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ORIGINAL ARTICLE

Preparation and characterization of microspheres based on blend of poly(lactic acid) and poly(ε-caprolactone) with poly(vinyl alcohol) as emulsifier

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Abstract In this paper, microspheres were prepared by oil-in-water (o/w) emulsion solvent evaporation method. Biodegradable polymer such as blend of poly (lactic acid) (PLA) and poly(ε-caprolactone) (PCL) with certain compositions and characteristics was used to prepare the microspheres with poly(vinyl alcohol) (PVA) as an emulsifier. This study observed the microspheres particle's size distribution at various concentrations of PVA (1%, 1.5%, 2%, and 2.5% PVA). The PVA volume variations effects during the process (50, 100, 150, 200, and 250 mL) were also observed. The blend of PLA and PCL is formed only by physical interaction between them. This can be seen from the FTIR spectrum which shows both PLA and PCL component. The microspheres physical size and appearance were observed by optical microscope (MO). The overall results of this study showed that the formula which used 50–150 mL of 2.5% polyvinyl alcohol produced the microspheres with the most uniform size distribution.

1. Introduction

Microsphere is a term used for small spherical particles, with diameters in the micrometer range (typically 1–1000 μm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary a lot in density and, therefore, are used for different applications. Microspheres can be made by a variety of ways including emulsification technique with single or double solvent evaporation system (Bao et al., 2006; Rizkalla et al., 2006), spray-dry technique (Blanco

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et al., 2005; Oster and Kissel, 2005), or phase separation technique. Jain explained that the microspheres can be prepared by dissolving the starting materials in volatile solvents and then dispersing them in another solvent which is not miscible with the previous. Later complete evaporation of the last solvent will produce a fine powder called microspheres which is soluble in water (Jain, 2000).

Good microspheres should meet these requirements: (1) able to preserve the stability and biological activity of the drug during the encapsulation process, (2) the size is not bigger than 250 μm, (3) the amount of frequently released drug must be within a specified limit, and (4) must be produced as pure powder that does not contain impurities and form aggregates or coagulant (Jain, 2000).

The main advantage of applying microspheres as drugs delivery system is the controlled release of the drug content. This feature made them suitable for carrying a particular drug which is frequently needed by the body in a small fixed amount. Today this application has been widely practiced; encapsulation of dexamethasone sodium phosphate with PLGA (Jaraswekin et al., 2007), and the use of PLGA microspheres as protein release system in the body (Ciombor et al., 2006; Wischke and Borchert, 2006) are just a few examples.

The use of synthetic biodegradable polymer as microspheres for drug delivery system application has been increasing since two decades. Some of the degradable polymers that can be used for this purpose is poly(lactic acid) (PLA) Lai et al., 2004; Sudirman and Aloma, 2003, poly(lactic-co-glycolic acid) (PLGA) Cao et al., 2006; Huy et al., 2006, and poly(ε-caprolactone) (PCL) Kim et al., 2003; Ramesh et al., 2002. PCL is aliphatic polyester that is biodegradable and biocompatible. PCL has been used in the drug delivery system because it has good permeability. PCL has high crystallinity but its rate of degradation is slow. Polylactide (PLA) in the form of D, L-PLA undergoes faster degradation than PCL, but it has 3–5% lower strain than PCL, thus PLA is more brittle compared to PCL (Porjazoska et al., 2004).

According to Gunatillake and Adhikari, the mixture of PCL with other polymers which have lower molecular weight can be used in various applications, such as modified polymers for drug delivery system. The mixture of PCL and PLA is expected to produce a compatible polymer which has a faster degradation time and better permeability. The use of this biodegradable polymer has many advantages because it can be easily absorbed by the body after hydrolysis and so will not poison the body (Gunatillake and Raju, 2003).

