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# Biodegradable and temperature-responsive polyurethanes for adriamycin delivery

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ABSTRACT

To develop biodegradable polymers with temperature-sensitivity, a series of polyurethanes consisting of poly (ethylene glycol) (PEG) and L-lysine ester diisocyanate (LDI) were synthesized, and the structure and molecule weight of the polymers were examined by $^1$H NMR, FT-IR, gel permeation chromatography (GPC). The solution properties of the copolymers were studied by turbidity measurement and size measurement. Polyurethanes could form nanoparticles by sonication in water. No temperature-sensitivity was observed with the polyurethane nanoparticles composed of PEG1000 and PEG1500. On the contrary, LDI-PEG600 exhibited a reversible temperature-responsive behavior in aqueous solution. The transition temperature ($T_c$) of LDI-PEG600 with methyl ester of LDI was higher than that of LDI-PEG600 with butyl ester side chain. The polymers were then used to encapsulate adriamycin (ADR) by the dialyzing method from dimethylformamide solution against water. ADR could be successfully encapsulated into the polyurethane nanoparticles. The ratio of ADR release from polymeric nanoparticles increased sharply above the $T_c$, while the release was suppressed below the $T_c$.



## 1. Introduction

Increased use of therapeutic molecules such as anti-cancer drugs is limited by toxicity: both target cancerous cells and healthy cells are exposed to drug non-selectively, leading to unwanted toxic side effects. (Bae and Kataoka, 2009; Thomas et al., 1990; Thornton et al., 2007). Therefore, persistent efforts have been made in the development of stimuli-responsive or site-specific drug delivery systems for controlled drug release. Typical biological stimuli exploited for triggered drug release include temperature, pH, redox, ionic strength, and enzymes (Bhattarai et al., 2003; Gong et al., 2010; Itaka et al., 2003; Lee et al., 2005, 2008).

Among the stimuli-responsive vehicles, biodegradable and biocompatible polymers have attracted much attention. Biodegradability offers several advantages, such as the excretion of the delivery vehicle after the release of bioactive molecules (Chiappetta and Sosnik, 2007; Du et al., 2010; Kataoka et al., 2000; Yang et al., 2008). Biodegradable polyurethanes, having extensive structure/property diversity, are one of the most bio- and blood-compatible materials known today. Polyurethanes have been used in the body for over 30 years. Properties such as biodegradability, facile formation, and acceptance or tolerance in the body during the healing, are often associated with polyurethanes (Bhattarai et al., 2007; Chung et al., 2006; Zheng et al., 2009). PEG is widely used as hydrophilic segments in many amphiphilic block copolymer systems. PEG-based polyurethanes are one of the most widely studied materials for biomedical applications, due to their non-immunogenicity and non-toxicity (Kim et al., 2000; Ommoleila et al., 2008; Petros et al., 2008). Recently, we observed that adjusting of hydrophilic/hydrophobic balance of polyurethanes could produce a series of temperature-sensitive aggregations, which is potentially useful as controlled drug delivery vehicles (Fu et al., 2011). In this study, another series of polyurethanes was designed and synthesized by selecting L-lysine diisocyanate with different side ester chains and PEG of different molecular weights via a condensation reaction. The aqueous solution properties of the polymers were studied by turbidity measurement and size measurement. The potential use of these polymers for pharmaceutical applications was also explored, using adriamycin (ADR) as a model peptide.

## 2. Materials and methods

### 2.1. Materials

Poly (ethylene glycol) (PEG) ($M_n$ = 600, 1000, 1500), L-lysine, dibutyltin dilaurate were purchased from Sigma–Aldrich. ADR was purchased from Beijing HuaFeng United Technology Co., Ltd. All

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other chemicals were obtained from Tianjin Chemical Reagent Co. (Tianjin, China) and used as received.

### 2.2. Synthesis of lysine diisocyanates

Lysine diisocyanate was synthesized in two steps, starting with lysine esterification followed by phosgenation (Han et al., 2009). L-Lysine was esterified by continuously passing dry HCl gas into the anhydrous methanol or n-butanol solution of lysine. The product was purified by precipitation in ethyl ether. The resulting L-lysine ester was suspended in the mixture of pyridine and $CHCl_3$ and stirred in an ice salt bath for 10 min. A solution of triphosgene in $CHCl_3$ was then added at temperature from −10 °C to −15 °C over a period of 10 min, and stirred for 5 h at 0 °C. The reaction mixture was extracted with cold aqueous solution of HCl. The aqueous layer was extracted twice with 200 mL of $CHCl_3$. The combined organic phases were dried over $MgSO_4$, filtered and concentrated by rotary evaporation to obtain the crude diisocyanate. The product was purified by distillation under reduced pressure.

