

# Further application of a modified spontaneous emulsification solvent diffusion method to various types of PLGA and PLA polymers for preparation of nanoparticles

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## Abstract

The purposes of this study were to expand the application of a new nanoparticle preparation method, i.e., the modified spontaneous emulsion solvent diffusion (modified-SESD) method, to polylactide (PLA) and poly(DL-lactide-co-glycolide) (PLGA) polymers with different molecular weights, copolymer ratios ( $L/G$  ratios) and original sources, and to find the optimal composition of binary organic solvents. Fifteen nanoparticles of different PLA and PLGA polymers were prepared by means of the modified-SESD method, and the yield, particle size and size distribution of these nanoparticles were evaluated. The phase separation points of PLGA and poly(vinylalcohol) (PVA) were examined by cloud point titration to clarify the effect of the affinity of solvent used in the system to polymers on nanoparticle productivity. The combination of binary organic solvents, i.e., acetone/alcohol, enabled the production of nanoparticles with good productivity when the  $L/G$  ratio was higher than 75/25. The 50/50 PLGA nanoparticles were prepared unsuccessfully in acetone/alcohol, because of poor solubility, but it became successful by replacing the solvents to acetonitrile/alcohol. All of the nanoparticles could be powderized via freeze-drying, and they showed narrow size distributions. The phase diagram study indicated that the balance of the affinity between binary organic solvents and each polymer had a very important role in the productivity of nanoparticles. The productivity was represented a function of  $\chi$ , a parameter representing the degree of phase separation of PLGA at the actual preparation condition against the ultimate cloud point. The yield of nanoparticles increased with the increase in the  $\chi$  value and attained almost 100% at more than 0.7 of  $\chi$  regardless of the difference in binary solvent combination. These results indicated that the optimal composition ratio of binary organic solvents coincided to near the cloud point and the optimal condition of binary organic solvents could be predicted by using their relation curve. It was found that the modified-SESD method was widely applicable to various types of PLGA polymers, by choosing optimal combination of binary organic solvents. © 2000 Elsevier Science S.A. All rights reserved.

**Keywords:** PLGA; Nanoparticle; Molecular weight; Copolymer ratio; Binary organic solvents

## 1. Introduction

Biodegradable materials for polylactide (PLA) and its copolymer with glycolic acid (poly(DL-lactide-co-glycolide), PLGA) have been utilized as a drug delivery system for controlling the release of various drugs. In many investigations concerning these polymers, almost all of the controlled release dosage forms were drug-incorporated carriers such as microspheres [1] or nanospheres [2,3].

Recently, however, the knowledge and skill of biodegradable polymer technology are progressing rapidly

and some attempts have been made to apply biodegradable polymers to other dosage forms such as rods [4–6], granules [7] and films [8,9]. One approach to the development of such new drug delivery systems involves the use of powdered biodegradable nanoparticles, taking advantage of their extremely small particle size and large specific surface area [10].

However, a preparation method for nanoparticles on an industrial scale has not yet been established. We have focused on the development of such a preparation method, in particular to produce powdered PLGA nanoparticles on a large scale [11–13]. We previously established a promising method for this purpose, named the modified spontaneous emulsification solvent diffusion method (modified-

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SESD method), using a PLGA polymer, Medisorb (85/15, Mw 46770) [13]. In the modified-SESD method, Medisorb was dissolved in the binary mixture of acetone and alcohol with a suitable ratio, and the resultant solution was dispersed in an aqueous poly(vinylalcohol) (PVA) solution under mild agitation. The dispersion prepared was then ultrafiltered and freeze-dried without using any cryoprotectant, resulting in powdered nanoparticles. In this preparation method, the use of binary organic solvents with the following properties was necessary; one (e.g., acetone) with affinity to PLGA but not to PVA, and the other (e.g., alcohol) with affinity to PVA but not to PLGA. The combination of acetone and alcohol resulted in improved productivity compared to the original SESD method, which was previously established in our laboratory by using  $\text{CH}_2\text{Cl}_2$  and acetone [2].

