Synthesis of Amorphous Polylactide and Poly (lactide-*co*-glycolide) Containing High L-form Enantiomer for Use in Controlled Release Drug Delivery

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ABSTRACT

In this work, the effect of L-lactide (LL) copolymerization on the properties of poly(D,L-lactide) (PDLL) and poly(D,L-lactide-*co*-glycolide) (PDLLG) copolymers and its drug release behaviors were determined and discussed. The copolymers were synthesized by ring-opening polymerization of DLL, LL, and G monomer mixtures. The PDLL with DLL/LL ratios of 100/0-50/50 by mole and the PDLLG with DLL/LL/G ratios of 75/0/25-37.5/37.5/25 by mole were investigated. All the copolymers were completely amorphous. The drug-loaded copolymer microparticles with a spherical shape and smooth surface were prepared by the oil-in-water emulsion solvent evaporation method. Indomethacin was used as a poorly-water soluble model drug. The copolymerization of the LL monomer did not change the *in vitro* drug release profiles of the PDLL and the PDLLG microparticles significantly. It is suggested that these amorphous PDLL and PDLLG copolymers that contain higher L enantiomer amounts have the potential to be developed further as a lower-cost PDLL and PDLLG, respectively, for use as controlled release drug delivery systems.

Keywords: Lactide, Glycolide, Copolymers, Microparticles, Drug delivery.

INTRODUCTION

Controlled release drug delivery systems made from biodegradable particles provide several benefits over traditional formulations.[1] Prior to release, the drug is protected from degradation or premature metabolism by the polymeric particle matrix. The release of the drug is sustained over days to months, thereby keeping the drug concentration in the plasma at an effective level for longer periods of therapy time and reducing the toxic side-effects from overdose of the drug. This decreases the frequency of administration and increases patient compliance.[2] Biodegradable microspheres for drug delivery have been widely made from a variety of biodegradable polyesters due to their biodegradability and biocompatibility. The removal of these biodegradable polyester-based microspheres at the end of the

therapy is not required. Administration of medication via such a system is advantageous because the microspheres can be ingested or injected[3-4]

Amorphous poly(D,L-lactide) (PDLL) and poly(D,L-lactide-*co*-glycolide) (PDLLG) are biodegradable and biocompatible polyesters that have been widely investigated for use as controlled release drug delivery systems.[4-6] This is due to the fact that good drug distribution into the amorphous PDLL and PDLLG matrices can be obtained. The semi-crystalline phases in the poly(L-lactide) (PLL) matrix may induce drug aggregation. A good distribution of the entrapped drug into the microparticle matrices could allow a consistent drug release rate. Controllable molecular weights of the PDLL and the PDLLG are usually synthesized by ring-opening polymerization of DLL and DLL/G monomers, respectively. The higher hydrophilic G units in the PDLLG resulted in a faster biodegradation rate than the PDLL.

An equivalent D-lactic acid/L-lactic acid mixture, called D,L-lactic acid, is used to prepare the DLL monomer. However, L-lactic acid, the monomer precursor of LL, is produced at a larger scale for supply to food, cosmetic, and pharmaceutical applications. Therefore, the L-lactic acid is easier to find and cheaper than the D,L-lactic acid. The DLL and LL monomers are prepared from the D,L-lactic acid and the L-lactic acid, respectively, by the same procedure. This has the benefit of offering a substantial reduction in cost by the addition of LL to produce lower-cost alternatives to the current commercial PDLL and PDLLG for use in controlled release drug delivery applications.

In the present paper, PDLL and PDLLG copolymers with different LL monomer contents were synthesized by ring-opening polymerization of the DLL/LL and the DLL/LL/G mixtures, respectively. We prepared drug-loaded copolymer microparticles using an oil-in-water emulsion solvent evaporation method. Indomethacin was used as the hydrophobic model drug. The characteristics of the drug-loaded PDLL and PDLLG microparticles containing high LL content and *in vitro* indomethacin release were determined and compared to the neat PDLL and PDLLG microparticles.