Yield of methyl ester diisocyanate (LDIM): 89%; bp, 142–144 °C (4 mmHg). $^1$H NMR [$CDCl_3$,δ,ppm]: 4.08(m, 1H, $CH_2CHNCO$), 3.83(s, 3H, $COOCH_3$), 3.35(m, 2H, $OCNCH_2CH_2$), 1.85(m, 2H, $CH_2CH_2CHNCO$), 1.65(m, 2H, $OCNCH_2CH_2$), 1.53(m, 2H, $OCNCH_2CH_2CH_2CH_2CHNCO$).

Yield of butyl ester diisocyanate (LDIB): 85%; bp, 160–161 °C (4 mmHg). $^1$H NMR [$CDCl_3$,δ,ppm]: 4.23(m, $COOCH_2CH_2$), 4.05 (m, $CH_2CHNCO$), 3.36(m, $OCNCH_2CH_2$), 1.85(m, $CH_2CH_2CHNCO$), 1.73–1.62(m, $OCNCH_2CH_2 + COOCH_2CH_2CH_2$), 1.55(m, $OCNCH_2CH_2CH_2CH_2CHNCO$), 1.43(m, $CH_2CH_2CH_3$), 0.97(m, $CH_3$).

### 2.3. Synthesis of polyurethanes

Polyurethanes could be synthesized from diisocyanate and PEG via a condensation reaction (Bouchemal et al., 2004) (Scheme 1). Typically, the LDIM (or LDIB) and PEG ($M_n$ = 600, 1000, 1500) were mixed at a ratio 1:1 in anhydrous toluene under nitrogen, using 0.5 wt.% dibutyltin dilaurate as a catalyst, followed by heating to 110 °C for 8 h. After cooling to 50 °C, an excess amount of methanol was added and stirred for 1 h. After cooling to room temperature, the resulting polymer was purified by precipitation in diethyl ether twice, washed with diethyl ether for 3 times, and eventually dried under vacuum at room temperature for 24 h. The yields of all resulting polymers were over 80%.

### 2.4. Polyurethanes characterization

IR spectra were recorded on a Bio-Rod 6000 (Thermo Electron, USA) spectrometer using KBr pellets. $^1$H NMR spectra were recorded on a Bruker AV-400 spectrometer (400 MHz, Bruker, Freemont, CA). Samples were dissolved in deuterated dimethyl sulfoxide. The molecular weight of polymers was determined in THF by gel permeation chromatography (GPC, Waters 2414 system Milford, MA). The weight- and number-average molecular weights ($M_w$ and $M_n$, respectively) were calibrated with standard polystyrene samples. The sample concentration in the THF was 2.5 mg/mL, at a flow rate of 1.0 mL/min and a temperature of 35 °C. The glass transition temperature ($T_g$) and melting temperature ($T_m$) of the polyurethanes was examined by differential scanning calorimeter (DSC, Netzsch PC-200) at a cooling and heating rate of 10 °C/min ranging from −50 to 200 °C. The DSC thermograms were recorded during the second heating run.

### 2.5. Nanoparticle formulation and characterization

The nanoparticles could be fabricated by dispersion of the polyurethanes in double distilled water with sonication for 5 min. Dynamic light scattering (DLS) measurements were carried out on a DLS spectrophotometer (DLS, Zetasizer Nano ZS90, Malvern Instruments, Southborough, MA) at temperatures ranged from 25 to 70 °C. The morphology of the nanoparticles was observed by scanning electron microscopy (SEM, JSM-6700F. Japan Jeol Electron Co.) using vertically polarized incident light with a wavelength of 410 nm from an Ar laser operated at 15 mW.

### 2.6. Temperature-responsive behavior

The optical transmittance of the polymer aqueous solution of various temperatures was measured at 410 nm using a UV–vis spectrometer (UV-2450 Shimadzu Co. Japan) equipped with a temperature-controllable cell. The measurement was performed at a heating and cooling rate of 3 °C/min ranging from 25 to 70 °C. The temperature at which the change in absorbance started decreasing was defined as the critical transition temperature ($T_c$). The concentration dependence of $T_c$ was investigated by transmittance measurements of polymer solutions with various polymer concentrations from 0.1 to 1.0 mg/mL.

