Effect of surfactant mixing in microspheres preparations using polyblend of poly(lactic acid) and polycaprolactone

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Abstract. Microencapsulation has an important role in the drug delivery system in the medical and pharmaceutical world. As an attempt to improve the therapeutic effect of the drug, microspheres materials are developed by optimizing the size of microspheres and their size distribution to be suitable for drug delivery applications. In this study, poly(lactic acid) and polycaprolactone polyblend with 60:40 (w/w) composition, have been used in the preparation of microspheres through the solvent evaporation (O/W) method using a mixed of common non-ionic surfactants, Tween 80 and Span 80 were used as emulsifier. The microspheres size distribution was observed at various compositions (60:40, 50:50, 40:60) and concentrations (0.5–2.5 % (v/v)) of Tween 80/Span 80. The resulting microspheres were round and have diameter distributed around 30.07 μm. Microspheres were also characterized by Fourier Transform Infrared (FTIR) and Particle Size Analyzer (PSA). The effect of mixing Tween 80 and Span 80 was shown in microspheres size formed, which was similar to the one of Tween 80 (0.375–43.67 μm) and larger than the one of Span 80 (0.375 - 0.791 μm). The distribution size of the resulting microspheres was slightly narrower than the one with the use of Tween 80. The microspheres physical appearances were observed by optical microscope (OM).

1. Introduction

Drug delivery system aims to release a treatment at specific desired anatomical location and to maintain drug concentration within therapeutic window as long as desired [1] and to optimize the therapeutic effects of the drugs, as well as minimizing the adverse effects if possible [2]. Polymer-based drugs delivery devices have been developed to provide a safe path for drugs to pass through the physiological areas that are not friendly inside the body. A controlled molecular structures polymer can be constructed to provide a well-defined response to external conditions [1]. The polymer biomaterials used were usually one single type of polymer or a polyblend, which deliberately blended to obtain the new material with combined superior properties of each polymer constituents, to be more suitable for the application [3].

One of polymer device applications such as microencapsulation, is a process when solids, liquids or gases are coated in the form of thin coating walls surrounding the substance to form microscopic particles called microspheres [4]. Solvent evaporation method is frequently used to encapsulate hydrophobic drugs in an oil-in-water emulsion (o/w) technique [5]. The polymer is dissolved in a soluble, volatile organic solvent. The resulting solution then emulsified into a large volume of water in the presence of a surfactant, followed by removal of solvent by evaporation, resulting in solid microspheres.

To produce small particle size microspheres, it is required the addition of surfactant to decrease the interfacial tension and reduce the coalition on droplets [6]. Mixing two or more different types of surfactants are designed to enhance the properties of the mixed-end products. Positive synergistic
The nature of mixed-end product is obtained from the interaction between two or more compatible surfactants which have better performance than those achieved by each component when used separately [7]. In most cases, combinations of commonly used surfactants consist of hydrophilic surfactant and lipophilic surfactant [7] are mixed between sorbitol ester (Span) and polyoxyethylene (POE) sorbitol ester (Tween). Due to the greater interaction of Tween with the water phase, the hydrophilic group in Tween extends further into the water than the unsubstituted ester with the polyoxyethylene chain in Span, and this is believed to allow the hydrophobic portion of the two surfactants to interact more closely with each other and with the interface layer than if it was used separately [8].

The aim of this paper is to study microspheres (blank microcapsules) prepared by solvent evaporation method, using polyblends of poly(lactic acid) and polycaprolactone with mixed of two non-ionic surfactants Tween 80 and Span 80 as emulsifier. And to study certain effect from using mentioned mixed surfactant to the microspheres size distribution and its polydispersity. The technical procedure in this study refers to what has been done by Elfrida [9] with modifications and adjustments in some parts.

2. Experimental

2.1. Synthesis of PLA.

PLA were synthesized from its monomer, lactic acid (LA) (Merck) by direct polycondensation method under nitrogen gas flow without adding catalysts, solvents, and initiator. Stirring was started by raising the starting material temperature to 120 °C. Then, continued by kept it constant for 1 h. After 1 h., the system was purged by nitrogen gas about 5–10 min and remained within nitrogen for the rest of the works. The temperature was further raised until reaches 150 °C, then, kept constant for 22 h. Afterwards the temperature was turned off but the system remained the same for approximately 2 h. Once the system temperature dropped, the PLA formed was transferred to the vapor plate and allowed to stand for 24 h until it is hardened [9].