Experimental section
Materials

Crude D,L-lactide (DLL) and L-lactide (LL) monomers were synthesized from D,L-lactic acid (85% w/v, 50/50 D-/L-form ratio, Acros Organics) and L-lactic acid (88% w/v, 5/95 D-/L-form ratio, Purac), respectively, by direct polycondensation at 180 °C followed by thermal decomposition at 220 °C under reduced pressure. Crude glycolide (G) monomer was synthesized from glycolic acid (99%, Acros Organics) by the same procedure. The reaction temperatures for the direct polymerization and the thermal decomposition stages were 220 °C and 320 °C, respectively, for preparing the crude G monomer. Crude lactide and glycolide monomers were purified by re-crystallization in ethyl acetate four times. The purified monomers were dried under vacuum at 55°C for 48 h before use in the polymerization. 1-dodecanol (98%, Fluka) containing a one-hydroxyl end group was purified by distillation under reduced pressure before use. Stannous octoate [$Sn(Oct)_2$, 95%, Sigma], indomethacin (99.95%, Sigma), and Tween80 (Acros Organics) were used without further purification. All reagents used were analytical grade.

Synthesis of copolymers

Poly(D,L-lactide) (PDLL) and poly(D,L-lactide-*co*-glycolide) (PDLLG) copolymers were synthesized by ring-opening polymerization of the DLL/LL/G mixtures in bulk at 165 °C for 2.5 h under a nitrogen atmosphere. $Sn(Oct)_2$ was used as a catalyst at 0.01 mol% and 1-dodecanol was used as an initiator. Copolymers with a theoretical number-average molecular weight ($M_{n, theoretical}$) of 50,000 g/mol were prepared. The 1-dodecanol concentrations of 0.28 and 0.27 mol% were used to synthesize the PDLL and the PDLLG, respectively. The crude copolymers were purified by dissolving in chloroform before precipitating in cool *n*-hexane. They were then dried to a constant weight in a vacuum at 50°C for 48 h.

Characterization of copolymers

The specific optical rotation of the PDLL copolymers was determined in chloroform at a concentration of 1 g/dL at 25°C with a Bellingham and Stanley Polarimeter ADP220 at a wavelength of 589 nm. The specific optical rotation of the PDLL

was used to calculate the D and L enantiomer contents.[7-8]

The chemical compositions of the PDLLG copolymers were measured by ^{1}H-NMR spectrometry using a Bruker Advance DPX 300 ^{1}H-NMR spectrometer at 25°C. $CDCl_3$ was used as the solvent, and tetramethysilane was used as the internal standard.

The number-average molecular weight (M_n) and molecular weight distribution (MWD) of the copolymers were determined by Gel Permeation Chromatography (GPC) with a Waters e2695 separations module equipped with PLgel 10 mm mixed B 2 columns operating at 40°C and employing a refractive index (RI) detector. Tetrahydrofuran was used as the solvent at a flow rate of 1.0 mL/min.

The thermal transition properties of the copolymers were determined with a Perkin-Elmer Pyris Diamond differential scanning calorimeter (DSC) under a nitrogen flow. For DSC, copolymers of 5 – 10 mg in weight were heated at 10°C/min over a temperature range of 0 to 200 C (1st heating scan) to observe their melting temperature (T_m). Then the samples were quenched to 0°C according to the

Table 1: Molecular weight characteristics of copolymers from GPC curves

Comonomer ratio (by mole)	M_n (g/mol)	MWD
DLL/LL ratio		
100/0	53,200	2.2
90/10	49,600	2.7
80/20	53,600	2.5
70/30	52,100	2.4
60/40	47,100	1.6
50/50	49,200	1.8
DLL/LL/G ratio		
75/0/25	51,500	1.6
67.5/7.5/25	56,400	1.5
60/15/25	53,600	2
52.5/22.5/25	47,600	1.7
45/30/25	48,700	1.9
37.5/37.5/25	51,200	1.7

DSC instrument's own default cooling mode before heating from 0 to 200°C (2nd heating scan) to observe their glass transition temperature (T_g). The T_m was measured as the peak value of the endothermal phenomena in the DSC curve. The T_g was taken as the midpoint or half of the heat capacity increment, associated with the glass-to-rubber transition.

Preparation of drug-loaded copolymer microparticles

The copolymer microparticles entrapping the indomethacin model drug were prepared by the oil-in-water emulsion solvent evaporation method. Dichloromethane was used as an organic solvent. 90 mg of copolymer and 10 mg of indomethacin were dissolved in 2.5 mL of dichloromethane (oil phase). The oil phase was slowly added-drop wise into 400 mL of a 2% w/v Tween80 solution in distilled water (water phase) under magnetic stirring. The organic solvents were evaporated in a fume hood for 6 h. The drug-loaded microparticles suspended in the water phase were obtained. The resulting microparticles were collected by centrifugation before freeze-drying.

