Preparation of Drug-Loaded Microspheres of Linear and Star-Shaped Poly(D,L-lactide)s and Their Drug Release Behaviors

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ABSTRACT: Linear (1-arm) and star-shaped (4-, 6-, and 16-arm) poly(D,L-lactide)s (PDLLs) were synthesized by ring-opening polymerization in bulk of D,L-lactide monomer. Hydroxyl end-group compounds and stannous octoate were used as the initiator and catalyst, respectively. The intrinsic viscosity and glass transition temperature (T_g) of the PDLLs decreased steadily as the branch arm number increased for similar molecular weights. However, the intrinsic viscosity and T_g values of the linear PDLL were less than the star-shaped PDLL for similar each PDLL arm lengths. Ibuprofen, a poorly water soluble model drug was entrapped in the PDLL microspheres. All drug-loaded PDLL microspheres were prepared by the oil-in-water emulsion solvent evaporation method, were spherical in shape, and had a smooth surface with fine dispersibility. *In vitro* drug release behaviors indicated that the drug release from the microspheres with higher branch arm number was faster than from those with lower branch arm number. Moreover, the drug release from the star-shaped PDLL microspheres was slower than that of the linear PDLL microspheres for similar PDLL arm lengths. The drug release behavior could be adjusted through both the branch arm number and arm length of PDLL. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 124: 3871–3878, 2012

Key words: poly(D,L-lactide); star-shaped polyesters; microspheres; controlled release

INTRODUCTION

Controlled release drug delivery carriers made from biodegradable particles provides several benefits over traditional formulations.[1] Prior to release, the drug is protected from degradation or premature metabolism by the polymeric particle matrix. Release of the drug is sustained over days to months, thereby maintaining plasma drug concentrations at therapeutic levels for longer periods of time. This reduces the frequency of administration and increases patient compliance.[2] Biodegradable drug carriers have been made from a variety of biodegradable polyesters.

Recently, star-shaped biodegradable polyesters containing branch arm numbers of three (or higher) have attracted much attention because of their particular properties resulting from their special three-dimensional structures.[3,4] The polyesters with different arm numbers have been synthesized using initiators containing different hydroxyl end-groups. The chemical structures in each arm are the same. The influences of arm number and arm length on crystallinity, melting temperature and degradation of these star-shaped polyesters have been widely reported for poly(L-lactide),[3,5–8] poly(D,L-lactide),[9,10] poly (ε-caprolactone)[11–14] and its block copolymers.[15,16] The microspheres of poly(D,L-lactide) (PDLL) and its copolymers have been widely investigated as controlled release drug delivery matrices due to its completely amorphous form.[17] Complete drug distribution into the PDLL matrices could be obtained due to its complete amorphous state. The semi-crystalline phases in poly(L-lactide) may induce drug aggregates into the poly(L-lactide) matrix. Complete distribution of entrapped drug into the microsphere matrices could allow a consistent drug release rate. Pentaerythritol, dipentaerythritol, and Boltorn H20 have been used as hydroxyl end-group initiators for synthesizing the biodegradable star-shaped polyesters containing 4, 6, and 16 arms, respectively.[8,18] However, comparison of these star-shaped and linear polyester microspheres as drug delivery carriers has been scarcely published.

For drug delivery systems it is necessary to carefully adjust the drug release rate. Drug release from the polylactide matrix is generally controlled by

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both drug diffusion and polymer erosion.[19] It is known that increased molecular mobility of PDLL (decreasing its glass transition temperature, T_g) causes a faster swelling of the microsphere matrix and, thereby, promotes faster drug release. The T_g of biodegradable polyesters can be tailored by adjusting their molecular architectures.[20] The star-shaped PDLLs may provide new controlled release drug carriers with interesting drug release behaviors.

In the present work, we report the influence of molecular architectures (arm number and arm length) of PDLLs on their thermal transitions, drug-loaded microsphere characteristics, and drug release behaviors of a hydrophobic model drug. The linear PDLLs and star-shaped PDLLs with arm numbers of 4, 6, and 16 were synthesized using different initiators and monomer/initiator mole ratios.