In the present study, the applicability of the modified-SESD method was further tested using various types of PLA and PLGA polymers with different molecular weights, copolymer ratios (*L/G* ratios) and original sources. We also attempted to find key factors affecting the productivity of nanoparticles with the modified-SESD method. Finally, the effect of the composition ratio of binary organic solvents was investigated by comparing acetone/alcohol with acetonitrile/alcohol, and experimental formula for determining the optimal conditions are proposed.

## 2. Experimental

### 2.1. Materials

PLA of various molecular weights (LA0005, 0010 and 0020, Wako, Japan, and Resomer 202H, Boehringer Ingelheim, Germany), 85/15 PLGA (Medisorb, DuPont, USA), 75/25 PLGA (LGA7505, 7510 and 7520, Wako), 50/50 PLGA (LGA5005, 5010 and 5020, Wako; Medisorb, DuPont; and Resomer RG504, Boehringer Ingelheim) were used as received, as shown in Table 1. PVA (Poval<sup>®</sup>-403, Kuraray, Japan) with 80% of hydrolyzation degree and 300 of polymerization degree was used as received. All other chemicals and solvents were of reagent grade.

### 2.2. Preparation of PLGA nanoparticles

The typical operating procedure was as follows.

(I) Quasi-emulsification: 5 g of PLGA or PLA was dissolved in 125 ml of the solvent mixture consisting of acetone or acetonitrile and alcohol. The polymer solution obtained was then added into 300 ml of aqueous PVA solution (4%, w/w) in a 1000-ml glass flask using a peristaltic pump at a flow rate of 10 ml/min with continuous stirring at 400 rpm by a propeller mixer.

(II) Purification: The dispersion formed was transferred into a 1000-ml glass flask and deionized water was added up to 500 ml. The dispersion was condensed to 25 ml by

means of an ultrafiltration (Minitan<sup>®</sup> system, Millipore, Japan), and deionized water was added up to 500 ml. This dilution–condensation process was repeated three times to remove the residual PVA and organic solvents.

(III) Freeze-drying: The aqueous dispersion condensed to 25 ml was passed through a 100-mesh sieve to remove aggregates and then freeze-dried in a vacuum to obtain powdered nanoparticles. The yield of nanoparticles was represented by the percent weight fraction of the powdered nanoparticles relative to the total weight of PLGA used for the preparation.

### 2.3. Particle size and size distribution measurement

The mean diameter and the size distribution of the nanoparticles in aqueous dispersion were measured by an electrophoretic light scattering spectrophotometer (ELS-800, Otsuka Electronics, Japan). The size of the freeze-dried nanoparticles was determined after dispersing in deionized water.

### 2.4. Measurement of molecular weight of PLGA

The molecular weight of the PLA or PLGA was determined by gel permeation chromatography. The measurements were performed with a high-performance liquid chromatography (HPLC) system at 40°C (oven, CO8010, Tosoh, Japan) at a flow rate of 1.0 ml/min (pump, COPM, Tosoh) detected with a refractive index meter (detector, RI8012, Tosoh). Two hundred microliters of the solution of PLA or PLGA dissolved in chloroform was separated with three TSK gel columns connected in series (Tosoh). The weight-average molecular weights were calibrated with an integrator (SC-8010, Tosoh) by the use of standard polystyrene (Standard S series, Shodex, Japan).

### 2.5. Cloud point titration for PLGA and PVA

To evaluate the affinity of PLGA to methanol and ethanol, the cloud points were determined applying the titration technique [14]. A total of 2 ml of PLGA acetonitrile solution at various concentrations was poured into a 20-ml glass test tube. The resultant PLGA solution was slowly titrated with either methanol or ethanol to the cloud point, where the PLGA began to precipitate, as noted by a faint but distinct cloudiness. The alcohol percentage in the PLGA solution at the cloud point,  $\text{CL}_{\text{alc}}$ , was determined as the index representing the affinity between PLGA and the solvent.