2.2. Preparation of 10 % polyblend solution.

A 10 % polyblend solution was prepared by weighing 0.5 g of polyblend with 60:40 (w/w) composition of PLA and PCL (Perstorp CAPA-6800) [9]. Then, it was dissolved into 5 mL dichloromethane (Merck) [9] followed by additions of Span 80 (TEGO SMO V from PT. Evonic) with volume variation as presented in table 1 and table 2. Continued by stirring for 50 min at 500 rpm to obtain 10 % polyblend solution [10].

2.3. Preparation of Tween 80 solutions.

The Tween 80 solutions were made in various concentrations by dilutions of Tween 80 solution. 10 mL of Tween 80 solution was dissolved in 80 mL aquadest (PT. Demin Indonesia) followed by stirring using magnetic stirrer. The solution was then added into a measuring flask and diluted with the rest of aquadest until the volume reach exactly 100 mL. From the solution, it can be obtained Tween 80 solutions with v/v concentrations 0.5 %, 1.5 %, 2 % and 2.5 % through further dilutions [9].

2.4. Preparation of microspheres.

Microspheres were prepared in sets of various concentrations and various compositions. 5 mL of 10 % polyblend solution was added into Tween 80 solution with each concentration and volume as shown in table 1 and table 2. For the stirring emulsion stage, the new solution was stirred at 700 rpm for 1 h.

Table 1. The various concentrations of surfactant used in preparation of microspheres

| Mixed surfactants composition (v/v) | Tween 80 concentrations ((v/v) %) | Tween 80 volume (mL) | Span 80 volume (mL) |
|-----------------------------------|----------------------------------|---------------------|--------------------|
| 50:50                             | 0.5                              | 8.5                 | 0.043              |
|                                   | 1.5                              | 8.5                 | 0.128              |
|                                   | 2.0                              | 8.5                 | 0.170              |
|                                   | 2.5                              | 8.5                 | 0.213              |
Table 2. The various compositions of surfactant used in preparation of microspheres

| Mixed surfactants composition (v/v) | Tween 80 volume (mL) | Span 80 volume (mL) |
|-------------------------------------|----------------------|---------------------|
| 60:40                               | 10.2                 | 0.136               |
| 50:50                               | 8.5                  | 0.170               |
| 40:60                               | 6.8                  | 0.204               |

*Tween 80 : Span 80.
*Tween 80 with 2 % concentration (v/v).

Table 3. The average diameter of microspheres at any variation concentration.

| Variation concentration (%) | Average diameter (μm) |
|-------------------------------|-----------------------|
| 0.5                           | 1.739                 |
| 1.5                           | 5.329                 |
| 2.0                           | 19.51                 |
| 2.5                           | 19.43                 |

Figure 1. FT-IR spectrum of PLA and PLA/PCL microsphere.

After 1 h, the emulsion formed was inserted into a spray bottle. For the dispersion stage, the solution was then sprayed into 350 mL of aquadest which already rotated at 900 rpm for 1 h. The microcapsules formed were then washed, filtered and dried at room temperature of approximately one night [9].

3. Results and discussion

3.1. Analysis of Functional Groups in Poly(lactic acid) by FT-IR.
Characterization by Fourier Transform Infra Red (FT-IR) is intended to determine the functional groups consisting the chemical structure of synthesized PLA. It could also prove the level of purity and shows whether most of the monomers (LA) have been polymerized into PLA, by comparing FT-IR spectra of the product (PLA) and starting material (LA). From the obtained results, there is a band shift related to vibration of the C = O carbonyl group from monomer spectrum at 1727.06 [11] compared to 1758.19 cm⁻¹ in the polymer spectrum. The band shift between the LA spectrum and the PLA also has a difference in the peak intensity which indicates that there is a structural change in the polymer chain which was carboxylic acid to ester. The spectrum of PLA is shown in figure 1.
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volume (%) which was 10.1 %, 9.98 % and 9.67 % for the sample 60:40, 50:50 and 60:40,

area around 30.07 μm. The three graphs were multimodal, with one narrow peak at the highest intensity

Figure 3a shows the measured data in graphical form of the particle diameter (μm) plotted against

