The effect of sorbitan monooleate as surfactant in preparation of polyblend polylactic acid and polycaprolactone microspheres

A N Ryofi and E Budianto
Department of Chemistry, Faculty of Mathematics and Natural Sciences (FMIPA), Universitas Indonesia, Kampus UI Depok, Depok 16424, Indonesia

Corresponding author’s e-mail: emilb@ui.ac.id

Abstract. Polyblend of polylactic acid (PLA) and polycaprolactone (PCL) microspheres with polymodal size distribution were synthesized through an emulsification-solvent evaporation method in water-in-oil (W/O) emulsions. Sorbitan monooleate was used as emulsion stabilizer and size controller in preparation of the microspheres. The effect of sorbitan monooleate addition in preparation on the size of the microspheres was studied by varying the volumes of sorbitan monooleate, the stirring speeds of emulsion formation, and dispersion times. The microspheres were characterized using Fourier Transform Infrared (FT-IR) and Particle Size Analyzer (PSA). The results show that there is no chemical interaction between PLA and PCL. This phenomenon can be seen from the FT-IR spectrum, which shows both PLA and PCL component. The particle size of microspheres decreased with the increasing volume of surfactant, emulsion stirring speed, and dispersion time. The size of microspheres obtained ranges from 0.4 µm to 10 µm. Physical forms of microspheres were observed using optical microscope. The result shows that some microspheres are spherical and others are in aggregates form.

Keywords: solvent evaporation, polyblend, polylactic acid, polycaprolactone, sorbitan monooleate

1. Introduction
Microspheres are very important in drug delivery system due to their tiny size as well as other superior characteristics. Microspheres are well-known as a perfect solution to formalize a potent dose for a drug control release simulation [1]. Microsphere is a term used for small spherical particles with diameter 1–1000 µm [2]. Microspheres are typically free flowing solid powders, which consist of proteins or synthetic polymer, known to be biodegradable in nature and can be delivered by several routes like oral, parenteral, nasal, ophthalmic, transdermal, colonial etc. [3].

Polylactic acid (PLA), originating from lactic acid and polycaprolactone (PCL) has biocompatibility and biodegradability characteristics and are excellent materials to use in the medical sciences [4]. PLA is aliphatic polyester, thermoplastic, hydrophobic, and has been used in medical application such as cell transplantation scaffold and PCL has been applied in drug delivery system due to its great permeability property [5,6]. PCL holds a high crystallinity characteristic; yet, its degradation rate is low [7]. D,L-PLA forms of PLA experience a more rapid degradation rate compared to PCL, however, it carries a 3-5% lower strain compared to PCL, thus PLA is more brittle than PCL [8].

The PCL mixture together with other polymers with lower molecular weight can be applied in the numbers of application, namely, polymer modification for drug delivery system [2]. The PCL mixture and PLA are counted to generate a suitable polymer with a more rapid degradation rate and better permeability. The application of this biodegradable polymer offers many benefits, since it can be...
conveniently absorbed by the body once the hydrolysis process is completed, hence, will not cause any poisoning in the body [9].

The requirements of microspheres for drug delivery systems must have a size not greater than 250 μm [2]. The size of the microsphere is the main determinant of the rate of drug release [10]. Thus, the rate and drug release duration depends on the surface area, thickness of the walls, and pores of the drug introducing microspheres, so that the size distribution of microspheres is a significant aspect in the microspheres characterization. In addition, particle size is vital parameter in the drug dosage preparation form, such as oral, parenteral and others [11]. By changing the size to be simpler it enables the localization of microspheres to specific organs or tissues. Microspheres that have a size in the range of 40-50 μm will produce efficiency of around 70-90% so that a uniform microsphere size will increase the efficiency and rate of drug release [12].

