Effect of surfactants mixing of Tween 80 and Nonidet RK-18 in preparation of microspheres based on polyblend of poly(lactic acid) and polycaprolactone

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Abstract. In preparation of microspheres process with solvent evaporation method, microspheres are formed from the oil in water (O/W) emulsion droplets as a template in which the type and concentration of surfactant will affect the stability of the emulsion. This research aims to investigate the effect of composition and concentration of a mixture of Tween 80 and Nonidet RK-18 as a mixed emulsifier in the preparation of microspheres based on polyblend of PLA/PCL. The solvent evaporation method involves emulsification and dispersing the polyblend emulsion in water. The microspheres obtained were characterized using FTIR, stereomicroscopes, and PSA instrumentations. The result of this research shows that the mixed emulsifier produces smaller microspheres compared to the result of using Tween 80 or Nonidet RK-18 individually because of the presence of synergistic effect. When the surfactants mixture is used, the larger Tween 80 ratio in the mixture will increase the ratio of smaller microspheres obtained because of the high hydrophilicity of Tween 80 that can stabilize O/W emulsion. On the other hand, the addition of Nonidet RK-18 in an increasing manner of ratio or concentration may destabilize the emulsion droplets through Ostwald ripening that can occur because Nonidet RK-18 has a low cloud point (17 °C).

Keywords: lactic acid, solvent evaporation, microspheres

1. Introduction
When microspheres are used as a controlled drug delivery carrier, before we evaluate the microencapsulation efficiency and drug loading of drug loaded microcapsules, a research to observe the size and particle size distribution of hollow microcapsules (microspheres) is needed to be done. This is due to the fact that if the required size and size distribution of microspheres as drug delivery device are not attained, the utilization of microspheres as a carrier will not be optimum [1].

According to Jain [2], the size of microspheres as drug delivery device is required to be less than 250 µm. Moreover, Kim and Pack [3] stated that the appropriate size of microspheres as controlled drug delivery device falls between the ranges of 1-100 µm with a narrow particle size distribution.

One of the important parameters that affect microspheres size obtained is the surfactant used [4]. It stems from the fact that in microspheres making process with solvent evaporation method, there is an emulsification process before dispersing the emulsion in water. This emulsification process is a stage of oil forming in water (o/w) emulsion droplets as a template in which the type and concentration of surfactant will affect the stability of the emulsion. A dual surfactants system is utilized in this research because of the synergistic interface stabilising effect between two surfactants with different properties found in previous studies.

Based on the explanation above, this research is conducted to investigate the effect of composition and concentration of a mixture of Tween 80 and Nonidet RK-18 as a mixed emulsifier in microspheres
making process based on blend of Poly(Lactic Acid) (PLA) and Polycaprolactone (PCL) with solvent evaporation method. The result of this research is expected to show the correlations between variations of composition and concentration of surfactants mixture and the microspheres size obtained.

2. Materials and methods

2.1. Materials
The subsequent compounds were employed as obtained: \(\text{L-}(+)\)-lactic acid (purity of \(\geq 98\%\)) was obtained from Sigma-Aldrich, Polycaprolactone CAPA-6800 (glass transition temperature of \(-60^\circ\)C) was obtained from Perstorp, dichloromethane and Tween 80 from Merck, Nonidet RK-18 was a gift from Evonik.

2.2. Instruments
Thermo Scientific Cimarec SP88857105 Stirring Hot Plate, Fourier Transform Infra Red (FTIR) IRPrestige-21 Shimadzu, and Particle Size Analyzer Beckman Coulter Light Scattering-100 (PSA LS-100).

2.3. Lactic acid polycondensation
Polymerizations were conducted in a three-neck flask completed with magnetic stirrer, thermometer, and a reflux condenser. Fifty millilitres of \(\text{L-}\)LA were added to the flask and then heated gradually to 120 \(^\circ\)C, after which the temperature was maintained at 120 \(^\circ\)C for an hour. After one hour, the temperature was then brought to 150 \(^\circ\)C with \(\text{N}_2\) flowed to the reactor. After that, this condition was kept for 22 hours. After the reaction finished, the reactor was cooled down to room temperature for two hours. The product was then removed from the three-neck flask and characterized with FT-IR.

2.4. Preparation of polyblend solutions
PLA and PCL polyblend was prepared with 60:40 (mole ratio) compositions. The polymers were wholly mixed in dichloromethane with the addition of Nonidet RK-18 and stirred until entirely dissolved to obtain the 10 \(\%\) polyblend solution.

2.5. Preparation of microspheres at different dual surfactants compositions and concentrations
Preparation of PLA/PCL microspheres was attained by a modified solvent evaporation technique [1]. Five millilitres of 10 \(\%\) polyblend solution were emulsified in Tween 80 with different compositions and concentrations. The emulsification process was carried out by stirring at 700 rpm for 1 hour. The emulsion was then dispersed in 400 mL distilled water and stirred for another hour. The microspheres formed were acquired by filtration, washed with distilled water, and dried in oven (\(\leq 40^\circ\)C) overnight. The variations of mixed surfactants compositions and concentrations used in this research are listed in table 1 and table 2.
Figure 1. Reaction scheme of lactic acid polycondensation reaction to produce PLA.

Figure 2. IR spectra of PLA, PCL, and PLA/PCL polyblend

2.6. Microspheres characterization
After microspheres were obtained by utilizing the mixture of Tween 80 and Nonidet RK-18 as the emulsifier, it was characterized using FTIR to ensure that microspheres were successfully formed from polyblend of PLA and PCL. The microspheres were also characterized using Particle Size Analyzer (PSA) to measure the particle size distribution of the microspheres produced.