### 2.7. Incorporation of adriamycin (ADR)

Polyurethanes (19 mg) and ADR hydrochloride (19 mg) were dissolved separately in 1.5 mL of dimethylformamide (DMF). The ADR solution was added to the polymer solution after triethylamine (6.0 μL) was added dropwisely. The solution was dialyzed against water at 35 °C for 24 h (Jeong et al., 1999). The NPs were lyophilized yielding a loosely packed powder. ADR-loaded nanoparticles were dispersed in water, the size of the nanoparticles was determined by DLS. The freeze-dried samples were dissolved in DMSO within the range of the standard curve and assayed for the ADR content by UV–visible spectrophotometry ($\lambda_{max}$ = 480 nm) using a UV-2450 (Shimadzu Co. Japan). Final drug loading and encapsulation efficiency (EE) were calculated from the following equations:

$$\text{Drug loading } (\%w/w) = \frac{\text{Mass of loaded guest}}{\text{Mass of NPs}} \times 100 \quad (1)$$

$$\text{EE } (\%) = \frac{\text{Final loading}}{\text{Initial loading}} \times 100 \quad (2)$$

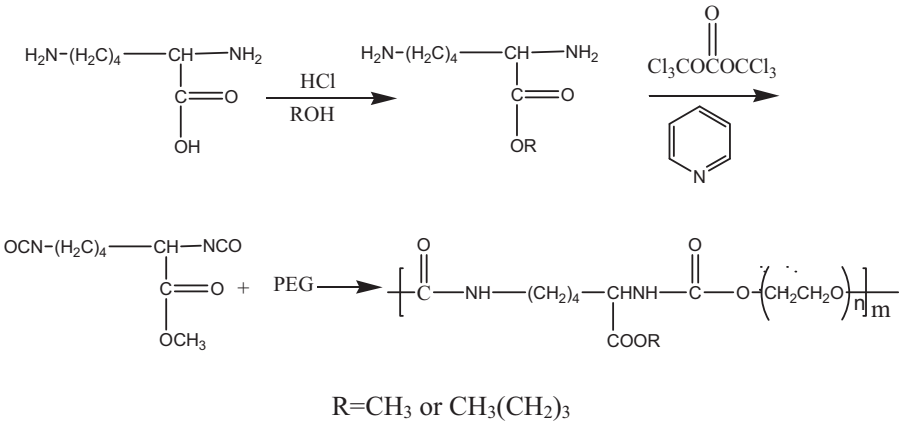
### 2.8. In vitro drug release

Freeze-dried drug-loaded nanoparticles (2 mg/mL) was dispersed in water and dialyzed against water in a capped beaker incubated at temperatures below and above $T_c$ under shaking (SHZ-88 Constant Temperature Water-bath Shaker, China). At designated intervals, 5 mL of water solutions in the beaker was taken out from the dialyzing solution and 5 mL of fresh water was added to keep a constant volume. The amount of ADR released into the water was analyzed using a UV spectrophotometer at a wavelength of 480 nm.

The cumulative drug release was calculated as:

$$\text{Cumulative drug release } (\%) = \frac{M_t}{M_\infty} \times 100 \quad (3)$$

where $M_t$ is the amount of drug released from nanoparticles at time $t$, and $M_\infty$ is the amount of drug released from the nanoparticles at time infinity. All release experiments were carried out in duplicate, and all data were averages of six determinations used for drawing figures.




**Scheme 1.** The synthesis route of polyurethanes.

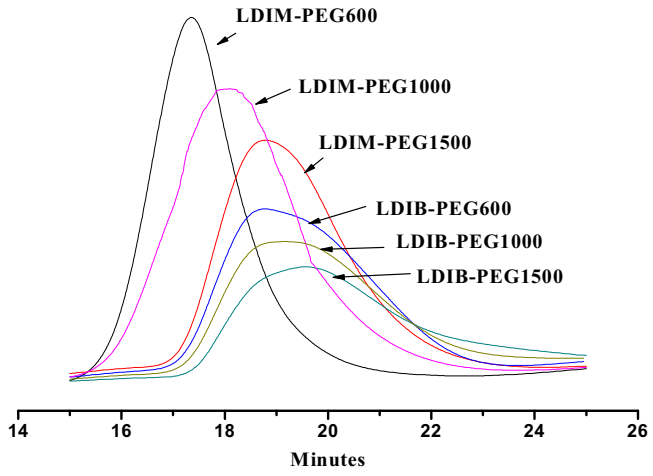



**Fig. 1.** GPC traces of the polyurethanes synthesized from LDIM or LDIB and different molecular weights PEG ($M_n$ = 600, 1000 and 1500).

