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Polymer 46 (2005) 9514–9522
polymer
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Thermo- and pH-sensitive dendrimer derivatives with a shell of poly (*N*,*N*-dimethylaminoethyl methacrylate) and study of their controlled drug release behavior

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Received 12 December 2004; received in revised form 26 April 2005; accepted 5 July 2005
Available online 8 August 2005

Abstract

Novel dendrimer derivatives combining the temperature- and pH-sensitivities are synthesized. At first, polyamidoamine (PAMAM) dendrimers with generations 1–5 are synthesized by the reaction of ethylenediamine with methyl acrylate, and then the dendrimers are acylated by chloroacetyl chloride to obtain PAMAM-Cl, which can act as a macroinitiator for further synthesizing functional dendrimers. For fulfilling this goal, the polymers consisting of a dendritic PAMAM core and poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMA) shell are synthesized by atom transfer radical polymerization (ATRP). Their macromolecular structures are characterized by FTIR, ^{1}H NMR, DSC and particle size analyses, and their aqueous solutions are inspected by UV spectroscopy for understanding their thermo- and pH-sensitivities. The results show that novel dendrimer derivatives exhibit clearly thermo- and pH-respondings in accordance with the change of the environment. Using chlorambucil (CLB) as a model drug, the behaviors of the controlled drug release from polymers with different average graft length of PDMA are studied. The results indicate that the rate of the drug release can be effectively controlled by the pH value.

Keywords: Polyamidoamine (PAMAM) dendrimers; Poly(*N*,*N*-dimethylaminoethyl methacrylate); Dendritic polymer

1. Introduction

Dendrimers are synthetic, highly branching, spherical, mono-disperse macromolecules with nanometer dimensions [1,2]. Since the pioneering work of Tomalia et al. on dendrimer synthesis in the mid-1980s [3,4], the research investigations for the synthetic methodology, physical and chemical properties of these macromolecules are increased rapidly in this field [5–10]. Potential applications for dendrimers are now forthcoming, especially, the properties associated with these parameters such as uniform size, water solubility, modifiable surface functionality and available internal cavities make them attractive for both biological and drug delivery applications [11,12].

The family of dendrimers most investigated for drug delivery is the polyamidoamine (PAMAM) dendrimer, which is biocompatible, nonimmunogenic [13], and possesses terminal-modifiable amine functional groups for binding various targeting or guest molecules [14,15]. The internal cavities of PAMAM dendrimers with tertiary amines and amide linkages can host metals or guest molecules because of their unique architectures [16,17]. Twyman et al. [18] have converted the ester-terminated half-generation PAMAM dendrimers into a more water-soluble hydroxyl surface by reacting with triis, and studied the complexing of these novel dendrimers with small hydrophobic guest molecules. Kojima et al. [19] have synthesized PAMAM dendrimers with PEG grafts on the surface and attempted making encapsulation for anticancer drugs including adriamycin and methotrexate. Although it is widely investigated and confirmed that this functional polymer has a sound ability to encapsulate various drugs, unfortunately, there are no enough researches, at the same time, to indicate and prove its capability of controlled drug release.

An important function of many controlled release systems is to effectively modify the drug release behavior in response to some external stimuli including the change of

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doi:10.1016/j.polymer.2005.07.034

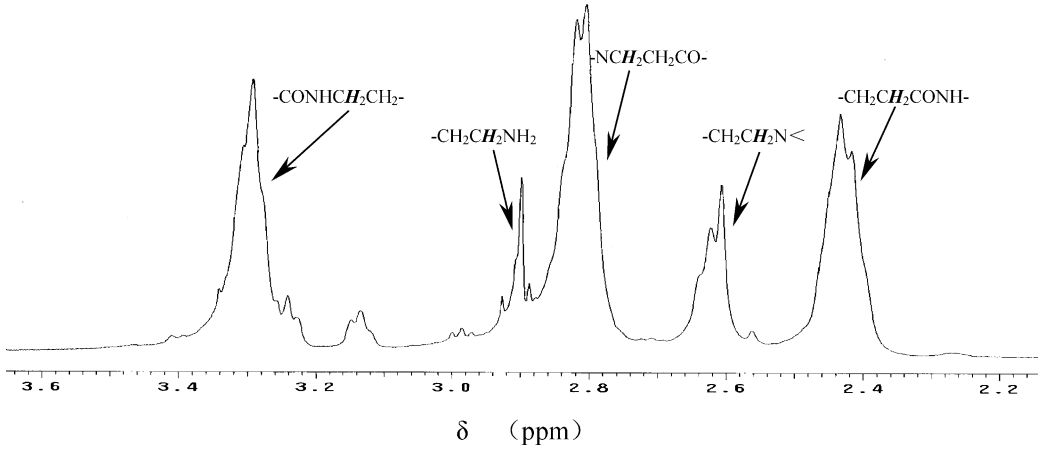

Fig. 1. ^{1}H NMR spectrum for G3 PAMAM dendrimer.

temperature or pH values [20–22]. It is well known that poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMA) can undergo a conformational transition from compact coil to random coil, and simultaneously, shows a drastic phase change due to hydrophobic or hydrophilic molecular chain interactions by varying the pH and temperature [23–27]. With controlled polymerization processes such as atom transfer radical polymerization (ATRP), it can readily allow the synthesis of PDMA with well-controlled molecular weights and defined topology [28]. If PDMA segments are incorporated into a dendrimer surface, this novel dendrimer derivative can be certainly becoming an interesting drug carrier in controlled release system due to the encapsulation of dendrimer and environmental sensitivity of PDMA.