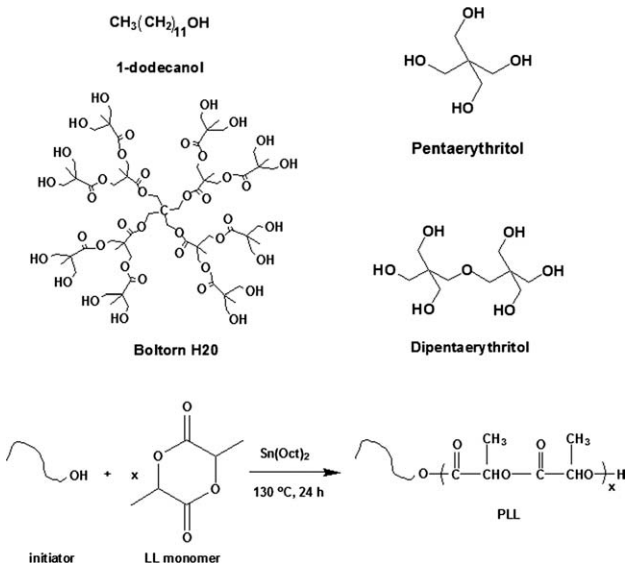
EXPERIMENTAL

Materials

D,L-lactide (DLL) monomer was synthesized by well-established procedures from D,L-lactic acid (90% Fluka, Switzerland). The DLL was purified by repeated recrystallization from distilled ethyl acetate and dried in a vacuum oven at 50°C for 48 h before use; 1-dodecanol (98%, Fluka, Switzerland) containing one hydroxyl end group was purified by distillation under reduced pressure before being stored over molecular sieves. It was used as an initiator for preparing 1-arm PDLL. Pentaerythritol (99%, Aldrich, USA), dipentaerythritol (99%, Aldrich, USA), and Boltorn H20 (Perstorp Specialty Chemicals, Sweden) were dried in a vacuum oven at 50°C for 48 h before use as initiators and contained 4-, 6-, and 16-hydroxyl end groups, respectively. Stannous octoate (95% Sigma, USA), $Sn(Oct)_2$, was used without further purification. Ibuprofen (99.95%) was used as a model drug. It was kindly supplied from the Government Pharmaceutical Organization, Thailand. All reagents used were analytical grade.

Synthesis of poly(D,L-lactide)s

Poly(D,L-lactide)s (PDLLs) with different arm numbers (1, 4, 6, and 16 arms) were polymerized in bulk at 130°C for 24 h under nitrogen atmosphere. A DLL/initiator ratio of 208/1 by mole was used. The theoretical molecular weights of these PDLLs were approximately 30,000 g/mol, designated as PDLL30,000. Hydroxyl end group compounds and $Sn(Oct)_2$ were used as the initiating system. The chemical structures of the initiators and polymerization reaction are illustrated in Scheme 1. $Sn(Oct)_2$ concentration was kept constant at 0.02 mol%. As-polymerized PDLLs were purified by being dissolved in chloroform and precipitated in cool *n*-hexane before drying to constant weight in a vacuum oven at room temperature. A linear PDLL with a theoretical molecular weight of 5000 g/mol, designated as PDLL5000, was also synthesized for comparison by using a 35/1 mole ratio of DLL/initiator and 0.02 mol% $Sn(Oct)_2$.



Scheme 1 Chemical structures of co-initiators and ring-opening polymerization reaction of lactide monomer.

Characterization of poly(D,L-lactide)s

Intrinsic viscosity, [η], of PDLLs was determined from flow-time measurements on a diluted series of solutions in chloroform ($CHCl_3$), as the solvent, at 30°C viscometrically.

Molecular weight characteristics of the PDLLs were characterized by ^{1}H-NMR spectrometry using a Bruker Avance DPX 300 ^{1}H-NMR Spectrometer and gel permeation chromatography (GPC) with a Waters 717 plus Autosampler GPC equipped with an Ultrastyragel® column operating at 40°C and employing universal calibration. ^{1}H-NMR spectra were obtained from polymer solutions in deuterated chloroform ($CDCl_3$) using tetramethysilane as the internal reference. For GPC analysis, tetrahydrofuran was used as the solvent at a flow rate of 1 mL/min.

Thermal properties of the PDLLs were determined by means of differential scanning calorimetry (DSC) using a Perkin-Elmer DSC Pyris Diamond. For DSC analysis, 5–10 mg of PDLL was heated at 10°C/min under helium flow in order to observe its glass transition temperature (T_g).

