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Thermosensitive polymeric vesicles self-assembled by PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers

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Abstract PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers were prepared by redox polymerization. The self-assembly behavior and thermosensitive property of the copolymers in water were studied using ^{1}H-NMR, TEM and a UV spectrophotometer. The results showed that the LCST of the copolymers was 32 °C, which was consistent with that of pure PNIPAAm. The copolymers could form a vesicular structure in an aqueous solution by self-assembly. The hollow structure of the PNIPAAm-b-PPG-b-PNIPAAm vesicles combined with the temperature-sensitive property may enable many potential applications of the vesicles.

Keywords Block copolymers · Poly(*N*-isopropylacrylamide) · Thermosensitive · Vesicles

Introduction

Polymeric vesicles are microscopic sacs that enclose a cavity with a polymeric shell. The polymeric shells are generally self-directed assemblies of amphiphilic block copolymers whose insoluble blocks are much larger than the soluble blocks. In the past few years, polymeric vesicles have received increasing attention because of their potential applications as confined reaction vessels, drug carriers, protective shells for enzymes or catalysts, artificial cells, etc. [1–6]. Compared with conventional polymeric micellar carriers, polymeric vesicles have the following advantages. Polymeric vesicles not only encapsulate soluble species in their cavities but also accumulate insoluble species in their shells. Furthermore, they may be made to possess a greater range of cavity sizes to enable the delivery of large species such as proteins and genes or more species.

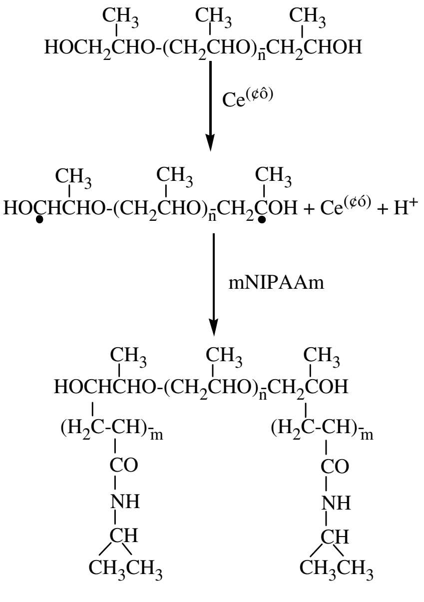
However, it is rather difficult to load or release substances from polymeric vesicles in a controlled way at the desired target. In order to solve this problem, the amphiphilic block copolymers containing thermosensitive blocks, Poly(*N*-isopropylacrylamide) (PNIPAAm), were introduced. It is well-known that PNIPAAm in aqueous solution exhibits a reversible thermosensitive phase transition at 32 °C. Block copolymers containing short PNIPAAm blocks and long hydrophobic blocks can self-assemble in aqueous solution to form stable vesicular structures below 32 °C. Changing the temperature of the environment to slightly above 32 °C can result in destabilization of the vesicles and trigger a burst-like release of the encapsulated substances. Thus, the loading and release of the vesicles can be intelligently controlled by changing the temperature of the environment. So far, no literature has reported thermosensitive polymeric vesicles.

In this work, Poly(propylene glycol) (PPG) was used as the long hydrophobic block. PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers were synthesized by a redox system consisting of ceric ion and PPG in an aqueous medium. They could form polymeric vesicles by self-assembly in aqueous solution. The hollow nanospheres showed the advantage of the thermosensitive property and were expected to load more and larger substances.

Experimental section

N-Isopropylacrylamide (NIPAAm, Acros) was purified by recrystallization in toluene/hexane and dried in vacuo at room temperature. Poly(propylene glycol) (PPG, Uni. Chem.) with a molecular weight of 4,000 was used without further purification. Ceric ammonium nitrate (CAN) was oven-dried at 105 °C for 1 h and then in a desiccator over phosphorous pentoxide prior to use. All other chemicals were reagent grade and used as received.

PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers were prepared by a redox polymerization, similar to the description in the literature (Scheme 1) [7]. The triblock copolymers were characterized by ^{1}H-NMR and GPC, and GPC in THF revealed a molecular weight of the triblock copolymers of $M_n = 6{,}596$ g/mol and a polydispersity of $M_w/M_n = 1.92$.



