Carbohydrate Polymers 89 (2012) 788–794

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Microwave-assisted solid-phase synthesis of pH-responsive polyaspartamide derivatives

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ARTICLE INFO

Article history:
Received 5 March 2012
Received in revised form 3 April 2012
Accepted 5 April 2012
Available online 13 April 2012

Keywords:
Dynamic light scattering
Functional poly(amino acid)s
Microwave-irradiation
Stimuli-sensitive polymers
Solvent-free

ABSTRACT

Biodegradable stimulus-responsive polymers have attracted more attention in biomedical fields. Here, a series of pH-responsive polyaspartamide derivatives are successfully synthesized from poly(*N*-substituted α/β-asparagines) by a facile, solvent-free and catalyst-free microwave-assisted method. The polymer structure is confirmed by ^{1}H NMR, IR and UV–Vis spectra. With much shorter reaction time (13–18 min), the degree of substitution (DS) of the anhydride-modified polyaspartamide derivatives obtained by microwave heating is two to three times higher as that obtained by conventional heating in DMF (24 h). In addition, pH-induced phase transition behavior of polyaspartamide derivatives is investigated by dynamic light scattering (DLS). The critical pH transition (pHtr) of the resulted polymers increases with increasing DS of the polymers. The hydrophile–lipophile balance (HLB) of the obtained polymers is evaluated to study the relationship between pHtr and polymer structure.

1. Introduction

Poly(amino acid)s and their derivatives have become increasingly attractive because of their superior biocompatible, biodegradable, protein-like nature and non-toxic properties, which are useful in biomedical fields, such as drug delivery, gene transfer, and tissue engineering (Lee et al., 2006; Lin & Kim, 2011; Moon, Kim, Kim, Jeong, & Kim, 2011; Park, Jin, Yang, & Kim, 2009; Seo & Kim, 2006; Sun et al., 2011; Wang et al., 2011b). One of the synthetic poly(amino acid)s, polyaspartamide based polymer, which can be easily synthesized from polysuccinimide (PSI), has been widely studied for drug carrier. The chemical modification of pendant groups either by the aminolysis reaction to PSI using functional amines and/or by further pendant group functionalization can provide diverse biodegradable functional polymers with specific properties (Moon et al., 2011; Park et al., 2011; Xu, Wang, Deng, & Chen, 2010).

In recent years, more attention has been focused on water-soluble stimulus-responsive polymers in response to external stimuli, such as changes at pH, temperature, magnetic field, and electric field in biotechnology and medicine (Chen, Meng, Cheng, & Zhong, 2010; Kojima, Yoshimura, Harada, Sakanishi, & Kono, 2009). Among them, pH-responsive polymers which undergo phase transition in response to changes at pH value have been widely investigated in drug delivery system (Felber, Dufresne, & Leroux, 2011; Kojima et al., 2009; Prabaharan, Grailer, Pilla, Steeber, & Gong, 2009). For instance, they could be used for colonic drug delivery as enteric coatings whose main function is to help the drug go through the stomach without leakage but only release their contents on arriving at the small intestine (Lai, Sun, Tian, Zhao, & Gao, 2008; Shukla & Tiwari, 2012; Sonaje et al., 2010).

The possibility to work efficiently without solvent is very attractive from a green chemistry perspective, especially in biomedical fields. Microwave heating has been proved to be more rapid and efficient technique for controlled solvent-free synthesis and modification in polymer materials (Chen et al., 2009; Ebner, Bodner, Stelzer, & Wiesbrock, 2011; Guo, Zhou, Song, & Zhang, 2009; Iannelli & Ritter, 2005; Roy, Ullah, & Sumerlin, 2009; Sosnik, Gotelli, & Abraham, 2010; Wang et al., 2008). Polyaspartamide derivatives prepared by microwave method were rarely reported so far. The purpose of the present investigation was to synthesize pH-responsive polyaspartamide derivatives by microwave-assisted solid-phase method, as shown in Scheme 1. Their pH-induced phase transition behavior was studied by dynamic light scattering (DLS). The relationship between the critical pH transition (pHtr) and the structure (side chain) of the polymers was discussed.

