Temperature-responsive Property of Star Poly((N,N-dimethylamino)ethyl methacrylate) with Hyperbranched Core: Effect of Core-Shell Architecture and β-Cyclodextrin Grafted via Covalent Bond or Ionic Electrostatic Attraction

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Temperature-responsive Property of Star Poly((N,N-dimethylamino)ethyl methacrylate) with Hyperbranched Core: Effect of Core-Shell Architecture and β-Cyclodextrin Grafted via Covalent Bond or Ionic Electrostatic Attraction

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The influence of macromolecular architectures on temperature-responsive properties of poly((N,N-dimethylamino)ethyl methacrylate) (PDMAEMA) was investigated to control the lower critical solution temperature (LCST) for promoting its potential application in the biomedical field. Temperature-responsive property of PDMAEMA was adjusted via β-cyclodextrin (β-CD) groups on polymers, the hyperbranched architecture, and the core-shell structure. The effect of β-CD groups, hyperbranched architecture, and core-shell structure on LCST was accomplished by comparing the amphiphilic hyperbranched polymers with and without β-CD groups, as well as their linear analogous. The β-CD groups grafted via ionic electrostatic attraction can increase the LCST value of PDMAEMA at different pH value and ionic strength. In contrast, the covalent β-CD groups result in the decrease of LCST at a wide range of pH value. Additionally, the LCST value is also prominently determined by core-shell structure. The core layer carrying the covalent β-CD groups increases LCST value, whereas the shell layer containing 2-Hydroxyethyl methacrylate (HEMA) component decreases LCST value.

Keywords: β-cyclodextrin, Core-shell structure, Hyperbranched, PDMAEMA, Temperature-responsive Property

Introduction

Stimuli-responsive polymers responding to external or internal stimuli including temperature, pH, light, ionic strength, and electric or magnetic fields are attractive for application in drug delivery, diagnostics, sensing, and so forth (1–6). As one of the typical stimuli-responsive polymers, poly((N,N-dimethylamino)ethyl methacrylate) (PDMAEMA) is well-known for its lower critical solution temperature (LCST)-type phase transition due to the hydrogen-bond effect with water of tertiary amine moieties and hydrophobic effect of gemini methyl groups. Normally, pH and ionic strength may significantly influence the phase transition behavior of PDMAEMA aqueous solution because it can be regarded as a weak polyelectrolyte. Thus, the PDMAEMA aqueous solution also exhibits multi-stimuli-responsive property under external stimuli, such as temperature, pH, or ionic strength (7–10).

The temperature-responsive property of PDMAEMA is influenced by its macromolecular architecture (4, 11–13). For example, though PDMAEMA was reported with a LCST of 50°C, the shift from 50°C to 4°C could be observed for the linear copolymer of DMAEMA and ethylacrylamide (EAAm). It is due to the formation of hydrogen bond between the DMAEMA and EAAm component resulting in a hydrophobic contribution to LCST (11, 14). However, the physiological condition for gene delivery or drug release in vivo is about 37°C, but the LCST of PDMAEMA may be higher or lower than 37°C. Obviously, its LCST is not always satisfied with the actual demand. Therefore, it is important to fully understand the relationship between the macromolecular architecture of PDMAEMA and the temperature-responsive property for adjusting LCST and promoting its potential application in biomedical field (15–21).

In general, PDMAEMA possesses linear (8, 11, 22, 23), brush-shaped (4, 24), star-shaped (12, 13, 25), or network architecture (26–29). There are many reports on linear PDMAEMA or its copolymers, where the molecular weight and monomer...
component change LCST (22, 23). For example, for the brush-shaped PDMAEMA, the hydrophilic/hydrophobic co-monomers affect the temperature, pH, and ionic strength responsiveness (4, 24). Furthermore, the LCST of star-shaped PDMAEMA is dependent on star architectures including arm number, arm length, or degree of polymerization (12, 25), which ranges from 29°C to 34°C. Recently, even the stimuli-responsive hydrogel of PDMAEMA with network architecture has become attractive for its unique physicochemical characteristic in aqueous solution (26–29).

Thus far, however, there are few reports on the relationship between the core-shell type PDMAEMA and its temperature-responsive property. Herein, for the first time, we report on the LCST of new star PDMAEMA with hyperbranched core and the effect of core-shell architecture and β-cyclodextrin (β-CD) grafted via covalent bond or electrostatic attraction on LCST. First, LCST of PDMAEMA was adjusted via β-CD groups, hyperbranched architecture, and core-shell structure. Then the effect of β-CD groups, hyperbranched architecture, and core-shell structure on LCST was investigated by comparing the amphiphilic hyperbranched polymers with and without β-CD groups, as well as their linear analogues.

