Effect of Nonidet SF-5 as surfactant in preparation of microspheres based on polyblend of poly(lactic acid) and polycaprolactone

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Abstract. Microspheres of biodegradable polymers have been widely investigated in delivery system for bioactive compounds. In this study, microspheres were prepared from polyblend of poly(lactic acid) and polycaprolactone using water-in-oil (w/o) emulsion solvent evaporation method with Nonidet SF-5 as surfactant. The effect of Nonidet SF-5 on the size of microsphere and its distribution was studied by varying the volume of surfactant (1, 1.5, and 2) mL. Additional variations such as emulsion stirring speed (700, 800, and 900) rpm and dispersion stirring time (0.5, 1, 1.5, and 2) h were also conducted. Microspheres were characterized using Particle Size Analyzer (PSA), Fourier Transform Infrared (FTIR), and optical microscope. The results showed that the addition of surfactant volume decreased the microspheres size from 34.58 µm to 28.70 µm and the most uniform microspheres size was obtained at 1 mL of Nonidet SF-5. While the microspheres that produced through variation of emulsion stirring speed showed the same size, that was 31.50 µm and the most uniform microspheres size was obtained at 800 rpm. Moreover, the increasing in dispersion stirring time also decrease the microspheres size from 31.50 µm to 19.76 µm, but it did not affect the microspheres size distribution.

Keywords: microspheres, poly(lactic acid), polycaprolactone, Nonidet SF-5, solvent evaporation method

1. Introduction
The rapid advancement in modern drug delivery system was begun with the use of biodegradable polymers as carriers to obtain a therapeutic effect by a simultaneous release of the drug within a certain period of time and appropriate dosage. Controlled drugs release has been widely developed which is capable of controlling the rate of release of drugs, maintaining the duration of therapeutic activity or targeting drug delivery to tissues [1]. Poly(lactic acid) (PLA) and poly(e-caprolactone) (PCL) are biodegradable polymers that are widely used in biomedical applications because they have good biodegradability and biocompatibility. In general, PLA presents good mechanical properties and high modulus strength, but the degree of its fragility is also high. Various ways to resolve the physical properties limitations of PLA have been investigated, one of which is mixing or blending [2]. The toughness properties of PLA can be improved by blending it with PCL [3]. PCL possesses a high crystallinity property, still with a low degradation rate. Poly(lactic acid) in the form of D, L-PLA is degraded more quickly than PCL [4]. Therefore, the development of drug delivery system based on the blend of PCL and PLA is presumed to generate a suitable polymer with a higher speed degradation rate and preferable permeability to improve the controlled release of drugs [5].

Microspheres of biodegradable polymers are one of the biomedical applications that have been widely investigated in delivery systems for bioactive compounds such as drugs. Microsphere is tiny...
spherical particle in the diameter size ranges from 1–1000 µm [6]. Kemala et al. [6] reported that the concentration and volume of PVA (an emulsifier) affected the size of microspheres that were synthesized from the blend of PLA and PCL by a modified (o/w) emulsion solvent evaporation method. In another study by Zhou et al. [7] microspheres of PLA and PCL were prepared by a modified double emulsion method using PVA as an emulsifier. The formed microspheres presented spheres contains small holes on the surface and a spongy porous inner structure [7]. In this study, microspheres were prepared from blend of PLA and PCL by a modification in water-in-oil (w/o) emulsion solvent evaporation method to see the effect of Nonidet SF-5 as surfactant on microspheres size and its distribution. Nonidet SF-5 is a nonionic surfactant with low foaming, which enhanced emulsification properties. Low foaming surfactant can be an alternative in microspheres production. In the process of emulsion, stirring with high-speed makes more air will enter into the emulsion and form foam which can disrupt the formation of microspheres and affect the size of the microsphere [6,8]. The size of microspheres and its distribution is one of the important factors that affect the process of drug delivery system. The uniform size of microspheres will provide good dissolution rates and efficiency of drug encapsulation [6].

2. Materials and methods

2.1. Materials

S-lactic acid (90%) was used as monomer which was purchased from Merck. Polycaprolactone was purchased from Perstop CAPA-6800. Distilled water (aquades) was purchased from PT. Brataco. Nonidet SF-5 was obtained from Evonik Indonesia, and dichloromethane was purchased from Merck.

2.2. Synthesis of poly(lactic acid)

Synthesis of PLA was performed by a modified direct polycondensation without a catalyst, initiator, or solvent [9]. 50 mL of lactic acid (LA) was poured into the three-neck flask and then put it in the reactor. LA was stirred and heated on the hotplate until the temperature of 120 °C, and the temperature was kept constant for 1 h. In this step, the nitrogen gas was flowed to the system. Furthermore, the temperature system was increased to 150 °C and maintained for 22 h. The nitrogen gas was continuously flowed to keep the system free of oxygen until the formed PLA was taken out from the reactor. After 22 h, the heating process was stopped, but the formed PLA was still stirred for 2 h. The formed PLA was cooled for 24 h at room temperature.