2. Experimental

2.1. Materials

Phthalic anhydride, maleic anhydride and L-aspartic acid were supplied by the Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). 5-Aminol-1-pentanol (AP) was purchased from Alfa

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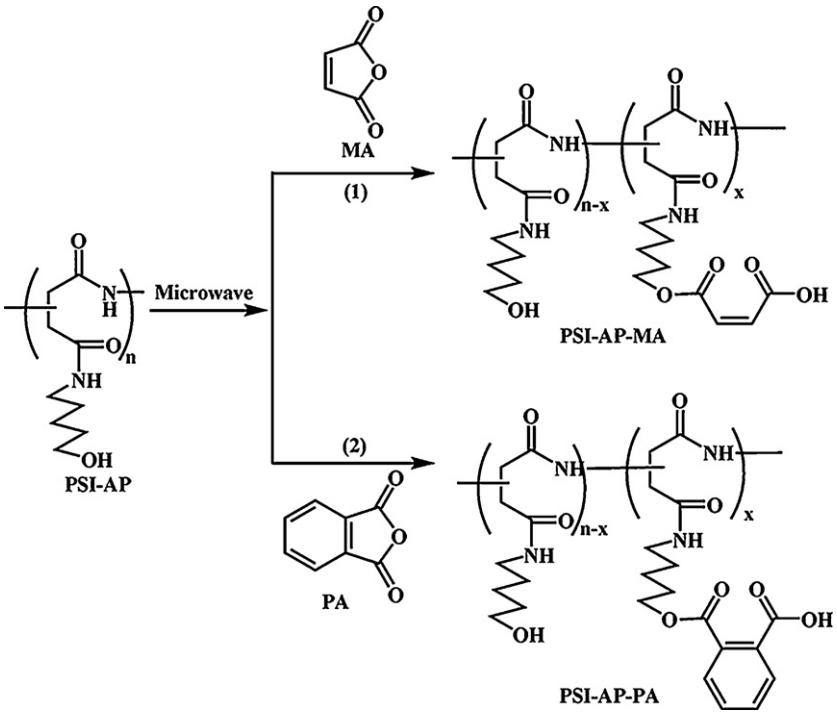
http://dx.doi.org/10.1016/j.carbpol.2012.04.012



Scheme 1. Reaction schemes of polyaspartamide derivatives PSI-AP-MA (1) and PSI-AP-PA (2) via microwave irradiation.

Aesar. *N,N*-Dimethylformamide (DMF) was obtained from Shanghai Reagent Chemical (Shanghai, China) and distilled under reduced pressure prior to use. All other reagents and solvents were of analytical grade and used without further purification.

2.2. Measurements

^{1}H NMR spectra were obtained by a Mercury VX-300 spectrometer at 300 MHz with DMSO-d_6 as the solvent. IR spectra were recorded on a Spectrum one spectrometer (Perkin-Elmer). UV–Vis spectra (400–200 nm) were determined by Perkin-Elmer Lambda Bio 40 UV/VIS spectrometer, and the polymer concentration of 0.2 mg/mL in PBS 8.0 was used. The molecular weights of the polymers were evaluated by size-exclusion chromatography-multi-angle light-scattering detector (SEC-MALS) system consisted of a Waters 2690D separations module, a Wyatt Optilab DSP differential refractometer detector and a Wyatt DAWN EOS MALS detector. Two chromatographic columns (Styragel HR3, HR4) with a precolumn were used in series. DMF containing 10 mM LiBr was used as the mobile phase at a flow rate of 0.3 mL/min at 30 °C. The data were processed with Astra software (Wyatt Technology). pH-Responsive characteristics of the obtained polyaspartamide derivatives were investigated by dynamic light scattering (DLS) using ZETA-SIZER Nano Series Nano-ZS, MALVERN Instrument. The polymer was first dissolved in PBS solution at pH 8.0 with polymer concentration of 1.0 mg/mL and filtered through a 0.45 μm filter. The pH of the polymer solution was gradually adjusted by adding 0.10 M HCl standard aqueous solution.

2.3. Synthesis of polyaspartamide derivatives

2.3.1. Synthesis of poly(N-substituted α/β-asparagine)s

Poly(succinimide) (PSI) was synthesized by a thermal polycondensation of L-aspartic acid in the presence of phosphoric acid as catalyst, as previously reported (Park et al., 2009). Reaction of PSI with an excess of 5-amino-1-pentanol (2 equiv.) at 50 °C in anhydrous DMF for 24 h according to the method reported in the literature (Tachibana, Kurisawa, Uyama, Kakuchi, & Kobayashi, 2003) produced poly(*N*-substituted α/β-asparagine)s, denoted as PSI-AP. Its structure was analyzed by ^{1}H NMR (Fig. 1A) and FTIR.

