 wt%, interior.

Table 1: Morphological parameters of the freeze-dried PLLA/rifampicin particles.

C_{PLLA}/wt%	Method	d/mm	r_v	σ/m^2 g^{-1}	A_v/A_t	R_∞
2.0	Drop	2.4	0.956	19.6	0.58	0.85
2.0	Spray	0.010–0.10		34.8	0.61	0.89
4.9	Drop	2.6	0.907	15.9	0.022	0.70
4.9	Spray	0.010–0.20		33.7	0.014	0.74

roughly estimated from the specific surface area σ to be 24–52 nm (the thickness of a thin film that has the same σ value as that of the sample). Figure 3 shows SEM images of the smaller particles that were prepared by the spray method. The results indicate the same trend observed for the particles created by the drop method.

The morphological parameters of the particles are listed in Table 1. The average particle diameter d depends strongly on the freezing method, as mentioned in the experimental section. The void fraction r_v is greater than 90%, which indicates that the particles are highly porous even with a high content of the drug (ca. 33%). The specific surface area σ for the smaller particles is approximately twice as large as that for the larger particles. This discrepancy may be understood simply by considering the contour size effect of the particles. In addition, the difference in the rate of freezing may be responsible for this finding: during the freezing process, the phase separation of the solutes from the solvent occurs as the solvent crystallizes; however, for smaller droplets, freezing occurs more rapidly due to faster thermal conduction, which prohibits the formation of large domains of solutes and thus results in a finer microporous morphology. We also note that σ decreases with increasing C_{PLLA}, which suggests that the phase separation of solutes and solvent occurs more slowly for higher values of C_{PLLA}.

Surface porosity A_v/A_t was evaluated from the SEM images, and the results are shown in Table 1, where A_v is the void area on the surface of a particle and A_t is the total surface area. The surface porosity for C_{PLLA} = 4.9 wt% is surprisingly lower than that for C_{PLLA} = 2.0 wt%. Considering the fact that the σ values are still high even for C_{PLLA} = 4.9 wt%, the low porosity must be limited to the surface region. Thus, we infer that a low-porosity skin exists on the surface of the higher-C_{PLLA} particles. Such a skin may be formed during the freezing process in liquid nitrogen: when the solution is frozen, the solvent crystallizes excluding the solutes (PLLA and rifampicin), and as a result, a solution phase with a higher concentration of the solutes is formed, which leads to a dense skin near the surface region. For a lower-C_{PLLA} solution, the amount of the solutes is too small to form a dense skin.

Figure 4 shows the WAXS profiles for the as-received rifampicin and the PLLA/rifampicin blend particles. The as-received rifampicin was in a crystalline state as evidenced by a number of diffraction peaks (curve (a)), but once it

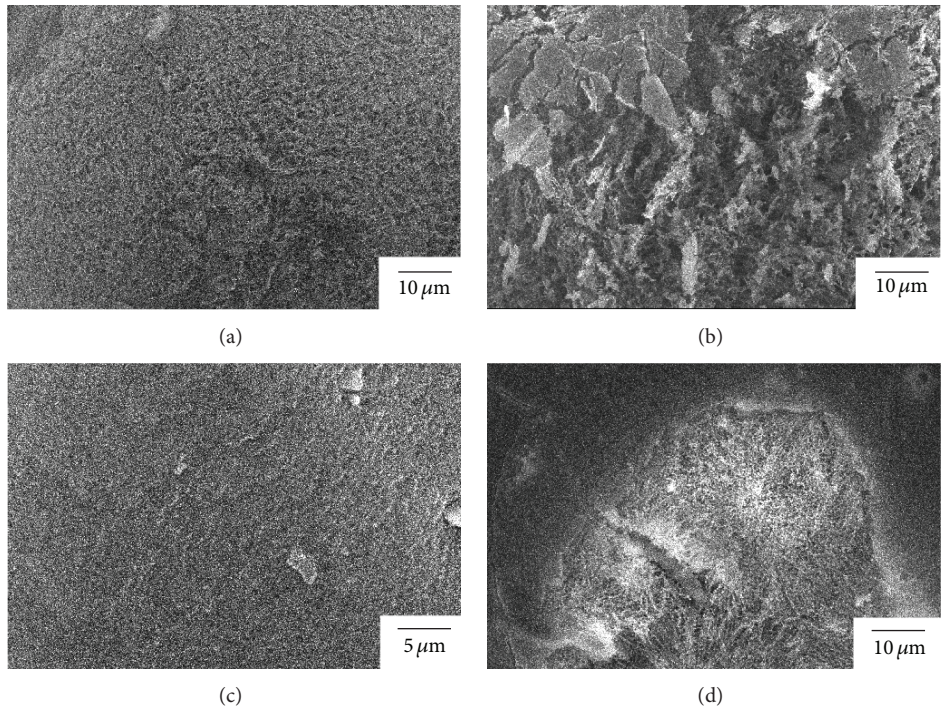

Figure 3: SEM images of the surface and interior of PLLA/rifampicin blend particles prepared by the spray freeze-drying method. (a) C_{PLLA} = 2.0 wt%, surface, (b) C_{PLLA} = 2.0 wt%, interior, (c) C_{PLLA} = 4.9 wt%, surface, and (d) C_{PLLA} = 4.9 wt%, interior.

