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Effects of the conformation of PLGA molecules in the organic solvent on the aerodynamic diameter of spray dried microparticles

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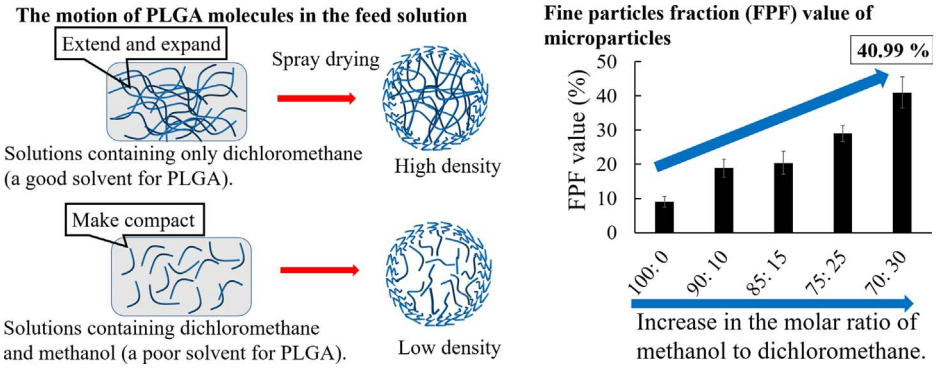
GRAPHICAL ABSTRACT



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ABSTRACT

The purpose of this study was to reveal the effects of the conformation of poly (DL-lactide-*co*-glycolide) (PLGA) molecules in the feed solution on the aerodynamic diameter of PLGA microparticles prepared by using spray drying method. We investigated the conformation of PLGA molecules in the feed solution using viscometry. The data provide information about the polymer coil radius (R_{coil}), the overlap concentration (c^*). Then, we prepared various rifampicin-loaded PLGA microparticles by changing the mixing ratio of dichloromethane and methanol. We used a cascade impactor and mice to measure the aerodynamic diameter of the microparticles *in vitro* and *in vivo*, respectively. The viscosity measurement showed that an increased molar ratio of methanol in the solvent compositions resulted in the decreased R_{coil} and increased c^*. Then, we found that the increased molar ratio of methanol in the solvent compositions resulted in the increased fine particle fraction value *in vitro* and delivery ratio to lung *in vivo*. The conformation of PLGA molecules in the feed solutions influences PLGA network in the microparticles, which would affect the aerodynamic diameter of the microparticles. In conclusion, the finding of our study suggests that solvent selection and connectivity of PLGA molecules of microparticles are associated with the aerodynamic diameter.

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1. Introduction

Poly (lactic-*co*-glycolic acid) (PLGA) has been widely used and studied of its biodegradability, biocompatibility, toxicological safety and release of drugs [1–4]. PLGA has also been used in studies of pulmonary drug delivery and treatment of tuberculosis [5–9]. Previously the authors have developed rifampicin (RFP)-loaded PLGA microparticles to kill Mycobacterium tuberculosis in alveolar macrophage [10,11]. However, it should also be pointed out that fine particle fraction (FPF) value of microparticles was very low (approximately 6%) [12]. It is needed to clarify the factors which influence aerodynamic diameter and make FPF value of particles higher. We hypothesize that the conformation of PLGA molecules in the organic solvent, feed solution, is important because the more compact PLGA molecular conformation would lead to having smaller aerodynamic diameter of microparticles. The aerodynamic diameter, d_{aer}, of the microparticles was calculated by the Eq. (1):

$$d_{aer} = d_{mass}\sqrt{\frac{\rho}{F}} \quad (1)$$

where d_{mass}, ρ and F are the geometrical particle diameter, the density of particle and the shape fraction, respectively [7]. We focused on the density of particles to improve aerodynamic diameter of microparticles. Our hypothesis relies on the previous studies. The studies revealed that the conformation of PLGA molecules influences the connectivity of PLGA and affects the drug release kinetics. Further, the reports suggest the importance of optimal solvent selection in designing polymeric microparticles with controlled release properties using spray drying method. It is found that an extended PLGA molecular conformational structure in a good solvent causes a slow release rate, which might be due to a high density of the stable PLGA network formed during the spray drying process. In contrast, the more compact PLGA molecular conformation in a poor solvent results in a burst release, which might be attributed to the weaker and a low density of PLGA network formed during spray drying process [13,14]. Thus, we hypothesize that the conformation of PLGA molecules is also important for pulmonary drug delivery because low density of PLGA network causes FPF value of microparticles higher.