In the present study, we report the synthesis and characterization of a novel dendrimer derivative, which can present molecular inclusion functionality, at the same time, can respond to different external stimuli. In order to fulfill this goal, we first synthesized PAMAM dendrimers with generations 1–5, and then dendrimers synthesized are modified by two step reactions to obtain PAMAM-Cl, which can be used as a macroinitiator for atom transfer radical polymerization (ATRP). Finally, the PAMAM dendrimer derivatives with a PDMA shell are synthesized by ATRP. The resultant PAMAM dendrimer derivatives show a good functionality with pH-, temperature sensitivities and molecular inclusion ability. Using chlorambucil (CLB) as a model drug [29], the drug release behaviors from the polymer matrix with different length of PDMA grafts are studied. The results indicate that the rate of the drug release can be effectively controlled by the pH value.

2. Experimental

2.1. Materials

N,*N*-dimethylaminoethyl methacrylate (DMA) was purchased from ACROS Chemical Industries (USA) and purified by distillation under reduced pressure. Chlorambucil (CLB) was purchased from Fluka

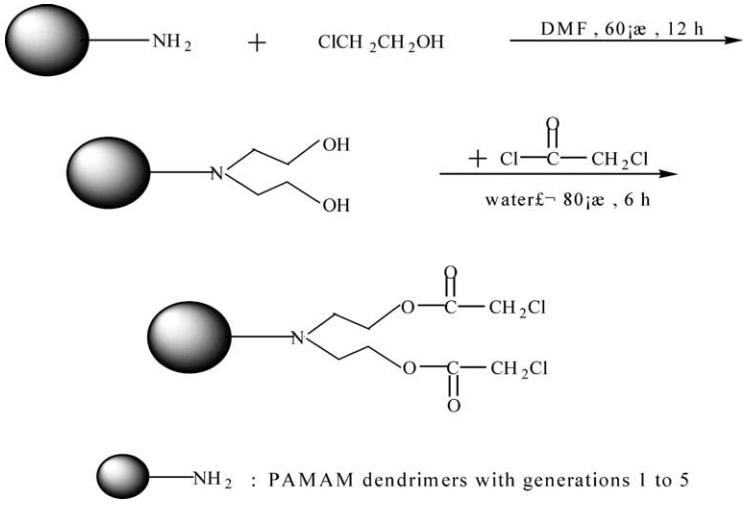

Fig. 2. Scheme of two-step modification reactions of PAMAM dendrimer.

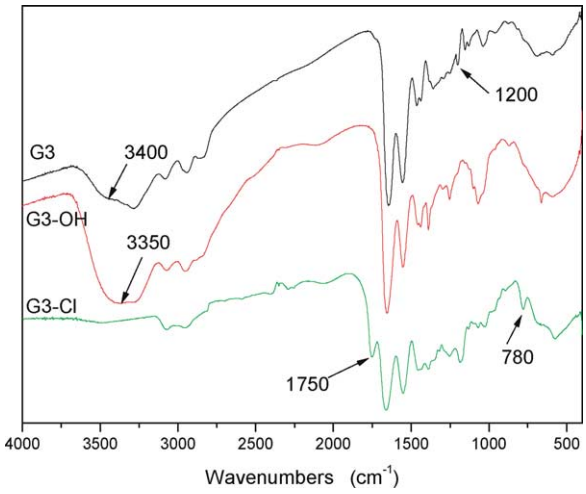

Fig. 3. IR spectra of the modified PAMAM dendrimers.

Chemika (more than 98% purity), All other reagents including ethylenediamine (EDA) and methyl acrylate (MA) were analytic grade made in China, and used as received without further purification.

2.2. Synthesis of PAMAM dendrimers with generation 1–5

The PAMAM dendrimers were synthesized on the basis of two consecutive chain forming reactions, that is, the exhaustive Michael addition reaction and the exhaustive amidation reaction as described elsewhere [3,4].

IR measurements (KBr, cm^{-1}): $\upsilon_{-NH_2}=1200\ cm^{-1}$; $\upsilon_{C=O}=1650\ cm^{-1}$; $\delta_{NH}+\upsilon_{C-N}=1558\ cm^{-1}$; $\upsilon_{C-N}=1250\ cm^{-1}$; $\upsilon_{(s)-CH_2-}=2860\ cm^{-1}$; $\upsilon_{(as)-CH2-}=2940\ cm^{-1}$.

^1H NMR (D_2O): δ(–CH_2CH_2CONH–)=2.36–2.48 (m); δ(–$CH_2CH_2N\langle$)=2.56–2.66 (m); δ(–NCH_2CH_2CO–)=2.68–2.74 (m); δ(–$CH_2CH_2NH_2$)=2.75–2.85 (m); δ(–$CONHCH_2CH_2$–)=3.10–3.40 (m).

Element analysis: Specifically, for a molecular structure of G3 PAMAM dendrimer, the theoretic calculation is C: 52.4; N:25.0; H:8.9%, and the actual measurements is C: 52.0; N:25.1; H:8.9% (Fig. 1).

