การเตรียมอนุภาคไมโครของพอลิดี,แอล-แล็กไทด์ผสมกรดเสตียริกที่สลายตัวได้ทางชีวภาพโดยวิธีการระเหยตัวทำละลายของอิมัลชันแบบน้ำมันในน้ำสำหรับนำส่งยา

Preparation of Biodegradable Poly(D,L-lactide)/Stearic acid Blend Microparticles by Oil-in-water Emulsion Solvent Evaporation Method for Drug Delivery

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บทคัดย่อ

อนุภาคไมโครของพอลิดี,แอลแล็กไทด์ผสมกรดเสตียริกที่สลายตัวได้ทางชีวภาพเตรียมโดยวิธีการระเหยตัวทำละลายของอิมัลชันแบบน้ำมันในน้ำที่มีอัตราส่วนผสมของพอลิดี,แอลแล็กไทด์และกรดเสตียริกต่างๆ โดยมีการศึกษาถึงอิทธิพลของอัตราส่วนผสมของพอลิดี,แอลแล็กไทด์และกรดเสตียริก ได้แก่ 100/0, 97.5/2.5, 95/5, 92.5/7.5, 90/10 และ 80/20 โดยน้ำหนัก ที่มีต่อลักษณะเฉพาะของอนุภาคไมโคร ซึ่งวิเคราะห์ด้วยเทคนิคอิเล็กตรอนแบบส่องกราด (SEM) การวิเคราะห์ขนาดอนุภาคด้วยการกระเจิงแสง และดิฟเฟอเรนเชียลสแกนนิงแคลอรีเมทรี (DSC) จากไมโครกราฟ SEM อนุภาคไมโครที่มีอัตราส่วนผสมของพอลิดี,แอลแล็กไทด์และกรดเสตียริกในช่วง 100/0-95/5 โดยน้ำหนักมีรูปร่างใกล้เคียงทรงกลม อนุภาคไมโครที่เตรียมได้มีร้อยละผลผลิตสูง (71-80%) และมีขนาดใกล้เคียงกัน (164-185 ไมครอน) การวิเคราะห์ด้วย DSC ยืนยันว่ามีอุณหภูมิเปลี่ยนสถานะคล้ายแก้วของพอลิดี,แอลแล็กไทด์และอุณหภูมิหลอมของกรดเสตียริก จากผลการทดลองที่ได้แสดงว่าสามารถเตรียมอนุภาคไมโครของพอลิดี,แอลแล็กไทด์ผสมกรดเสตียริกสำหรับเป็นตัวนำส่งยาต่อไป

คำสำคัญ: พอลิเมอร์สลายตัวได้ทางชีวภาพ, พอลิเมอร์ผสม, อนุภาคไมโคร, สัณฐานวิทยา

Abstract

Biodegradable poly(D,L-lactide) (PDLL)/stearic acid blend microparticles were prepared by an oil-in-water emulsion solvent evaporation method with various PDLL/stearic acid blending ratios. The influence of PDLL/stearic acid blend ratios of 100/0, 97.5/2.5, 95/5, 92.5/7.5, 90/10 and 80/20 (w/w) on the microparticle characteristics were studied. The microparticles were analyzed using a combination of scanning electron microscopy (SEM), light scattering particle size analysis and differential scanning calorimetry (DSC). From

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their SEM micrographs, the blend microparticles with a PDLL/stearic acid blend ratio in the range of 100/0-95/5 (w/w) were nearly spherical in shape. Blend microparticles with a high percentage yield (71-80%) and similar size (164-185 μm) were obtained. The DSC analysis confirmed that the blend microparticles consisted of the glass transition temperature of PDLL and melting temperature of stearic acid. The overall results indicated that it was possible to prepare the PDLL/stearic acid blend microparticles for use as drug delivery carriers.

Keyword: biodegradable polymers, polymer blends, microparticles, morphology

Introduction

Controlled-release drug delivery is a term referring to drug delivery in response to time. Sustained release, prolonged release and delayed release are terms used to identify drug delivery systems that are designed to deliver the precise amount of a drug at a pre-programmed rate in order to achieve the drug level necessary for the treatment after administration of a single dose.[1,2] Controlled-release drug delivery also attempts to maintain drug levels within the therapeutic window to avoid potentially hazardous peaks in drug concentration following injection or ingestion.[3] Biodegradable polymers have been widely investigated as a matrix for controlled-release drug delivery systems in film, particle, gel and fibre forms. The removal of these biodegradable polymeric matrices at the completion of therapy is not required. Drug release mechanisms from a biodegradable polymeric matrix consists of drug diffusion out and matrix erosion processes.