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.1–1.5 (*e*, $CH_2CH_2CH_2CH_2CH_2$), 2.5–2.7 (*b*, $CHCH_2CONH$), 3.0 (*d*, $NHCH_2CH_2$), 3.2–3.4 (*f*, CH_2CH_2OH), 4.2–4.8 (*a*, $NHCH(CO)CH_2$), 7.5–8.5 (*c*, NH).
FTIR (KBr): 1645, 1538 (s, ν(amide)), 2931, 2859 (w, $\nu(CH_2)$) cm^{-1}.

2.3.2. PSI-AP grafted with maleic anhydride by microwave irradiation

PSI-AP 100 mg (0.50 mmol) and maleic anhydride (0–1 mg, 0–0.5 mmol) were mixed in an agate mortar. The mixture was transferred into a 5 mL cylindrical glass vessel. The reaction vessel was placed in the microwave oven (2.45-GHz microwave oven, G70D20CSP-D2(S0), Galanz company, Guangzhou, China). An interval heating way was carried out in this work. For example, the reagent mixture was first irradiated in microwave for 6 min with the microwave powers of 350 W, then cooled down to room temperature. This heating and cooling process was repeated several times. After being cooled to room temperature, the reaction product was dissolved in DMF and precipitated in ethyl ether in order to remove unreacted anhydride and side products. The polymer structure was analyzed by ^{1}H NMR (Fig. 1B) and FTIR.

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.1–1.5 (*e*, $CH_2CH_2CH_2CH_2CH_2$), 4.1 (*g*, $CH_2CH_2O(CO)$), 6.4 (*h*, $(CO)CH{=}CH(CO)$).
FTIR (KBr): 1645, 1538 (s, ν(amide)), 2931, 2859 (w, $\nu(CH_2)$), 1714 (s, $\nu(C{=}O)$) cm^{-1}.

2.3.3. PSI-AP grafted with phthalic anhydride by microwave irradiation

PSI-AP 100 mg (0.5 mmol) and phthalic anhydride (0–1 mg, 0–0.5 mmol) were mixed in an agate mortar. The mixture was transferred into a 5 mL cylindrical glass vessel, which was placed in the microwave oven and irradiated for total 13 min (the reaction mixture was cooled down to room temperature every 4 min, but 5 min for the last reaction time) at the power of 490 W. Then the reaction product was dissolved in DMF and precipitated in ethyl

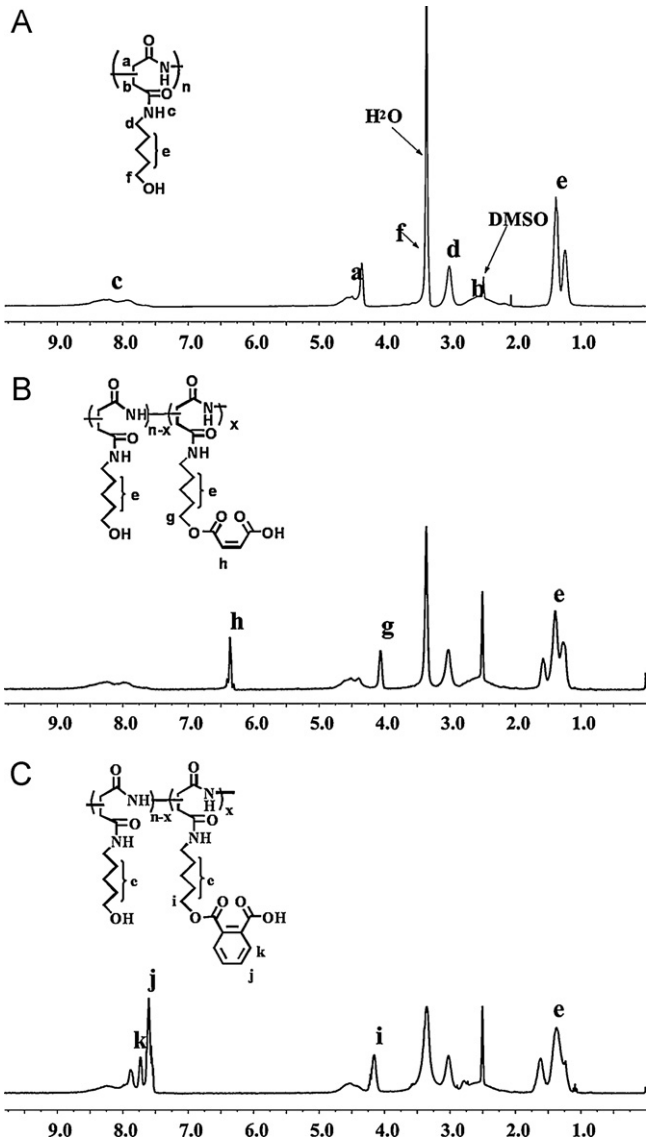


Fig. 1. ^{1}H NMR spectra of PSI-AP (A), PSI-AP-MA (B) and PSI-AP-PA (C) in DMSO-d_6.