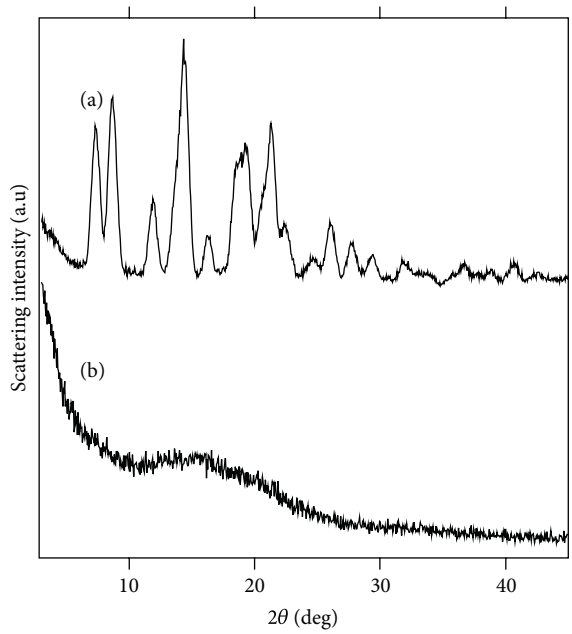

Figure 4: WAXS intensity profiles for (a) as-received rifampicin, and (b) PLLA/rifampicin blend particle prepared by the drop method from the C_{PLLA} = 4.9 wt% solution. The wavelength of the X-rays was 0.154 nm. The vertical axis is appropriately shifted.

was freeze-dried together with PLLA, the rifampicin became completely amorphous (curve (b)). This result suggests that the compatibility of PLLA with rifampicin is rather high such that PLLA prevents the formation of rifampicin domains that are large enough to allow for crystallization. Figure 4(b) indicates that the PLLA in the blend particles was also in an amorphous state. The same result has already been confirmed for pure freeze-dried PLLAs.

3.2. Release Kinetics. Figure 5 shows the time evolution of rifampicin release in water for the PLLA/rifampicin blend particles. The curves indicate that the degree of release $M(t)/M_\infty$ reached an ultimate value within 24 h. The total amount of the drug released in water after 24 h was estimated to be 70 − 89% of that initially existing in the PLLA particles; the values of the final release ratio $R_\infty = M_\infty/M_{fed}$ are shown in Table 1, where M_{fed} is the mass of rifampicin that initially existed in the PLLA/rifampicin particle. The results indicate that there existed a fraction of rifampicin that could not be extracted in the release experiment, because the drug was completely surrounded by PLLA in this case. Considering the mass ratio of rifampicin/PLLA (=1.0/2.0) for the present blend particles, it is likely that PLLA exists as a continuous phase. Because of the hydrophobicity of PLLA, water hardly penetrates into the PLLA phase, which consequently prevents the fraction of the drug surrounded by the PLLA phase from being released as long as PLLA remains intact.

It was observed that the time required to reach the ultimate value of $M(t)$ is generally shorter for low values of C_{PLLA}. The result may be due to the higher porosity of the lower-C_{PLLA} samples, as revealed by the values of r_v and A_v/A_t in Table 1. Assuming that the interior pore space of the particles during release is filled with an aqueous phase

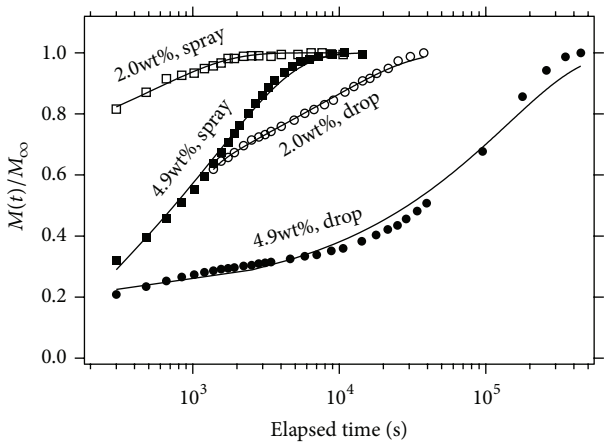

Figure 5: Time evolution of drug release $M(t)/M_\infty$ from the PLLA/rifampicin blend particles in water at 37.0°C. C_{PLLA} and method of preparation are indicated in the figure. The solid curves indicate the results of the fitting analysis.