For PVA, 2 ml of aqueous PVA solution (4%, w/w) in the 20-ml glass test tube was titrated with the solvent mixture of methanol/acetonitrile or ethanol/acetonitrile. The volume of solvent mixture required for reaching the cloud point was determined. The volume percentage of solvent mixture at the cloud point,  $\text{CL}_{\text{binary}}$ , was deter-

mined as the index representing the affinity between PVA and the solvent mixture.

### 3. Results

#### 3.1. Application of the modified-SESD method for preparation of nanoparticles with various types of PLGA and PLA

The basic concept of the modified-SESD method consists of the use of succeeding coacervation process of two polymers, PLGA in the organic phase and PVA in the aqueous phase, when PLGA dissolved in binary organic solvents is dispersed in an aqueous PVA solution. The combination of binary organic solvents is required as; one with affinity to PLGA but not to PVA and the other with affinity to PVA but not to PLGA.

In our previous study, we showed that nanoparticles of Medisorb (85/15, Mw 46770) could be obtained at a high yield with the binary organic solvents of acetone/ethanol or acetone/methanol at the mixing ratio of 6/4 (alcoholic concentration ( $\Phi_{\text{alc}}$ ): 40%). We therefore applied these preparation conditions for various types of PLA and PLGA polymers, which varied in molecular weight,  $L/G$  ratio and original source. The properties of the 15 polymers used are shown in Table 1 together with the properties of nanoparticles obtained. The diameter “before” in Table 1 indicates that of nanoparticles before the freeze-drying, i.e., immediately after the purification in the preparation process. On the other hand, the diameter “after” indicates that of nanoparticles after the freeze-drying, i.e., immedi-

ately after the rehydration of the freeze-dried nanoparticles. In all of these cases, the mean diameters of the nanoparticles were less than 300 nm and did not change during their freeze-drying and rehydration process. The small polydispersity index suggested that their size distributions were monomodal. The differences in molecular weight and original sources did not have a significant influence on the productivity. Thus, polymer nanoparticles were produced successfully at high yields when the  $L/G$  ratio was more than 75/25.

On the other hand, because of their poor solubility to acetone/ethanol (6/4), 50/50 PLGAs did not dissolve completely in acetone/ethanol solvent used in the preparation condition shown in Table 1. In our general preparation method, PLGA is dissolved in six parts of acetone, and then four parts of alcohol are added, resulting in 4% (w/v) of PLGA solution. However, 50/50 PLGAs in acetonic solution were precipitated by the addition of alcohol. Then, nanoparticles were not produced, although the binary organic solvents, i.e., acetone of affinity to 50/50 PLGA but none to PVA and alcohol of affinity to PVA but none to 50/50 PLGA, fulfilled the necessary condition of nanoparticle formation. To investigate the reason for this result, we conducted cloud point titration and determined the  $CL_{\text{alc}}$  of each polymer. The results are plotted against the polymer molecular weight in Fig. 1. The  $CL_{\text{alc}}$ s increased as the  $L/G$  ratio increased and decreased with the increase of molecular weight. It should be noted that the  $CL_{\text{alc}}$  values of 50/50 PLGA were below 30% and were the lowest values of all of the polymers. This means that the phase separation of 50/50 PLGA was generated most easily from acetonic solution by the addition of ethanol.

Table 1

Properties of PLGA and PLA nanoparticles prepared by the modified-SESD method, using binary organic solvents of acetone/ethanol or acetone/methanol

Polymer	$L/G$ ratio	Mw	Types of alcohol <sup>*1</sup>	Diameter (nm)		Polydispersity index
				Before <sup>*2</sup>	After <sup>*3</sup>	
LA0005	100/0	4350	EtOH	201	198	0.076
LA0010	100/0	8950	EtOH	204	182	0.091
LA0020	100/0	14790	EtOH	206	215	0.069
Resomer R202H	100/0	15830	EtOH	225	231	0.003
85/15 Medisorb	85/15	12280	EtOH	258	264	0.034
85/15 Medisorb	85/15	46770	EtOH	261	264	0.057
			MeOH	266	263	0.024
85/15 Medisorb	85/15	54110	EtOH	238	240	0.046
LGA7505	75/25	4960	EtOH	238	254	0.054
LGA7510	75/25	8690	EtOH	234	237	0.059
LGA7520	75/25	15810	EtOH	250	250	0.013
LGA5005	50/50	4170	EtOH			
LGA5010	50/50	6800	EtOH			
LGA5020	50/50	11350	EtOH			
50/50 Medisorb	50/50	47700	EtOH			
Resomer RG504	50/50	47670	EtOH			