2.3. Synthesis of PAMAM dendrimer macroinitiator

PAMAM dendrimers are modified by two-step reactions to obtain PAMAM-Cl, which acts as a macroinitiator for ATRP. Fig. 2 outlines the chemical routes for two-step modifications of functional PAMAM dendrimer.

2.3.1. Synthesis of PAMAM-OH

In a 3-neck round bottomed flask equipped with a thermometer, dropping funnel and magnetic stirring, 10 g of PAMAM dendrimer of one generation was dissolved in 80.4 g (1.1 mol) of DMF, and then, 32.2 g (0.4 mol) of chlorohydrin was added dropwise under vigorous stirring at room temperature for 30 min. The mixture solution was heated at 60 °C for 12 h under vigorous stirring. At the same time, nitrogen gas was in bubbling for removing HCl byproduct. After the reaction was completed, the mixture was purified by distillation under the vacuum of 0.093 MPa at 75 °C. The PAMAM-OH product of generation 1 was kept in vacuum glassware at room temperature. PAMAM dendrimer of generation 2–5 modified with peripheral hydroxyl were obtained according to the same process. Feed composition: $-NH_2$ in dendrimer/chlorohydrin is 1/5 (mol/mol).

2.3.2. Synthesis of PAMAM-Cl

In a 3-neck round bottomed flask equipped with a thermometer, dropping funnel and magnetic stirring, 5 g of PAMAM-OH with generation 1 was dissolved in 1.5 g of water following put 10.4 g (0.092 mol) of chloroacetyl chloride at room temperature for 30 min under vigorous stirring. Then the mixture solution was heated at 80 °C for 6 h, at the same time, nitrogen gas was in bubbling in order to remove HCl byproduct. After the reaction was completed, the mixture was purified by distillation under the vacuum of 0.093 MPa at 75 °C. The product obtained was redissolved in methanol and precipitated from cold acetone as oily viscid lumps, which then was dried in a vacuum oven at room temperature for a week. PAMAM dendrimer of generation 2–5 modified with peripheral alkyl chlorine was obtained according to the same process above.

Table 1
IR spectra parameters of the modified PAMAM dendrimers with generations 1–5

Sample[a]	υ_{-CH_2-}	δ_{-CH_2-}	υ_{C-N}	$\upsilon_{C=O}$	$\delta_{NH}+\upsilon_{C-N}$	υ_{-OH}	$\upsilon_{C=O}$	υ_{C-Cl}
G1-OH	2891	1455	1254	1652	1554	3330		
G2-OH	2864	1456	1254	1651	1552	3300		
G3-OH	2844	1458	1254	1651	1554	3300		
G4-OH	2854	1458	1252	1651	1552	3300		
G5-OH	2840	1460	1252	1651	1550	3280		
G1-Cl		1456	1257	1660	1558		1753	779
G2-Cl		1456	1254	1660	1554		1755	777
G3-Cl		1456	1250	1660	1554		1751	779
G4-Cl		1456	1254	1660	1552		1753	779
G5-Cl		1454	1254	1660	1552		1747	781

[a] G1-OH, G2-OH, G3-OH, G4-OH, G5-OH are modified PAMAM dendrimers with peripheral hydroxy; G1-Cl, G2-Cl, G3-Cl, G4-Cl, G5-Cl are modified PAMAM dendrimers with peripheral alkyl chlorine.

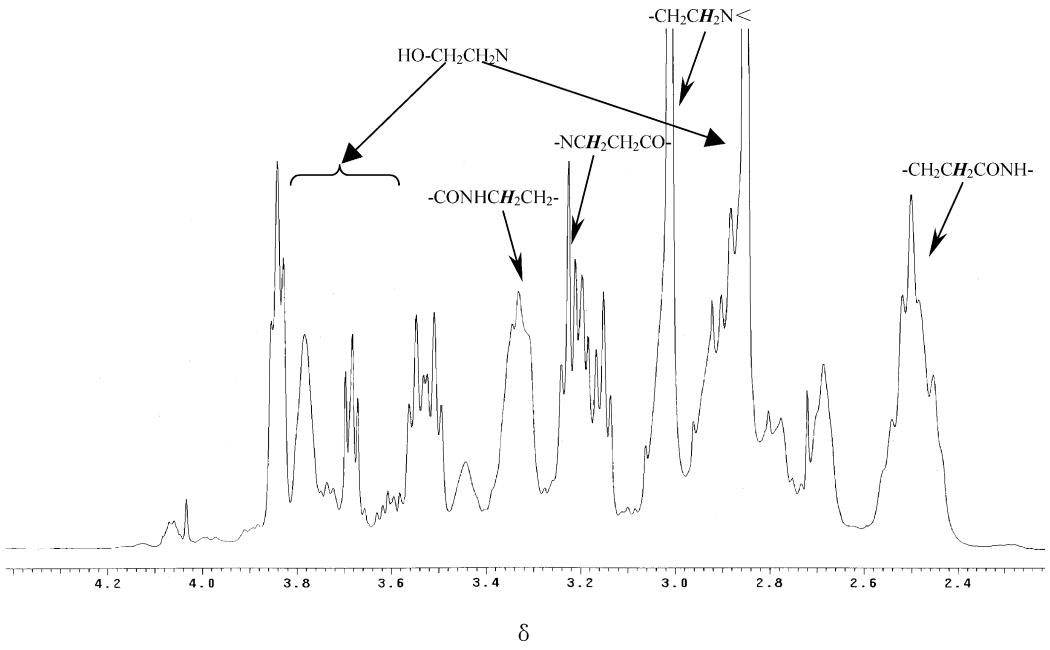

Fig. 4. ^{1}H NMR spectrum for G3-OH.