Recently, many researchers have investigated the preparation of microspheres with various surfactants. However, there have been few reports on research on the control of polyblend PLA-PCL microsphere size [13] using a non-ionic hydrophobic surfactant, so in this study, the preparation of the blend of polylactic acid and polycaprolactone microspheres with sorbitan monooleate as surfactants has been studied by the method of water-in-oil (w/o) emulsion solvent evaporation. The use of sorbitan monooleate as an emulsion stabilizer was selected because sorbitan monooleate has biocompatibility properties and has been used in biomedical applications, oral drug pharmaceutical formulations, and food industries. In addition, the sorbitan monooleate acts as a microsphere size controller with a uniform size distribution. The effect of sorbitan monooleate in the control of size in the formation of microspheres is studied through variations in volume sorbitan monooleate, stirring speeds of emulsion formation, and dispersion times. The size distribution is affected by the agitation process throughout the emulsion process in the w/o system [12–14].

2. Materials and methods

2.1. Materials
Lactic acid (90%) and dichloromethane were purchased from Merck, while polycaprolactone was purchased from Pestorp CAPA-6800, and sorbitan monooleate was purchased from Evonic with the commercial name is span 80.

2.2. Synthesis of polylactic acid
The reaction was performed in a 250 mL, three-necked flask reactor completed with a magnetic stirrer, thermometer, and a water-cooling condenser. A volume of 50 mL lactic acid was added in to the reactor. The temperature was gradually increased to 120 °C and kept constant for 1 hour. During the reaction, the solution was stirred continuously. After that, the reactor was flowed with nitrogen gas for 15 min. At the same time, the temperature was raised up to 150 °C and kept at constant temperature for 22 h. After the reaction finished, it was cooled down at room temperature for 2 h, while stirring. White-yellow sticky solids were obtained.

2.3. Preparation of 10% polyblend solutions
The amount of 0.5 g polyblend of PLA and PCL with 60:40 ratio was prepared. The polymers were perfectly mixed in dichloromethane and stirred for 30 min to acquire the 10% polyblend solution.

2.4. Preparation of microspheres
5mL 10% polyblend solution and sorbitan monooleate with different volumes were added as an emulsifier; this was stirred at 700 rpm for 1 h. The emulsion product was then dispersed in 250 mL distilled water, and stirred (900 rpm) for 1 h. At the same time, in dispersion phase was occurred evaporation of dichloromethane. The produced microsphere was obtained by filtration, cleaned with distilled water, and dried in an oven at temperature maximum 40 °C or at room temperature. The particle size of the microspheres products generated from each formula were studied by Particle Size Analyzer (PSA), optical microscope and the microspheres’ functional group was analyzed by Fourier Transform Infrared (FT-IR). Details of the various preparation conditions are described below.

3. Results and discussion
In this study, polylactic acid was obtained with direct polycondensation without catalyst and solvent. In this reaction lactic acid acts as self-catalyzed polymerization. Without exogenous strong acid, the
The lactic acid dehydrative polycondensation is promoted by self-catalysis from carbonyl group, the condensation progress declined as the number of carboxylic group in the lactic acid decreased in the polycondensation reaction [16,17].

3.1. Characterization of poly(lactic acid)

Figure 1a shows FT-IR spectra of lactic acid and poly(lactic acid) synthesized at 150 °C for 22 h. In Figure 1a IR spectra of PLA presented absorption peaks characteristic of ester (1759 cm⁻¹ and 1191 cm⁻¹ for –COO– and C–O–C respectively) and CH₃ groups (2996 cm⁻¹). According to Laonuad et al. [18] as lactic acid was polymerized, the hydroxyl group will react with carboxylic group from another molecule, therefore the broad –OH stretch peak at 3428 cm⁻¹ assigned for PLA will be reduced. The hydroxyl absorption peak (in case of PLA) is almost vanished, suggesting that the amount of hydroxyl groups was decreased and the sharper absorption peak of C=O stretching (1759 cm⁻¹) was presented as the polymer was continuously synthesized.