Scheme 1 The synthesis of PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers

To prepare the colloidal solutions, deionized water, as a precipitant, was added at a rate of 0.3 wt%/10 s with vigorous stirring of the copolymers solution in the common solvent, THF. More water was added until the water content reached ca. 50 wt%. Finally, the organic solvents were removed by dialysis of the colloidal solutions against pure water for 3 days.

Transmission electron microscopy (TEM) was carried out on a JEM-100CX instrument at an acceleration voltage of 80 kV and at room temperature. TEM specimens were prepared by aspirating an aqueous sample onto a copper EM grid. A few minutes after the deposition, the aqueous solution was blotted away with a strip of filter paper and dried in air at room temperature for a few hours.

The chemical compositions of the triblock copolymers were determined by a Varian Unity 300 MHz NMR spectrometer using $CDCl_3$ and D_2O as the solvents at 25 °C.

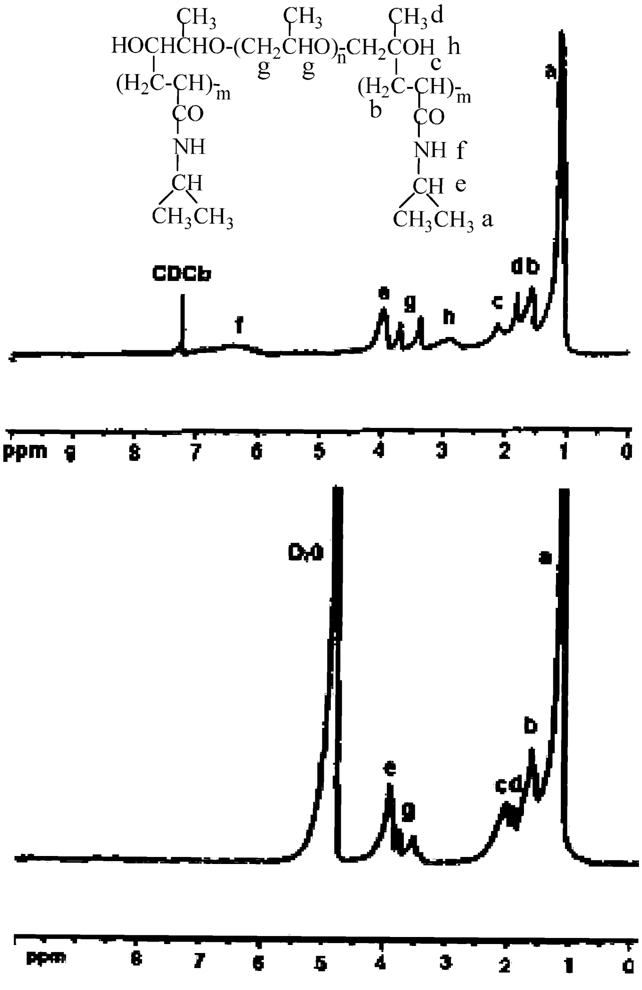


Fig. 1 ^{1}H-NMR spectra of PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers in $CDCl_3$ and D_2O

Optical transmittance of polymer aqueous solution (0.25 wt%) at various temperatures was measured at 500 nm with a UV spectrophotometer (VARIAN CARY100 Conc, USA). Sample cells were thermostated with a circular water jacket from 27 to 35 °C. The LCST of polymer solution was defined as the temperature producing a 50% decrease in optical transmittance.