Element analysis: For a molecular structure of G3-OH with 100% substituent degree, the theoretic calculation is C: 53.1; N:17.4; H:9.0%, and the actual measurements is C: 52.7; N:18.1; H:8.0%; for a molecular structure of G3-Cl with 100% substituent degree, the theoretic calculation is C: 45.6; N:11.4; H:6.3%, and the actual measurements is C: 44.3; N:10.5; H:6.9%. IR spectra of the modified PAMAM dendrimers of G3 were shown in Fig. 3, and the detailed FT-IR peak assignments of the modified PAMAM dendrimers were showed in Table. 1. ^{1}H NMR spectra for sample G3-OH and G3-Cl was shown in Figs. 4 and 5. These results indicated the ratio of modification of C–Cl groups in dendrimers should be close to 100%.

2.4. Synthesis of PAMAM-g-PDMA with a shell of PDMA grafts on the surface of PAMAM dendrimer

In a flask equipped with magnetic stirring, 0.20 g of macroinitiator PAMAM-Cl of generation 1, 0.05 g of CuCl and 0.175 g of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiehylenetriamine (PMDETA) were dissolved in 4 g of water, and then added 4.00 g of DMA into the flask under vigorous stirring. The

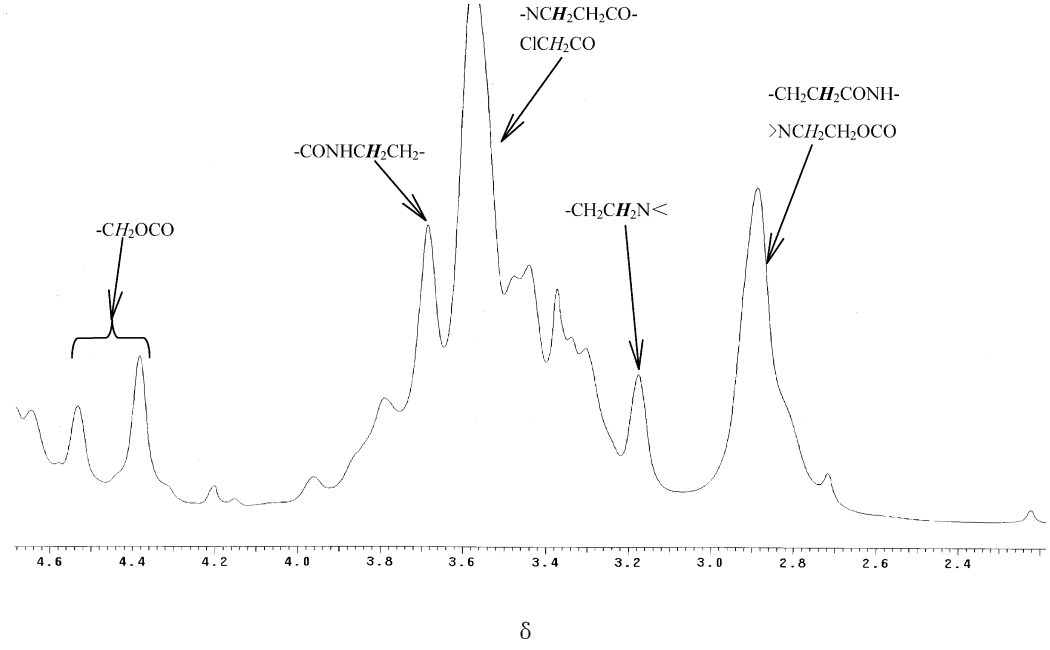

Fig. 5. ^{1}H NMR spectrum for G3-Cl.

Table 2
Parameters of dendrimer derivative PAMAM-*g*-PDMA

Sample	G3–Cl (g)	CuCl (g)	PMDETA (g)	Water (g)	DMA (g)	Product yield (wt%)	Diameter[a] (nm)	PDI[a]	LCST (°C)
G3-PDMA-2	0.200	0.051	0.175	4.01	2.02	47.5%	3.07	0.14	34.9
G3-PDMA-4	0.200	0.050	0.176	4.30	4.01	45.6%	3.46	0.12	31.4
G3-PDMA-6	0.204	0.051	0.178	4.01	6.00	40.7%	3.99	0.08	30.6

PDI, polydispersity index.
[a] Measured by means of laser particle size analyzer.

mixed solution was bubbled with nitrogen gas for 45 min. The flask was sealed under vacuum. The polymerization was conducted at 80 °C for 20 h. After the reaction was completed, the mixture was dialyzed in a dialysis bag (molecular weight cut off: 8000–10,000) against distilled water for 96 h. It was refreshed at a interval of 5 h. The dialyzed product was lyophilized and kept in vacuum glassware for further characterization. PAMAM-*g*-PDMA products with generations 2–5 were obtained according to the same procedures above.

