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Facile technique for the preparation of monodispersed biodegradable polymer nanospheres using a solvent evaporation method

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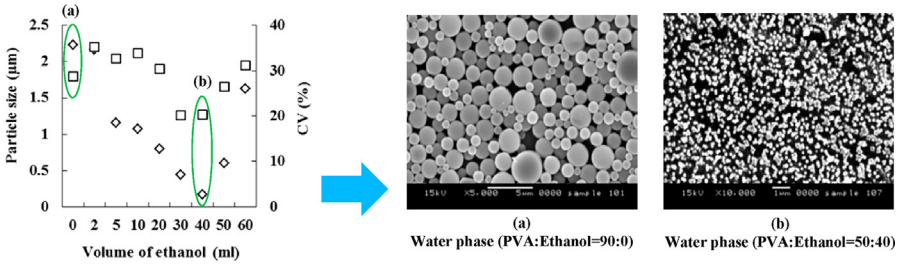
HIGHLIGHTS

- Size of prepared emulsion droplets in PVA/ethanol water phase was smaller ones.
- PLGA nanospheres by solvent evaporated the smaller droplets were prepared.
- Monodispersed 170-nm PLGA nanospheres were prepared using a simple method.

GRAPHICAL ABSTRACT



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ABSTRACT

A facile technique was developed for the preparation of monodispersed nanospheres composed of poly(lactide-*co*-glycolide) (PLGA) for use as a biodegradable polymer in a liquid–liquid system. The preparation of PLGA particles by solvent evaporation from an emulsion prepared by adding a nonionic or reactive surfactant to the water phase was examined. The size of the PLGA particles gradually decreased as the surfactant concentration in the water phase increased. However, nanosized PLGA particles were difficult to prepare using this procedure. Preparation of nanosized particles of PLGA by solvent evaporation from a mixture of an aqueous solution of polyvinylalcohol (PVA) and ethanol was also examined. As the amount of ethanol was increased relative to the amount of PVA solution, the size of the PLGA particles decreased. At a ratio of 50:40 v/v% PVA(aq):ethanol, monodispersed spherical PLGA particles, 170 nm in diameter, were generated. Nanosized PLGA particles in liquid–liquid systems are generally prepared using solvent evaporation methods after emulsion droplets are first prepared using a particulate disperser apparatus (e.g., an ultrasonic homogenizer), although the resulting particles are polydispersed. In this study, monodispersed nanosized PLGA particles were generated even though we used a simple high-speed rotary homogenizer, which is usually not capable of preparing nanosized particles, without the use of a particulate mechanical disperser or a combination of particulate emulsion techniques. The technique used in this study may also be applicable to the preparation of other types of polymers and emulsion particles.

1. Introduction

Particles composed of poly (lactide-co-glycolide) (PLGA) as biodegradable and biocompatible polymers have been investigated in the research and development of advanced drug delivery systems (DDS) and biomaterials [1–3]. Preparation of PLGA parti-

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cles in liquid–liquid systems has typically been done via solvent evaporation [4–6]. We have been developing PLGA particles in liquid–liquid systems for use in the fabrication of new DDS formulations [7–14]. Monodispersed PLGA microspheres containing hydrophobic or hydrophilic drugs have been prepared by combining a membrane emulsification process and a solvent evaporation method [7–9]. Control of the drug loading efficiency and drug release behavior using PLGA particles prepared by this technique have been examined [10–11]. In addition, PLGA particles containing low-molecular-weight hydrophilic drugs in liquid–liquid systems have been prepared using a newly established technique to enclose hydrophilic drugs within microspheres [12–14]. For these applications, we recently developed a facile technique for the preparation of monodispersed PLGA nanospheres using conventional solvent evaporation.

In general, PLGA nanospheres have been prepared by solvent evaporation using a specific disperser apparatus, such as an ultrasonic homogenizer [15–17]. PLGA nanospheres using a solvent diffusion method were also prepared, although an ultrasonic homogenizer was not used [18]. The common opinion regarding these techniques was that the resulting PLGA particles were polydispersed, not monodispersed. We have previously presented a method for the preparation of monodispersed PLGA nanospheres by combining a solvent diffusion method and a membrane emulsification technique [19]. This approach utilized emulsion preparation techniques. Therefore, the study of the preparation of monodispersed PLGA nanospheres by simple solvent evaporation without using a particulate disperser apparatus or an emulsion unit has not been previously reported.