Nanoparticles could not be prepared due to poor solubility in this binary solvents

\*<sup>1</sup> Mixing ratio of alcohol in binary organic solvents,  $\Phi_{\text{alc}}$ , is 40%.

\*<sup>2</sup> Before freeze-drying.

\*<sup>3</sup> After rehydration of freeze-dried nanoparticles.

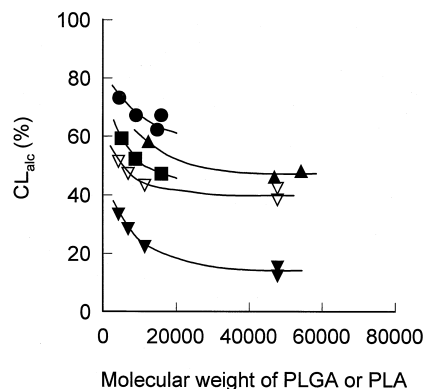


Fig. 1. Relationship between the  $CL_{alc}$  values of various PLGAs and PLAs and their molecular weights.  $L/G$  ratio: (●) 100/0, (▲) 85/15, (■) 75/25, (▼) 50/50 determined in acetone/ethanol, (▽) 50/50 determined in acetonitrile/ethanol.

### 3.2. Preparation of 50/50 PLGA nanoparticles using acetonitrile / alcohol

As another pair of binary organic solvents satisfying the conditions necessary for the modified-SESD method, the combination of acetonitrile/alcohol was found instead of acetone/alcohol. The  $CL_{alc}$ s were determined for 50/50 PLGAs in acetonitrile/ethanol, as shown in Fig. 1, and compared with those in acetone/ethanol. In acetonitrile/ethanol, the  $CL_{alc}$ s of the 50/50 PLGAs also decreased with the increase of molecular weight similarly to acetone/ethanol, but they were larger than those in acetone/ethanol. This indicates that the phase separation of PLGA proceeded more slowly in acetonitrile/ethanol than in acetone/ethanol by the addition of ethanol. The new combination seemed to be suitable for the preparation of 50/50 PLGA nanoparticles, because the rapid coacervation of 50/50 PLGA was not able to occur due to its high affinity to acetonitrile.

Thus, the preparations of nanoparticles were successful for 50/50 PLGAs when binary organic solvents of acetonitrile/ethanol with the various  $\Phi_{alc}$ s being near to their cloud points were used. The properties of the 50/50 PLGA nanoparticles prepared are shown in Table 2. High yields of nanoparticles could be obtained for all of the

Table 2

Properties of 50/50 PLGA nanoparticles prepared using the binary organic solvents of acetonitrile/ethanol

Polymer	$\Phi_{alc}$ (%)	Diameter (nm)		Polydispersity index	Yield (%)
		Before <sup>*1</sup>	After <sup>*2</sup>		
LGA5005	50	244	253	0.017	85
LGA5010	40	258	238	0.058	88
LGA5020	40	260	282	0.013	91
50/50 Medisorb	40	240	255	0.007	95
Resomer RG504	30	247	233	0.004	100

<sup>\*1</sup> Before freeze-drying.

<sup>\*2</sup> After rehydration of freeze-dried nanoparticles.

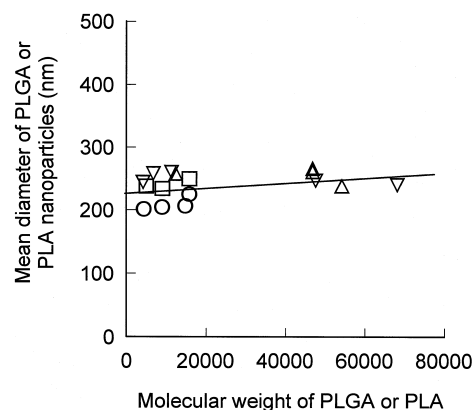


Fig. 2. Dependency of particle size on the molecular weight of PLGA or PLA.  $L/G$  ratio: (○) 100/0, (△) 85/15, (□) 75/25, (▽) 50/50.

