Effect of nonionic surfactant in the preparation of microsphere based on blend of poly(lactic acid) and polycaprolactone

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Abstract. Microspheres of poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL) were blended and prepared using the water in oil (w/o) emulsion solvent evaporation method. The PLA/PCL blend was formulated with the composition of 60:40 (w/w), nonionic surfactant was utilized as the emulsifier. This study observed the distribution of the microspheres particle size by varying the nonionic surfactant volumes, emulsion stirring speed, and dispersion stirring time. The microspheres were characterized using Fourier Transform Infrared (FTIR) and Particle Size Analyzer (PSA). Physical forms of microspheres were observed using an optical microscope as well. The IR spectra of PLA/PCL blend showed that only physical interaction was occured between them. Moreover, the result of this study showed that when 2.0 mL nonionic surfactant was added, the uniform size distribution of the formed microspheres was observed at 31.50 μm. Furthermore, the microspheres that formed through emulsion stirring speed at 900 rpm revealed that the formed microspheres have a uniform size distribution at 31.50 μm, while the uniform size distribution at 34.58 μm was observed in the microspheres that formed during the dispersion stirring time at 90 minutes.

1. Introduction
Microspheres are commonly used in the drug delivery systems because they have small size and efficient properties as particles carrier. Microspheres are small spherical particles with diameters 1–1000 μm [1]. The size of microspheres for drug delivery systems should not be greater than 250 μm, ideally less than 125 μm [2]. Biodegradable polymers are used as coatings or agent (drug or protein) in the form of microspheres or microcapsules [3]. The notable examples of biodegradable polymers have been widely used for the drug delivery systems are poly (lactic acid) (PLA), polycaprolactone (PCL), poly (glycolic acid), and poly (lactic-co-glycolic acid) [4]. Meanwhile, PLA has low permeability compared to PCL, although the degradation time is shorter than PCL [5]. The PCL and PLA’s mixture is supposed to generate a suitable polymer with higher speed degradation period as well as preferable permeability [6].

According to results of experiments, it showed that the performance of the microspheres is highly affected by the amount and types of surfactants [7]. Nonionic surfactant is frequently used in the preparation of microsphere using solvent evaporation method. They are generally imparted with good stability and compatibility [8–10]. The microsphere yielded from PLA-PCL was produced using Nonidet RK-18 as nonionic surfactant. Nonidet RK-18 is a low foaming nonionic surfactant with high emulsification and has biocompatible properties, which can control microsphere size distribution. This study aims to determine the effect of nonionic surfactants by varying the Nonidet RK-18’ (nonionic surfactant) volumes, emulsion stirring speed and dispersion stirring time on the microsphere size distribution.

2. Materials and methods
Table 1. The variations were used for prepared microsphere using 10 % polyblend solution

| Composition formulation | Variations |
|-------------------------|------------|
|                         | Volumes of Surfactant (mL) | Stirring Speed (rpm) | Dispersion Stirring Time (min) |
| 60 PLA : 40 PCL        | 1.0         | 700             | 30           |
|                        | 1.5         | 800             | 90           |
|                        | 2.0         | 900             | 120          |
|                        | 2.5         |                 |              |

2.1. Materials

Lactic acid (90 %) and dichloromethane from Merck, polycaprolactone Perstop CAPA-6800, and Nonidet RK-18 were obtained from Evonik Indonesia: Specialty chemicals.

2.2. Synthesis of poly(lactic acid)(PLA)

50 mL of lactic acid was added into 250 mL glass reactor equipped with a mechanical stirrer and thermometer [11]. The reactor was heated in an oil bath until the temperature reached 120 °C and was made it constant for 1 hour. The reaction was continued at 150 °C for 22 hours under the flow of nitrogen gas. After 22 h, the sample was cooled and characterized by Fourier Transform Infrared (FTIR) Shimadzu Prestige-21 spectrometer.

2.3. Preparation of 10 % polyblend solution

The PLA and PCL blend were prepared with the ratio of 60:40 (w/w). The polymers were blended in dichloromethane and stirred for 15 min to obtain the 10 % polyblend solutions [12].

2.4. Various Paratermeters in preparation of microsphere

Microspheres were prepared using water in oil (w/o) emulsion solvent evaporation method. 5 mL of 10 % polyblend solution was emulsified in 2 mL surfactant and 1 mL distilled water with stirring speed of 700 rpm for 1 hour. Furthermore, the organic phase was dispersed into 300 mL of the aqueous phase and stirred at 900 rpm for 1 h to completely evaporate dichloromethane. The produced microspheres were filtrated with distilled water and dried in an oven [13]. Variations of nonionic surfactant are listed in table 1. The particle size distribution and appearance of the produced microspheres were determined by an optical microscope (OM) and particle size analyzer (PSA). The functional groups of microspheres were analyzed by FTIR.

3. Results and discussion

Microsphere was prepared by using single water in oil (w/o) emulsion the solvent evaporation method. Initially, the aqueous external phase was added with organic phase and emulsified [13]. The organic phase employed in the research is dichloromethane, because it has a low boiling point at 39 °C [12]. This study utilized Nonidet RK-18 as the surfactant to stabilize the emulsion. Nonidet RK-18 is a low foaming surfactant with high emulsification properties and has a HLB value of 6.