Experimental Section

Materials

*N,N*-dimethylamino)ethyl methacrylate and 2-hydroxyethyl methacrylate monomers were purchased from ACROS Chemical Industries (USA) and purified by distillation under reduced pressure before use. *N,N,N',N''*,N'''-pentamethyl diethylene triamine (PMDETA) was supplied by Yutian Chemical Ltd. (Liyang City, China) and used as received without further purification. Dimethylformamide (DMF) (HPLC grade) used as the eluent for SEC/MALLS was received from Dima Tech (USA). Other chemical reagents were purchased from Tianjin Kermel Chemical Reagents Development Center (Tianjin City, China).

Measurements

The ^1H NMR and ^13C NMR spectra were conducted on a Bruker Avance 300 spectrometer (Bruker BioSpin, Switzerland) operating at 300 MHz in DMF-d6. The molecular structure parameters of hyperbranched polymers were determined on DAWN EOS size exclusion chromatography/multangle light scattering (SEC/MALLS) instrument equipped with viscometer (Wyatt Technology, USA), HPLC grade DMF containing LiCl (0.01 mol L^-1) (at 40°C) was used as eluent at a flow rate of 0.5 mL min^-1. The chromatographic system consisted of a Waters 515 pump, differential refractometer (Optilab rEx) and one column, MZ 103 Å 300 × 8.0 mm. MALLS detector (DAWN EOS), quasi-elastic light scattering (QELS), and differential viscosity meter (ViscoStar) were placed between the SEC and the refractive index detector. The molecular weight (M_n) and molecular weight distribution (MWD) were determined by SEC/DAWN EOS/Optilab rEx/QELS model. ASTRA software (Version 5.1.3.0) was utilized for acquisition and analysis of data. UV–vis spectroscopy measurement was performed on a Shimadzu UV-2550 model spectroscopy (Shimadzu, Japan).

Atomic Force Microscopy (AFM) images were recorded on a Digital Instruments Dimension 3100 microscope equipped with a Nanoscope V controller operated in tapping mode. The samples were prepared by drop-coating from dilute solutions in toluene onto fresh-cleaved mica. Transmission Electron Microscopy (TEM) images were recorded in bright field mode with a LEO 922 Omega electron microscope operated at 200 kV. A 5-μL droplet of a dilute solution was dropped onto a copper grid (200 mesh) coated with carbon film, followed by drying for 2 h at room temperature.

Synthesis of PDMAEMA with Core-Shell Architecture and β-Cyclodextrin

HBP-g-PDMAEMA (P0), HBP-g-PDMAEMA-β-CD (P1), and HBP-g-P(DMAEMA-co-GMA-EDA-β-CD) (P2)

The first type of PDMAEMA is consisting of a dendritic polycarbosilane core and PDMAEMA shell with or without β-CD groups. The schematic synthesis route is described in Scheme 1 and the detailed synthesis procedure can be seen in literature (20). In general, for P0 (M_n = 2.6 × 10^6, M_w/M_n = 1.48), the shell layer is composed of the pure PDMAEMA chains prepared via atoms transfer radical polymerization (ATRP) of DEMAEMA monomer. With the same dendritic polycarbosilane core (M_n = 2.4 × 10^5 Da, M_w/M_n = 1.77, degree of branching: 0.62) of P0, P1 (M_n = 3.5 × 10^5, M_w/M_n = 1.37) and P2 (M_n = 4.3 × 10^5, M_w/M_n = 1.06) are constructed from the shells of PDMAEMA chains immobilized by iodide substituted β-CD, and the copolymer of DEMAEMA and GMA-EDA-β-CD monomers, respectively. In another word, the PDMAEMA in P1 is immobilized with the iodide-substituted β-CD group with content of 28.6% and the shell of P2 is the copolymer immobilized by the covalent β-CD groups with 96.2/3.8 molar ratios of DMAEMA and GMA-EDA-β-CD.