ether in order to remove unreacted anhydride and side products. The polymer structure was analyzed by ^{1}H NMR (Fig. 1C) and FTIR.

^{1}H NMR (300 MHz, DMSO-d_6, δ): 1.1–1.5 (*e*, $CH_2CH_2CH_2CH_2CH_2$), 4.1 (*i*, $CH_2CH_2O(CO)$), 7.5–7.7 (*j*, *k*, Arom).
FTIR (KBr): 1645, 1538 (s, ν(amide)), 2931, 2859 (w, $\nu(CH_2)$), 1714 (s, ν(C=O)) cm^{-1}.

2.3.4. PSI-AP grafted with anhydrides by conventional thermal heating

PSI-AP 50 mg (0.25 mmol) was dissolved in 1.0 mL of anhydrous DMF, and a calculated amount of maleic anhydride or phthalic anhydride was added. The reaction mixture was stirred at 70 °C for 24 h, then the product was precipitated in ethyl ether in order to remove unreacted anhydride and side products.

3. Results and discussion

3.1. Microwave-assisted solid-phase synthesis of polyaspartamide derivatives

Polysuccinimide (PSI) was synthesized by a thermal polycondensation of L-aspartic acid in the presence of phosphoric acid as catalyst, as previously described (Park et al., 2009). The obtained PSI dissolved in anhydrous *N,N*-dimethylformamide (DMF) was reacted with an excess of 5-amino-1-pentanol to give poly(*N*-substituted α/β-asparagines), denoted as PSI-AP, according to the method reported in the literature (Tachibana et al., 2003). Then, pH-responsive polyaspartamide derivatives PSI-AP-MA and PSI-AP-PA were synthesized by mixing solid PSI-AP with anhydride (maleic anhydride, MA or phthalic anhydride, PA, respectively) at the irradiation of microwave, as shown in Scheme 1. The structure of the obtained polymers was analyzed by ^{1}H NMR, FTIR and UV–Vis spectroscopy.

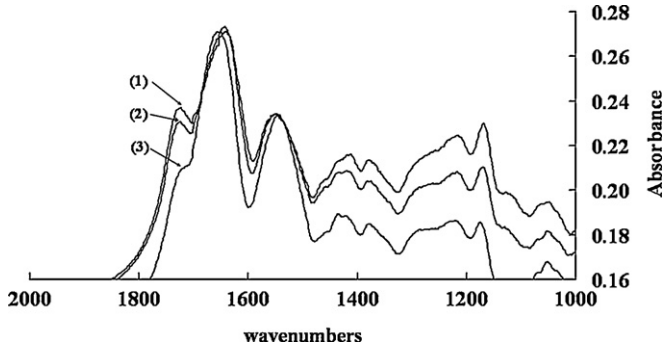


Fig. 2. IR spectra of PSI-AP-MA with the DS of 0.64 (1), 0.37 (2), 0.26 (3).

Fig. 1 shows the ^{1}H NMR spectra of PSI-AP, PSI-AP-MA and PSI-AP-PA. It can be seen from Fig. 1B that the signal at 6.4 ppm corresponds to maleic double bond of PSI-AP-MA, and the new signal at 4.1 ppm is attributed to methene protons connected with the new ester bond. Similarly, as illustrated in Fig. 1C for the ^{1}H NMR spectrum of PSI-AP-PA, the new signal at 4.1 ppm is due to the methene protons connected with the new ester bond, the signal at 7.5–7.7 ppm is from the aromatic protons, which indicates the introduction of the PA pendant group. The degree of substitution (DS) of the resulting polymer PSI-AP-MA was defined as the molar ratio of MA to all of the repeating succinimide units in the PSI polymer and was calculated by ^{1}H NMR spectrum using the ratio of the integral of the peak at 6.4 ppm (*h* in Fig. 1B, 2*H*, alkene protons) to the integral of the peak at 1.1–1.5 ppm (*e* in Fig. 1B, 6*H*, methene protons). Similarly, the DS of PSI-AP-PA was estimated by the aromatic protons (*j*, *k* in Fig. 1C, 4*H*) at 7.5–7.7 ppm to the methene protons (*e* in Fig. 1C, 6*H*) at 1.1–1.5 ppm. The DS of PSI-AP-MA and PSI-AP-PA continued to increase with increasing the feed molar ratio of anhydride reagents (Table 2).