3. Results and discussion

3.1. Lactic acid polycondensation
Condensation polymerization is used in this research as a PLA synthesis method from lactic acid (figure 1), which this polymerization occurs without the presence of catalyst and solvent thus classified as an economic reaction. However, this simple polycondensation reaction has some downsides such as difficult to obtain the desired polymer with high molecular weight (Mw), produces PLA with inferior mechanical strength, and it manifests PLA degradation reaction simultaneously at high temperature [5–6].

When the reaction takes place, water molecules are also produced as the by-product, which is necessary to be removed because it can diffuse into the amorphous fragments of PLA followed by random hydrolysis of the ester bonds. Fragmented PLA will produce Oligomer Lactic Acid (OLA) and reduce molecular weight of PLA subsequently. Hence, N₂ is flowed to the reactor to drive the water vapor away.

3.2. Preparation of microspheres based on polyblend of PLA/PCL
Polyblend is a mixture of two or more different polymers or copolymers, which are associated physically (without the presence of covalent bonds) [7]. The absence of chemical bonds implies that there will be no new vibrations observed in the IR spectra of the polyblend compared to the polymers (figure 2). The mentioned vibrations identified from the IR spectra are C-H sp³ stretching on a region of 2850-3030 cm⁻¹, C=O stretching on 1725 cm⁻¹, and stretching of saturated ester (C-O) on 1130 cm⁻¹.
3.3. Preparation of microspheres at different dual surfactants compositions

This research studies particle size distribution of microspheres prepared at various compositions of Tween 80 and Nonidet RK-18 as mixed emulsifier with 40:60; 50:50; and 60:40 Tween 80:Nonidet RK-18 ratios (figure 3), which compared to the size distribution of microspheres prepared using sole surfactant (Tween 80 or Nonidet RK-18) (figure 4). Microspheres prepared with dual surfactants displays smaller particle size of microspheres (< 25 µm) compared to the utilization of sole surfactant (a peak is observed at 40 µm). This might be owing to the presence of synergistic effect between Tween 80 and Nonidet RK-18 that produces an interfacial layer, which protects emulsion droplets during emulsification process [4]. The synergistic effect itself is defined by Rosen as a condition where the properties of the mixture are exceeding the properties obtainable from the single surfactant system [8].

To get a better understanding on the roles of each surfactant constituents in dual surfactants system, particle size distributions of microspheres prepared with Tween 80:Nonidet RK-18 ratios of 60:40; 65:35 and 73:30 are observed in figure 5. The particle size distributions indicate that larger Tween 80 ratio in the surfactants mixture will produce higher quantity of the smaller microspheres obtained (0.4–1 µm) whereas an increase in Nonidet RK-18 will decrease the quantity of smaller microspheres (0.4–1 µm) and increase the quantity of bigger microspheres obtained (2–4 µm). This might be for the
Figure 5. Particle size distribution of microspheres based on polyblend of PLA/PCL with Tween 80: Nonidet RK-18 ratios of 60:40 (blue); 65:35 (green); and 73:30 (red).

Figure 6. Particle size distribution of microspheres based on polyblend of PLA/PCL at different dual surfactants concentration.

reason that Tween 80 has high hydrophilicity (HLB 15.0 ± 1.0) while Nonidet RK-18 has low hydrophilicity (HLB 6). Tween 80 with its hydrophilic property will dissolve readily in water and according to Bancroft rule will produce a stable emulsion when water serves as the dispersing phase. To put it another way, higher Tween 80 ratio will stabilize O/W emulsion and will produce smaller microspheres.

3.4. Preparation of microspheres at different dual surfactants concentrations

After the investigation of surfactants compositions effect, the microspheres produced with various surfactant concentrations (0.25 %; 0.5 %; 1.0 %; 1.5 %; 2.0 % and 2.5 %) were studied. In figure 6, dual surfactants 0.25 % produced microspheres with monomodal size distribution with a single peak at 0.688 µm, dual surfactants 0.5 % exhibited bimodal size distribution with peaks at 0.474 µm and 2.539 µm, dual surfactants 1.0 % exhibited trimodal size distribution with peaks at 0.520 µm, 2.539 µm, and 5.878 µm, respectively. For dual surfactants with concentrations from 1.5 % to 2.5 %, microspheres size distributions produced broad distributions compared to the others. The formations of new peaks in bigger size from the utilization of dual surfactants 0.25 % to 0.5 % and 1.0 % implied that there were droplets destabilization that might be due to the fact that Nonidet RK-18 has a low cloud point (17 °C) whilst the cloud point of Tween 80 is higher at 65 °C. Cloud point itself defines as a temperature above which the surfactant solution becomes turbid due to phase separation and destabilization. When exceeding its cloud point, Nonidet RK-18 that consists PEO copolymer block will undergo an excessive dehydration resulting in the domination of hydrophobic attraction to hydrophilic repulsion and prompt the micelles aggregation. This micelles aggregation or flocculation leads a direct contact between oil droplets and drives an Ostwald ripening by decreasing the diffusion path length. Ostwald ripening itself covers a diffusive transfer of the dispersed phase from smaller to larger droplets [9–10].

4. Conclusions

Microspheres based on polyblend of PLA/PCL has been successfully prepared with solvent evaporation method implied from the synergic IR spectra of the microspheres and the polymer constituents. The mixed emulsifier produces smaller microspheres compared to the result of using Tween 80 or Nonidet RK-18 individually because of the presence of synergistic effect. When the surfactants mixture is used, the larger Tween 80 ratio in the mixture will increase the ratio of smaller microspheres obtained because of the high hydrophilicity of Tween 80 that can stabilize O/W emulsion. On the other hand, the addition of Nonidet RK-18 in an increasing manner of ratio or concentration may destabilize the emulsion droplets through Ostwald ripening that can occur because Nonidet RK-18 has a low cloud point (17 °C).

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