HBP-(B_2+AB_x)-g-PDMAEMA (P3), HBP-AB_2-g-PDMAEMA (P4), HBP-AB_2-g-P(DMAEMA-co-HEMA) (P5)

The second type of PDMAEMA systems is consisting of hyperbranched β-CD based polymers core and PDMAEMA shell or copolymer of DMAEMA and HEMA shell. The schematic structure is described in Scheme 2. P3 and P4 are composed of a hyperbranched poly(β-CD) core from AB_2 (M_n = 6.47 × 10^5 Da, M_w/M_n = 1.74, degree of branching: 0.83) or AB_2 (M_n = 3.67 × 10^4 Da, M_w/M_n = 1.89, degree of branching: 0.40) type β-CD monomers. The detailed synthesis procedure can be seen in literature (30) and the molecular structure parameters are listed in Table 1. With a little difference, P5 is composed of a hyperbranched poly(β-CD) core from AB_2 β-CD monomers with degree of branching of 0.40 and the copolymer of DMAEMA and HEMA shell. P5 was synthesized via the similar procedure with P4 using the same macroinitiator in ATRP. For the shell layer of P(DMAEMA-co-HEMA), the molar ratio of DMAEMA and HEMA is 49.2/50.8 (feed ratio: 1/1). 1)

P5: ^1H NMR (DMF-d6, δ, ppm): 4.07 (—O—CH2—CH3—); 3.75 (—CH2—CH2—OH); 2.57 (—CH2—CH2—N—); 2.26 (CH3—N—); 1.91—1.96 (—CH2—); 0.94—1.30 (CH3—). ^13C NMR (DMF-d6, δ, ppm): 175.05—175.88
Scheme 1. Schematic route of synthesis and molecular structures of star PDMAEMA with dendritic polycarbosilane core and PDMAEMA shell (P0, P1, and P2) (color figure available online).

Scheme 2. Schematic route of synthesis and molecular structures of star PDMAEMA with hyperbranched $\beta$-CD based polymer core and PDMAEMA shell (P3, P4, and P5) (color figure available online).
Table 1. The molecular weight and distribution, degree of polymerization of polymer P3, P4, and P5 with core-shell architecture.

<table>
<thead>
<tr>
<th>Sample index</th>
<th>(M_n^a) (KDa)</th>
<th>MWD(^b)</th>
<th>DP(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3</td>
<td>256.6</td>
<td>1.21</td>
<td>36</td>
</tr>
<tr>
<td>(P_4)(<em>{\beta\text{-CD}}) (</em>{10})</td>
<td>79.3</td>
<td>1.10</td>
<td>19</td>
</tr>
<tr>
<td>(P_4)(<em>{\beta\text{-CD}}) (</em>{21})</td>
<td>88.7</td>
<td>1.20</td>
<td>21</td>
</tr>
<tr>
<td>(P_4)(<em>{\beta\text{-CD}}) (</em>{42})</td>
<td>138.1</td>
<td>1.23</td>
<td>42</td>
</tr>
<tr>
<td>P5</td>
<td>186.4</td>
<td>1.46</td>
<td>52</td>
</tr>
</tbody>
</table>

\(^a\)the parameters are measured by SEC/MALLS.
\(^b\)DP is calculated from molecular weight.

\(\cdots\text{COO--}\); 64.98 (\(\cdots\text{O--CH}_2\text{--CH}_2\text{--OH}\)); 57.73 (\(\cdots\text{O--CH}_2\text{--CH}_2\text{--OH}\)); 61.20 (\(\cdots\text{O--CH}_2\text{--CH}_2\text{--N}\)); 55.54 (\(\cdots\text{O--CH}_2\text{--CH}_2\text{--N}\)); 50.12, 52.62 (\(\cdots\text{CH}_2\cdots\)); 43.50 ((CH\(_3\)_2\(--\text{N}\--\cdots\));

14.93, 16.84 (\(--\text{CH}_3\)).

**Results and Discussion**

**Effects of \(\beta\)-CD Groups and Hyperbranched Architecture on LCST**

To adjust LCST and investigate the effect of \(\beta\)-CD groups and hyperbranched architecture on LCST of PDMAEMA, the new star PDMAEMA with hyperbranched core was constructed according to our previous work (Scheme 1) (20, 30). Here, BP-\(g\)-PDMAEMA (\(P_0\)), HBP-\(g\)-PDMAEMA-\(\beta\)-CD (\(P_1\)), and HBP-\(g\)-P(PDMA-Co-GMA-EDA-\(\beta\)-CD) (\(P_2\)) consisted of the hyperbranched polycarbosilane core \(M_n=2.4\text{ KDa,} \ M_n/M_a=1.77,\) degree of branching: 0.62) and PDMAEMA shell with or without \(\beta\)-CD groups, respectively. \(P_0\) possesses a pure PDMAEMA shell layer, whereas \(P_1\) and \(P_2\) have the PDMAEMA shell layer with \(\beta\)-CD groups formed via ionic electrostatic attraction or covalent bond, respectively. For comparison, the linear analogous \(L_1\) and \(L_2\) of PDMAEMA shell of \(P_1\) and \(P_2\), respectively, were employed (Scheme 3) (31).