Poly(D,L-lactide) (PDLL) is a synthetic biodegradable polyester. PDLL is an amorphous polymer. This induces uniform drug distribution in the PDLL matrix. PDLL microparticles have been widely studied for use in controlled-release drug delivery applications.[4-7] The oil-in-water emulsion solvent evaporation method has been usually used to prepare the PDLL microparticles containing hydrophobic model drugs.[4,7] Drug release from polyester particles depended upon the polyester molecular weight, initial drug content, particle size and polymer blending.[8,9,10] Lipids are inexpensive biocompatible substances that have been widely investigated as a matrix for drug delivery.[11,12,13] Solid lipid microparticles attain high encapsulation efficiency for hydrophobic drugs due to their hydrophobic nature. Stearic acid is a solid lipid. Stearic acid microparticles combine the advantages of liposome and polymer microparticles, while avoiding some of their disadvantages such as toxicity, biodegradability problems and raw material costs.[14] However, microparticles of PDLL/stearic acid blends for use as drug delivery systems have not been reported.

In the present study, the PDLL/stearic acid blend miroparticles were prepared by the oil-in-water emulsion solvent evaporation method. The influence of PDLL/stearic acid blend ratio on morphology, yield, particle size and thermal transition properties of the blend microparticles was determined.

Materials and Method

Materials

Poly(D,L-lactide) (PDLL) with an average-viscosity molecular weight of 20,000 g/mol was synthesized by ring-opening polymerization of a D,L-lactide monomer at 140°C for 24 h using 1-dodecanol

(98%, Fluka, Switzerland) and stannous octoate (95% Sigma, USA) as the initiator and catalyst, respectively. The 1-dodecanol was distilled under reduced pressure before use. Stannous octoate, stearic acid (95%, Sigma-Aldrich, USA) and Tween80 (Labchem, Australia) were used without further purification.

Preparation of PDLL/stearic acid blend microparticles

Blend microparticles were prepared by the oil-in-water emulsion solvent evaporation method. Briefly, 0.1 g of PDLL/stearic acid blend was dissolved in dichloromethane (2.5 mL). After complete dissolution, it was poured into 400 mL of 2 wt% Tween80 solution in water. The solution was then emulsified by a magnetic stirrer at 800 rpm to form an oil-in-water emulsion. The dichloromethane was evaporated in a fume hood for 6 h. The obtained microparticles were filtered and washed with distilled water. The microparticles were then freeze-dried overnight and stored in a desiccator before characterization.

Characterisation of PDLL/stearic acid blend microparticles

Morphology of the microparticles was investigated by scanning electron microscopy (SEM) using a JEOL JSM-6460LV SEM. The microparticle samples were coated with gold to enhance conductivity before scanning. The average size and size distribution of the microparticles were determined using the light scattering (LS) technique with a Coulter LS230 particle size analyzer at 25^{o}C in a water medium. Thermal transition properties of the microparticles were determined by means of differential scanning calorimetry (DSC) using a Perkin-Elmer DSC Pyris Diamond. For DSC analysis, 5–10 mg of sample was heated at 10^{o}C/min under a helium flow.

Results

The morphology of the blend microparticles was investigated from their SEM micrographs as shown in Figure 1. Blend microparticles with fine dispersibility were seen. The resulting blend microparticles with PDLL/stearic acid blend ratios of 100/0, 97.5/2.5 and 95/5 (w/w) were nearly spherical in shape with a smooth surface. While the 92.5/7.5, 90/10 and 80/20 (w/w) PDLL/stearic acid blend microparticles were irregular in shape with a broken surface. The morphology of the blend microparticles can be better observed from their expanded SEM micrographs in Figure 2.

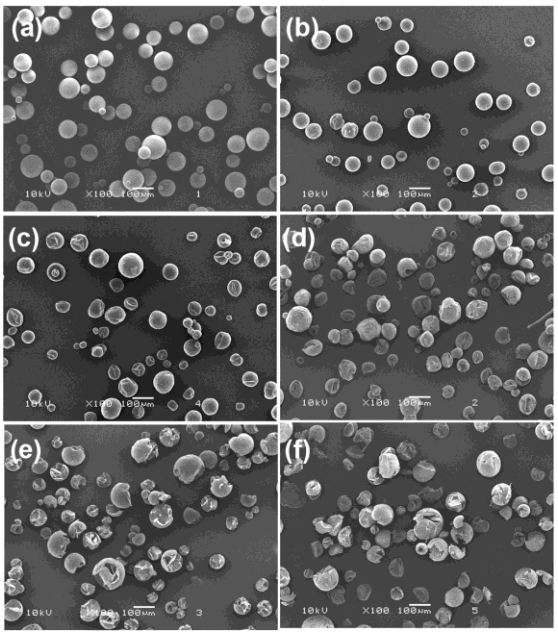

Figure 1 SEM micrographs of blend microparticles with PDLL/stearic acid blend ratios of (a) 100/0, (b) 97.5/2.5, (c) 95/5, (d) 92.5/7.5, (e) 90/10 and (f) 80/20 (w/w).