Characterization of drug-loaded copolymer microparticles

The morphology of the microparticles was observed by scanning electron microscopy (SEM, JEOL JSM-6460LV). The microparticles were sputter-coated with gold to enhance the surface conductivity before scanning. The average size of the microparticles was determined from several SEM images by counting a minimum of 100 particle diameters using the smile view software (version 1.02).

The drug loading of the microparticles was measured by UV-vis spectrophotometry (Lamda 25, Perkin Elmer). For this purpose, the drug-loaded microparticles were completely dissolved in dichlorometane before analysis with a UV-vis spectrophotometer at λ_{max} = 319 nm.[9] The amount of indomethacin was calculated by comparison with a standard equation of indomethacin solution in dichloromethane. The standard equation and R^2 were y = 0.0181x + 0.0158 and 0.9996, respectively.

The theoretical drug loading content (DLC$_{theoretical}$), actual drug loading content (DLC$_{actual}$), and drug loading efficiency (DLE) were calculated form Equations (1) – (3), respectively. The DLC$_{actual}$ was an average value from three measurements.

$$DLC_{theoretical}\ (\%)\ =\ \frac{Weight\ of\ feed\ drug}{Weights\ of\ feed\ drug\ and\ PDLLA} \times 100$$

...(1)

$$DLC_{actual}\ (\%)\ =\ \frac{Weight\ of\ entrapped\ drug\ in\ microparticles}{Weight\ of\ microparticles} \times 100$$

...(2)

$$DLE\ (\%) = \frac{DLC_{actual}}{DLC_{theoretical}} \times 100$$

...(3)

where the weight of the entrapped drug in the microparticles was measured by dissolving the drug-loaded microparticles in dichloromethane before analysis with UV-vis spectrophotometry at λ_{max} = 319 nm.

In vitro drug release tests

An *in vitro* drug release test with the microparticles was performed. About 10 mg of drug-loaded microparticles were placed in a pretreated dialysis bag before being incubated in a flask containing 200 mL of 0.02 M phosphate buffer saline (PBS, pH 7.4). The flasks were kept in a shaker incubator at 37°C and 100 rpm for 48 h. At each desired time, some supernatant was withdrawn and replaced with an equal volume of fresh PBS medium. The release concentration of the indomethacin in the supernatant was determined by a UV-vis spectrophotometer at λ_{max} = 319 nm[9].

The amount of indomethacin model drug was calculated by comparison with a standard equation of indomethacin solution in PBS. The standard equation and R^2 were y = 0.02x + 0.0047 and 0.9994, respectively. The cumulative release

Table 2: Enantiomer ratios and chemical compositions of copolymers

Comonomer ratio (by mole)	Feed X_D/X_L ratio (by mole)[a]	Final X_D/X_L ratio (by mole)[b]	Feed DLL-LL/G ratio (by mole)[c]	Final DLL-LL/G ratio (by mole)[d]
DLL/LL ratio				
100/0	50/50	50/50	-	-
90/10	45/55	45/55	-	-
80/20	40/60	41/59	-	-
70/30	35/65	37/63	-	-
60/40	30/70	32/68	-	-
50/50	25/75	27/73	-	-
DLL/LL/G ratio				
75/0/25	-	-	75/25	75/25
67.5/7.5/25	-	-	75/25	76/24
60/15/25	-	-	75/25	78/22
52.5/22.5/25	-	-	75/25	76/24
45/30/25	-	-	75/25	72/28
37.5/37.5/25	-	-	75/25	72/28

[a] Calculated from feed DLL/LL ratio based on 50/50 D-/L-form ratio and 5/95 D-/L-form ratio for D,L-lactic acid and L-lactic acid, respectively.
[b] Determined from polarimetry method.
[c] Calculated from feed DLL/LL/G ratio.
[d] Calculated from ^{1}H-NMR spectra.

percentage of indomethacin (% drug release) was calculated based on the ratio of the drug release at each time and the initial drug content in the microparticles. The drug release profiles were plotted

Fig. 1: ¹H-NMR spectrum of PDLLG with feed DLL/LL/G mole ratio of 67.5/7.5/25 in CDCl₃ (peak assignments as shown)

between %drug release and release time. The *in vitro* drug release tests were performed in triplicate.