In order to stabilize the emulsion formed between polymer and drug solution with water, polyvinylalcohol (PVA) is usually used. In this investigation, the PVA solution stabilizes the emulsion between polyblend (PLA and PCL) and drugs with water. The polyblend is soluble in dichloromethane but they cannot be mixed with water due to differences in density and polarity. An emulsion will be formed when they are mixed together in high speed rotation resulting them to appear in one phase. Unfortunately this emulsion is not stable. To overcome this problem, emulsifier must be added to the emulsion. In this study, we used poly(vinyl alcohol) (PVA) as the emulsifier. The hydroxyl groups in PVA will interact with the water phase while the vinyl chain will interact with the dichloromethane thus making the formed emulsion more stable. Variation in PVA concentration and volume will affect the emulsion stability. Thus, the addition of PVA will affect the stability of emulsion; in this case, PVA concentration will affect the size of the microspheres. The microspheres of uniform size will increase the dissolution rate of drugs loaded. Zhu et al. explained that the microspheres in the size of 40–50 μm to ibuprofen-loaded microcapsules have the efficiencies of 70–90% (Zhu et al., 2005).

The objective of this paper is to obtain uniform microspheres using various concentrations and volume of poly vinyl alcohol as emulsifiers. Microspheres' particle size distribution is influenced by the stirring speed during the emulsification process in the o/w system. (Zhu et al., 2005; Berchane et al., 2006).

Another important factor that greatly influenced the process of drug delivery system is the microspheres' size and their distribution. The uniform particle sizes will produce good dissolution rate and efficiency. Zhu et al. reported that 40–50 μm-sized microspheres have good efficiency of 70–90% (Berchane et al., 2006).

2. Materials and methods

2.1. Material

PCL (Mw = 42,000) was obtained from Sigma–Aldrich, PVA (Mw = 75,000) and dichloromethane from Merk. PLA (Mv = 10,241) obtained from the Laboratory of Chemistry, Bogor Agricultural University was used in study.

2.2. Preparation of 10% polyblend solutions

The polyblend between PLA and PCL was prepared with 9:1 (A1) composition. The polymers were completely mixed in dichloromethane and stirred for 30 min to obtain the 10% polyblend solutions.

2.3. Preparation of 10% PVA stock solution

A 10 g PVA was dissolved in 90 mL distilled water and stirred with a magnetic stirrer at 60 °C until completely dissolved. The solution was then cooled to room temperature.

2.4. Optimization of concentration and volume of PVA in microspheres preparation

The microspheres were prepared by a modified solvent evaporation technique (Zhu et al., 2005; Garkhal et al., 2007). Five milliliters of 10% polyblend solution (A1) were emulsified in 100 mL PVA solutions with different concentrations and stirred at 500 rpm for 15 min. The resulted emulsion was then dispersed in 500 mL distilled water and stirred for another 15 min. After this, the stirring was continued for 1 h to completely evaporate the dichloromethane. The produced microspheres

Table 1 The concentration variations of PVA were used for making microspheres of polyblend 10%.

Formulation variables	Concentration of PVA (%)
PLA:PCL 9:1, the volume of PVA 100 mL	0.5
	1
	1.5
	2
	2.5

Table 2 The volume variations of PVA were used for making microspheres of polyblend 10%.

Formulation variables	Volume of PVA (mL)
PLA:PCL 9:1, the concentration of PVA 1%	50
	100
	150
	200
	250

were collected by filtration, washed with distilled water, and dried in oven.

The variations of PVA concentration and volume used in this study are listed in Tables 1 and 2. The particle sizes of the microspheres produced from each formula were determined by optical microscope and the functional group of microspheres was analyzed by FTIR.

3. Results and discussion

Polyblend is a physical mixture of two or more different polymers or copolymers which are not linked covalently. Blending techniques are an extremely promising approach which can improve the original properties of the polymers (Kim et al., 2003). Polyblend microspheres containing were prepared by the o/w emulsion solvent evaporation process. It has been found that emulsification by using oil-in-water (o/w) is better than using oil in oil (o/o) in preparation of microcapsules of polymers (Kim et al., 2003). In the first step, the organic phase was emulsified in the aqueous external phase.