The purpose of this study was to clarify the effects of the conformation of PLGA molecules in the feed solution on the aerodynamic diameter of microparticles prepared using spray drying method. To examine the conformation of PLGA molecules in the feed solution, we performed viscosity measurement experiment. Then, we prepared RFP-loaded PLGA microparticles in mixtures of dichloromethane (DCM) and methanol (MeOH) at various ratio by using spray drying method. DCM was chosen as a proper solvent for PLGA [15] and MeOH was as a poor solvent [16]. It is easy to prepare microparticles using spray drying because boiling point of MeOH (62 °C) is lower than others. To investigate effects of the conformation of PLGA molecules in the feed solution on the aerodynamic diameter of spray dried microparticles, FPF value and delivery ratio to the lung were conducted *in vitro* and *in vivo*, respectively.

2. Materials and methods

2.1. Materials

PLGA with a molecular weight of 20,000 and a DL-lactic acid/glycolic acid monomer composition of 75/25 (PLGA7520), acetonitrile (for HPLC, purity ≥ 99.9%), dichloromethane (DCM, CH_2Cl_2, purity ≥ 99.0%), methanol (MeOH, CH_3OH, purity ≥ 99.8%) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Rifampicin (RFP, $C_{43}H_{58}N_4O_{12}$, purity ≥ 97.0%) was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Table 1
Characterization of PLGA molecules in the feed solution (n = 3).

Solvent compositions (DCM: MeOH)	[η] (dL/g)	R_{coil} (nm)	V_{coil} (nm^3)	c^* (g/dL)	Entanglement index
100: 0	0.33	1.02	4.44	3.03	1.32
90: 10	0.32	1.00	4.19	3.14	1.27
85: 15	0.29	0.97	3.82	3.43	1.17
75: 25	0.24	0.92	3.26	4.10	0.98
70: 30	0.18	0.82	2.31	5.52	0.72

Table 2
Characterization of rifampicin-loaded PLGA microparticles (n = 3, mean ± S.D.).

Solvent compositions (DCM: MeOH)	Mean volume diameter (μm)	Drug loading (%)	Entrapment efficiency (%)
100: 0	4.71 ± 2.61	20.21 ± 0.08	101.1 ± 0.42
90: 10	4.98 ± 2.72	20.13 ± 0.07	100.6 ± 0.34
85: 15	4.47 ± 2.57	20.11 ± 0.18	100.5 ± 0.93
75: 25	4.65 ± 2.59	19.11 ± 0.21	99.55 ± 1.06
70: 30	4.37 ± 2.51	19.92 ± 0.02	99.62 ± 0.12

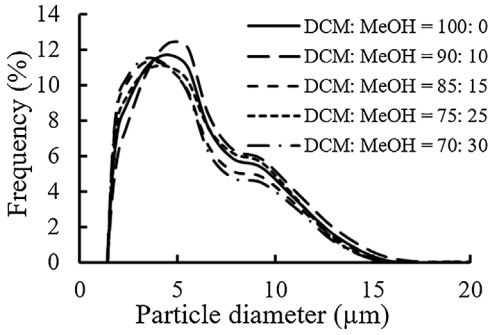

Fig. 1. Size distributions of microparticles prepared using various solvent compositions.

Hydroxypropyl methylcellulose (HPMC) capsules were purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Other chemicals were of the highest grade commercially available.

2.2. Viscosity measurement of the feed solutions

In order to measure the conformation of PLGA molecules in the feed solution, viscometer (TV-20, Toki Sangyo Co., Ltd., Tokyo, Japan) was introduced. The experiment was carried out at 25 °C in a water bath because viscosity tends to affect the temperature [13]. The intrinsic viscosity ([η]) of PLGA in the various solvent compositions (DCM: MeOH = 100: 0, 90: 10, 85: 15, 75: 25, 70: 30) was determined by using the following Eq. (2):

$$[\eta] = \lim_{c\to 0}\left(\frac{\eta_{sp}}{c}\right) \quad (2)$$

where η_{sp} is the specific viscosity and c is the concentration of the polymer solution [17].

The polymer coil radius, R_{coil}, in the solvent compositions was calculated using [η] using Eq. (3):

$$R_{coil} = [3[\eta]\bullet M\mathrm{w}/10\pi\bullet N_{AV}]^{1/3} \quad (3)$$

where M_w is the molecular weight of the polymer and N_{AV} is Avogadro's number [18].

Volume per polymer coil, V_{coil}, in the various solvents was

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