RESULTS AND DISCUSSION

Characterization of copolymers

The yields of all the copolymers obtained from the precipitation method were higher than 85%. Table 1 reports the number-average molecular weight (M_n) and molecular weight distributions (MWD) of the copolymers obtained from the GPC curves. All the GPC curves were unimodal. The M_n and MWD values were in the ranges of 47,100-56,400 g/mol and 1.5-2.7, respectively. The M_n values obtained from the GPC were close to the values of the theoretical M_n (50,000 g/mol). The M_n of the copolymers was then controlled by the 1-dodecanol concentration.

The PDLL copolymers with different DLL/LL ratios were polymerized from the mixtures of DLL and LL monomers. The feed DLL/LL ratios were 100/0, 90/10, 80/20, 70/30, 60/40, and 50/50 by mole, which corresponded to the feed X_D/X_L ratios
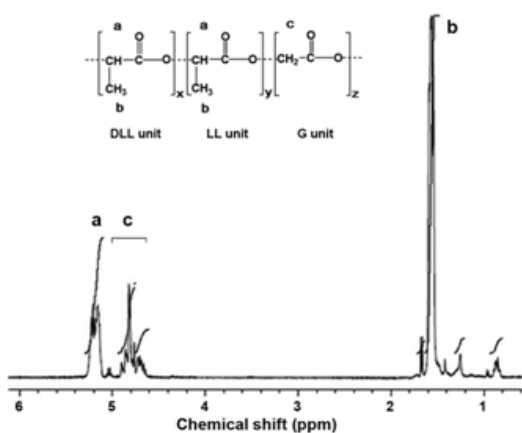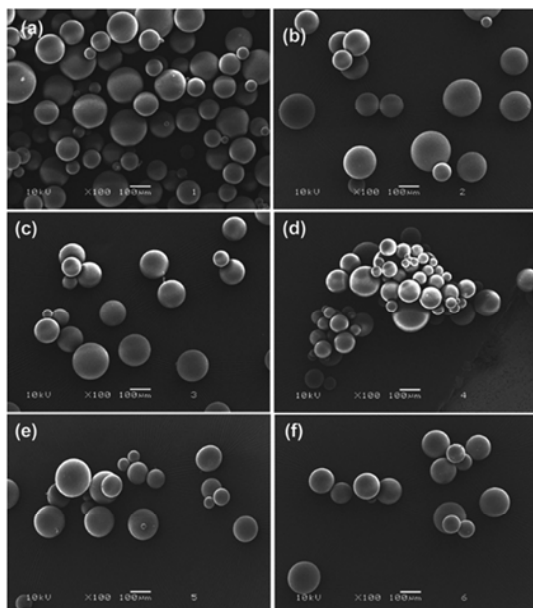

Fig. 2: SEM images of drug-loaded PDLL microparticles before drug release test prepared from PDLL with feed DLL/LL ratios of (a) 100/0, (b) 90/10, (c) 80/20, (d) 70/30, (e) 60/40, and (d) 50/50 by mole (all scale bars = 100 mm)
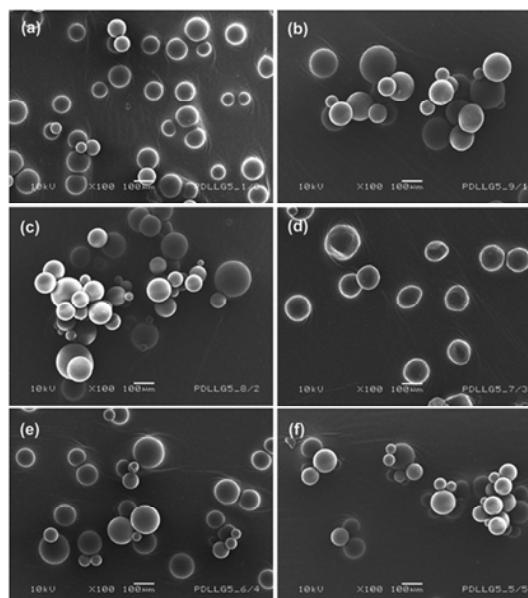

Fig. 3: SEM images of drug-loaded PDLLG microparticles before drug release test prepared from PDLLG with feed DLL/LL/G ratios of (a) 75/0/25, (b) 67.5/7.5/25, (c) 60/15/25, (d) 52.5/22.5/25, (e) 45/30/25, and (f) 37.5/37.5/25 by mole (all scale bars = 100 mm)

of 50/50, 45/55, 40/60, 35/65, 30/70, and 25/75 by mole, respectively, as summarized in Table 2. The final X_D/X_L ratios of the PDLL copolymers determined from the polarimetry are also reported in Table 2. They were very close to the values of the feed X_D/X_L ratios. The results suggest that the PDLL copolymers with different X_D/X_L ratios can be synthesized from the DLL/LL mixtures.