The structure of the anhydride-modified polyaspartamide derivatives was confirmed by the FTIR spectra. The characteristic strong bands at 1645 cm^{-1} (amide I) and 1538 cm^{-1} (amide II) corresponding to the aspartamide backbone, the band at 1714 cm^{-1} originating from the stretching frequencies of carbonyl groups can be seen in Fig. 2, which indicates the attachment of MA onto the resulting polymer successfully through the ring-opening reaction of maleic anhydride with PSI-AP. It was observed that the absorption at 1714 cm^{-1} from carbonyl group increased with increasing the anhydride feed ratio.

The UV–Vis spectra of the obtained polymers PSI-AP-PA with various DS were shown in Fig. 3. It can be seen from this figure that an obvious absorption peak at 280 nm, the characteristic absorption of aromatic group, indicating the attachment of the PA pendant group. It was also observed that the characteristic absorption peak of aromatic group at 280 nm increased with the increase of DS of PSI-AP-PA. Both of the IR and UV results mentioned above were in good accordance with the ^{1}H NMR results. All the above indicate the successful synthesis of PSI-AP-MA and PSI-AP-PA by solvent-free microwave-assisted solid-phase method.

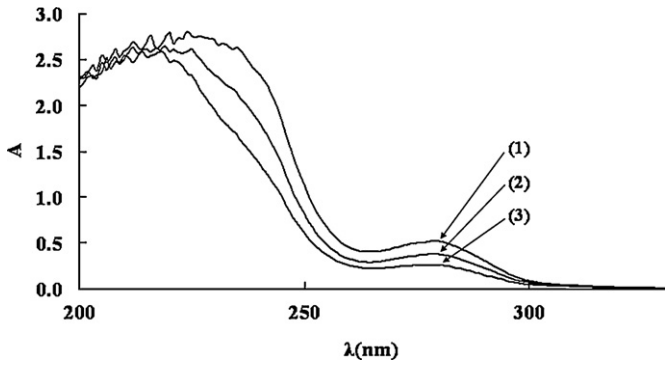


Fig. 3. UV spectra of PSI-AP-PA in phosphate buffer (pH = 8.0) with the DS of 0.60 (1), 0.39 (2), 0.20 (3) (polymer concentration 0.2 mg/mL).

Table 1
Effect of microwave energy and reaction time on DS values for PSI-AP-MA.[a]

Sample	Power (W)	Time (min)	DS
P1	210	6	0.20
P2	280	6	0.30
P3	350	6	0.40
P4	350	3	0.18
P5	350	4	0.29
P6	350	5	0.34
P7	350	12[b]	0.53
P8	350	18[b]	0.64
P9	350	24[b]	0.66
P10	350	30[b]	0.66

[a] The molar ratio of maleic anhydride to PSI-AP unit was 1.0.
[b] Total irradiation time with 6 min for each time.

3.2. Optimization of microwave irradiation

To investigate the effect of microwave energy on the degree of substitution (DS) of PSI-AP-MA, different reaction time and power outputs were examined.

3.2.1. Output power of microwave

When the microwave output powers were 210, 280, and 350 W with an irradiation time of 6 min and MA/PSI-AP molar unit ratio of 1.0, PSI-AP-MAs with different DS were obtained as shown in Table 1. It can be seen from Table 1 that the DS of PSI-AP-MA increased with increasing output power in the range of 210–350 W (for polymers P1–P3). When the output power was above 350 W, unfavorable charing of polymer and sublimation of MA were observed, which was mentioned in the literature (Liu, Li, & Fang, 2004). Thus, 350 W was used as the optimum output power in the later investigation.