The yield of the blend microparticles was calculated from the weight ratio of the resultant microparticles and feed polymer blend. Light

scattering analysis was used to determine the average particle size. All of the particle size graphs exhibited similar unimodal particle size distributions, as an example of which is shown in Figure 3 for the 92.5/7.5 (w/w) PDLL/stearic acid blend microparticles. The yield and the average particle size of the blend microparticles, as summarized in Table 1, are in the range of 71–80% and 164–185 μm, respectively. Both yield and average particle size did not change significantly with the PDLL/stearic acid blend ratio.

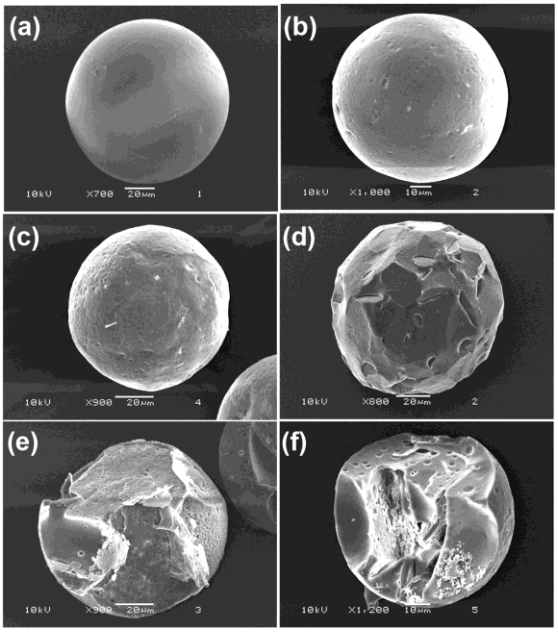

Figure 2 Expanded SEM micrographs of blend microparticles with PDLL/stearic acid blend ratios of (a) 100/0, (b) 97.5/2.5, (c) 95/5, (d) 92.5/7.5, (e) 90/10 and (f) 80/20 (w/w).

The thermal transition properties of the blend microparticles were investigated by DSC. The DSC curves of the blend microparticles are compared in Figure 4. The DSC curve of PDLL microparticles in Figure 4(a) showed a single glass transition temperature (T_g) at 44°C. The DSC curves of the blend microparticles in Figures 4(b)–4(f) also showed a single T_g in the range of 41-47°C. It should be noted that the DSC curves of the 92.5/7.5, 90/10 and 80/20 (w/w) PDLL/stearic acid blend microparticles in Figures 4(d)–4(f) exhibited a shoulder peak of stearic acid character. The area of the shoulder peak increased as the stearic acid blend ratio increased.

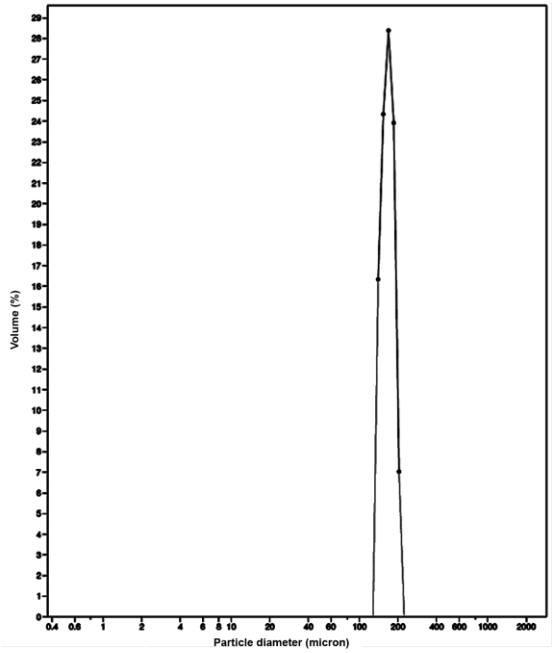

Figure 3 Particle size graph for the 92.5/7.5 (w/w) PDLL/stearic acid blend microparticles.

Table 1 Yield and size of the blend microparticles.