The PDLLG copolymers with different DLL/LL/G ratios were synthesized from the mixtures of DLL, LL, and G momomers. The DLL/LL/G ratios were 70/0/25, 62.5/7.5/25, 60/15/25, 52.5/22.5/25,

45/30/25, and 37.5/37.5/25 by mole, as reported in Table 2. The feed DLL-LL/G ratio was constant at 75/25 by mole. The final DLL-LL/G ratios were determined from the ^{1}H-NMR spectrum, an example of which is shown in Figure 1 for the 62.5/7.5/25 DLL/LL/G copolymer including peak assignments. It can be seen that the half DLL and LL units exhibited the same peaks as the methine protons (-CH; peak a) and methyl protons (-CH$_3$; peak b) at 5.2 and 1.5 ppm, respectively.[10] The DLL/LL ratios of the PDLL copolymers could not be determined from the ^{1}H-NMR spectra. The half G units showed peaks of methylene protons (-CH$_2$; peak c) in the range 4.6-
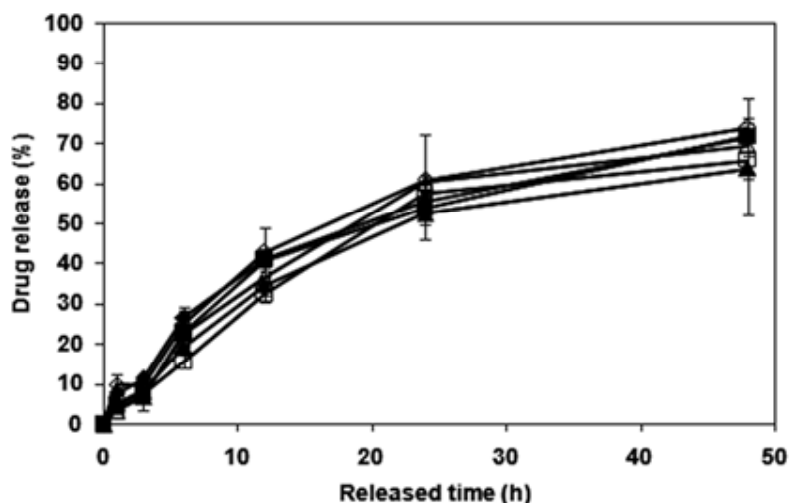

Fig. 4: *In vitro* **drug release profiles of PDLL microparticles prepared from PDLL with feed DLL/LL ratios of (◊) 100/0, (△) 90/10, ( ) 80/20, (♦) 70/30, (▲) 60/40, and (■) 50/50 by mole**
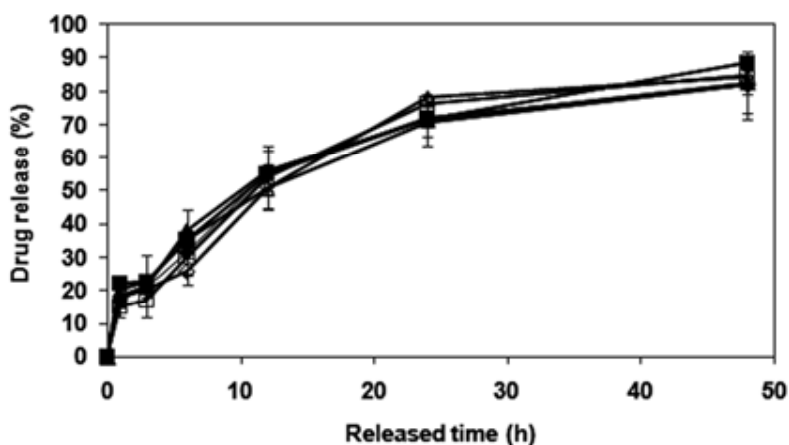

Fig. 5: *In vitro* **drug release profiles of PDLLG microparticles prepared from PDLLG with feed DLL/LL/G ratios of (◊) 75/0/25, (△) 62.5/7.5/25, ( ) 60/15/25, (♦) 52.5/22.5/25, (▲) 45/30/25, and (■) 37.5/37.5/25 by mole**

5.0 ppm.[11] The final DLL-LL/G ratios of the PDLLG copolymers calculated from the integral peak areas of the peaks a and c are also reported in Table 2. They were nearly the same values as with the feed DLL-LL/G ratio (75/25 by mole).