The organic phase used in this study is dichloromethane. Besides dichloromethane, chloroform can also be used, but the time required for the evaporation of chloroform is longer than that of dichloromethane. Chloroform is evaporated at a temperature of 61 °C, while the dichloromethane is evaporated at a temperature of 39 °C. Microspheres will be formed faster when using the solvent dichloromethane. Following the evaporation of the organic solvent from the surface of droplets, the concentration of the polymer increased, reaching a critical point at which the polymer concentration exceeded its solubility in the organic phase and then precipitated to produce microspheres (Bolourtchian et al., 2005). Microspheres of the polyblend of PLA and PCL are made by this method. When two or more liquids are mixed to form a homogeneous mixture, they are said to be compatible. In this research, we have shown that PLA and PCL are compatible.

Analysis of FTIR aims to determine and compare the functional group of the constituent components of polyblend. Process mixture of physics will produce different FTIR spectrum with mixture of chemically. Alloy physics will show the combined spectrum of the constituent components of polyblend, whereas chemical alloy will show a different spectrum of constituent components, due to chemical interaction that will produce new compounds. PLA and PCL are all aliphatic polyesters with similar structures. The C═O, C–O–C, and C–C peaks were clearly visible at 1754, 1175 and 1200 cm^{-1}, respectively, in the IR spectra (Chen et al., 2003).

In Table 3 can be seen that the spectra of PCL and PLA reappear in the spectra of microspheres. This indicates that functional groups in microspheres of polyblend are a combination of constituent components. In addition, the spectra of microspheres had no new peaks. Therefore, it can be concluded that the microspheres produced was the result of the blend of PLA and PCL is formed only by physical interaction between them. It can also be seen from the FTIR spectrum which shows both components of PLA and PCL. Thus the FTIR spectra of polyblend of PLA and PCL are merely a mixture of PLA and PCL. The spectra of PLA, PCL, and polyblend are shown in Fig. 1.

Table 3 Analysis of functional group using FTIR.

Sample	Wave number (cm^{-1})	Functional groups	Reference (Stuart 2003)
PCL	2866–2943.2	Stretching of C–H	2840–3000
	1728.1	Stretching of C═O carbonyl	1715–1730
	1168.8–1242.1	Stretching of C–O saturated ester	1163–1210
PLA	3432	O–H	3330–3500
	2948–2999	Stretching of C–H	2840–3000
	1758	C═O carbonyl	1715–1730
	1387–1459	Bending of C–O–H	1395–1440
	1133–1213	Stretching of C–O saturated ester	1163–1210
Microspheres	2873–3001	Stretching of C–H	2840–3000
	1759	C═O carbonyl	1715–1730
	1387–1458	Bending of C–O–H	1395–1440
	1134–1214	Stretching of C–O saturated ester	1163–1210

3.1. Optimization of concentration and volume of PVA on the making of microspheres polyblend 10%

Microspheres were prepared by the emulsion method. Basic materials of microspheres PLA with PCL were dissolved in a volatile organic solvent of dichloromethane then was emulsified, and dispersed in another solvent that do not interfere each other to form microparticles called microspheres. Emulsion formed by mixing with water is not stable. PVA was used to stabilize the emulsion between the organic and water phase. In this experiment, the polyblend/dichloromethane solution is the dispersed phase while the PVA solution is the continuous phase. As the stirring speed increased, more air was entrained and foam was formed. To avoid excessive foaming, anti-foam of silicon and non-silicon constituents was used (0.1% v/v) that served to increase the rate at which air bubbles were dissipated (Zhu et al., 2005). An aluminium foil lid was also used to seal the top of the beaker to reduce air entrainment. This was necessary as the entrained bubbles can damp turbulence intensity and affect the size of the microspheres.