Preparation of microspheres

Drug-loaded PDLL microspheres were prepared by the oil-in-water emulsion solvent evaporation method. Briefly, 0.18 g of PDLL and 0.02 g of

TABLE I
Viscosity and Molecular Weight Characteristics of Linear and Star-Shaped PDLLs

PDLLs	[η] (dL/g)	$M_{n,\ yield}$[a] (g/mol)	$M_{n,\ NMR}$[b] (g/mol)	$M_{n,\ GPC}$[c] (g/mol)	MWD[c]
1-arm linear PDLL5000	0.098	4600	4900	4900	1.5
1-arm linear PDLL30,000	0.524	28,200	29,500	33,139	1.5
4-arm star-shaped PDLL30,000	0.349	27,300	30,100	29,058	1.4
6-arm star-shaped PDLL30,000	0.259	27,900	29,800	27,400	1.4
16-arm star-shaped PDLL30,000	0.115	26,400	30,300	22,115	1.3

[a] Calculated from theoretical M_n × (%yield/100); [theoretical M_n was determined from monomer/initiator feed ratios].
[b] Calculated from ^{1}H-NMR spectra.
[c] Obtained from GPC curves; MWD = molecular weight distribution.

ibuprofen were dissolved in dichloromethane (5 mL). After complete dissolution, it was poured into 100 mL of 2 wt% Tween80 solution in water. The solution was then emulsified by a magnetic stirrer at 900 rpm to form a W/O emulsion. The dichloromethane was evaporated in a fume hood for 6 h. The drug-loaded microspheres were centrifuged at 3000 rpm for 20 min and washed three times with distilled water. The microspheres were then freeze-dried overnight and stored at 4°C before characterization and drug release testing.

Characterization of microspheres

Morphology of the microspheres was investigated by scanning electron microscopy (SEM) using a JEOL JSM-6460LV SEM. The microsphere samples were coated with gold for enhancing conductivity before scanning. The average particle size and size distribution of the microspheres were determined by light-scattering (LS) technique using a Coulter LS230 particle size analyzer at 25°C. Thermal properties of the drug-loaded microspheres were measured by the DSC method, as described above.

Actual drug loading content (DLC_{actual}) of the entrapped ibuprofen in the PDLL microspheres was determined by dissolving 20 mg of drug-loaded PDLL microspheres in dichloromethane (1 mL). The ibuprofen concentration in clear solution was calculated from absorbance at λ_{max} = 264 nm by UV–vis spectrophotometry compared to a standard curve of ibuprofen. Theoretical drug loading content ($DLC_{theoretical}$), actual drug loading content (DLC_{actual}), and drug loading efficiency (DLE) were calculated from eqs. (1)–(3), respectively. The DLC_{actual} is an average value from three measurements.

$$DLC_{theoretical}\ (\%) = \frac{\text{Weight of feed drug}}{\text{Weight of feed drug and PDLL}} \times 100 \quad (1)$$

$$DLC_{actual}\ (\%) = \frac{\text{Weight of drug in PDLL microspheres}}{\text{Weight of drug} - \text{loaded PDLL microspheres}} \times 100 \quad (2)$$

$$DLE\ (\%) = \frac{DLC_{actual}}{DLC_{theoretical}} \times 100 \quad (3)$$

In vitro drug release tests

In vitro drug release test of the microspheres was performed as follows. About 20 mg of drug-loaded microspheres were placed in the 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 an incubator shaker at 37°C and 100 rpm. At each desired time, the supernatant was withdrawn and replaced with an equal volume of fresh PBS medium. The release concentration of ibuprofen in the supernatant was determined by a UV–vis spectrophotometer at λ_{max} = 220 nm. The release of pure ibuprofen was also measurement for comparison. For this purpose, the ibuprofen powder was placed in PBS under the same conditions as in the release test. At each time interval, the drug solution was centrifuged at 5000 rpm for 10 min. Then the drug concentration in the supernatant was determined. The drug release profile was plotted according to the cumulative release percentage of ibuprofen (by weight). *In vitro* drug release tests were performed in triplicate.

RESULTS AND DISCUSSION

Characterization of poly(D,L-lactide)s

1-dodeccanol, pentaerythritol, dipentaerythritol, and Boltorn H20 were used as initiators containing hydroxyl end-groups for synthesizing 1-, 4-, 6-, and 16-arm PDLLs, respectively, via ring-opening polymerization. The 1-arm PDLL is a linear PDLL. The PDLLs consisting of 4, 6, and 16 branch arms are called star-shaped PDLLs. The all linear and star-shaped PDLLs had 88–94% yields.

Table I reports the [η] values and the molecular weight characteristics of the PDLLs. For PDLL30,000, the [η] decreased significantly as the arm number increased. The [η] of PDLL solution was directly related to the hydrodynamic volume of the PDLL