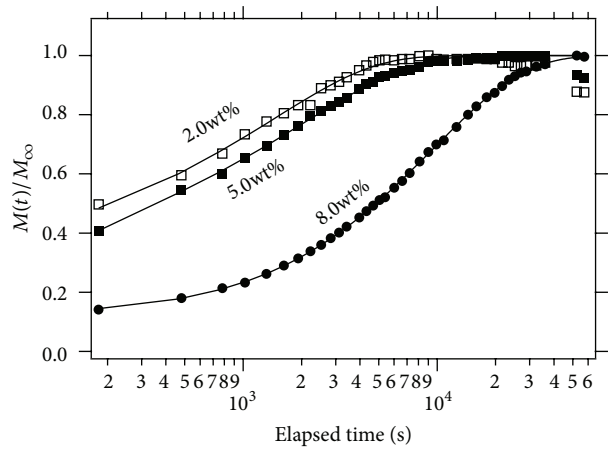

Figure 6: Time evolution of drug release $M(t)/M_\infty$ in water at 37.0°C from the rifampicin-adsorbed FDPLLAs. The values of C_{PLLA} are indicated in the figure. The solid curves indicate the results of the fitting analysis.

and that this phase provides a diffusion path for the drug, the larger r_v promotes drug transport. It is also noted that the time required to reach the ultimate value of $M(t)$ is longer for larger particles. For the smaller particles, the diffusion path in the interior of the particle is shorter, which makes the completion of release occur more rapidly.

In this section, we analyze the time-evolution data of release. Assuming a Fickian diffusion model for a non-swellable sphere, $M(t)/M_\infty$ is expressed as [18]

$$\frac{M(t)}{M_\infty} = (1-b)\left\{1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left[-\frac{Dn^2\pi^2(t-t_i)}{a^2}\right]\right\} + b, \quad (1)$$

where D is the diffusion coefficient of the drug in the particle, a is the radius of the particle ($d/2$), b is a baseline parameter that accounts for very rapid release at an early stage (initial burst), and t_i is the induction period for the second step of the release after the initial burst. We performed nonlinear least-squares fitting analysis in which D, b, and t_i were treated as variable parameters. Note that the obtained D values do not include a contribution from the initial burst and that the analysis is based on the assumption that the interior of the particle is regarded as a homogeneous medium. The latter assumption implies that the estimated D actually denotes the average diffusion coefficient over the PLLA/rifampicin solid phase and aqueous phase in the particle.

The results of the analysis are shown in Table 2. The apparent diffusion coefficient D is greater for the particles with C_{PLLA} = 2.0 wt% than those with C_{PLLA} = 4.9 wt%. This difference may be due to the higher surface porosity of the former samples, as evidenced by the A_v/A_t values. It is also noted that D is smaller for the smaller particles. For the smaller particles, the penetration of the aqueous phase into the particle interior may be incomplete because of the very fine structure of the hydrophobic PLLA surface, which results in the suppression of drug diffusion.

Table 2: Best-fit parameters obtained from the analysis of release profiles.

C_{PLLA}/wt%	Method	b	$t_i/10^2$ s	D/m^2 s^{-1}
2.0	Drop	0.55	12.5	1.2×10^{-11}
2.0	Spray	0.64	0.4	8.7×10^{-14}
4.9	Drop	0.16	0	8.9×10^{-13}
4.9	Spray	0	1.4	2.6×10^{-14}
2.0	Adsorption	0.26	0	2.2×10^{-10}
5.0	Adsorption	0.31	0	1.4×10^{-10}
8.0	Adsorption	0	0	3.8×10^{-11}

We observed an initial burst of release for the blend systems studied. The baseline parameter b is a measure of the initial burst. It is likely that the initial burst reflects the rapid release from the region near the surface of the particles. The initial burst observed was less prominent for the samples with C_{PLLA} = 4.9 wt% than for those with C_{PLLA} = 2.0 wt%. This difference may be related to the high surface porosity of the former, that is, release from the near-surface region requires only a very short path for the drug to diffuse, but the existence of the denser skin at the surface still suppresses the diffusion for the higher-C_{PLLA} particles.