## 3. Results and discussion

### 3.1. Synthesis of polyurethanes

By choosing LDIM or LDIB and different molecular weights of PEG ($M_n$ = 600, 1000 and 1500), a series of polyurethanes were obtained. The molecular weight of polyurethanes was determined by GPC. GPC traces of polyurethanes are shown in Fig. 1. The molecular weights and polydispersity index (PDI) of polyurethanes are listed in Table 1. The molecular weight of polyurethanes composed of the same kind of diisocyanate declined as the molecular weights of PEG increasing. While the molecular weight of copolymers composed of the PEG bearing the same molecular weight decreased with the ester chain extending in L-lysine diisocyanate (LDI). The concentration of PEG and LDI, as well as reaction time was kept the same for each polymerization. Increased PEG chain resulted in decreased initial hydroxyl concentration, which caused a lower polymerization. Similarly, increase in LDI side chain length resulted in a lower a concentration of isocyanate, causing a lower molecular weight. In addition, the increasing in the length of carbon side chain of LDI induced the increased steric hindrance during the process of condensation reaction.

**Table 1**
Molecular weights of polyurethanes.

| Type of diisocyanate | $M_n$ of PEG[a] | $M_n$ of polyurethanes[b] | PDI[b] |
|---|---|---|---|
| LDIM | 600 | 51,600 | 1.44 |
| LDIM | 1000 | 32,100 | 1.47 |
| LDIM | 1500 | 26,700 | 1.32 |
| LDIB | 600 | 26,300 | 1.51 |
| LDIB | 1000 | 21,300 | 1.54 |
| LDIB | 1500 | 19,100 | 1.59 |

[a] Provided by Sigma–Aldrich.
[b] Obtained by GPC.

### 3.2. Characterization of polyurethanes

The chemical structure of synthesized polyurethanes was examined by FT-IR and $^1$H NMR. There is an identifiable change between LDI (LDIM or LDIB) and synthesized polyurethanes in FTIR spectrum (Fig. 2). The absorbance at 2260 cm$^{-1}$ assigned to the group of NCO in LDIB and LDIM all disappear in the polyurethanes (LDIB-PEG600 and LDIM-PEG1500). Instead, the stretching vibration of N–H peak emerged at 3400 cm$^{-1}$. $^1$H NMR spectroscopy (Fig. 3) also confirmed the chemical structure of LDIB-PEG1500.

### 3.3. Thermal analysis of polyurethanes

The thermal properties of synthesized polyurethanes (LDIM-PEG and LDIB-PEG) were studied by DSC (Fig. 4, Table 2). The glass transition temperature ($T_g$) of the LDIM-PEG series ranges from −37 °C to −36 °C, while that of LDIB-PEG series ranges from −43 °C to −40 °C. The LDIM-based polyurethanes exhibited higher $T_g$ than that of the LDIB-based polyurethanes containing the same PEG segments. LDIM exhibited higher hydrophilicity than LDIB, resulting in that LDIM showed stronger microdomain mixing with PEG. The $T_g$