50/50 PLGA polymers. These combinations of binary organic solvents provided discrete PLGA nanoparticles with a small size distribution without aggregation. These results indicated that the selection of the combination of binary organic solvents is very important for the preparation of nanoparticles.

### 3.3. Properties of nanoparticles prepared by the modified-SESD method

The particle sizes of all nanoparticles prepared in acetone/ethanol and acetonitrile/ethanol are plotted against the molecular weights of PLA or PLGA in Fig. 2. The mean diameter increased slightly with the increase of molecular weight, and the difference of  $L/G$  ratio and original source seemed not to affect this propensity. This could be regarded as a technical advantage of the modified-SESD method, since the formability would not be influenced by such factors as the  $L/G$  ratio and the polymer species.

The relationship between the yield of nanoparticles and the molecular weight of PLA or PLGA is shown in Fig. 3. Although there was no aggregation of nanoparticles in the

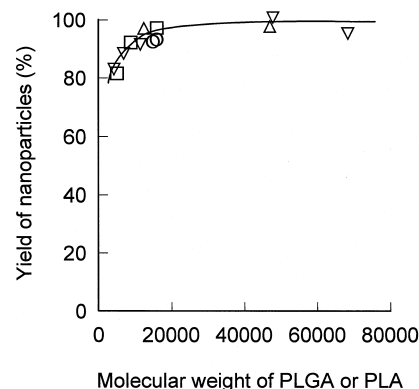


Fig. 3. Relationship between yield of nanoparticles and the molecular weight of PLGA or PLA.  $L/G$  ratio: (○) 100/0, (△) 85/15, (□) 75/25, (▽) 50/50.

dispersion process, the yield of nanoparticles decreased slightly with the decrease of molecular weight. Mehta et al. [15] reported that the water-soluble fraction in PLGA increased with the decrease of the molecular weight of PLGA, resulting in a low yield of PLGA microspheres. In the present study, the water-soluble fraction in PLGA or PLA could be transferred from the organic phase to the aqueous phase during the dispersion process. The modified-SESD method afforded nanoparticles at a high yield (more than 80%) irrespective of the polymer species and can thus be considered an excellent method for preparing nanoparticles.

#### 4. Discussion

As shown above, an acetonitrile system can further expand the applicability of the modified-SESD method. Therefore, to clarify the effect of binary organic solvents on the productivity of nanoparticles, the following investigation was conducted using 85/15 Medisorb, as in our previous study [13].

The 85/15 Medisorb nanoparticles were prepared by using acetonitrile/ethanol and acetonitrile/methanol with various alcoholic concentrations. In Fig. 4, the yields are plotted against the alcohol concentration ( $\Phi_{\text{alc}}$ ) in the binary organic solvents. The results of these experiments are compared with those obtained using acetone/ethanol and acetone/methanol in the previous study [13]. The PLGA concentration in binary organic solvents was fixed at 4% in all the experiments. The yields of nanoparticles increased with the increase of  $\Phi_{\text{alc}}$  in every binary organic solvent condition and attained the maximum values at more than 30% of  $\Phi_{\text{alc}}$  in the acetone systems and at more than 40% of  $\Phi_{\text{alc}}$  in the acetonitrile systems.