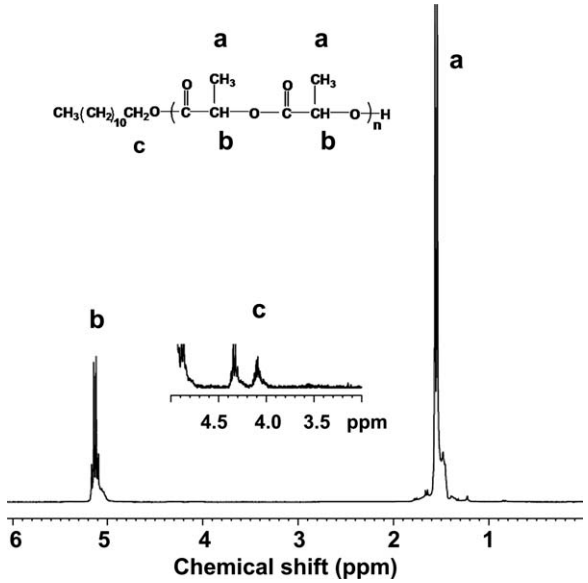


Figure 1 ^{1}H-NMR spectrum of 1-arm linear PDLL30,000 in $CDCl_3$ (peak assignments as shown).

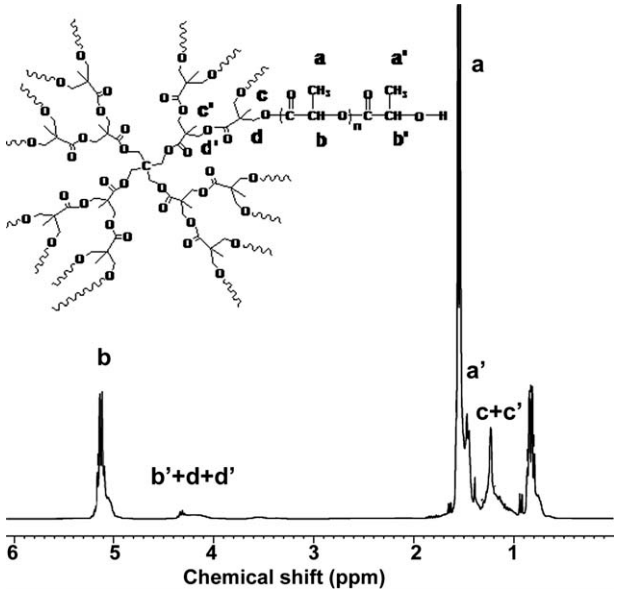


Figure 2 ^{1}H-NMR spectrum of 16-arm star-shaped PDLL30,000 in $CDCl_3$ (peak assignments as shown).

molecules in solution. Higher arm number polyesters exhibited smaller hydrodynamic volume for a similar molecular weight.[7] The viscosity results can be explained due to the hydrodynamic volume of the PDLL in solution decreasing as the arm number increased (or the arm length decreased). Therefore, the higher arm numbered PDLLs induced lower [η]. It should be noted that the [η] of 1-arm PDLL5000 was lower than that of the 6-arm star-shaped PDLL30,000. Each PDLL arm length of the 6-arm star-shaped PDLL30,000 was estimated as 5000 g/mol. This suggests that a star-shaped structure can increase the [η] value due to it being a larger molecule.

Figures 1 and 2 show the ^{1}H-NMR spectra of the 1-arm linear and 16-arm star-shaped PDLLs, as examples. Number-average molecular weights (M_n) of the PDLLs can be calculated based on integral peak areas of the ^{1}H-NMR spectra. From the ^{1}H-NMR spectrum in Figure 1, the ethylene protons (CH_2, peak c) of the initiator at 3.9–4.2 ppm and the methine protons (CH, peak b) of the DLL units at 4.9–5.3 ppm were used to measure the M_n.[9] The M_ns of 4- and 6-arm star-shaped PDLLs were also calculated using these integral proton peak areas from their ^{1}H-NMR spectra. Whereas the overlapped integral peak areas of peaks b′, d, and d′ at 3.9–4.4 ppm and the methine protons (CH, peak b) of DLL units at 4.9–5.3 ppm in the ^{1}H-NMR spectrum of the 16-arm star-shaped PDLL (Fig. 2) were used for this purpose, which corresponded to the literature.[8]

As shown in Table I, the M_ns of PDLL5000 and PDLL30,000 calculated from feed ratios ($M_{n,\ \mathrm{yield}}$) and ^{1}H-NMR spectra ($M_{n,\ \mathrm{NMR}}$) are nearly 5000 and 30,000 g/mol, respectively. However, the M_ns obtained from GPC curves slightly decreased as the arm number increased. Molecular weight distributions of the linear and star-shaped PDLLs showed narrow values in a range of 1.3–1.5. The GPC curves of all the PDLLs showed a unimodal type, as an example of which is shown in Figure 3 for the 6-arm star-shaped PDLL30,000.