2.5. Instrument analyses

^{1}H NMR measurements were conducted on Varian INOVA-400 spectrometer, USA, at room temperature using D_2O as solvent. Infrared spectroscopy measurements were preformed on a Specode 75 model, Germ, and the samples were prepared by casting of the sample solution onto a piece of KBr slice. UV spectroscopy measurements were preformed on shimadzu UV-2550 model, Japan. Differential scanning calorimetry (DSC) was conducted on TA instrument model MDSC 2910, USA, heating from −50 to 200 °C with a rate of 20 °C/min. Elemental analyses were carried out on a Vario EL III Instrument, Germ. Particle size analyses were preformed on a laser particle size analyzer (Zetasizer Nano ZS), England.

2.6. Transmittance measurement

Optical transmittances of 1 wt% polymer solutions in pH 10 buffer solutions (0.1 mol/L) were recorded at 500 nm using a UV–visiable spectrometer (shimadzu UV-2550) at different temperature. Sample cells were thermostated with an external constant temperature-controller. All measurements were repeated for three times. The temperature-raising rate was set at 1 °C/min. The LCST values of polymer solution were determined as the onset temperatures of the cloud point curves.

Optical transmittances of 1 wt% polymer aqueous solutions were measured at 500 nm with a UV–visible spectrometer at various pH. The pH of the sample solution was adjusted with 1 M NaOH solution. All determinations were repeated for three times and in good agreements.

2.7. Drug loading into dendrimer derivatives

Both CLB and dendrimer derivative (5/100, wt/wt) were dissolved in appropriate tetrahydrofuran under vigorous stirring. The solvent was volatilized at room temperature, and sample slices with 0.2 mm in thickness consisting of both PAMAM dendrimer derivatives and CLB were prepared. They were then dried under ambient temperature for 1 day, and in a vacuum oven at room temperature for 4 days.

2.8. CLB release studies

The sample slices loading with CLB were sealed separately using a dialysis bag with 4 cm in length. The dialysis bag was used because PAMAM-*g*-PDMA has a significantly higher molecular weight, so that polymers would stay inside the dialysis bag, whereas the drug with small molecular weight would readily diffuse out. At 37 °C, the bags were immersed into 40.0 ml of a buffer solution with pH = 10.0 and ionic strength = 0.1 mol l^{-1}. In a certain time interval, 5.0 ml of buffer solution was withdrawn and replaced with 5.0 ml of fresh buffer solution. After a sample's cumulative release time reached to 4.5 h, the old solution was replaced by a fresh buffer solution with pH = 1.4. Every 2 h, the old buffer solution with pH = 1.4 was replaced with another buffer solution with pH 10, alternatively. The CLB released was analyzed by spectrophotometer using 211.5 nm (pH = 1.4) and 242.0 nm (pH = 10.0) as characteristics bands, respectively. All solutions withdrawn were kept at 37 °C for 48 h prior to measurements. All release measurements were carried out in triplicate for each sample, and an average value was adopted. The cumulative release was calculated by using Eq. (1) as follows.

$$\text{Cumulative release}(\%) = \frac{100 \times (40.0\, C_{\mathrm{CLB}(n)} + 5.0 \sum C_{\mathrm{CLB}(n-1)})}{W_0} \quad (1)$$

W_0 (mg), weight of drug in the polymer; $C_{\mathrm{CLB}(n)}$ (mg/ml), the concentration of CLB in buffer solution which was withdrawed for n times; $C_{\mathrm{CLB}(n-1)}$ (mg/ml), the concentration of CLB in buffer solution which was withdrawed for $n-1$ times.

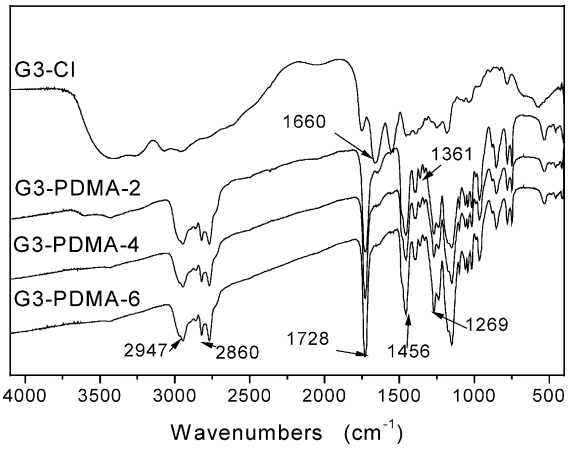

Fig. 6. IR spectra of dendrimer derivatives PAMAM-*g*-PDMA based G3 PAMAM.

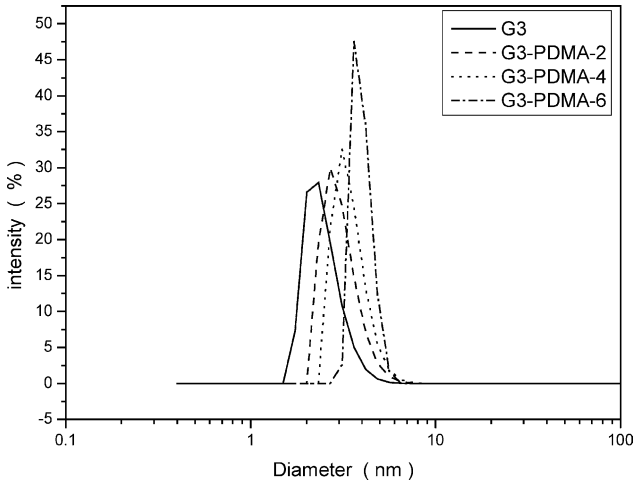

Fig. 8. Size distributions of dendrimer derivatives PAMAM-*g*-PDMA in aqueous solutions (2.0 mg ml^{-1}) at 25 °C.