An increase in the alcohol concentration in the binary organic solvents accelerated the phase separation rate of PLGA during the dispersion process, since alcohol is a

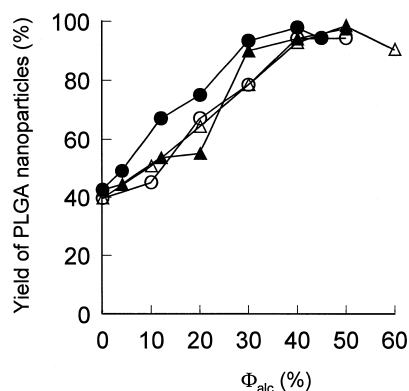


Fig. 4. Yield of PLGA ( $L/G$  ratio = 85/15, Mw 46770) nanoparticles prepared with various binary organic solvents. Binary organic solvents: (○) acetonitrile/ethanol, (△) acetonitrile/methanol, (●) acetone/ethanol, (▲) acetone/methanol.

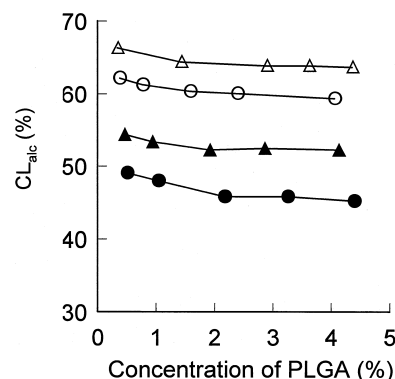


Fig. 5. Dependency of  $CL_{\text{alc}}$  on the concentration of PLGA ( $L/G$  ratio = 85/15, Mw 46770) in various binary organic solvents. Binary organic solvents: (○) acetonitrile/ethanol, (△) acetonitrile/methanol, (●) acetone/ethanol, (▲) acetone/methanol.

poor solvent for PLGA. Therefore, the alcohol percentage at which the coacervation of PLGA was generated, i.e., the  $CL_{\text{alc}}$ , was determined by cloud point titration in acetone/alcohol and acetonitrile/alcohol for 85/15 Medisorb. The  $CL_{\text{alc}}$  values are plotted against the PLGA concentration in Fig. 5. The  $CL_{\text{alc}}$  values scarcely changed with the concentration of PLGA but were significantly changed by the combinations of binary organic solvents in all systems. The  $CL_{\text{alc}}$  values in acetonitrile/alcohol were higher than those in acetone/alcohol. This implies that more alcohol is required for the phase separation of PLGA in acetonitrile/alcohol than in acetone/alcohol. This difference could be the reason why the  $\Phi_{\text{alc}}^{\text{max}}$  values, at which the yield attained the maximum values, were higher in acetonitrile/alcohol (approximately 40%) than in acetone/alcohol (approximately 30%) (Fig. 4).

We clarified in previous study [13] that the phase separation of PVA dissolved in the aqueous phase is also an important factor in the formation of nanoparticles, and that it is markedly affected by the combination of binary organic solvents. Therefore, cloud point titration with binary organic solvents was conducted using an aqueous 4% PVA solution, and the volume percentage of binary organic solvents, at which the aqueous phase became cloudy, i.e., the  $CL_{\text{binary}}$  value, was determined. The  $CL_{\text{binary}}$  values are plotted against the  $\Phi_{\text{alc}}$  of the binary organic solvents in Fig. 6, together with those in acetone/alcohol. The  $CL_{\text{binary}}$  increased with the increase of  $\Phi_{\text{alc}}$ , and the dependency of  $CL_{\text{binary}}$  on  $\Phi_{\text{alc}}$  showed similar propensities in acetonitrile/alcohol and acetone/alcohol. The increase of  $CL_{\text{binary}}$  implies that the phase separation rate of PVA is slower as the  $\Phi_{\text{alc}}$  increased. The difference of  $CL_{\text{binary}}$  between the binary organic solvents containing acetonitrile and acetone could be attributed to the difference of their affinity to PVA.