2.3. Preparation of 10% (w/v) polyblend solution

The polyblend of PLA and PCL was made from the composition of 60:40 (PLA:PCL) with the blend weight of 0.5 g. The polymers were mixed in dichloromethane (DCM) and stirred with a magnetic stirrer until completely dissolved to obtain the 10% (w/v) polyblend solution [6].

2.4. Variations in preparation of microspheres

Microspheres were made by using a modified w/o emulsion solvent evaporation method [6]. In the preparation of microspheres, three variations were used to see their effect on microspheres size and its distribution, i.e. variations of surfactant volume, emulsion stirring speed, and dispersion stirring time. First, 5 mL of 10% polyblend solution was emulsified in 1 mL of distilled water and 1.5 mL of Nonidet SF-5. The solution was stirred at 700 rpm for 1 h. The emulsion was then dispersed in 350 mL of distilled water and stirred at 900 rpm for 1 h to evaporate DCM. The formed microspheres were filtrated, washed with distilled water, and dried in the oven at 40 °C for 24 h. The variations that were used in this study are listed in table 1.

| Volume of Nonidet SF-5 (mL) | Emulsion stirring speed (rpm) | Dispersion stirring time (h) |
|-----------------------------|-----------------------------|----------------------------|
| 1                           | 700                          | 0.5                        |
| 1.5                         | 800                          | 1                          |
| 2                           | 900                          | 1.5                        |

Table 1. The three variations in preparation of microspheres.
Characterization of PLA and microspheres

The functional groups of PLA and microspheres were analyzed using Fourier Transform Infrared (FTIR) Shimadzu Prestige-21 spectrophotometer. The size of microspheres produced from each formula, as well as its distribution, were measured using Particle Size Analyzer (PSA) LS-100 Shimadzu. The microspheres shape and appearance were observed by optical microscope at 13.5x magnification.

Results and discussion

3.1. Synthesis of poly(lactic acid)

Synthesis of poly(lactic acid) has been successfully performed using a modified direct polycondensation method without a catalyst, initiator, or solvent. Figure 1 shows the schematic representation of PLA synthesis. The uncatalyzed direct polycondensation method is a simple method, but does not produce high molecular weight PLA (Mw <10000) [9]. The state of the system is made oxygen-free by flowing the nitrogen gas during the polymerization process. The flow of nitrogen gas can eliminate the oxygen gas contained in the system. Oxygen may oxidize the reagent (lactic acid), which causes the color of poly(lactic acid) turns to dark brown. The color change of PLA indicates that the formed PLA has damaged.

The FTIR spectrum of PLA synthesized is shown in figure 2a. IR spectrum of PLA showed characteristic absorption peaks of C-H sp stretching at 2996 cm⁻¹, C=O carbonyl at 1756 cm⁻¹, and C-O ester at 1192 cm⁻¹. The results indicated that the functional groups of formed PLA are in accordance with the results of previous research by Choksi and Desai [10]. They characterized the PLA that was synthesized from lactic acid by polyesterification process, which showed the absorption peaks of CH sp, C=O, and C-O at 2988.70, 1716.98, and 1119.50 cm⁻¹ in IR spectra, respectively.
3.2. Variations in preparation of microspheres
Microspheres were made by a modified w/o emulsion solvent evaporation method. PLA and PCL were dissolved in a volatile organic solvent (dichloromethane). The solution is then emulsified in other solvent to form droplets and dispersed in continuous phase to precipitate microparticles called microspheres [6]. The emulsion is not a stable system thermodynamically because of the unfavorable interactions between hydrophobic and hydrophilic molecules in the interface [11]. Nonidet SF-5 was applied to stabilize the emulsion between the organic and water phase to prevent coalescence of the droplet, which later can damage the formation of microspheres.

The functional groups of microspheres were characterized by FTIR spectrophotometer to see the interaction between PLA and PCL in microsphere. Poly(lactic acid) and polycaprolactone are aliphatic polyesters with identical structures. The C=O, C-O-C, and C-C peaks are obviously shown at (1754, 1175, and 1200) cm⁻¹ in the IR spectra [12]. The IR spectrum of microspheres is shown in figure 2b. Gokalp et al. [13] have been successfully synthesized PCL through ring opening polymerization. IR spectra of PCL in their results revealed the same absorption peaks (CH sp³, C=O, and C-O at (2945.32, 1720.78, and 1238.73) cm⁻¹, respectively) as PLA. The microspheres spectrum was also compared with PCL spectrum from the result of their research. The results showed that the C-H sp³, C=O, and C-O peaks in PLA and PCL spectra reappeared on the microsphere spectrum at (2933, 1756, and 1192) cm⁻¹, respectively, and there were no new absorption peaks on it. Thus, it indicates that the functional groups in the microspheres are a combination of constituent components of PLA and PCL, so it can be concluded that the interaction of PLA and PCL in microspheres is physical interaction.