3.2. Analysis of functional groups in microspheres PLA/PCL by FT-IR.

Specific interactions that are often found in polyblends are hydrogen bonding, dipole-dipole

3.3. Effect of surfactant concentration variation on microsphere size distribution.

Particle size diameter of the microspheres formed were measured using the LS 100Q Beckman Coulter

3.4. Effect of variation of mixed surfactant composition on microsphere size distribution.

Figure 3a shows the measured data in graphical form of the particle diameter (μm) plotted against

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Figure 3. Graphic of (a) particle diameter size distributions with variation of mixed surfactant compositions, (b) comparison of microspheres size distributions based on different surfactant and microspheres formed with each surfactant concentrations (c) Span 80, (d) Tween 80/ Span 80 (50:50), (e) Tween 80 observed with optical microscope at 25x magnification.

Figure 3b shows the comparison of microspheres size distribution based on different surfactant usage and composition between Tween 80 and Span 80. The microspheres formed using Tween 80 have a relatively high polydispersity and wide size distribution area ranging from 0.375 to 43.67 μm. The size range resembles the ones formed using mixed surfactants. However, microspheres with mixed surfactants have lower polydispersity levels and one of the highest peaks is narrower than those of Tween 80 microspheres have. It is indicated that the microspheres are dominated by a certain size. For microspheres using Span 80 surfactants, only have two groups of particle size distributions based on peaks seen in the graph (0.375-0.751 μm and 1.520-2.920 μm). It is shown a relatively smaller size. However, its polydispersity was lower due to its relatively narrow size range (0.375-0.791 μm), when compared to those microspheres formed with mixed surfactants, which still varied in size. From the different surfactant forms in figure 3c, figure 3d and figure 3e it is obtained that mixing Tween 80 with Span 80 can also affect the different forms of microspheres particle.

If the graph in figure 4a is enlarged around the highest peak area (30.07 μm), it would show difference intensity in the form of volume (%) is 10.1 %, 11.0 % and 9.65 % for sample 700, 800 and 900 rpm, respectively. All three graphs were similar, but when viewed in the form of a group of sizes made based on peaks shown in figure 4a (0.375–3.205, 3.205–5.610 and 5.610–43.67 μm). There are differences in volume (%) between three microsphere sample charts. It was obtained that in 900-rpm sample, the amount of particles with size less than 3.5 μm was more abundant than those found in 700 and 800 rpm samples. According to Heisnaken et al. [6] and Gabor et al. [17] the increasing of stirring speed will increase the shear force, which would work to break up the droplet to form a smaller one. In this study, it might cause a few portion of bigger droplets in 900 rpm sample to split into smaller droplets.

3.5. Effect of varied stirring time on microsphere size distribution.
If the graph is inspected around the highest peak area (30.07 μm), which can be seen in figure 4b there were intensity differences in the form of volume (%) between every samples. There are 11.6 %, 10.1 %, 10.5 % and 9.95 % for each samples 0.5, 1.0, 1.5 and 2.0 h, respectively. Sample of 0.5 hours has the highest amount of % volume distributed around 30.07 μm area, which is 11.6 %, indicating that the 0.5 sample has more microspheres with diameter around 30.07 μm. This might be related to
the duration of stirring. It is possible that there may be some portion of microspheres in which the size has not reduced yet according to evaporation of the solvent. Thus, means there are still few amount of solvents that have not been evaporated from the surface of the microspheres which eventually affecting the size of the microspheres formed. As for the other three variation samples, there are no significant differences between one another.

4. Conclusions
Microspheres formed using polyblend of poly(lactic acid) and polycaprolactone through the solvent evaporation method (o/w) were spherical, having a small size of < 50 μm and were fine as powder but the particle size distribution was still not uniform. The uniformity of microspheres might be related to the pressure given during spraying or stirring which could affect the distribution of the droplet size formed. The usage of mixed surfactants Tween 80 and Span 80 in microspheres preparation process affected the size of microspheres formed and its polydispersity. The size of the microspheres produced using mixed surfactants with compositions (60:40, 50:50, and 40:60) were similar to the Tween 80 microspheres sizes (0.375–4.67) μm and greater than microspheres produced using Span 80 surfactants (0.375–0.791) μm. The mixed surfactants microspheres polydispersity were lower compared to Tween 80 microspheres but is relatively higher if compared to 80 Span microspheres.

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