3. Results and discussion

3.1. Synthesis and characterization of PAMAM-g-PDMA with PDMA grafts on the surface

Using PAMAM-Cl based dendrimers as a macroinitiator, CuCl as a catalyst and PMDETA as the ligand, the PAMAM dendrimer derivatives (PAMAM-*g*-PDMA) are synthesized via ATRP. Table. 2 shows the parameters of PAMAM-*g*-PDMA based third-generation PAMAM dendrimer.

IR spectra for PAMAM-*g*-PDMA based G3 PAMAM are shown in Fig. 6. The bands occurring between 2800 and 2947 cm^{-1} are associated with the symmetric and asymmetric C–H stretching vibrations of the aliphatic CH_2 and CH_3 groups. Other bands including the C=O stretching vibration at 1728 cm^{-1} and C–N stretching vibration at 1271 cm^{-1} are the characteristic of the segment of PDMA. The peak at 1660 cm^{-1} can be attributed to the amide-I vibration, indicating the existence of dendritic PAMAM unit. The intensity of the band at 1660 cm^{-1} gradually decreases as feed ratio of sample G3-Cl decreasing, which reveals that dendritic PAMAM unit decreases due to the feed ratio of macroinitiator G3-Cl decreasing, namely, dendrimer derivatives having different graft length of PDMA can be controlled by changing the molar ratio of DMA to macroinitiator.

^{1}H NMR spectrum for sample G3-PDMA-2 is shown in Fig. 7. The chemical shifts are attributed to protons originated from PDMA segment. As can be seen, no chemical shift for the amide protons of dendrimer appears in its ^{1}H NMR spectrum. This is because the methyl protons of PDMA component can overlap with CH_2 protons in PAMAM dendritic component.

Fig. 8 displays the particle size distributions of dendrimer derivatives PAMAM-*g*-PDMA in aqueous solutions at 25 °C. G3 PAMAM dendrimer and PAMAM-*g*-PDMA present unimodal and relatively narrow distributions. The

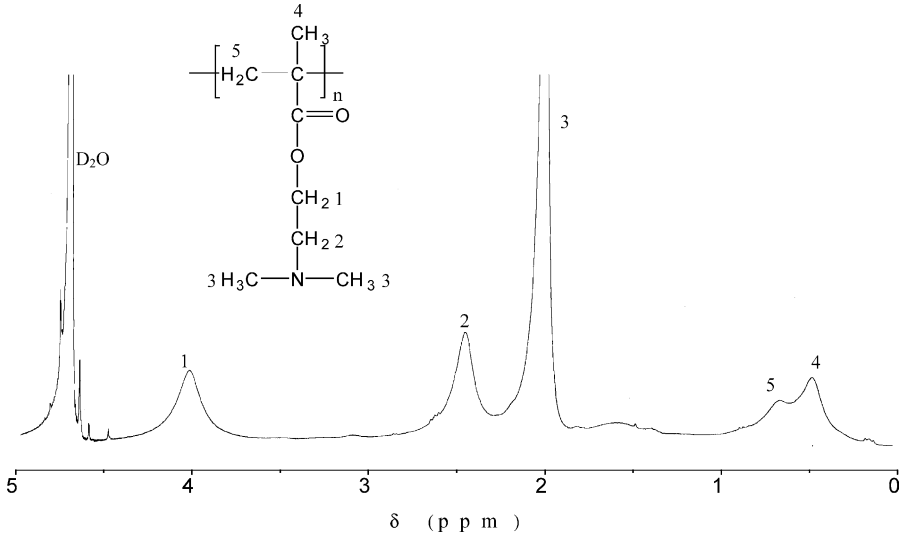

Fig. 7. ^{1}H NMR spectrum for G3-PDMA-2.

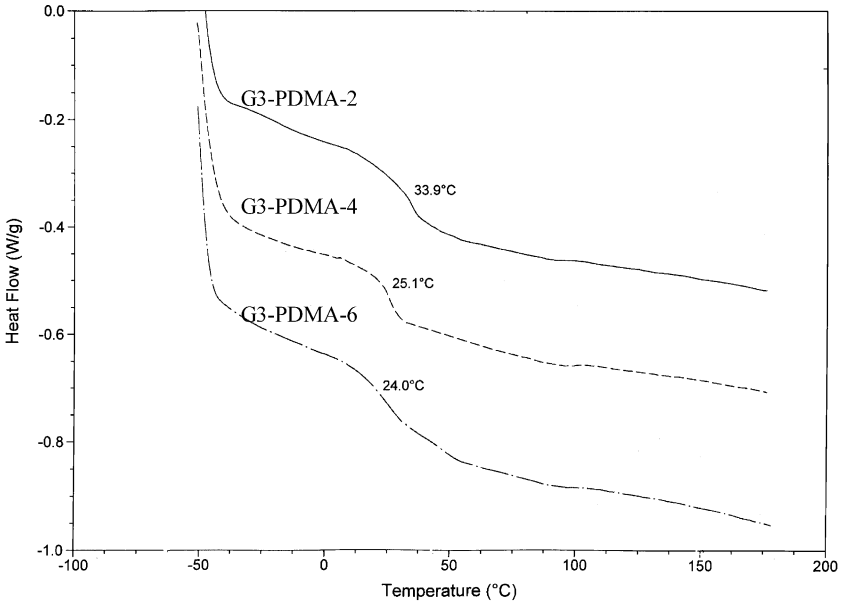

Fig. 9. DSC thermograms of dendrimer derivatives PAMAM-*g*-PDMA.