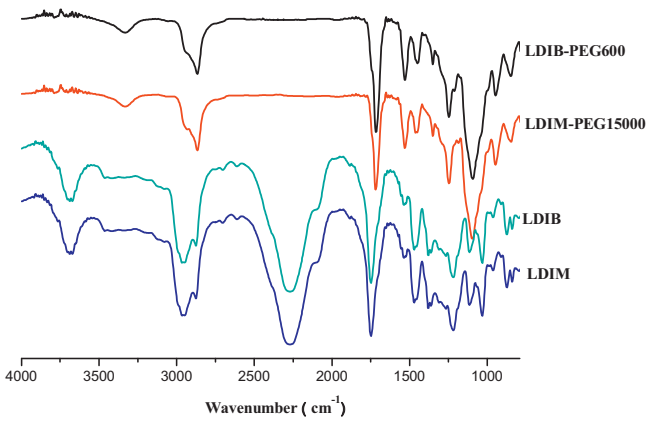



**Fig. 2.** FTIR spectra of LDIM, LDIB, LDIM-PEG1500 and LDIB-PEG600.

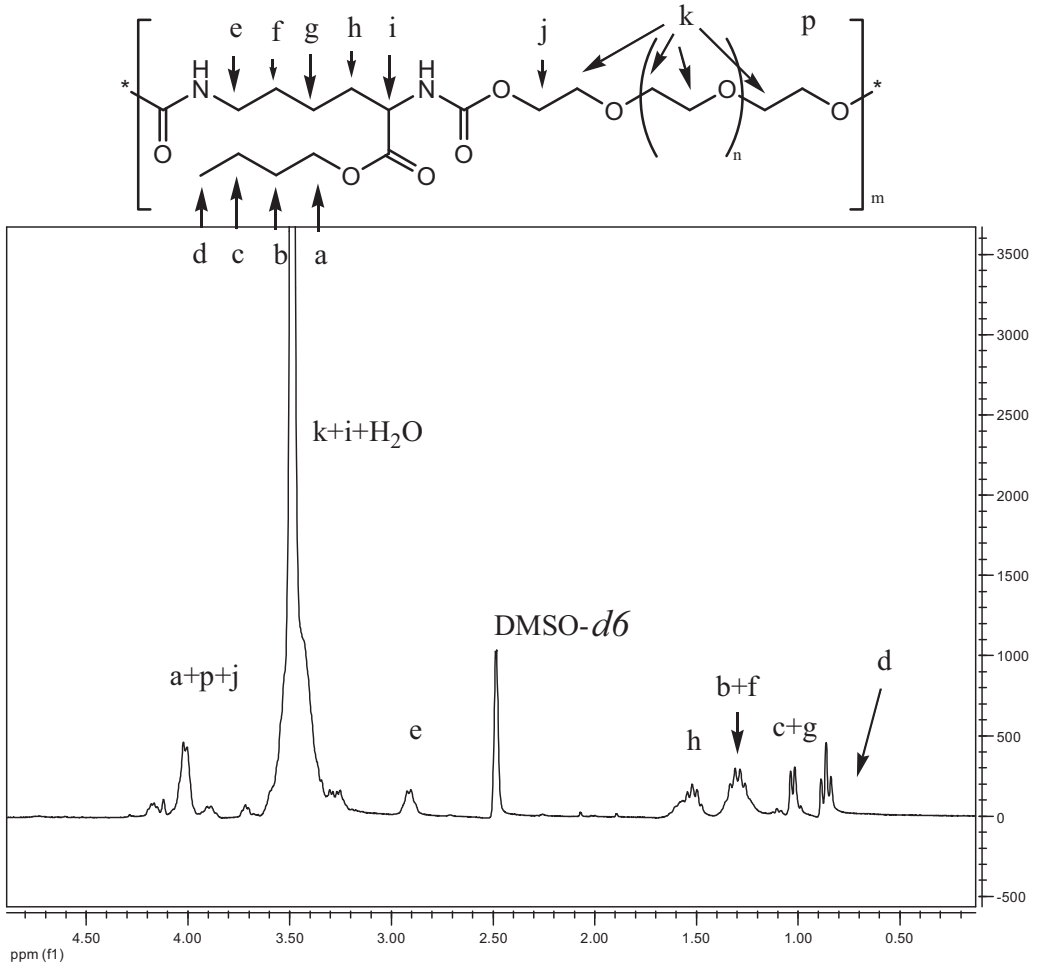



**Fig. 3.** $^{1}$H NMR spectrum of LDIB-PEG1500 polyurethanes in DMSO-*d6*.

of the two series of polyurethanes all increased with the increasing molecular weight of PEG in polyurethanes. In the range of measurement temperature, no melting pointing ($T_m$) could be found with LDIM-PEG600 and LDIB-PEG600. The other polyurethanes exhibited similar $T_m$ values. Usually, $T_m$ of PEG homopolymer increased with molecular weight. However, in this study, the molecular weight of LDI-PEG1500 is lower than that of LDI-PEG1000, which may cause a lower $T_m$ of LDI-PEG1500. With regard to these two factors, LDI-PEG1000 and LDI-PEG1500 showed similar $T_m$.

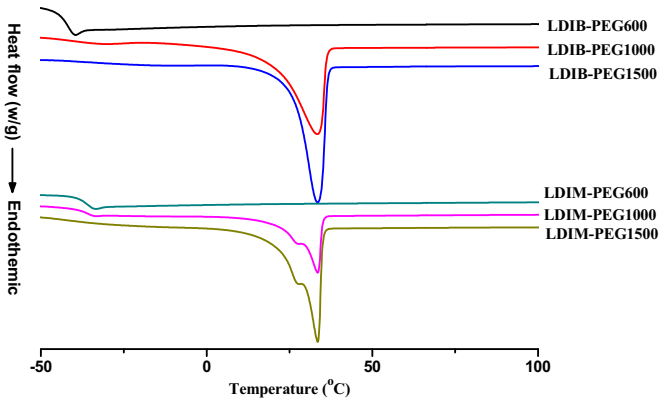



**Fig. 4.** DSC thermograms (second heat run) of polyurethanes.

### 3.4. Temperature responsibility of polyurethanes in aqueous solution

The polyurethane is not well soluble in double distilled water, so sonication was used to breakup of polymer particle to form nanoparticles. The temperature-responsive behavior of the polyurethane nanoparticles in aqueous solution was investigated by UV–vis turbidity measurements at a wavelength of 410 nm during both heating and cooling process (Fig. 5). LDIM-PEG600 and LDIB-PEG600 exhibited a reversible temperature-responsibility. The aggregation could occur upon heating for polymers with proper hydrophilic–hydrophobic balance. Apparently, LDIM-PEG600 and LDIB-PEG600 are more hydrophobic than other polyurethanes composed of PEG1000 and PEG1500, indicating that the hydrophobic interaction is the driving force for temperature-sensitive transition.