From the 1st heating scan DSC curves, the melting peaks of all the PDLL and the PDLLG copolymers were not found (DSC thermograms not shown). This suggests that the copolymers with the DLL/LL and the DLL/LL/G ratios in the ranges of this study were completely amorphous. It is well known that amorphous polyesters are more appropriate for use in drug delivery. The entrapped drug could be uniformly distributed into the amorphous matrix better than the semi-crystalline matrix. This enhances the consistent drug release. The glass transition temperatures (T_g) of the copolymers obtained from the 2nd heating scan DSC curves were similar and in the ranges of 53-54°C and 48-49°C for

the PDLL and the PDLLG copolymers, respectively. The results indicate that the DLL/LL and DLL/LL/G ratios do not affect the T_g values of the copolymers. The T_g values of the PDLLG copolymers were slightly lower than the PDLL copolymers because the T_g of the homopolymers of polyglycolide (37°C) was lower than the polylactide (55°C).

Characterization of copolymer microparticles

The drug-loaded copolymer microparticles of PDLL and PDLLG were prepared by the oil-in-water emulsion solvent evaporation method. The yields of the microparticles, based on the weights of the feed copolymer and drug, were in the range of 82.4-93.7%. The morphology of the drug-loaded microparticles was observed from the SEM images, as shown in Figures 2 and 3 for the PDLL and the PDLLG, respectively. They were spherical in shape with a smooth surface. The average particle sizes determined from several SEM images are summarized in Table 3. They were in the range of 89-113 mm. The morphology results suggest that the monomer ratio of the copolymers did not significantly affect their particle morphology and size.

The theoretical drug loading content ($DLC_{theoretical}$) of all the copolymer microparticles calculated from Equation (1) was 10 wt %. The actual drug loading content (DLC_{actual}) and the drug loading efficiency (DLE), as summarized in Table 3, were in the ranges of 5.39–6.60% and 53.9–66.0%, respectively. Both DLC_{actual} and DLE did not change significantly with the DLL/LL and the DLL/LL/G ratio.

***In vitro* drug release**

The *in vitro* drug release test was performed in PBS at 37°C for 48 h. The release profiles of indomethacin are illustrated in Figure 4 for the PDLL microparticles. All PDLL microparticles with different DLL/LL ratios showed similar sustained drug release patterns. An initial burst release of the drug near the particle surfaces was detected within the first 12 h followed by a slower drug release. The initial burst release of the PDLL microparticles was in the range of 30-40%. The drug release was in the range of 60-70% at 48 h of release time.

Figure 5 shows the drug release profiles of the PDLLG microparticles. All PDLLG microparticles
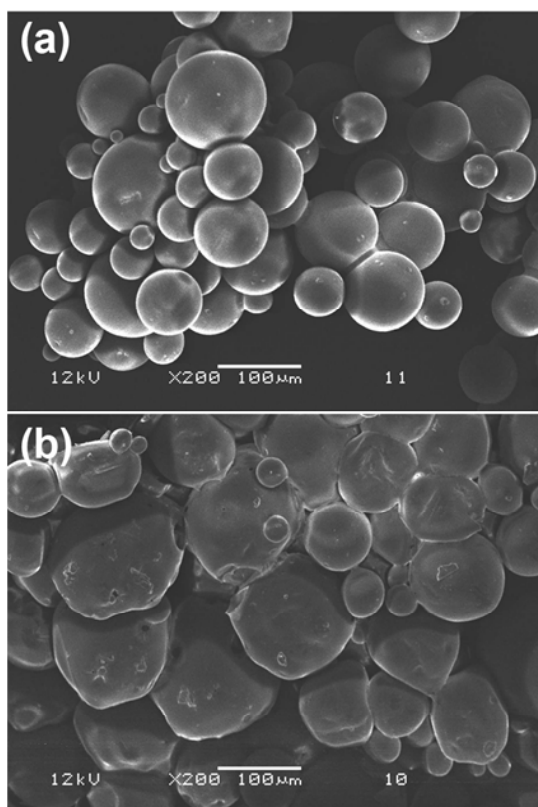