particle size and PDI are showed in Table 2. As can been seen, the size of G3 PAMAM dendrimer is the smallest, and following the increase in molar ratio of DMA to G3-Cl, the particle size distributions for PAMAM-*g*-PDMA shifts gradually to a higher value with increasing the graft length of PDMA. The result further confirms that the graft length of PDMA on PAMAM surfaces can be controlled by the change of the molar ratio of DMA to macroinitiator.

Fig. 9 shows DSC thermograms of dendrimer derivatives PAMAM-*g*-PDMA with different feed ratio of DMA components. The glass transition temperatures (T_g) gradually decrease following the increase in feed ratio of DMA. Based on the analysis above, the increasing feed ratio of DMA can lead to a longer graft chain on the surface of dendrimers. Moreover, the longer graft can increase the free volume in polymers, and results in a lower glass transition temperature.

3.2. Temperature- and pH-sensitive characters of PAMAM-g-PDMA

Fig. 10 shows the dependence of temperature on the light transmittance at 500 nm of the PAMAM-*g*-PDMA in buffered solution with pH = 10.0. As seen from Fig. 10, the increasing temperature to a certain critical value can cause PAMAM-*g*-PDMA solutions from transparency to opacity. It is a typical temperature-sensitive character. The results can be explained that at lower temperature PAMAM-*g*-PDMA polymers appear an expansible chain configuration, however, as the temperature is raised to a critical value, which is known as 'lower critical solution temperature' (LCST), polymer chains could shrink into a globular configuration because of the hydrophobic interaction between *N*,*N*-dimethylaminoethyl groups. Table 2 presents

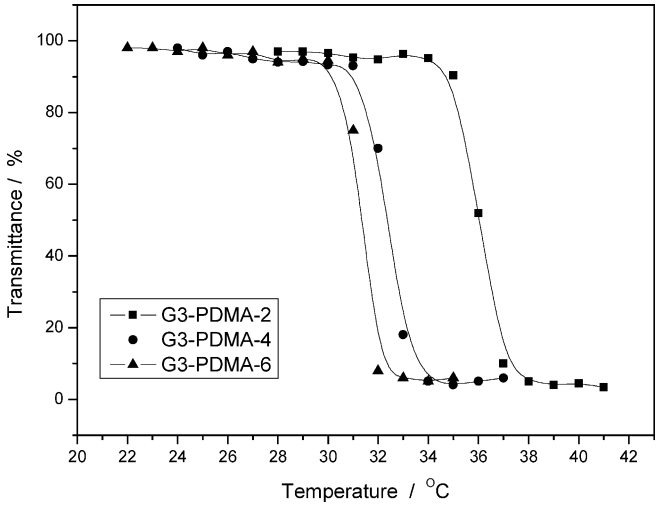

Fig. 10. Effect of temperature on transmittance of PAMAM-*g*-PDMA dissolved in pH 10.0 buffered solution (1 wt%).

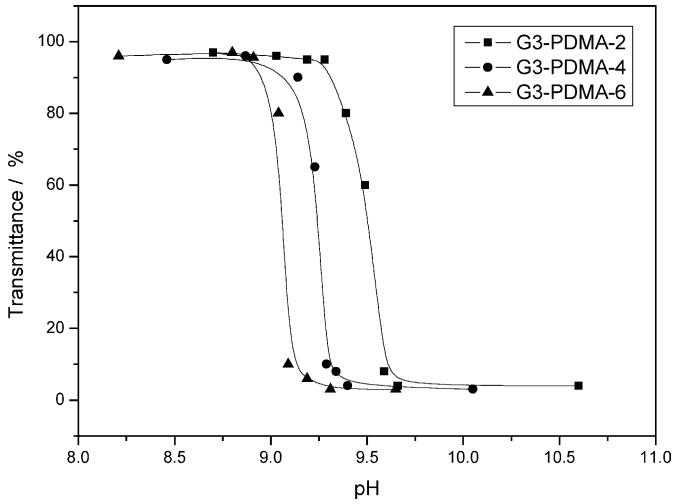

Fig. 11. Effect of pH on transmittance of PAMAM-*g*-PDMA solution (1 wt%) at 37 °C.

the LCST data of PAMAM-*g*-PDMA based third-generation PAMAM dendrimer. Obviously, the LCST of PAMAM-*g*-PDMA shifts to a lower temperature with the increase in the graft length of PDMA on PAMAM surface. Taylor and Cerankowski [30] proposed that the LCST should decrease with increasing hydrophobicity of the polymers, and in the case of PAMAM-*g*-PDMA, following the increase in the graft length of PDMA on PAMAM surface, the polymer becomes more hydrophobic due to the formation of hydrogen bonding between amide and *N*,*N*-dimethylamino groups [31]. This process can prevent *N*,*N*-dimethylamino groups from contacting water and result in a significant hydrophobic interaction causing LCST to a lower temperature.