3.2. Characterization polyblend of PLA-PCL by FT-IR

FT-IR spectroscopy was used to ensure that no chemical interaction between the polymers had occurred. From the inspection of FT-IR spectra of blend of PLA and PCL in Figure 1b, it showed a characteristic of ester group (C=O) at 1758 cm⁻¹ with stretching vibration and C–O–C at 1189 cm⁻¹. The C–H stretching of methyl occurs in the 2947 cm⁻¹ region. According to Jung et al. [19] polycaprolactone has ester carbonyl group at 1729 cm⁻¹ with stretching vibration and C–O–C at 1185 cm⁻¹. The FT-IR spectrum corresponds to microspheres formulation was almost identical to polymer spectra. The interaction between PLA and PCL is only physical interaction [2]. The proposed physics interaction is the van der Waals force that resulted from the presence of momentary dipoles or London forces in non-polar molecules of PLA and PCL.

3.3. Effect of emulsifier volume on the size of the PLA and PCL microspheres

For this experiment, the volume of sorbitan monooleate was varied from 0.5 to 1.5 mL, the W/O ratio was 1:5, the emulsion stirring speed was 700 rpm for 1 h, and the stirring time of dispersion was 900 rpm for 1 h. Figure 2 shows the effect of emulsifier volume on the size of the PLA and PCL microspheres. Bimodal size distributions are obtained and can be seen in table 1. The results indicated
Table 1. Blend of PLA-PCL microsphere size distribution obtained with different variations

| Variations                      | Microsphere size distribution (μm) |
|---------------------------------|-------------------------------------|
|                                 | 1        | 2          | 3          |
| Volumes of sorbitan monooleate  |          |            |            |
| (mL) 0.5                        | 0.393-0.755 | 1.748-2.787 |
| 1.0                             | 0.393-0.829 | 1.748-3.358 |
| 1.5                             | 0.393-0.755 | 1.748-2.539 |
| Stirring speeds of emulsion     |          |            |            |
| (rpm) 700                       | 0.393-0.755 | 1.748-2.787 |
| 800                             | 0.393-0.910 | 1.451-3.059 |
| 900                             | 0.393-0.829 | 1.321-2.539 |
| Dispersion times (hour)         |          |            |            |
| 0.5                             | 0.393-1.592 | 1.748-4.443 | 4.877-7.370 |
| 1.5                             | 0.393-1.592 | 1.748-4.877 | 5.354-10.290|
| 2.0                             | 0.393-0.829 | 1.592-2.787 |

Figure 2. (a) Size distribution of PLA and PCL microspheres of variation of volume surfactant and optical microscope images (11.25×) of microspheres with volume of sorbitan monooleate: (b) 0.5, (c) 1 and (d) 1.5 mL.

that as the volume of the emulsifier increased, the average size decreased. This can be explained on the basis that the primary function of the emulsifier in stabilization of droplets is to generate a thin film around the droplets to avoid their coalescence. Emulsifier is one of the critical aspects that can influence the microspheres’ particle size and its shape. Emulsifier can reduce the interfacial tension of W/O in order to produce a smaller and more stable droplets in the dispersed phase. So, when the emulsifier (sorbitan monooleate) volume was increased from 0.5 mL to 1.5 mL, the size of the microspheres decreased from 1.128 μm to 0.764 μm.
Figure 3. (a) Size distribution of microspheres with different emulsion stirring speed and optical microscope images (11.25×) of microspheres with emulsion stirring speed of: (b) 700, (c) 800 and (d) 900 rpm.