Figure 1a shows the temperature dependence of light transmittance of \(P_0\), \(P_1\), and \(L_1\) at wavelength of 550 nm in pH = 10 buffer solution. The increase of temperature to a certain critical value causes the change of the polymer solution from transparency to opacity, which is a typical temperature-responsive characteristic. An appropriate explanation for this result is that these polymers appear an expansible chain configuration at lower temperature, however, when the temperature is raised to a critical value, PDMAEMA segments could shrink into a globular configuration because of the hydrophobic interaction among \(N,N\)-dimethylaminoethyl group (3, 13, 32). The schematic transition process is suggested in Scheme 4. Furthermore, compared with \(P_0\), LCST of \(P_1\) is observed to shift to a higher temperature. This result indicates that the incorporation of the ionic \(\beta\)-CD groups decreases the LCST of PDMAEMA. It can be attributed to the ionic electrostatic attraction and large amount of hydroxyl from \(\beta\)-CD groups that increase the hydrophilicity of \(P_1\), resulting in the increase of LCST. In contrast, LCST of \(P_2\) is shifted to a lower temperature in comparison with \(P_0\) (Fig. 1b). It may be attributed to the covalent \(\beta\)-CD groups in P(PDMA-Co-GMA-EDA-\(\beta\)-CD) segments that result in the formation of hydrogen...
Scheme 4. The schematic transition process of P1 near the LCST (color figure available online).

Fig. 1. Temperature dependences of light transmittance of P0, P1, L1 (a), P0, P2, L2 (b), P0, P3 (c), P4, P5 (d), and P4 with different DPs (e) at 550 nm in pH = 10 buffer solution (color figure available online).
bonds, which gives a hydrophobic contribution to the LCST (11). From Fig. 1a and b, compared with the linear polymers L1 and L2, LCST of P1 shifted to a higher temperature, which is in contrast to P2. The result indicates that the hyperbranched architecture also affects the temperature-responsive property of PDMAEMA to some degree.

Figure 2a illustrates the effect of pH on LCST of P0, P1, and L1. From Fig. 2a, LCST values of these polymers decrease sharply with the increase of pH values ranging from 8.5 to 9.5, while the tendency slowly becomes 10 to 13. This behavior can be attributed to the protonation of the tertiary amine functional groups resulting in the enhancement of hydrophobic interactions in solution (33, 34). Interestingly, almost no LCST behavior for P1 or L1 was observed when pH value was lower than 8.5, although many PDMAEMA-based polymers still present LCST behavior even in neutral solution (3, 11, 13, 32). The result indicates that the ionic β-CD groups play a determined role in this phase transition process. The aforementioned conclusion can be further confirmed by the similar study on the influences of pH on LCST of P0, P2, and L2 in Fig. 2b. LCST values of these polymers also decrease with the increase of pH value. However, it should be pointed out that P2 cannot be well-dissolved to form a homogenous solution even at room temperature when the pH value was set as 13. A suggested explanation is that the hydrophobic interaction of the covalent β-CD groups and N,N-(dimethylamino)ethyl groups dominates the intramolecular and intermolecular interaction in this case (10).

Figure 3a demonstrates the effect of ionic strength in buffer solution on LCST of P1 and P2. Obviously, the LCST value of P1 decreases with the increase of ionic strength, but no significant change is observed for P2. It is well-known that PDMAEMA is regarded as a weak cationic polyelectrolyte. Accordingly, for P1, with the addition of NaCl, the electrostatic repulsion among the ionic β-CD groups and the repeating units drive PDMAEMA segments to a more coiled conformation resulting in the phase separation that shifted to a lower temperature. Zhai and coworkers also reported that a high ionic strength in PDMAEMA aqueous solution can induce a lower LCST due to the polyelectrolyte effect (10). However, the electrostatic repulsion becomes very weak when the covalent β-CD groups are incorporated into the PDMAEMA segments. As a result, the LCST value of P2 does not show obvious change with the increase of ionic strength.