Fig. 11 shows the dependence of pH on the optical transmittance at 500 nm for the PAMAM-*g*-PDMA solution. As can be seen, PAMAM-*g*-PDMA solutions exhibit pH-sensitive behavior due to protonation/de-protonation of *N*,*N*-dimethylaminoethyl groups in PDMA component. With the increase in graft length of PDMA on PAMAM surface, the polymer's phase transition shifts to a lower pH value. This is due to the same reason as the temperature-sensitive behavior analyzed above.

3.3. The release of CLB from PAMAM-g-PDMA

Compared to linear PDMA, PAMAM-*g*-PDMA contains a dendritic core and a PDMA shell. The internal cavities of dendrimers can act as drug reservoirs to encapsulate drug molecules [14]. In addition, the PDMA grafts on the dendrimer surface can form complexes or conjugates with drug molecules or ligands. On the other hand, due to environmental sensitivity of PDMA component, PAMAM-*g*-PDMA can be expected to become an intelligent carrier in controlled drug release system. To investigate the potential of PAMAM-*g*-PDMA used as a controlled drug release carrier, chlorambucil (CLB), a anticancer drug, is employed as a model drug. The behaviors of the drug release from the PAMAM-*g*-PDMA with different length of grafts of PDMA are studied. All release experiments are carried out under the conditions of pH 1.4 and 10.0 at 37 °C. Fig. 12 presents the cumulative release of CLB from loading samples of G3-PDMA-2, G3-PDMA-4, G3-PDMA-6 and G3. Using sample G3 as a comparison, as can be seen from Fig. 12, the release rate for CLB from the PAMAM-*g*-PDMA is faster at pH 1.4 than at pH 10.0. This suggests that the release of CLB from dendrimer derivative can be controlled by varying pH value. It is also observed from Fig. 12 that the release of CLB from dendrimer derivative is apparently slower compared to loading sample of pure dendrimer G3. With the increase in the length of chain grafts of PDMA on the dendrimer surface, the release rate for CLB are gradually slow. This may be attributed to a special macromolecular structure of PAMAM-*g*-PDMA in which the PDMA grafts are radially aligned on the three-dimensional

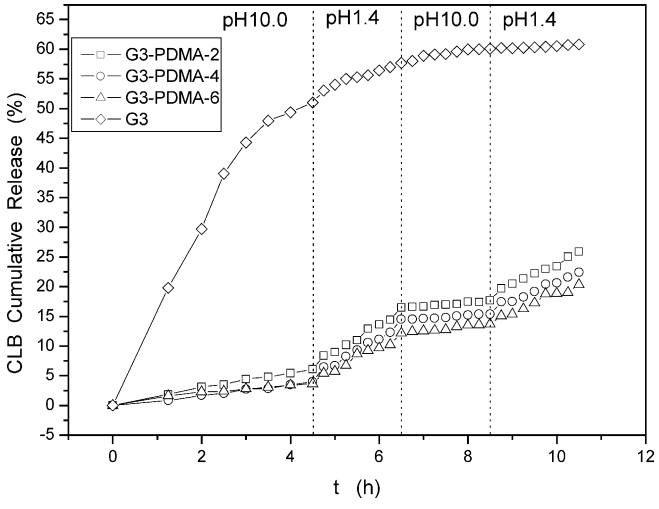

Fig. 12. Release profile of CLB from dendrimer derivatives PAMAM-*g*-PDMA under the conditions of pHs 1.4 and 10.0 at 37 °C.

core of dendrimer. It is well known that PDMA has a conformational transition from a expanding shape to a compact coil in accordance with the variation of the surrounding pH value. It is therefore expected that the release rate of CLB can also be changed during the conformational change of the PDMA grafts. At higher pH value (i.e. pH = 10.0), PDMA grafts take a compact coil conformation, which prevents CLB releasing from dendritic polymers. When pH value reduces to pH = 1.4, PDMA segments show a completely expanding conformation resulting in CLB to diffuse out from the dendritic polymer. These data can explain why the surrounding pH value can control the release rate of CLB from the PAMAM-*g*-PDMA, and why the longer grafts of PDMA can lead to the decrease in the release rate of CLB.

4. Conclusions

1. PAMAM dendrimers with generations 1–5 can be synthesized on the basis of repeatedly using two consecutive chain forming reactions, the exhaustive Michael addition reaction and the exhaustive amidation reaction. PAMAM dendrimer can be modified by two-step reactions to obtain dendrimer with peripheral alkyl chlorine (PAMAM-Cl).
2. Using PAMAM-Cl as macroinitiators, the PAMAM dendrimer derivatives (PAMAM-*g*-PDMA) with PDMA grafts on the surface can be synthesized via ATRP.
3. UV spectroscopy investigations show that the novel dendrimer derivatives exhibit clearly thermo- and pH respondings in accordance with the change of both the temperature and pH value.
4. Using chlorambucil (CLB) as a model drug, the behaviors of the controlled drug release from the dendrimer derivatives can be studied, and the results indicate that the release rate of the drug can be effectively controlled by the pH value of its environment.

Acknowledgements

This work was supported by the National Nature Science Foundation of China (No.20374040).

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