The T_gs of PDLLs obtained from the DSC curves in Figure 4 are summarized in Table II. It can be seen that the T_gs decreased as the arm number for the PDLL30,000 increased. This may be explained as the shorter arms of the PDLL30,000 were easier to rotate than the longer arms. The estimated arm lengths were in order 1-arm > 4-arm > 6-arm > 16-arm PDLL30,000 as reported in Table II. Thus the shorter PDLL arm lengths induced a lower T_g. This indicates that the T_g of PDLLs can be controlled with the PDLL molecular architecture (or branch arm number).[7–9] Therefore, star-shaped polymerization is an alternative method for adjusting the T_g of

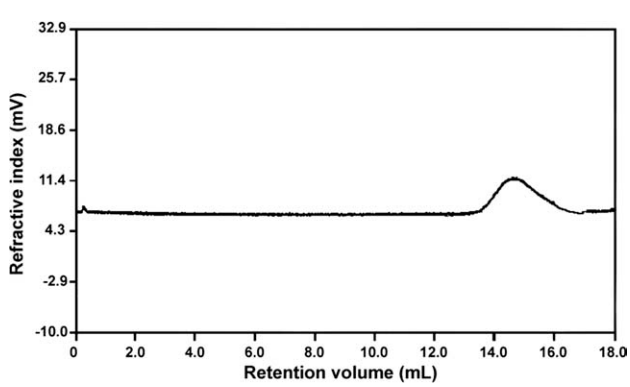


Figure 3 GPC curve of 6-arm star-shaped PDLL30,000.

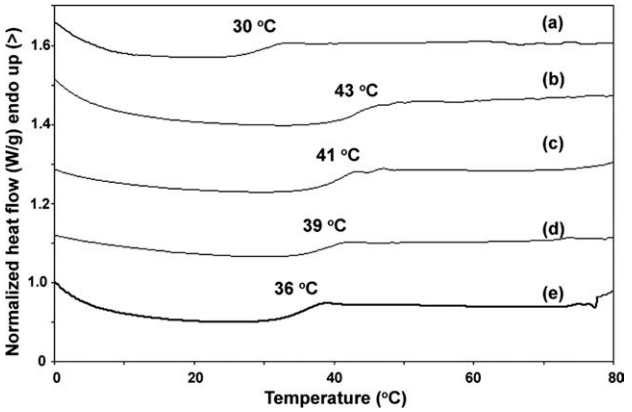


Figure 4 Second heating scan DSC thermograms of (a) 1-arm PDLL5000, (b) 1-arm PDLL30,000, (c) 4-arm PDLL30,000, (d) 6-arm PDLL30,000, and (e) 16-arm PDLL30,000.

TABLE II
T_g of Linear and Star-Shaped PDLLs

PDLLs	PDLL arm length[a] (g/mol)	T_g[b] (°C)
1-arm linear PDLL5000	4900	30
1-arm linear PDLL30,000	29,500	43
4-arm star-shaped PDLL30,000	7525	41
6-arm star-shaped PDLL30,000	4500	39
16-arm star-shaped PDLL30,000	1894	36

[a] Calculated from $M_{n,\ NMR}$/arm number.
[b] Measured from DSC curves.

PDLL. In addition, each PDLL arm may be difficult to rotate when it is connected to other PDLL arms in the star-shaped structure. This induces a higher T_g