Fig. 6: SEM images of drug-loaded copolymer microparticles after 48 h release time prepared from (a) 100/0 DLL/LL, and (b) 75/0/25 DLL/LL/G copolymers (all scale bars = 100 mm)

Table 3: Characteristics of drug-loaded copolymer microparticles

Comonomer ratio (by mole)	Average particle size (mm) [a]	DLC$_{actual}$ (%) [b]	DLE (%) [c]
DLL/LL ratio			
100/0	104 ± 34	5.93 ± 0.04	59.3
90/10	109 ± 30	5.50 ± 0.10	55
80/20	111 ± 32	6.08 ± 0.03	60.8
70/30	94 ± 23	5.75 ± 0.34	57.5
60/40	101 ± 37	5.76 ± 0.14	57.6
50/50	113 ± 27	5.39 ± 0.18	53.9
DLL/LL/G ratio			
75/0/25	89 ± 16	5.63 ± 0.02	56.3
67.5/7.5/25	102 ± 21	6.21 ± 0.17	62.1
60/15/25	93 ± 23	6.09 ± 0.33	60.9
52.5/22.5/25	103 ± 13	6.27 ± 0.18	62.7
45/30/25	92 ± 29	6.12 ± 0.14	61.2
37.5/37.5/25	92 ± 22	6.60 ± 0.08	66

[a] Determined from several SEM images
[b] Calculated from Equation (2)
[c] Calculated from Equation (3)

with different DLL/LL/G ratios exhibited similar sustained drug release profiles; an initial burst release effect within the first 12 h followed by slower drug release. However, the ranges of the initial burst release and drug release at 48 h of the PDLLG microparticles were 50-60% and 80-90%, respectively. It can be concluded that the DLL/LL and DLL/LL/G ratios did not significantly influence the drug release behaviors of the PDLL and the PDLLG microparticles, respectively. However the PDLLG microparticles exhibited a faster drug release than those of the PDLL microparticles. The drug release results suggest that the PDLL and PDLLG copolymers with different monomer mole ratios showed potential for use as controlled release drug delivery systems. The concentrations of the drug in the plasma could be maintained at the therapeutic level for longer periods of time. Therefore, the frequency of drug administration could be reduced.

The predominant drug release mechanism of the PDLL microparticles was proposed to be the drug diffusion process. This was supported by the SEM image of the PDLL microparticles in Figure 6(a). The PDLL microparticles after 48 h release were still spherical in shape and had a smooth surface. Meanwhile the PDLLG microparticles had surface erosion, as shown in Figure 6(b). Thus the drug release mechanisms of the PDLLG microparticles within 48 h may include both drug diffusion and surface erosion.[10] This may be due to the higher hydrophilicity and the lower T$_g$ of the PDLLG microparticle matrices that gave easier water penetration into the particle matrices. Therefore, higher water penetration induces faster surface erosion.

CONCLUSIONS

PDLL and PDLLG copolymers with different DLL/LL and DLL/LL/G mole ratios, respectively, were successfully synthesized via ring-opening polymerization of the mixtures of DLL, LL, and G monomers. They were completely amorphous. The drug-loaded copolymer microparticles of the PDLL and the PDLLG were prepared by the oil-in-water emulsion solvent evaporation method. These amorphous microparticles could be used to entrap a poorly-water soluble model drug, indomethacin with a 89-113 mm size and a 53.9–66.0% loading efficiency for drug delivery. All the copolymer microparticles were spherical in shape and had a

smooth surface. The copolymerization of the LL units was as high as 50 and 37.5 mol% for the PDLL and the 75/25 PDLLG copolymers, respectively, did not induced PLLA crystallization, and did not affect the drug release profiles significantly. The PDLLG microparticles showed faster drug release than the PDLL microparticles.

In conclusion, the results presented here show that the amorphous PDLL and PDLLG copolymers synthesized in this work have the potential to be developed further as drug delivery systems. The amorphous PDLL and PDLLG copolymers with a high L enantiomer content could provide a viable lower-cost alternative to the commercial PDLL and PDLLG.

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