PDLL/stearic acid (w/w)	Yield (%)	Particle size (μm)
100/0	75	185 ± 67
97.5/2.5	72	169 ± 57
95/5	78	178 ± 48
92.5/7.5	71	164 ± 18
90/10	77	171 ± 56
80/20	80	180 ± 68

Discussions

The particles of the polymer blends have been studied for use as drug delivery systems. The rate of drug release from the blend particles can be adjusted for each patient by varying the blend ratio.[10] Different polymer types of particle matrix usually exhibited different drug release rates from the particles. The drug release behavior of the polymer matrix depended upon polymer hydrophobicity and polymer-drug interaction. The aim of this work was the preparation of PDLL/stearic acid blend microparticles. Six PDLL/stearic acid blend ratios were investigated.

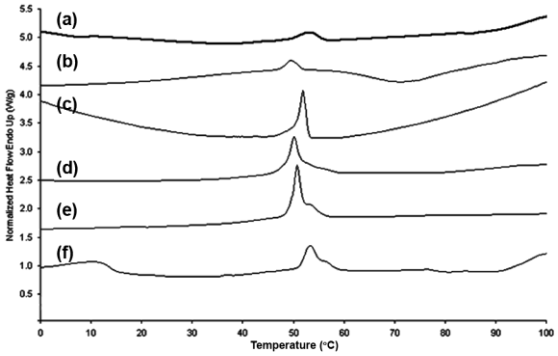

Figure 4 DSC thermograms of blend microparticles with PDLL/stearic acid blend ratios of (a) 100/0, (b) 97.5/2.5, (c) 95/5, (d) 92.5/7.5, (e) 90/10 and (f) 80/20 (w/w).

The morphology of the blend microparticles from Figures 1 and 2 showed a spherical shape with a smooth surface for the 100/0, 97.5/2.5 and 95/5 (w/w) PDLL/stearic acid blend microparticles and an irregular shape with a broken surface for the 92.5/7.5, 90/10 and 80/20 (w/w) PDLL/stearic acid blend microparticles. The self-aggregation of stearic acid molecules may induce a phase separation between PDLL and stearic acid phases and a break in the microparticle matrix. However, the drug release from the drug-loaded particles with a spherical shape usually exhibited a more consistent rate than from the irregular shaped particles.[9] From the morphology results, the 100/0, 97.5/2.5 and 95/5 (w/w) PDLL/stearic acid blend microparticles are appropriate for drug delivery applications.

The yields of the blend microparticles were in the range of 71–80% as reported in Table 1. This indicates that the preparation conditions, including polymer concentration, volumes of oil and water phases, stirring speed and evaporation time for the oil-in-water emulsion solvent evaporation method were appropriate for producing the blend microparticles with a high yield. In addition, the PDLL/stearic acid blend ratio did not significantly affect the yield of the microparticles. This may be due to the water-insoluble or hydrophobic properties of both PDLL and stearic acid. The particle sizes of the blend microparticles are also similar in the range of 164 – 185 μm (Table 1). This indicates that the stearic acid blend ratios in the range of 2.5 – 20% did not affect the particle size.

Thermal transition properties have been used to identify the blend particles.[15] Each blend component showed its thermal transition properties, such as glass transition temperature (T_g) and melting temperature (T_m). The PDLL has a T_g at 40-50°C. The stearic acid has a T_m at 55°C. The T_g of the PDLL microparticles in Figure 4(a) is 44°C. While the T_g of the blend microparticles is in the range of 41-47°C as shown in Figures 4(b)-4(f). The T_g of the PDLL blend component did not change significantly as the stearic acid blend ratio increased. The melting peak of the stearic acid characteristic appeared as a shoulder peak at higher temperatures of T_g of PDLL and was detected when the stearic acid blend ratio increased up to 7.5 wt% [see Figure 4(d)]. The area of the shoulder peak increased

with the stearic acid blend ratio. This may be explained by the stearic acid molecules aggregating to form crystalline structures for higher stearic acid blend ratio.

Conclusions

The present work demonstrated that PDLL/stearic acid blend microparticles were successfully prepared by the oil-in-water emulsion solvent evaporation technique. The microparticles with PDLL/stearic acid blend ratios in the range of 100/0 - 92.5/7.5 (w/w) exhibited a spherical shape with a smooth surface. Yields and particle sizes of the PDLL and all the blend microparticles were very similar. Further experiments are needed to study the effect of the drug encapsulation on the characteristics and drug release behaviors of these blend microparticles.

Acknowledgements

This research was financially supported by Mahasarakham University, Mahasarakham, Thailand.

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