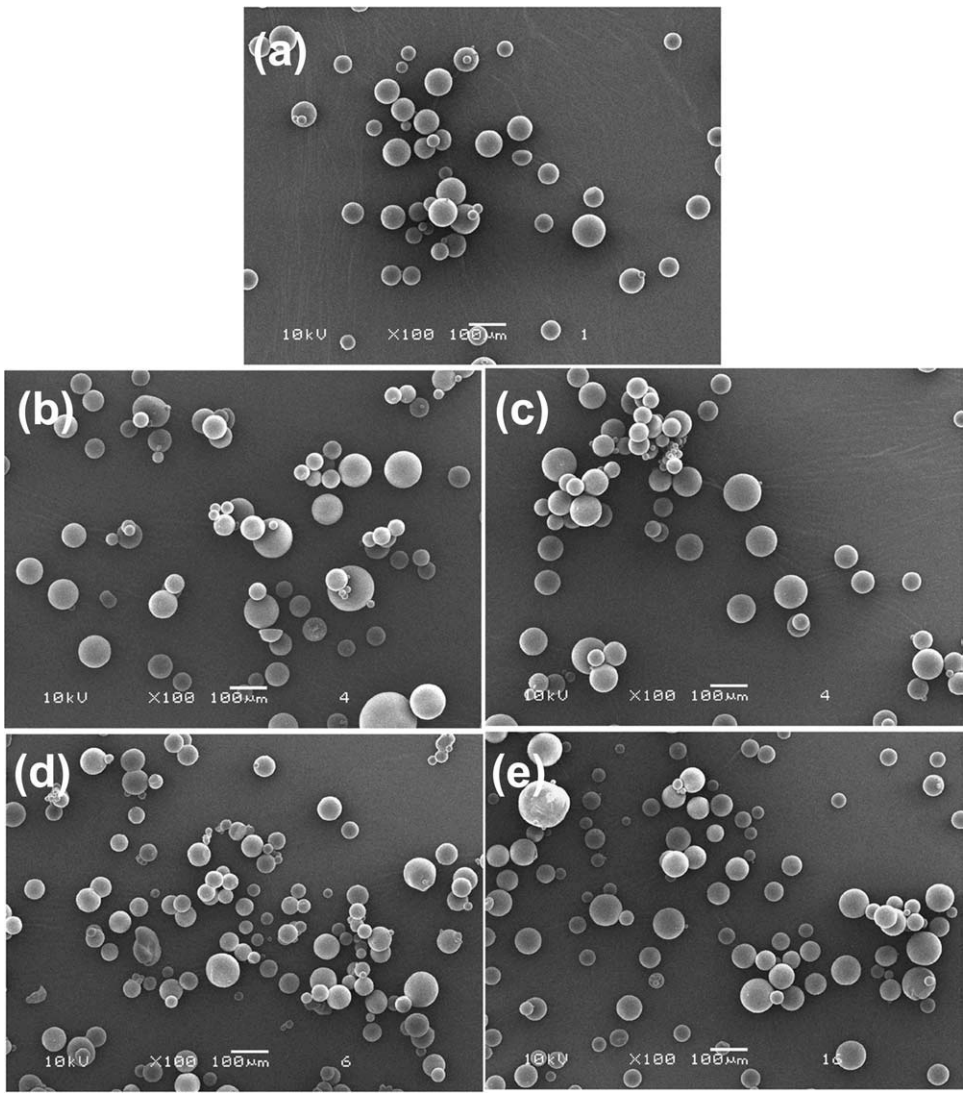


Figure 5 SEM images of drug-loaded microspheres of (a) 1-arm PDLL5000, (b) 1-arm PDLL30,000, (c) 4-arm PDLL30,000, (d) 6-arm PDLL30,000, and (e) 16-arm PDLL30,000. All bars = 100 μm.

TABLE III
Thermal and Drug Loading Properties of Linear and Star-Shaped PDLL Microspheres

PDLL microspheres	Average size[a] (μm)	T_g[b] (°C)	DLC_{actual}[c] (%)	DLE[d] (%)
1-arm linear PDLL5000	54 ± 12	30	6.1	61
1-arm linear PDLL30,000	80 ± 16	43	6.3	63
4-arm star-shaped PDLL30,000	85 ± 11	40	7.3	73
6-arm star-shaped PDLL30,000	75 ± 18	39	6.9	69
16-arm star-shaped PDLL30,000	81 ± 15	36	7.1	71

[a] Measured from light-scattering analysis.
[b] Determined from DSC curves.
[c] Calculated from eq. (2).
[d] Calculated from eq. (3).

value. This effect was found from the comparison the T_gs of the 1-arm linear PDLL5000 (30°C) and the 6-arm star-shaped PDLL30,000 (39°C), as reported in Table II. Although each arm length of the 6-arm star-shaped PDLL30,000 is similar to the 1-arm linear PDLL5,000. The T_g of the 6-arm PDLL is higher than the 1-arm PDLL.

Characterization of microspheres

The morphology of the drug-loaded microspheres was investigated from the SEM images as shown in Figure 5. The resulting drug-loaded PDLL microspheres with different branch arm numbers were spherical in shape with a smooth surface. The microspheres with fine dispersibility were obtained. The average microsphere sizes determined from the light-scattering analysis are summarized in Table III. They were less than 100 μm. The internal morphology of the microspheres was observed from broken microspheres. The microsphere matrices had a tight structure, as shown in Figure 6, for the broken microsphere of the 6-arm PDLL30,000. The morphology results suggest that the arm number of PDLL30,000 did not significantly affect the microsphere morphology and size. In addition, the PDLL5000 microspheres is the smallest in size. This due to the viscosity of the PDLL5000 solution in dichloromethane and it is the lowest. The viscosity of polymer solution directly related to its molecular weight. For the O/W emulsion solvent evaporation method, the polymer solution with a lower viscosity was emulsified to smaller droplets before solvent evaporation and particle solidification processes.

The $DLC_{theoretical}$ of all PDLL microspheres is 10 wt %. The DLC_{actual} and the DLE, as summarized in Table III, are in the range of 6.1–7.3 wt % and 61–73%, respectively. Both DLC_{actual} and DLE did not change significantly with the arm length and the arm number.