The difference in PVA concentration will produce different microspheres sizes. Smaller microspheres particle sizes were obtained from the greater PVA concentrations. The particle size of microspheres seems to be dependent on the PVA concentration in continuous phase (Bolourtchian et al., 2005). This result was observed during optical microscope observation at 50× magnification (Fig. 2).

Dispersion into the water to evaporate of dichloromethane and formed microspheres which will precipitate out. Microspheres are obtained and then rinsed with distillation water several times to remove the PVA of the microspheres.

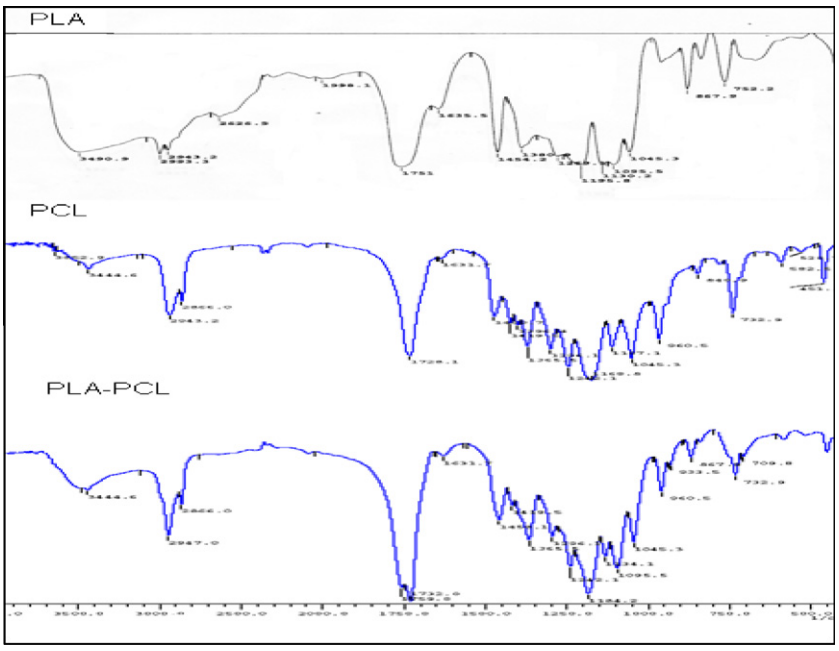

Figure 1 FTIR spectra of PLA, PCL, and their polyblend.

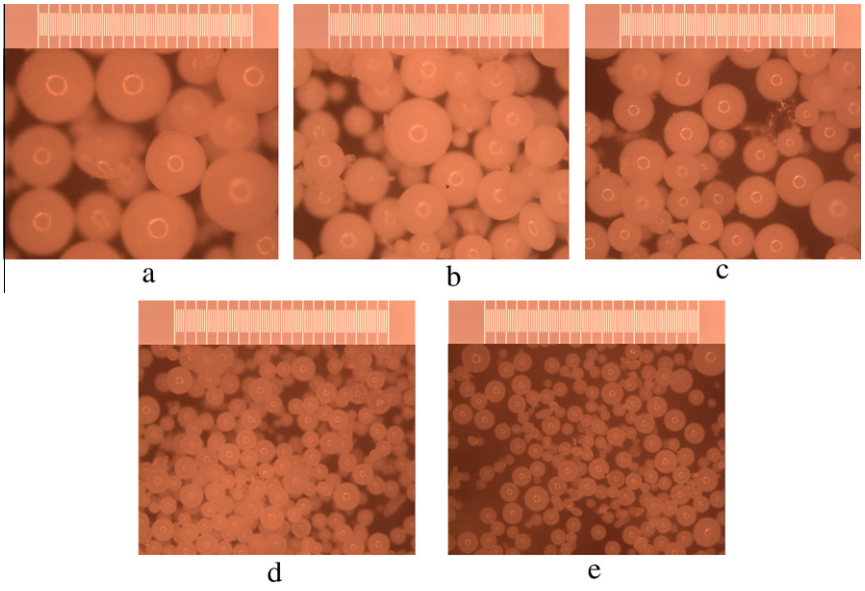

Figure 2 Optical microscope images microspheres produced with PVA concentrations of: (a) 0.5%, (b) 1%, (c) 1.5%, (d) 2%, and (e) 2.5% (50×).