The technical characteristic of the modified-SESD method consists of the combination of two water-miscible organic solvents; one (as acetonitrile or acetone) has higher affinity to PLGA than to PVA and the other (as alcohol)

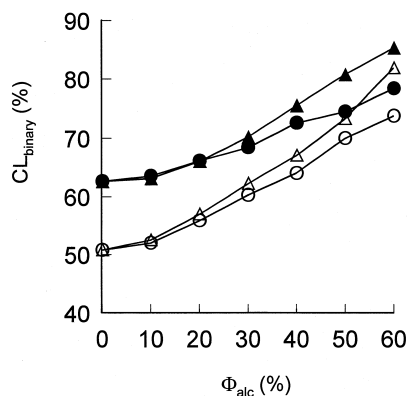


Fig. 6. Dependency of  $CL_{binary}$  on  $\Phi_{alc}$  when a 4% aqueous PVA solution was titrated with binary organic solvents. Binary organic solvents: (O) acetonitrile/ethanol, ( $\Delta$ ) acetonitrile/methanol, (●) acetone/ethanol, ( $\blacktriangle$ ) acetone/methanol.

has higher affinity to PVA than to PLGA. Therefore, the following mechanism of the nanoparticle formation is speculated and is schematically proposed in Fig. 7.

The PLGA solution is in a state that the addition of alcohol to the acetonitrile or acetic solution makes PLGA easy to induce deposition. When the PLGA solution is dispersed into the aqueous PVA solution (stage 1), the perturbation of the interface spontaneously produces a larger interfacial area, which leads to nanosized quasi-emulsion droplets of PLGA solution. This interfacial turbulence would be governed by the well-known Marangoni effect [16]. Thus, the alcohol preferentially diffuses out of the droplets since the affinity of alcohol to PLGA is lower than that of acetonitrile or acetone (stage 2). Continuously, acetonitrile or acetone diffuses out of the droplets and the coacervation of PVA is induced by the increasing concentration of acetonitrile or acetone (stage 3). In addition, the PLGA concentration inside increases to induce the PLGA deposition (stage 4). Finally, the subsequent solidification

of PLGA and PVA adsorption are completed simultaneously (stage 5). As these deposition processes are conducted almost instantaneously and spontaneously, the uniform nanoparticle dispersion can always be attained even by mild agitation.

When the  $\Phi_{alc}$  value became higher, the phase separation rate of PVA became slower, resulting in the high yield of nanoparticles due to the easy dispersion of PLA or PLGA quasi-emulsion droplets from the organic phase.

The use of the combination of binary organic solvents with high  $\Phi_{alc}$  value was desirable for the preparation of PLGA nanoparticles. In contrast, however, there is an upper limit for the  $\Phi_{alc}$  reaching its  $CL_{alc}$  of PLA or PLGA. Thus, the ratio ( $\chi$ ) of  $\Phi_{alc}$  in preparation condition to the cloud point ( $CL_{alc}$ ) appears to markedly influence the productivity. This parameter was defined as;

$$\chi = \frac{\phi_{alc}}{CL_{alc}}$$

where  $CL_{alc}$  is the alcohol percentage of cloud point extrapolated at 4% (w/v) PLGA in Fig. 5. The  $CL_{alc}$  values of PLGA in acetonitrile/ethanol, acetonitrile/methanol, acetone/ethanol and acetone/methanol were 59%, 64%, 45% and 52%, respectively. The  $\chi$  value represents the degree of phase separation of PLGA at the actual preparation condition. Thus,  $\chi = 1$  corresponds to an ultimate condition that the actual composition of binary solvents is the same as a threshold of cloud point.

In Fig. 8, the yields of nanoparticles are plotted against the  $\chi$  values. Almost all points were on the same curve regardless of the combination of binary organic solvents. The yield of nanoparticles increased with the increase in the  $\chi$  value and attained almost 100% when  $\chi$  approached 1.0 (0.7–1.0). This means that the optimal composition ratio of binary organic solvents coincided to near the cloud point. The curve in Fig. 8 could be regarded as a