3.2.2. Irradiation time

When the molar ratio of MA/PSI-AP molar unit was 1.0 and the microwave power was 350 W, the effect of microwave irradiation time on the DS of PSI-AP-MA was studied, as summarized in Table 1. It can be seen from Table 1 that the DS of PSI-AP-MA increased with increasing irradiation time from 3 to 6 min (for polymers P3–P6). However, too long irradiation time, such as above 6 min, charing of polymer was observed and thermal degradation of polymer could occur due to overheating (Feng, Li, Wu, He, & Ma, 2010). To further enhance the DS of PSI-AP-MA, an interval heating way was carried out in this work, i.e. the reagent mixture was first irradiated in microwave for 6 min, then cooled down to room temperature. This heating and cooling process was repeated several times. As seen in Table 1, when the total irradiation time is 18 min, the DS of PSI-AP-MA achieved up to 0.64. However, the DS hardly changed when further irradiation by microwave was applied. This is mainly due to sublimation of most unreacted reagent MA. The characteristic absorptions at about 1830 cm^{-1} and 1760 cm^{-1} of anhydride were not detected from the IR spectrum of the reaction mixture after 18 min irradiation, which indicated the reagent MA was absent. Therefore, total 18 min of irradiation time was applied.

The similar investigation process was carried out to obtain the optimal condition for PSI-AP-PA. The microwave output power was 490 W with the total irradiation time of 13 min (the reaction mixture was cooled down to room temperature every 4 min, but 5 min for the last time) when the PA/PSI-AP molar unit ratio was 1.0. The DS of the obtained PSI-AP-PA was up to 0.60.

3.3. Comparison of microwave irradiation and conventional heating method

A series of pH-responsive polyaspartamide derivatives with varying composition were prepared by the irradiation of microwave at the optimal conditions. The same reactions were carried out in DMF by conventional thermal heating in an oil bath at 70 °C and the molecular weight of the resulting polymers were measured by size-exclusion chromatography in DMF at 30 °C using online multi-angle light-scattering detector (SEC-MALS) (Table 2).

Generally speaking, microwave-assisted synthesis can proceed in a very fast and efficient manner (Sosnik et al., 2010). Indeed, synthesis of the polyaspartamide derivatives PSI-AP-MA and PSI-AP-PA under microwave irradiation needed significantly shorter time, resulting in higher degree of substitution, compared with conventional thermal heating process, as seen from Table 2. For example, PSI-AP reacted with maleic anhydride (1.0 equiv.) for 24 h at 70 °C in an oil bath, resulting in a polyaspartamide derivative with DS of 0.23, whereas the same reaction under microwave heating for 18 min brought about DS of 0.64.With much shorter reaction time, the DS of PSI-AP-MA obtained by microwave heating was two to three times higher as obtained by conventional heating with the molar ratio of anhydride to PSI-AP unit from 0.4 to 1.0. Although the DS obtained by conventional heating can be improved to some extent by adding catalyst or increasing the anhydride feed molar ratio extraordinarily, the efficiency of conventional heating can never be up to that of microwave heating at present. The reason of such high efficiency with microwave irradiation reaction may be originated from the formation of ionic intermediate (II), as shown in Scheme 2 (Bezdushna & Ritter, 2005), which can absorb the microwave energy very effectively.

3.4. pH-Responsive characteristics of polyaspartamide derivatives

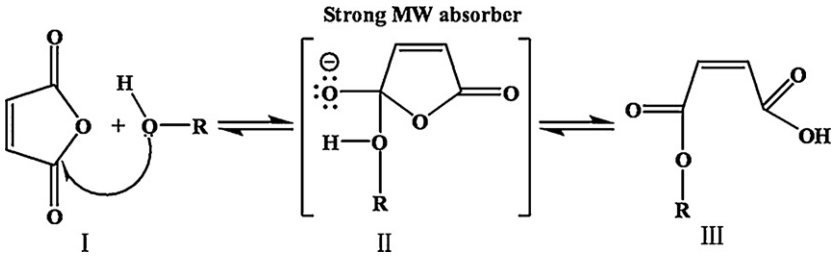
A pH-induced phase transition is a unique property that has been observed with polymers containing ionizable groups. Ionizable groups such as bases or acids which act as hydrophilic or hydrophobic parts of a polymer at various pH in water play an important role in pH-sensitive behavior (Kim et al., 2006; Liu & Urban, 2010). A basic group such as imidazole becomes charged at pH below its pKa value, whereas an acidic group such as carboxylic acid becomes ionized at pH above pKa. Meanwhile, when the pH is changed such that a less ionizing environment is created, the proportion of charged groups (hydrophilicity of the polymer) decreases, which causes a soluble–insoluble transition (Kang & Bae, 2002).