On pictures 2, more uniform sized and small microspheres on the concentration of PVA 2.5% when compared with other concentrations. The use of PVA 3% shows that damage to the microspheres, although of the small size, may be caused by an excessive amount of emulsifiers that cause the fragility of the microspheres during the process of dispersion.

The sizes of the resulting microspheres range from 40 to 350 μm. Microsphere size distribution at various concentrations of PVA can be seen in Table 4. The most uniform size distribution was obtained from the formula that used 2.5% PVA.

Table 4 Distribution of microspheres size on various concentrations of PVA.

Concentration of PVA (%)	Distribution of microspheres size (μm)
0.5	200–350
1	140–320
1.5	100–200
2	50–100
2.5	40–75

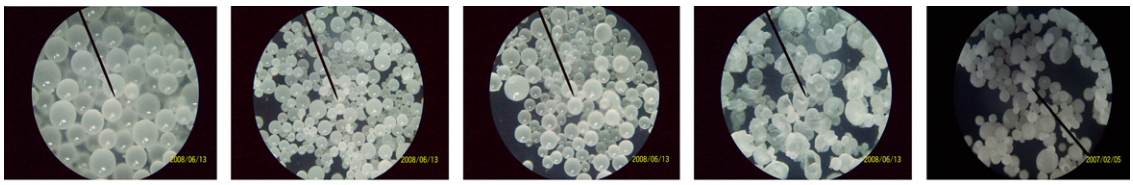

Figure 3 Optical microscope images of microspheres produced with PVA volumes of: (a) 50 mL (b) 100 mL (c) 150 mL (d) 200 mL, and (e) 250 mL.

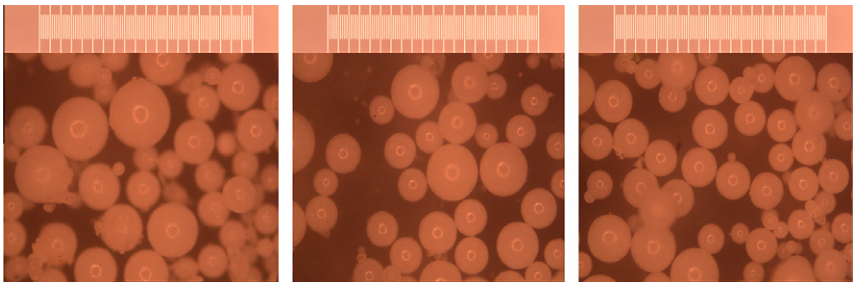

Figure 4 Optical microscope images of microspheres produced in three times repetition (50×).

According to Jain, microspheres' size must be less than 250 μm when they are used for drug delivery system (Jain, 2000)

The variation of PVA volumes produces different sizes of microspheres (Fig. 3). The formulae that used 200 and 250 mL of PVA produced deformed microspheres. The use of excessive amount of PVA will decrease the produced microspheres' stability.

The microspheres were produced three times to ensure the accuracy of the method. The results are shown in Fig. 4. From these images, it can be seen that three times repetition of this method was able to produce microspheres with a relatively same size and appearance.

4. Conclusions

The microspheres produced were the result of blend of PLA and PCL is formed only by the physical interaction between them. The FTIR spectra of polyblend of PLA and PCL are merely a mixture of PLA and PCL.

PVA concentration of 2.5% has produced the most uniform microspheres particle sizes (average = 70 μm) and PVA volumes range which produce the homogenous microspheres was 50–150 mL. We have shown that the o/w emulsion solvent evaporation method is able to produce microspheres with a relatively same size and appearance in three times repetition.

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