For the preparation of smaller PLGA particles by simple solvent evaporation without using a particulate disperser apparatus or an emulsion unit, we generated smaller polymer emulsion droplets by controlling the interfacial tension between the oil and water phases in a liquid–liquid system. In previously published work, we examined the relationship between particle size and drug-loading efficiency by evaluating the interfacial tension between the organic solvent used to dissolve PLGA, and the water phase [10]. In this earlier work, the effect of the oil phase on control of the interfacial tension between the oil and water phases was investigated in order to control the size of the PLGA particles. We now need to examine the effect of the water phase on the control of the interfacial tension between the oil and water phases. We started this part of our work by addition of a hydrophilic surfactant or solvent into the PVA solution. Adding surfactant into the water phase reduces the interfacial tension between the oil and water phases. The addition of a hydrophilic solvent to the PVA solution allows easy control of the interfacial tension between the oil and water phases. Ethanol was selected as the hydrophilic solvent since it has a low interfacial tension (6.78 mN/m) [10] and low toxicity. In the present study, these conditions for preparation of PLGA particles with sizes less than 200 nm were investigated. Hence, this is the first report on the preparation of monodispersed biodegradable polymer nanospheres without using a specific disperser apparatus or an emulsification unit technique.

2. Experimental

2.1. Materials

PLGA7520 (poly(lactic-*co*-glycolide), 75:25, Mw 20,000) (Wako Pure Chemical Industry, Japan) was purchased and stored at −80 °C prior to use. Polyvinyl alcohol (PVA) (degree of polymerization: 500; saponification: 86–90 mol%) (Wako Pure Chemical Industry, Japan) was purchased and used as a dispersant in the water phase of the emulsion and for the preparation of PLGA particles. A nonionic surfactant, HCO-60 (HLB: 14, NIKKOL) as a hydrogenated castor oil and reactive surfactant, Aquaron RN-30 (HLB: 16.7, Dai-ich Kogyo Seiyaku Co., Ltd.) were used as additives to control the size of the emulsion droplets formed in the water phase. The other chemicals used were of the highest commercially available grade.

2.2. Preparation of PLGA particles by solvent evaporation

The oil phase was prepared by dissolving 0.5 g of PLGA7520 in 10.0 mL of dichloromethane (DCM) in a 10.0-mL test tube. A small amount of surfactant (HCO-60 or RN-30) was added to the 1.0 wt% polyvinyl alcohol (PVA) solution. This mixture was used as the water phase. The oil phase was poured into 90.0 mL of the water phase (1.0 wt% PVA solution with surfactant added). The oil in water (o/w) emulsion was prepared by homogenization of 30,000 rpm for 60 s using a micro homogenizer (Microtec Nition Co., Ltd.). PLGA particles were prepared by solvent evaporation using impeller stirring (BL 1200, Shinto Scientific Co., Ltd.) at 250 rpm for 1.0 h at room temperature and 1 atm pressure.

A flow chart is shown in Fig. 1 illustrating the preparation of PLGA particles by adding ethanol into the PVA solution. PLGA7520 (0.5 g) was dissolved in 10.0 mL of dichloromethane (DCM) in a 10.0-mL test tube. This solution was used as the oil phase (Fig. 1(a)). A mixture of 1.0 wt% PVA solution and ethanol was used as the water phase (Fig. 1(b)). PLGA dissolved in DCM (oil phase) was added to the PVA/ethanol mixture (water phase). An o/w emulsion was prepared by agitation at 30,000 rpm for 60 s using a micro homogenizer (Fig. 1(c)). PLGA particles were prepared by solvent evaporation using impeller stirring at 250 rpm for 1.0 h at room temperature and 1 atm (Fig. 1(d)).

2.3. Collection and washing of PLGA particles

PLGA particles having different sizes were obtained by varying the centrifugation speed (2000, 3500, 5000, and 10,000 rpm for 5 min) (3700, Kubota Co., with a centrifugal separator). The supernatant was removed and fresh distilled water was added. The resulting PLGA particles were washed three times with distilled water.

2.4. SEM observation of PLGA particles

A droplet of the PLGA particle suspension was placed on an aluminum sample stage and dried for 1 day in a vacuum desiccator. Platinum sputtering was performed using an ion-sputtering device (Auto Fine Coater, JFC-1600, JEOL Ltd.). PLGA particles were examined using scanning electron microscopy (SEM, JSM-6060LA, JEOL Ltd.). Images of the particles were observed at 5000 and 10,000 magnification.

2.5. Measurements of PLGA particle size and particle size distribution

The average particle diameter and the coefficient of variation (CV) were calculated using data from 200 particles observed in SEM photographs. The value of CV was calculated using Eq. (1).

$$CV = \sigma / D_p \times 100 \quad (1)$$

where σ is the standard deviation and D_p is the average particle diameter. A low CV value indicates the presence of uniform monodispersed particles.