**Effect of the Core-Shell Structure on LCST**

From Scheme 1 and Scheme 2, P0 and HBP-(Bγ + ABγ)-g-PDMAEMA (P3) possess a similar PDMAEMA shell layer only with a different core, where β-CD groups are incorporated into the core layer of P3. Therefore, the effects of core layers on the temperature-responsive property of PDMAEMA can be investigated under the similar shell layer condition. Additionally, TEM and SEM images of P3 are presented in Fig. 4 and Fig. 5, respectively, where the spherical unimolecular micelles, with a size of 8–10 nm, were formed in pH = 9 aqueous solution. Figure 1c shows the temperature dependence of light transmittance of P0 and P3 at 550 nm in pH = 10 buffer solution. Compared with P0, LCST of P3 is observed to shift to a higher temperature, and the light transmittance is not significantly changed after decreasing to about 50%. The result indicates that the core structure with β-CD groups decreases the temperature-responsive property of PDMAEMA compared with the core without β-CD groups. Furthermore, the similar phenomenon occurs at different...
Fig. 3. Effect of ionic strength on LCST of P1, P2 (a), P0, P3 (b), and P4, P5 (c) in pH = 10 buffer solution (color figure available online).

Fig. 4. TEM image of P3 in pH = 9 aqueous solution (a), magnification image (b) (color figure available online).

Fig. 5. AFM image of P3 in pH = 9 aqueous solution (a), magnification image (b) (color figure available online).
pH values ranging from 8.5 to 13 (Fig. 2c), and different ionic strength from 0.1 mol·L⁻¹ to 0.5 mol·L⁻¹ (Fig. 3b).

HBP-AB₂-g-PDMAEMA (P4) and HBP-AB₂-g-P(DMA-co-HEMA) (P5) consist of the same hyperbranched poly(β-CD) core layer and different shell layers (Scheme 2 and Table 1). The shell layer of P4 is composed of the pure PDMAEMA segments, but the shell layer of P5 possesses P(DMA-co-HEMA) segments with two kinds of components. Figure 1d presents the temperature dependence of light transmittance of P4 and P5 at 550 nm in pH = 10 buffer solution. LCST of P4 is shifted to a lower temperature in comparison with P5. The reason is that the introduction of HEMA component in the shell layer induces the formation of hydrogen bonds between DMAEMA and HEMA segments, which makes a hydrophobic contribution to the LCST. It is in accordance with the results in the literature (11), where a LCST shifts from 50°C to 4°C was observed for the copolymers of DMAEMA with EAAm. The reason is also the formation of hydrogen bonding between DMAEMA and EAAm residues with a hydrophobic contribution to the LCST. Furthermore, it can be further proven by the investigation of different pH values ranging from 8.5 to 13 (Fig. 2d). In contrast, from Fig. 3c, with the increase of ionic strength, the LCST value of P4 decreases, whereas the LCST value of P5 increases and even obtains a higher value than that of P4 at 0.4 mol·L⁻¹. In general, a higher ionic strength promoted the phase separation of PDMAEMA at lower LCST due to the polyelectrolyte effect (10). The abnormal phenomenon may be attributed to the electrostatic repulsion existing in PDMAEMA segments that is weakened due to the introduction of the HEMA component when the ionic strength increases.

Is the arm length of star PDMAEMA with hyperbranched core able to influence the temperature-responsive property? A series of P4 with the same hyperbranched poly(β-CD) cores and with the shells possessing different arm lengths were prepared (Table 1) (21, 31). The average degree of polymerization (DP) per arm of P4 with different arm lengths is 19, 21, and 42, respectively. Figure 1e shows the temperature dependence of light transmittance of P4 with the different DP at 550 nm in pH = 10 buffer solution. The LCST value of P4 decreases with the increase of DP. The result indicates that the arm number length has certain influence on the LCST of PDMAEMA. In general, the LCST value should decrease when the hydrophobicity of polymer is increasing (35). P4 becomes more hydrophobic due to the formation of hydrogen bonding between the amide and N,N-dimethylamino groups. The effect is enhanced with the increase of arm length of PDMAEMA. Accordingly, the significant hydrophobic interaction causes the LCST to a lower temperature. It is in accordance with the result in literature (13), where the star-shaped PDMAEMA with a longer arm shows lower LCST than the polymer with the shorter arm.

Conclusion

The temperature-responsive property of PDMAEMA can be influenced and adjusted by macromolecular architectures, such as the β-CD groups in polymers, the hyperbranched architecture, and the core-shell structure. The ionic β-CD groups can increase the LCST value of PDMAEMA at different pH values and different ionic strengths. In contrast, the covalent β-CD groups result in the LCST value decreasing at different pH values, but have no significant influence on it when the ionic strength increases. The hyperbranched architecture can also affect the temperature-responsive property of PDMAEMA to some degree. Furthermore, the effect of the core-shell structure on the LCST is also quite prominent. The core layer carrying the β-CD groups can increase LCST, whereas the shell layer containing the HEMA component decreases LCST. The full comprehension is helpful for designing and controlling the LCST-type polymers via macromolecular architecture to promote their potential application in biomedical field.

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