The formation of a non-uniform particle size can be caused by the properties of sorbitan monooleate, which has a cloud point far below room temperature. The non-ionic surfactant’s solubility decreases as the temperatures increases, and these surfactants are probably start to lose the surface-active properties at a higher transition temperature – known as cloud point [20]. This phenomenon takes place due to at a higher temperature of the cloud point, the surfactant-rich phase of the swollen micelles will be separated and transition can be observed by the increase of dispersion turbidity. The system consists of an almost micelle-free dilute solution and a surfactant-rich micellar phase [20,21]. This separation is due to a significant increase in aggregation amount and a decrease in intermicellar repulsions [21,22] that generates a different density of the micelle-rich and micelle-poor phases so that the more surfactant volume added the more agglomeration formed and the solution looks more turbid.

3.4. Effect of emulsion stirring speed on the size of the PLA and PCL microspheres

Variations of emulsion stirring speeds were performed at speeds of 800 and 900 rpm. Other conditions were made constant (0.5 mL volume of sorbitan monooleate, 1 h emulsion stirring time, and dispersion stirring speed 900 rpm for 1 h). The emulsion stage is the step that determines the size of the microsphere because at this stage droplet formation will occur which will become solid microspheres.

The effect of stirring speed of emulsion formation on the size of the PLA-PCL microsphere has been characterized using PSA and can be seen in figure 3a. The result data of the variation was compared with the initial stirring speed of emulsion (700 rpm). Based on figure 3a, bimodal size distributions were obtained. There are two main size groups of microspheres. The details size distribution can be seen at table 1.
Figure 4. (a) Size distribution of microspheres with different stirring time dispersion and optical microscope images (11.25×) of microspheres with stirring time of dispersion of: (b) 0.5, (c) 1.5 and (d) 2 hours.

The average size of the microspheres at a variation in stirring speed of 800 rpm is 1.178 μm and the stirring speed of 900 rpm is 0.839 μm. On the other hand, sample with a speed of 700 rpm has an average size of 1.128 μm. At a speed of 700 rpm it appears that the distribution size is smaller than the speed of 800 rpm so that the average size becomes smaller. The effect of variations in the speed of the emulsion stirring on the average size of the microspheres shows that as the emulsion-stirring rate increases (800 rpm and 900 rpm) the resulting microsphere size becomes smaller. The decrease in the average size of the microsphere is due to an increase in stirring rate, the energy applied to the water phase increases, and the collision increases so that it can break the droplet into smaller droplets. In addition, droplets that are not easily to be flocculated or precipitated are supported in the presence of strong stirring centrifugal forces resulting in smaller microspheres. Whereas, with slower stirring the force applied to the water phase is less so that the microspheres are divided into droplets and some aggregates [10]. Droplets can join one another and obtained agglomeration.

3.5. Effect of dispersion time on the size of the PLA and PCL microspheres

With the other parameters is kept at constant (sorbitan monooleate volume 0.5 mL, emulsion stirring speed 700 rpm for 1 h, varying of stirring time of dispersion on (0.5, 1.5 and 2 h) stirring speed of dispersion 900 rpm, and the ratio of W/O 1:5), the effect of stirring time of dispersion on size of the PLA and PCL microspheres was studied. As shown in table 1 and figure 4a, bimodal and polymodal size distributions are obtained. Based on figure 4, the average size seemed as the dispersion time increased, the average size decreased. Stirring time of dispersion for 0.5 to 2 hours obtained the size of PLA and PCL microspheres 2.233, 1.918, and 1.045 μm respectively.

The reason is unclear but may be related to the dispersion step there is evaporation of solvent from droplet to continuous phase, then from continuous phase to free air [23]. A decrease in the average size of the microspheres may occur as the longer contact time between the droplets and the continuous phase allows the more complete solvent evaporation of the droplets diffusing into the continuous phase.
phase and the deposition of droplets into solid microspheres is also better so that the resulting average microsphere size is smaller. However, when droplets are in continuous phase in a short time, the solidification of the microspheres is yet to be perfect, and the residual solvent is constantly present in the droplets [24].