**Table 2**
DSC data of the polyurethanes.

| Polymer | $T_g$ (°C) | $T_m$ (°C) |
|---|---|---|
| LDIM-PEG600 | −37.1 | – |
| LDIM-PEG1000 | −36.8 | 33.6 |
| LDIM-PEG1500 | −35.9 | 33.2 |
| LDIB-PEG600 | −42.8 | – |
| LDIB-PEG1000 | −40.3 | 33.3 |
| LDIB-PEG1500 | −39.6 | 32.9 |

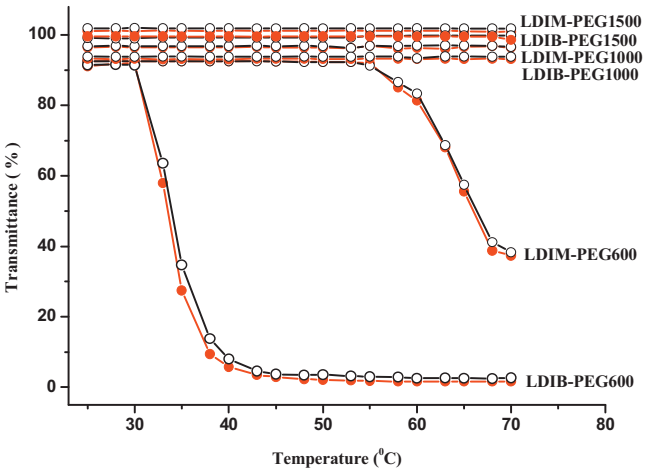



**Fig. 5.** Temperature dependence of the optical transmittance (410 nm) for LDIM-PEG (600, 1000 and 1500) and LDIB-PEG (600, 1000 and 1500) in aqueous solutions during heating (filled circle) and cooling (open circle). Polyurethane concentration: 1 mg/mL.

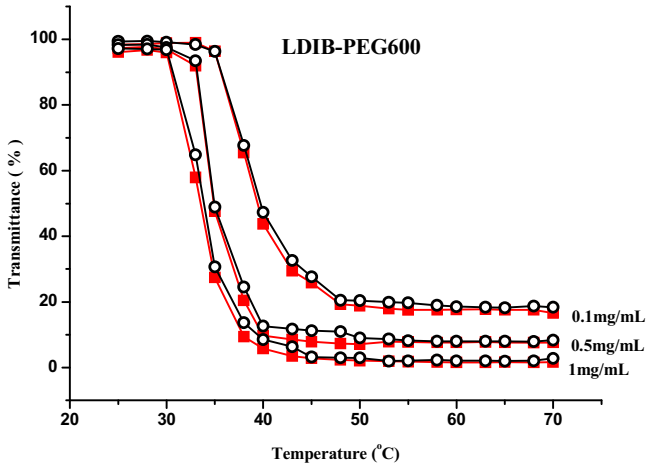



**Fig. 7.** Temperature dependence of the optical transmittance (410 nm) for the synthesized polyurethanes LDIB-PEG600 in aqueous solutions during heating (filled square) and cooling (open circle). Polyurethane concentration: 0.1 mg/mL, 0.5 mg/mL and 1.0 mg/mL.

The $T_c$ of LDIM-PEG600 and LDIB-PEG600 is about 55 °C, and 33 °C, respectively, while that of LDIE-PEG600 is about 45 °C as we reported previously (Fu et al., 2011). Above the $T_c$, water becomes a thermodynamically poor solvent and the interaction between the hydrophobic segments becomes stronger, which induced the aggregation. The $T_c$ of polyurethanes increased with the decreasing chain length of ester side chain, indicating that the polyurethanes with longer side hydrophobic chain are more ready to aggregate upon heating.

The particle size of LDIB-PEG600 and LDIM-PEG600 is 313 nm and 225 nm at 25 °C, respectively, as determined by DLS (Fig. 6a). The butyl ester side chain is more hydrophobic than the methyl one, so the size of LDIB-PEG600 is larger than that of LDIM-PEG600 in aqueous solution. Upon heating, the particle size enlarged when temperature reached $T_c$. Data of LDIE-PEG600 also illustrated here for comparison (Fu et al., 2011). The starting temperature of size enlargement was in good agreement with $T_c$ determined by UV-turbidity. The size distribution of all polyurethanes was 0.22–0.32 at room temperature, and enlarged significantly to over 0.38 when temperature reached 70 °C (Fig. 6b). This multi-distribution of aggregation at high temperature may reflect different aggregation number of polyurethane particles.