In this work, carboxylic acid is the ionizable groups, the phase transition corresponds to the beginning of the protonation of the –COOH groups on the MA or PA segments. The DLS measurement was performed to investigate the pH-responsive phase transition of the PSI-AP-MA and PSI-AP-PA polymers, as shown in Fig. 4. The transparent polymer solutions were observed at moderate and high pH because the neutralization of the –COOH groups provided hydrophilic –COO– groups. By decreasing the pH, the polymer

Table 2
Comparison of microwave irradiation and conventional heating method.

Sample	Reactant	Molar ratio[c]	Microwave irradiation[a]				Conventional heating[b]		
			DS	pHtr[d]	Mn ($\times 10^4$)	PDI	DS	Mn ($\times 10^4$)	PDI
1	MA	1.0	0.64	2.9	1.76	1.35	0.23	1.65	1.58
2	MA	0.7	0.37	3.2	2.29	1.50	0.21	1.43	1.61
3	MA	0.4	0.26	3.4	1.97	2.51	0.14	1.29	1.61
4	PA	1.0	0.60	4.4	3.83	1.51	0.25	2.46	1.66
5	PA	0.7	0.39	4.7	3.41	1.93	0.18	2.08	1.58
6	PA	0.4	0.20	4.9	2.43	2.41	0.12	1.78	1.69

[a] Reaction condition: 18 min, 350 W for MA and 13 min, 490 W for PA, respectively.
[b] Reaction condition: 24 h, 70 °C in DMF.
[c] Molar feed ratio of MA or PA to PSI-AP unit.
[d] Critical pH transition (pHtr), determined by DLS measurement.



Scheme 2. Mechanism of the ring open reaction by ionic intermediates.

solutions became turbid progressively due to less hydrophilic –COO– groups present (Dai, Ravi, Tam, Mao, & Gan, 2003).

It can be seen from Fig. 4 that the critical pH transition (pHtr) of all the polymers increased with increasing DS of the polymers. This indicates that the pHtr of the polymers can be adjusted by controlling the polymers' DS for different applications. Furthermore, the pHtr of PSI-AP-MA ranged from 2.9 to 3.4, which was lower than those of PSI-AP-PA (from 4.4 to 4.9). This is attributed to the hydrophilic differences of the side chains for PSI-AP-MA and PSI-AP-PA. Here, the hydrophile–lipophile balance (HLB) is introduced to discuss the relationship between the pHtr value and the structure of the polymers (Belbekhouche, Ali, Dulong, Picton, & Le Cerf, 2011; Wang, Klaikherd, & Thayumanavan, 2011).

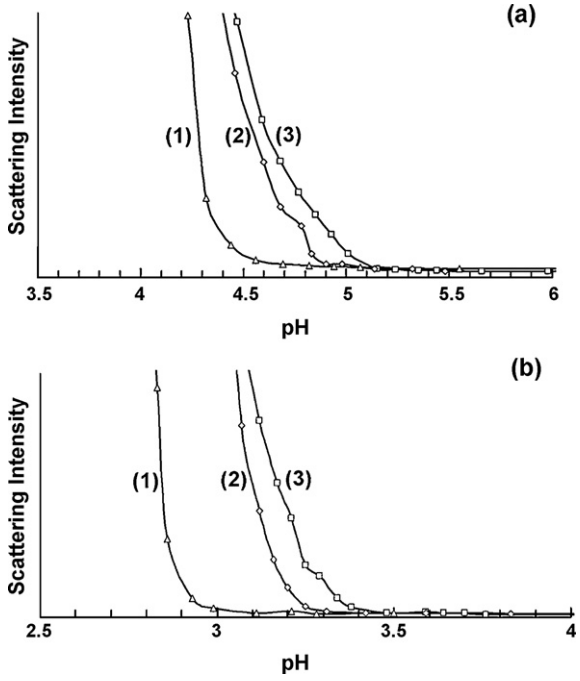


Fig. 4. DLS of PSI-AP-MA (a) with DS of 0.64 (1), 0.37 (2), 0.26 (3) and PSI-AP-PA (b) with DS of 0.60 (1), 0.39 (2), 0.20 (3) in phosphate buffer (pH = 8.0) (polymer concentration 1.0 mg/mL).