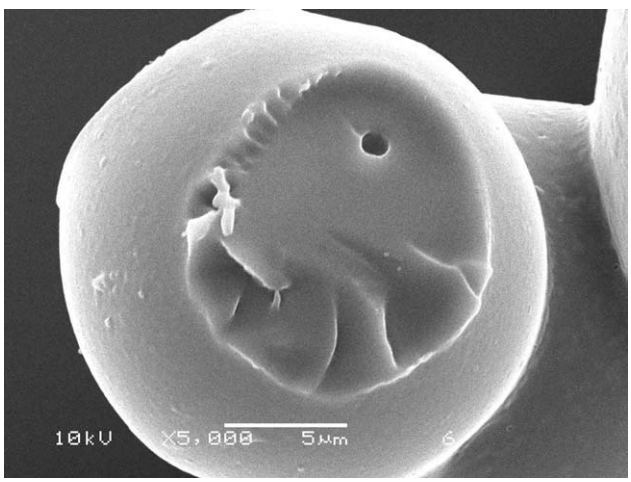


Figure 6 SEM image of drug-loaded microsphere matrix of 6-arm PDLL30,000. Bar = 5 μm.

In vitro drug release

Ibuprofen release profiles are illustrated in Figure 7. Ibuprofen powder showed complete dissolution in the medium solution within the first 6 h of release time. Drug-loaded PDLL microspheres exhibited sustained release profiles. The release profile results suggested that the linear and star-shaped PDLLs showed potential for use in controlled release drug

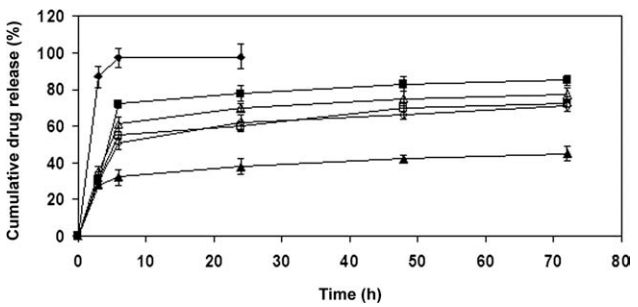


Figure 7 Release profile of (◆) ibuprofen powder, and ibuprofen from microspheres of (■) 1-arm PDLL5000, (▲) 1-arm PDLL30,000, (◇) 4-arm PDLL30,000, (□) 6-arm PDLL30,000, and (△) 16-arm PDLL30,000.