3.1. Characterization by FTIR

Poly(lactic acid) was synthesized through the direct polycondensation of lactic acid under vacuum without catalyst using nitrogen gases. Analysis of FTIR aims to determine the functional group of PLA [12]. Figure 1 shows the FTIR spectrum of the PLA obtained from synthesis that C=O bond was visible at 1758 cm⁻¹ which resembles the characteristic of carbonyl ester, 1992 cm⁻¹ is characteristic of C-O bond and at 2996 cm⁻¹ which shows the existence of C-H sp. The result of PLA spectrum was compared with the LA spectrum obtained from the previous research [14]. The formation of poly(lactic acid) was characterized by the band shift at 1730 to 1758 cm⁻¹ show exist C=O stretch in the carboxylic acid to ester.

The purpose of FTIR analysis is to investigate and match the functional group of the polyblend’s constituent components [12]. According to figure 1, the C=O, C–O–C, and C–C peaks were clearly observed at 1754, 1175 and 1200 cm⁻¹ respectively, in the IR spectra of PLA and PCL [14]. Based on the analysis of functional groups, the PLA and PCL spectra reappeared in the microspheres spectra. It shows that the functional groups of polyblend as microspheres were the combination of their constituent components. There was a physical interaction between PLA and PCL because there were no new peaks [12].
3.2. Particle size distribution of microsphere prepared with variation of nonionic surfactant volumes

The distribution of microspheres particle size was performed by varying the nonionic surfactant volumes at 1.0 mL, 1.5 mL, 2.0 mL, and 2.5 mL. Figure 2 and figure 3 shows that the increase of surfactant volumes will affect the stability of emulsion and resulted in smaller particle size with uniform size distribution [15]. The addition of surfactant will reduce the continuous phase surface and will make the diffusion layer thicker around the microdroplet, intended to prevent the coalescence [16,17]. This phenomenon can be seen in figure 2 and figure 3, nonionic surfactant volumes of 1.0 mL and 1.5 mL resulted in the size distribution of formed microspheres at 37.97 μm, and 34.58 μm. When 2.0 mL nonionic surfactant was added, the uniform size distribution of the formed microspheres was observed at 31.50 μm. However, the use of nonionic surfactant volumes of 2.5 mL revealed that the distribution was not uniform. The size of the formed microsphere is depended on the size and the stability of the emulsion droplets [18].

3.3. Particle size distribution of microsphere prepared with variation of emulsion stirring speed

The emulsion stirring speed was varied to determine the effect of nonionic surfactant on microsphere particle size distribution. As shown in figure 4 and figure 5, the particle size distribution decreases with an increase in stirring speed [15]. The lower stirring speed will produce larger size microspheres. While at low stirring speed 700 rpm the particle size distribution was obtained at 37.97 μm. As the stirring speed is increased to 800 rpm, the particle size distribution is reduced to 34.58 μm. A further increase in the stirring speed to 900 rpm formed particle size distribution with a uniform size distribution at 31.50 μm. The high stirring speed of emulsion can easily break down the emulsion into small droplets where there is a high impact between the stirrer and emulsion droplets [19].
Figure 3. Variation of nonionic surfactant volumes - Optical Microscope (6.75 ×) 
(a) 1.0 mL, (b) 1.5 mL, (c) 2.0 mL and (d) 2.5 mL

Figure 4. Variation of emulsion stirring speed - particle size analysis of microsphere

Figure 5. Variation of emulsion stirring speed (a) 700 rpm, (b) 800 rpm and (c) 900 rpm 
Particle Size - Optical Microscope (6.75 ×)
Figure 6. Variation of dispersion stirring time - particle size analysis of microsphere

Figure 7. Variation of dispersion stirring time (a) 30 min, (b) 90 min, and (c) 120 min
Particle Size - Optical Microscope (6.75 x)

3.4. Particle size distribution of microsphere prepared with variation of dispersion stirring speed
Dispersion stirring time will affect the particle size distribution of microspheres as well. Longer stirring time will produce a collision between the particles, resulting in a smoother dispersion. In addition, stirring time will determine whether the dichloromethane has completely evaporated or not. The result from figure 6 and figure 7 showed that the uniform size distribution at 34.58 μm was observed in the microspheres, which formed during the dispersion stirring time at 90 minutes. Whereas, the sample with 30 minutes and 120 minutes resulted the size distribution of the formed microsphere at 28.70 μm and 37.97 μm, respectively.

4. Conclusions
Microspheres of polyblend PLA and PCL with nonionic surfactants have been successfully carried out by a solvent evaporation method. The interaction occurs between PLA and PCL in polyblend of microspheres was a physical interaction based on the FTIR spectra. In this research, the effect of nonionic surfactant on the particle size distribution was found to be decreased with the increasing volume, stirring speed and dispersion stirring time. The variation of nonionic surfactant volumes, emulsion stirring speed and dispersion stirring speed resulted in the size of microspheres with a uniform distribution at 31.50 μm with a volume of 2.0 mL, 31.50 μm with the stirring speed at 900 rpm and dispersion stirring time at of 90 minutes at 34.58 μm.

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