In 1957, Davies suggested a method calculating a hydrophile–lipophile balance (HLB) value based on the chemical groups of the molecule (Davies, 1957), which has been widely used (Guo, Rong, & Ying, 2006). He assumed that the HLB value was an additive and constitutive indicator and the group numbers were assigned to various structural elements. Then the HLB value was given by Eq. (1).

$$\mathrm{HLB} = 7 + \sum(\text{hydrophilic group numbers}) - \sum(\text{hydrophobic group numbers}) \quad (1)$$

The dissociation of the polymer pendant carboxyl groups will produce two different structures of –COO– and –COOH, which can influence the HLB value. We can use Eq. (1) to get the relationship of HLB and the dissociation degree of –COOH in different pH values to obtain Eq. (2) for PSI-AP-PA and Eq. (3) for PSI-AP-MA (see Supplementary data).

$$\mathrm{HLB}_{(\mathrm{PSI\text{-}AP\text{-}PA})} = 10.725 + \frac{20.038x + 0.938}{1+x}n \quad (2)$$

$$\mathrm{HLB}_{(\mathrm{PSI\text{-}AP\text{-}MA})} = 10.725 + \frac{20.75x + 1.65}{1+x}n \quad (3)$$

where x is $[A^-]/[HA]$, n is the DS of PA and MA.

In order to get the relationship of HLB and pH values, the Henderson–Hasselbalch equation (4) is used.

$$\mathrm{pH} = \mathrm{pKa} + \log\frac{[A^-]}{[HA]} \quad (4)$$

The pKa of PSI-AP-$MA_{0.37}$ (PSI-AP-MA with the DS of 0.37) determined by acid–base titration was 4.15 and the pKa of PSI-AP-$PA_{0.39}$ (PSI-AP-PA with the DS of 0.39) determined was 5.0.

The HLB values of PSI-AP-$MA_{0.37}$ and PSI-AP-$PA_{0.39}$ calculated by Eqs. (2)–(4), as a function of pH were shown in Fig. 5. It can be seen from this figure that both the critical pH transition (pHtr) for PSI-AP-$MA_{0.37}$ (3.3) and PSI-AP-$PA_{0.39}$ (4.5) corresponded to the

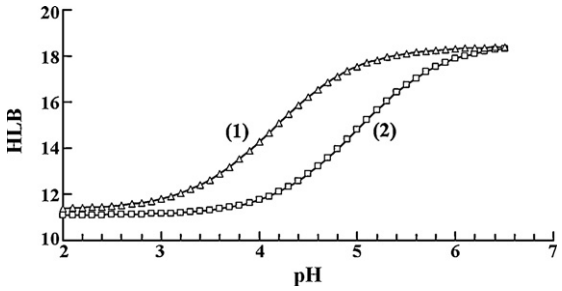


Fig. 5. The relationship between the calculated HLB and solution pH value for PSI-AP-$MA_{0.37}$ (1) and PSI-AP-$PA_{0.39}$ (2).

similar HLB around 12–13. Therefore, theoretically speaking, if the pendant groups (MA or PA) of the polymers are replaced by any other groups, the pHtr of the new polymers may be predicted and the new polymer with desired pHtr can be designed in advance.

4. Conclusions

In this study, synthesis of pH-responsive polyaspartamide derivatives from poly(*N*-substituted α/β-asparagines) using phthalic anhydride or maleic anhydride by an efficient microwave-assisted solid-phase method is described. ^{1}H NMR, IR and UV–Vis analysis is used to confirm the polymer structure. With much shorter reaction time (13–18 min), the degree of substitution (DS) for the anhydride-modified polyaspartamide derivatives synthesized by solvent-free microwave irradiation is two to three times higher compared with conventional thermal heating in DMF at 70 °C (24 h). The DLS measurement is performed to investigate the pH-responsive phase transition of the polyaspartamide derivatives PSI-AP-MA and PSI-AP-PA. The critical pH transition (pHtr) of the polymers increases with increasing DS for the two investigated polymers PSI-AP-MA and PSI-AP-PA. Furthermore, the pHtr of PSI-AP-MA ranged from 2.9 to 3.4, which was lower than those of PSI-AP-PA (from 4.4 to 4.9). Based on the hydrophile–lipophile balance (HLB) value, the polymer pHtr can be predicted and adjusted by controlling the polymer structure for different applications. Further study of these pH-responsive polymers for colonic drug delivery as enteric coatings is ongoing and will be reported elsewhere.

Acknowledgments

This research was financially supported by the National Natural Science Foundation of China (21174109, 21074100), the National Key Basic Research Program of China (2011CB606202, 2009CB930300), and Program for Changjiang Scholars and Innovative Research Team in University of China (IRT1030).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2012.04.012.

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