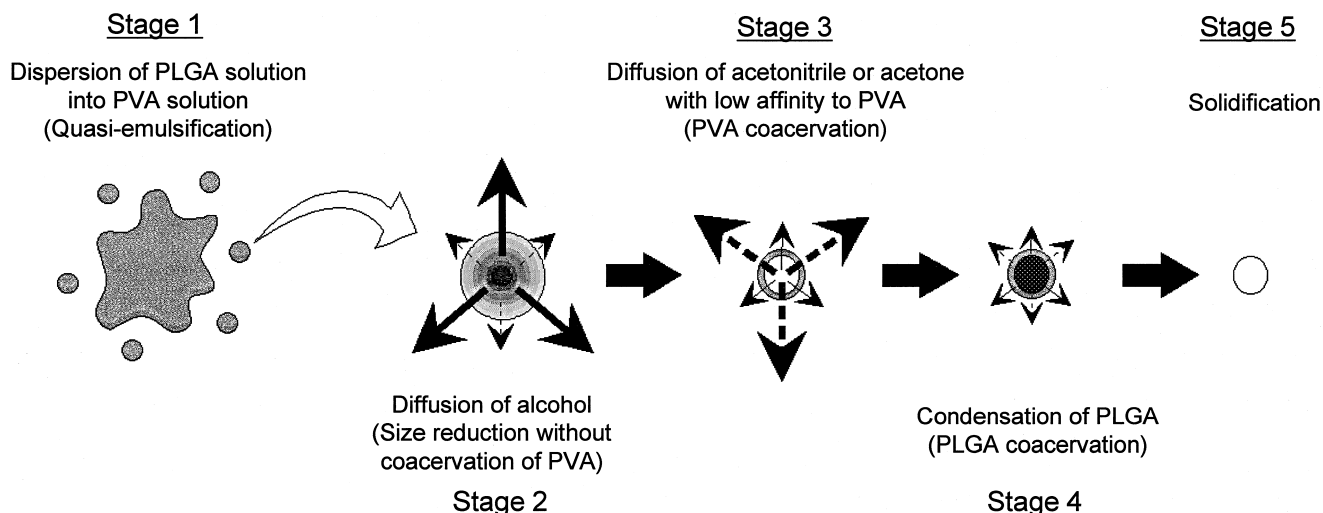


Fig. 7. Possible mechanism of nanoparticle formation by the modified-SESD method. Solid lines: the diffusion of alcohol, dotted lines: the diffusion of acetonitrile or acetone, bold lines: rapid diffusion, narrow lines: slow diffusion.

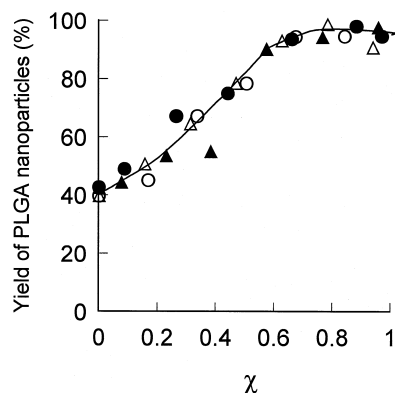


Fig. 8. Relationship between the yield of PLGA ( $L/G$  ratio = 85/15, Mw 46770) nanoparticles and the  $\chi$  values. Binary organic solvents: (○) acetonitrile/ethanol, (△) acetonitrile/methanol, (●) acetone/ethanol, (▲) acetone/methanol.

predicting curve of the yield of nanoparticles, as a function of  $\chi$  value regardless of the difference in the combination of binary organic solvents. In addition, the optimal composition ratio of the solvents could be estimated by using this predicting curve if the  $CL_{alc}$  is determined preliminarily.

## 5. Conclusions

The present study was conducted to explore the applicability of the modified-SESD method to various types of PLA and PLGA polymers for preparation of nanoparticles, using another combination of binary organic solvents (acetonitrile/alcohol). This method afforded nanoparticles at a high yield irrespective of molecular weight,  $L/G$  ratio and original source of the polymer, and was found to be an excellent preparation method with respect to productivity. In addition, the nanoparticles obtained showed small variation in size distribution and good powderization via freeze-drying, avoiding the need for the use of a high-speed homogenizer and chlorinated solvent. The combination of

binary organic solvents affected the balance of the phase separation of PLGA in the organic phase and PVA in the aqueous phase, and thus has an important role in the productivity of nanoparticles. It was found that the optimal condition of binary organic solvents could be predicted by using the curve of the yield representing as a function of  $\chi$  if the  $CL_{alc}$  is determined preliminarily.

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