4. Conclusions
Polyblend of polylactic acid and polycaprolactone microspheres with sorbitan monoooleate as surfactant were successfully synthesized. There is no chemical interaction between blend of PLA and PCL, its only physical interaction. The FT-IR spectra of polyblend of PLA and PCL are combinations of PLA and PCL. The effect of sorbitan monoooleate as surfactant on the size of microspheres by increasing the amount of surfactant volume, the stirring speed of emulsion formation, dispersion time of PLA and PCL, its only physical interaction. The size of microspheres obtained in range from 0.4 μm to 10 μm. Physical form of microspheres was observed using optical microscope. The result shows that some microspheres are spherical and others in aggregates form.

Acknowledgements
The authors would like to thank Universitas Indonesia for funding this research through PITTA Grant Universitas Indonesia with contract No:233/UN2.R3.1/PPM.00/2018.

References
[1] Sharma N, Purwar N and Gupta P C 2015 International Journal of Pharmaceutical Sciences and Research (IJPISR) 6 4579–87
[2] Ramteke K H, JadHAV V B and Dhoke S N 2012 IOSR Journal of Pharmacy (IOSRPHR) 2 44–8
[3] Kemala T, Budianto E and Soegiyono B 2012 Arab. J. Chem. 5 103–8
[4] Ramot Y, Haim-Zada M, Domb A J and Nyska A 2016 Adv. Drug Deliv. Rev. 107 153–62
[5] Thomson R C, Wake M C, Yaszemski M J and Mikos A G 1995 Biodegradable polymer scaffolds to regenerate organs Biopolymers II (Advances in Polymer Science vol 122) ed N A Peppas and R S Langer (Berlin: Springer) pp 245–74
[6] Pillai C K S and Sharma C P 2010 J. Biomat. Appl. 25 291–366
[7] Woodruff M A and HutmacHER D W 2010 Prog. Polym. Sci. 35 1217–56
[8] Porjazoska A, Karal-Yilmaz O, Kayaman-Apohan N, CvEtkovska M and Baysal B M 2004 Croat. Chem. Acta 77 545–51
[9] Gunatillake P A and Adhikari R 2003 Eur. Cell. Mater. 5 1–16
[10] Peng Z Y, Shen Y Q and Li Z P 2012 J. Macromol. Sci. B 51 12–21
[11] Sun R, Shi J, Guo Y and Chen L 2009 Front. Chem. Chin. 4 222–8
[12] Zhu K J, Li Y, Jiang H L, YAsuda H, Ichimaru A, Yamamoto K, Lecomte P and Jerome R 2005 J. Microencapsul. 22 25–36
[13] Achmad F, Yamane K, Quan S and Kokugan T 2009 Chem. Eng. J. 151 342–50
[14] Esposito E, Cortesi R and Nastruzzi C 1996 Biomaterials 17 2009–20
[15] BercHane N S, Jebrail F F, Carson K H, Rice-Ficht A C and Andrews M J 2006 J. Microencapsul. 23 539–52
[16] Odian G 2004 Principles of Polymerization 4+ ed (NewYork: John Wiley & Sons)
[17] Moon S I, Lee C W, Miyamoto M and Kimura Y 2000 J. Polym. Sci. A 38 1673–9
[18] Laonoud P, Chaiyut N and Ksapabur B 2010 Optoelectron. Adv. Mater. 4 1200–02
[19] Jung J W, Lee H, Hong J M, Park J H, Shim J H, Choi T H and Cho D W 2015 Biofabrication 7 045003
[20] SchramM L L, Stasiuk E N and Marangoni D G 2003 Annu. Rep. Prog. Chem. Sect. C 99 3–48
[21] Staples E J and TIDDy G J T 1978 J. Chem. Soc. Faraday Trans. I 74 2530–41
[22] TIDDy G J T 1980 Phys. Reports 57 1–46
[23] Li M, Rouaud O and Poncelet D 2008 Int. J. Pharm. 363 26–39
[24] Tiwari S and Verma P 2011 International Journal of Pharmacy and Life Science 2 998–1005