Figure 6 shows the release profiles for the rifampicin-adsorbed PLLAs; the corresponding best-fit parameters are shown in Table 2. The results show that the time required to reach the ultimate value of $M(t)$ lies between that of the blend sample created using the spray method and that of the sample created using the drop method. On the other hand, the diffusion coefficient D is greater than that for the blend samples. It is reasonable to consider that the rifampicin simply adsorbed to the surface of FDPLLA can be easily desorbed, which leads to an apparently higher D value. We also observed that the final release ratio $R_\infty = M_\infty/M_{fed}$ reaches nearly 100%. This finding suggests that there is no fraction of rifampicin that is completely surrounded by the PLLA phase. For the sample with C_{PLLA} = 8.0 wt%, an initial

burst was not observed (Table 2), likely due to the very low amount of rifampicin loaded (0.4 wt% with respect to PLLA) compared with the amount loaded in the other two samples (6.2 and 5.6 wt%), as mentioned in the experimental section. Indeed, the porosity of the FDPLLA particles with C_{PLLA} = 8.0 wt% is extremely low ($\sigma = 8.4\ m^2\ g^{-1}$, and $A_v/A_t = 3.0\%$), and this low porosity may be responsible for the low drug loading.

4. Conclusions

We observed that the present PLLA/rifampicin blend particles exhibit effective drug release into an aqueous phase. The release rate significantly depends on the morphology of the particles, specifically the particle size, specific surface area, and surface porosity. We confirmed that the morphology can be modified by the concentration C_{PLLA} and by the method of freezing; in particular, the latter can control the size of the resulting particles. Furthermore, the amount of drug loaded into the blend particles was observed to be prominently higher than that loaded into the rifampicin-adsorbed PLLAs; thus, the present blend system is a promising candidate as a drug carrier. The final release ratio R_∞ did not reach 100% over the time range investigated, but the remaining fraction of the drug could be released after the degradation of PLLA. Controlling the phase-separated structure of rifampicin and PLLA in the blend to obtain the desired fraction of the drug surrounded completely by PLLA would allow us to achieve drug delivery over a longer time span, where the release is dominated by the decomposition of the PLLA phase.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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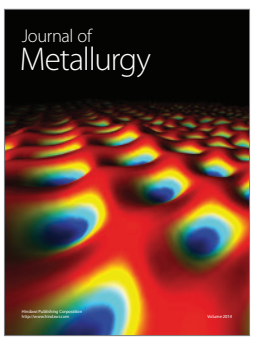

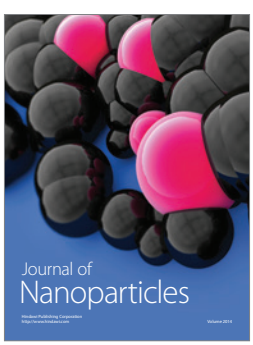

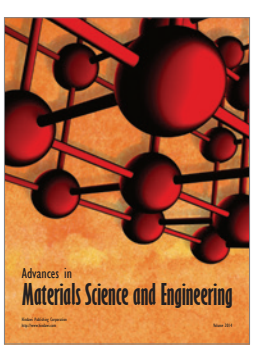

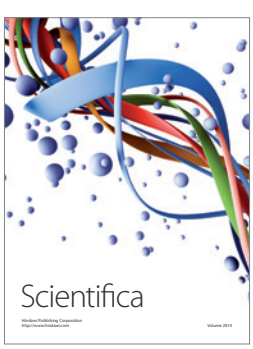

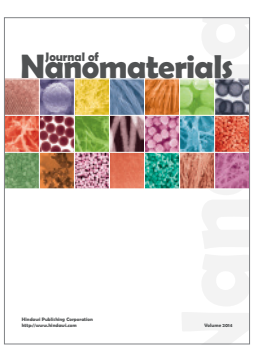

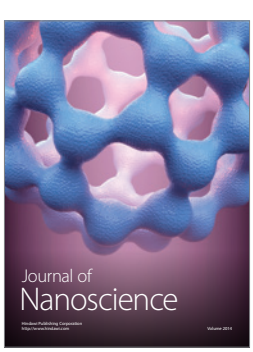

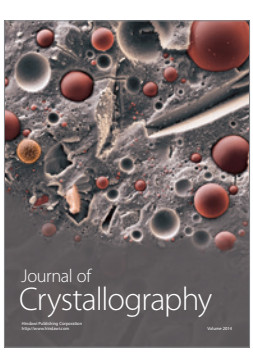

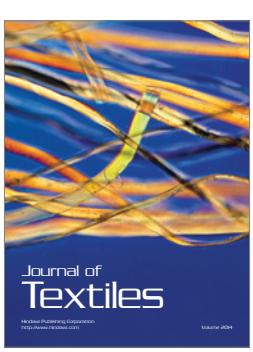

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