To investigate the effect of concentration of polyurethanes on the temperature-responsivity, the LDIB-PEG600 aqueous solution was prepared at different concentrations (from 0.1 to 1.0 mg/mL). The transmittance of the polymer aqueous solution at different concentrations decreased sharply in the similar temperature range (from 30 °C to 40 °C) during heating. The $T_c$ of the polyurethanes increased slightly with the concentration decreasing, indicating that increased concentration led to the stronger tendency for copolymer association (Fig. 7).

### 3.5. SEM analysis

The shape of the polyurethanes LDIB-PEG600 was investigated both below and above $T_c$ by SEM (Fig. 8). LDIB-PEG600 nanoparticles are spherical at 25 °C and 40 °C. While the size of the nanoparticles increased from 200 nm to 450 nm, which was in good accordance with the results measured with DLS.

### 3.6. ADR incorporation into polyurethane nanoparticles

Dialyzing method was tried to encapsulate ADR with the polymers. Equal mass of ADR and polymer were dissolved in DMF and then dialyzing against water. However, the ADR encapsulation effi-

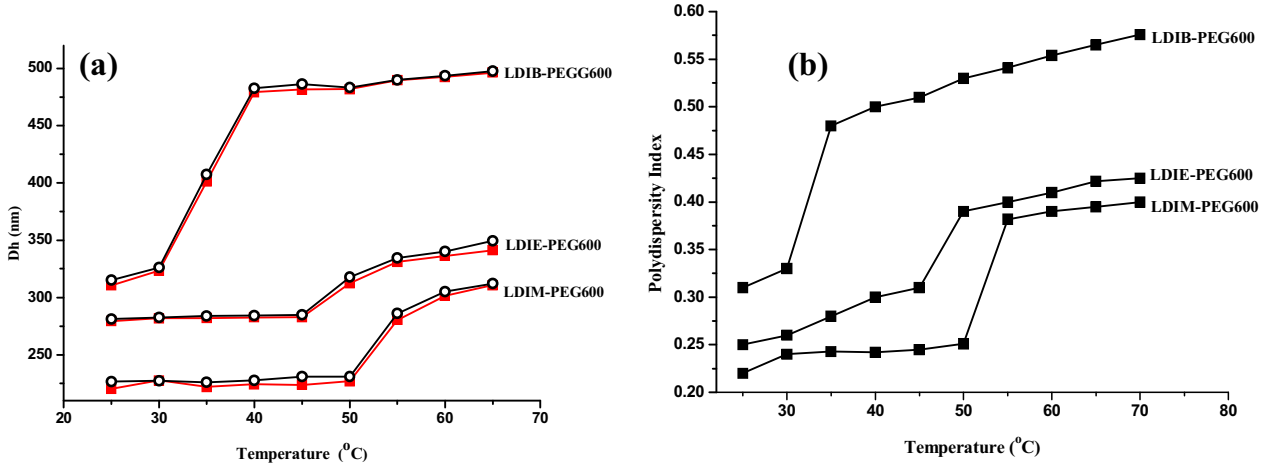



**Fig. 6.** Temperature dependence of the hydrodynamic diameter (a) and polydispwrsity index (b) for LDIM-PEG600, LDIE-PEG600 and LDIB-PEG600 in aqueous solutions during heating (filled square) and cooling (open circle). Polyurethane concentration: 1 mg/mL.