3.2.1. Volume of Nonidet SF-5. Microspheres size and its distribution that have been measured from the variations of Nonidet SF-5 volume can be seen in figure 3a. The result indicated that the addition of Nonidet SF-5 volume affected the microspheres size and its distribution. The microspheres size of 34.58 µm, 31.50 µm, and 28.70 µm was obtained at 1 mL, 1.5 mL, and 2 mL of Nonidet SF-5, respectively. The addition of surfactant volume decreased the microspheres size. It may be caused by the formed droplet on the emulsion process becomes smaller along with the addition of surfactant volume. The broader size distribution concomitant the addition of Nonidet SF-5 volume was also observed in the PSA graph. The excessive volume of Nonidet SF-5 can cause the microspheres to become more brittle, so it will decrease the stability of the formed microspheres and affect the size distribution. The most uniform microspheres size was obtained from the formula that used 1 mL of Nonidet SF-5.

Figure 3. The results of Nonidet SF-5 volume variation (a) The PSA graph of microspheres diameter size and its distribution. Optical microscope images of microspheres (b) 1 mL, (c) 1.5 mL, (d) 2 mL. (13.5x).
3.2.2. Emulsion stirring speed. Microspheres size and its distribution that have been measured from experiments with variations of emulsion stirring speed can be seen in figure 4a. The results indicated that the increased emulsion stirring speed did not affect the size of microspheres but affected the size distribution. It can be caused by the range of stirring speed is too near, so it does not affect the formation of droplet and the size of microspheres. The same microspheres size of 31.50 µm was obtained at 700 rpm, 800 rpm, and 900 rpm. The size distribution of microspheres at 800 rpm and 900 rpm did not differ significantly. But, if it was compared with the size distribution of microspheres at 700 rpm, the increase emulsion stirring speed produced more uniform sized microspheres. The most uniform microspheres size was obtained at 800 rpm.

Optical microscope images for variation of Nonidet SF-5 surfactant volume can be seen in figure 4b and figure 4c. The results showed there were no significant differences in the shape and appearance of the microsphere surface between the speed variations of 800 rpm and 900 rpm. However, when it was compared with the optical microscope results for emulsion stirring speed of 700 rpm in figure 3c, the increase emulsion stirring speed produced microspheres with coarser surface.

3.2.3. Dispersion stirring time. The variation of dispersion stirring time was used to see the effect of solvent evaporation time on the size of microspheres during the solidification process. The size of microspheres and its distribution from the experiment with variations of dispersion stirring time can be seen in figure 5a. The results indicated that the increased dispersion stirring time affected the microspheres size, but it did not affect the size distribution. The microspheres size of 31.50 µm, 31.50 µm, 23.81 µm, and 19.76 µm was obtained at 0.5 h, 1 h, 1.5 h and 2 h, respectively. The decrease in the size of the microspheres by increasing the dispersion time can be due to the droplet contact time with the continuous phase and dichloromethane diffusion rate to evaporate into the atmosphere. The longer the droplet is in the continuous phase; the solvent evaporation is more completed so that the size of the microsphere is getting smaller. Optical microscope images for variation of dispersion stirring time can be seen in figure 5b, figure 5c, and figure 5d. The results showed that the microspheres were not perfectly formed and had a rough surface obtained at 0.5 h. Meanwhile, the surface of the microsphere at the dispersion stirring time of 1.5 h was noticeably smoother than at the dispersion stirring time of 0.5 h. While at dispersion stirring time of 2 h, the surface of the microspheres became rougher and more perforated compared to the dispersion stirring time of 1.5 h. The duration of the diffusion contact with the droplet affects the microsphere solidification process in
the continuous phase. When the droplets are in continuous phase in less time, the microsphere solidification process is incomplete and the solvent residue still entrapped in the droplet [14]. Whereas, if the contact time of the continuous phase with microspheres and the stirring time of dispersions are too long, it can cause the microsphere to become more brittle and easily damaged so that holes and rough surfaces formed on the microspheres.

4. Conclusions
Poly(lactic acid) has been successfully synthesized using a modified direct polycondensation method. The microspheres were formed based on polyblend of PLA and PCL with physical interaction therein. The FTIR spectrum of microspheres showed that the functional groups in the microspheres are a combination of constituent components of PLA and PCL. The results of variations in preparation of microspheres showed that the volume of Nonidet SF-5 (a surfactant) affected the microspheres size, size distribution, and structure of the microspheres surface. The most uniform microspheres size was generated from the formula that used 1 mL of Nonidet SF-5. The stirring speed of emulsion affected the size distribution and structure of the microspheres surface. The most uniform microspheres size was obtained at 800 rpm. The stirring time of the dispersion affected the size and structure of the microspheres surface.

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