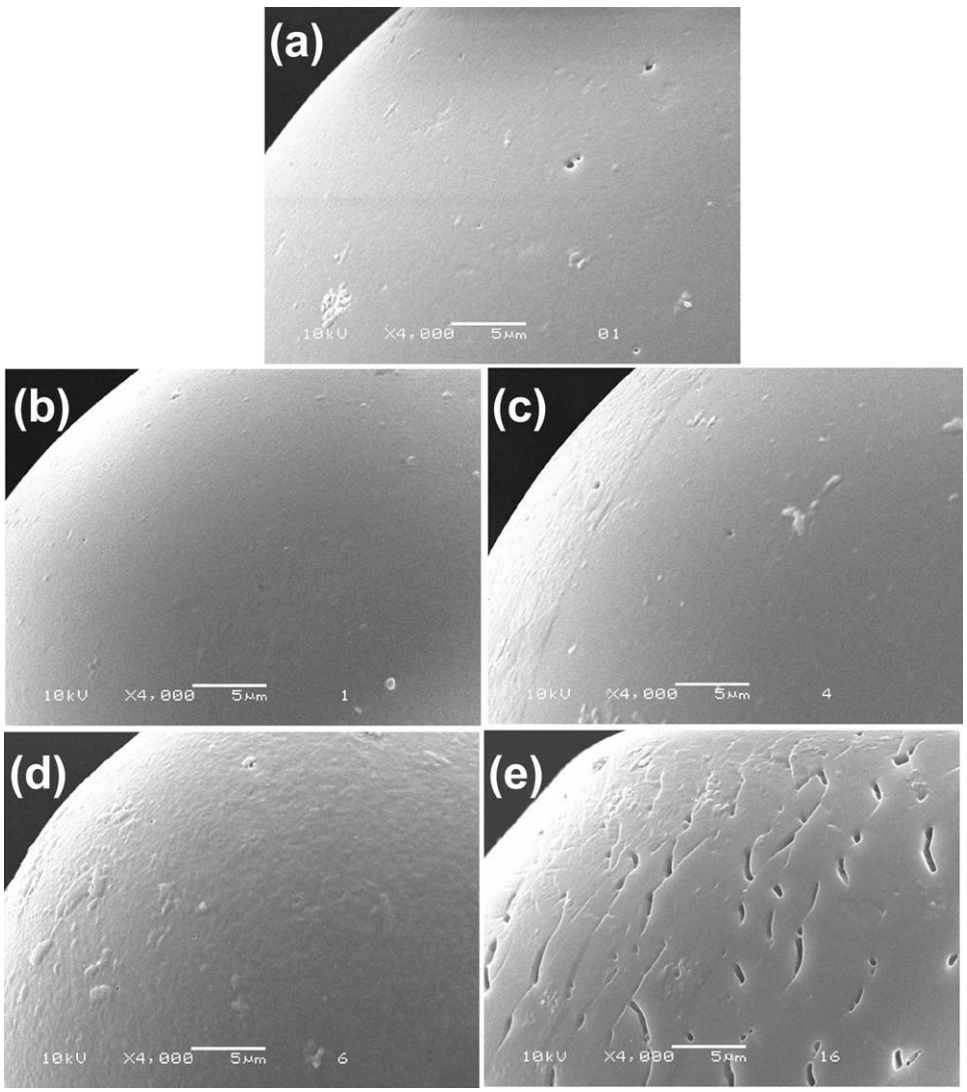


Figure 8 SEM images of microsphere surfaces after drug release test of (a) 1-arm PDLL5000 (b) 1-arm PDLL30,000, (c) 4-arm PDLL30,000, (d) 6-arm PDLL30,000, and (e) 16-arm PDLL30,000. All bars = 5 μm.

delivery applications. The plasma drug concentrations could be maintained at therapeutic levels for longer periods of time than pure ibuprofen. So the frequency of drug administration could be reduced.

Each drug release from PDLL microspheres consisted of an initial burst release within the first 6 h followed by slower drug release. The burst release of the 4-, 6- and 16-arm PDLL30,000 microspheres was in the range of 51–61%. In the 1-arm PDLL30,000 microspheres, the initial burst release is reduced to 32%. The drug release behaviors from the microspheres of 4- and 6-arm PDLL30,000 were similar. This may be due to their arm lengths and T_gs being so similar. The %cumulative drug releases at the 72 h release time from the PDLL30,000 microspheres was in the order of 16-arm $>$ 6-arm $\sim$ 4-arm $>$ 1-arm. The PDLL5000 microspheres exhibited the fastest drug release. The drug release results suggest that the star-shaped PDLLs would exhibit faster drug release than the linear PDLL for a similar molecular weight.

The predominant drug release mechanism was proposed to be the drug diffusion process. This was confirmed from the SEM images of the microsphere surfaces in Figure 8. After 72 h of drug release test, the PDLL30,000 microspheres were still spherical in shape and had a smooth surface, except for some of the surfaces of 16-arm PDLL30,000 microspheres in Figure 8(e) where surface erosion was observed. This may be explained as the higher hydroxyl groups of the 16-arm PDLL30,000 inducing higher hydrophilicity. Moreover, the lower T_g of PDLL gave easier water penetration into the microsphere matrix. Therefore, higher water absorption and penetration induces faster surface erosion. The drug release mechanisms of the 16-arm PDLL microspheres may include both drug diffusion and surface erosion mechanisms.

Indeed a fast burst release (72%) of the drug from the microspheres of 1-arm PDLL5,000 was observed compared to the 6-arm PDLL30,000 (55%). This indicates that the conversion of linear molecules to star-shaped molecular structure can reduce both the initial burst release effect and sustain drug release rate. This data indicates that the arm number and length are important factors for adjusting the drug release behaviors of PDLL microspheres. For PDLLs with similar molecular weight, the drug release content from PDLL microspheres increased as the arm number of PDLL increased. Finally, the drug release content from PDLL microspheres decreased when the linear PDLL chains were formed as star-shaped PDLL.

CONCLUSIONS

The biodegradable PDLLs with different branch arm numbers and arm lengths were successfully synthesized via ring-opening polymerization using hydroxyl end-group initiators and stannous octoate as the initiating system. The arm number and arm length of PDLLs were controlled through adjusting the initiator type and the DLL feed ratio. The T_gs decreased as the arm number increased and the arm length decreased. The drug-loaded PDLL microspheres prepared by the O/W emulsion solvent evaporation technique can be used as carriers of ibuprofen, a poorly water soluble model drug with 61–73% loading efficiency. The microspheres with a higher arm number and/or a shorter arm length exhibited faster drug release. The drug release from these microspheres may be tailored by adjusting the PDLL molecular architecture and arm length.

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