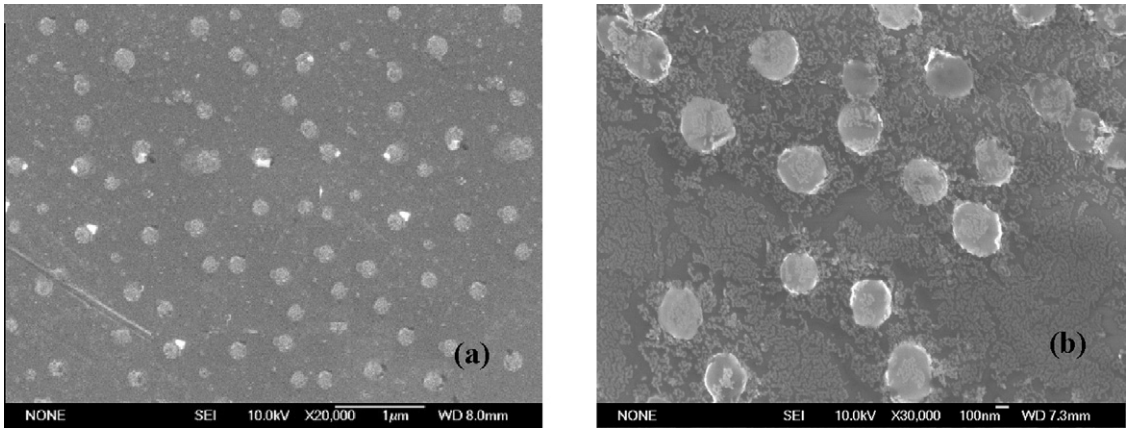



**Fig. 8.** SEM images of LDIB-PEG600 at 25 °C (a) and 40 °C (b).

ciency was rather low (less than 3%), which may be caused by the good water-solubility of ADR hydrochloride salt and resulting fast diffusion of ADR upon dialyzing. In order to remove hydrochloride salt groups from ADR, 1.3 molar equivalent TEA was added to the ADR solution dropwisely prior to mixing with the polymer solution (Chung et al., 1999). LDIM-PEG600, and LDIB-PEG600 was successfully for encapsulation of ADR with encapsulation efficiency of 23.2 wt.% and 26.5 wt.% and drug loading of 46.4% and 53.0%. The average diameter of LDIM-PEG600 and LDIB-PEG600 nanoparticles loading drug (ADR) was about 500 nm and 530 nm. Interestingly, the particles could well be dispersed in water; the PEG600 segments may protect the particles from being aggregation in the dialysis procedure.

### 3.7. Thermo-responsive ADR release

ADR release profiles from polymeric nanoparticles showed drastic differences with temperature changes below and above the $T_c$ (Fig. 9). The release of ADR for LDIB-PEG1500 nanoparticles was slow at both 25 °C and 60 °C, which did not show temperature sensitivity. For LDIB-PEG 600 and LDIM-PEG600, ADR release was selectively accelerated upon heating, while ADR release was well suppressed below the $T_c$. This was probably because the density of temperature-responsive nanoparticles was not so high, so that the interspace between the polymer chains increased after they shrunk due to the high temperature (Shen et al., 2008). In addition, the hydrogen-bonding or hydrophobic interaction between polyurethanes and ADR probably weakened upon heating. Above the $T_c$ of polyurethanes, it took only 4 h to release 80% of ADR from LDIM-PEG600, and it took 7 h to release 80% of ADR from LDIB-PEG600. At 37 °C, LDIB-PEG600 could release 75% of ADR in 8 h and reached a plateau. Butyl ester side chain increased the stability of polymer aggregation and it took more time to release the cargo.

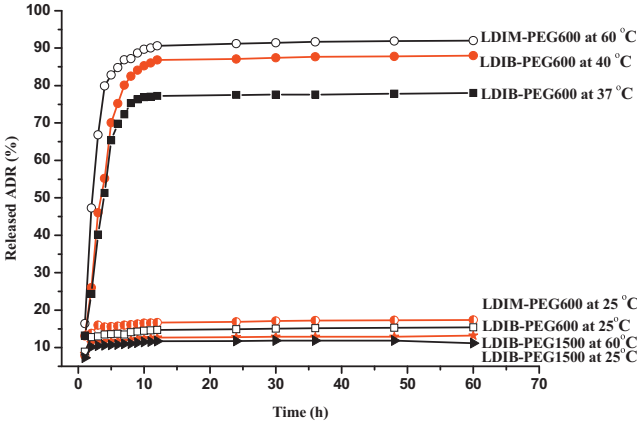



**Fig. 9.** Drug (ADR) release from polyurethanes.

## 4. Conclusion

Biodegradable polyurethanes composed of PEG and LDI were successfully synthesized. DSC shows that the $T_g$ and $T_m$ of the polyurethanes mainly depends on the molecular weight of PEG in polyurethanes. Polyurethanes composed of PEG600 showed temperature-responsibility, while those composed of PEG1500 and PEG1000 was not temperature-sensitive, indicating the hydrophobic interaction was the driving force for the temperature-sensitive aggregation. $T_c$ of the polyurethanes decreased with the side-chain extending in LDI, and increased slightly with the decreased concentration. LDIM-PEG and LDIB-PEG copolymers formed nanoparticles by dispersing in water. ADR could be successfully encapsulated into the nanoparticles by dialyzing method. Polymeric nanoparticles incorporated with adriamycin showed a dramatic temperature-responsive drug release on/off switching behavior according to the temperature responsive structural changes, which opens up opportunities to construct a novel drug delivery system for site-specific delivery of drugs using changes in temperature as a trigger.

## Acknowledgements

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