Results and discussion

The formation of PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers has been confirmed by ^{1}H-NMR and GPC. In an attempt to gain insight into the nature of the aggregation of PNIPAAm-b-PPG-b-PNIPAAm copolymers in aqueous solution, the proton NMR spectra of the copolymers in a good solvent and a selective solvent were monitored. Shown in Fig. 1 are ^{1}H-NMR spectra of the copolymers in $CDCl_3$ and D_2O, respectively. The proton assignments in $CDCl_3$ are consistent with the chemical structure of the copolymers. The proton signals from the amide (peak f) and the hydroxide (peak h) disappear in D_2O, which, as suggested by other authors [8], may be due to a fast exchange with D_2O. A comparison of the spectrum taken in D_2O with that taken in $CDCl_3$ shows that the integration ratios of peak g (belong to PPG)/ peak e (belong to PNIPAAm) and peak d (belong to PPG)/ peak b (belong to PNIPAAm) decrease from 0.83 and 0.72 in $CDCl_3$ to 0.45 and 0.17 in D_2O, respectively. This suggests that the copolymer chains keep stretching state in a good solvent, $CDCl_3$, whereas the copolymers form micelles by self-assembly in a selective solvent, D_2O, which is a good solvent for PNIPPAm chains and a precipitant for PPG chains. As a result, the relaxation time of some PPG chains inside the micelles becomes too short to be detected by the NMR technique, leading to a decrease of the signals from the PPG chains [9]. Furthermore, it is found that the positions of peak g and d change from 3.33–3.69 ppm and 1.77 ppm in $CDCl_3$ to 3.53–3.91 ppm and 1.88 ppm in D_2O, respectively. These results indicate that PPG chains may aggregate together in D_2O through the relatively weak solvent-associated forces. Therefore, the positions of the peaks belonging to PPG shift to low field.

The self-assembly process of block copolymers is a key point in the formation of polymeric vesicles. The morphology of the block copolymer aggregates depends on the initial copolymer concentration, the nature of the common solvent, the copolymer composition, the water content and many other conditions [10–12]. To obtain polymeric vesicles, deionized water, as a precipitant, was added at a rate of 0.3 wt%/10 s with vigorous stirring to the PNIPAAm-b-PPG-b-PNIPAAm solution of THF at a initial copolymer concentration of 0.5 wt%. After the formation of polymeric vesicles, more water was added until the water content reached ca. 50 wt%. The hollow structure of the polymeric vesicles was obtained and can be clearly observed by TEM, as illustrated in Fig. 2. Figure 2 is a typical TEM image of the vesicles. The outer diameter of the particles is between 30 and 80 nm. Compared with polymeric micelles, polymeric vesicles possess a greater range of cavity sizes to enable the delivery of large species, such as proteins and genes, and more species.

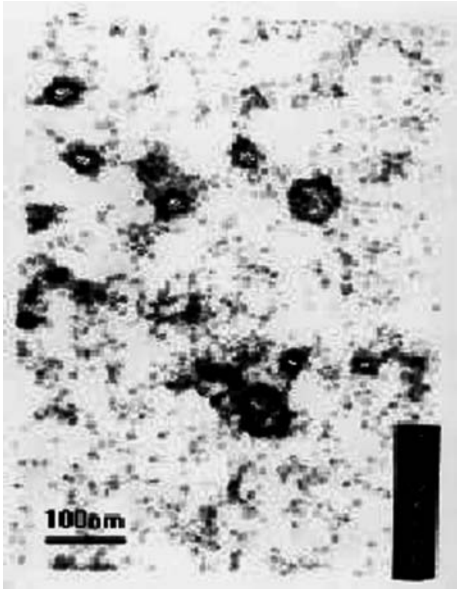


Fig. 2 Transmission electronic microscopic images of PNIPAAm-b-PPG-b-PNIPAAm vesicles at 25 °C

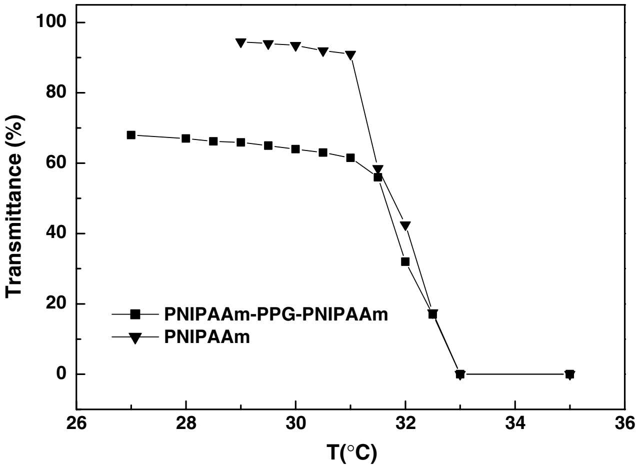


Fig. 3 LCST profiles for PNIPAAm and PNIPAAm-b-PPG-b-PNIPAAm determined by transmittance at 500 nm, [polymer] = 0.25 wt%

The thermosensitive property of the PNIPAAm-b-PPG-b-PNIPAAm vesicles in water was investigated using transmission spectra at a polymer concentration

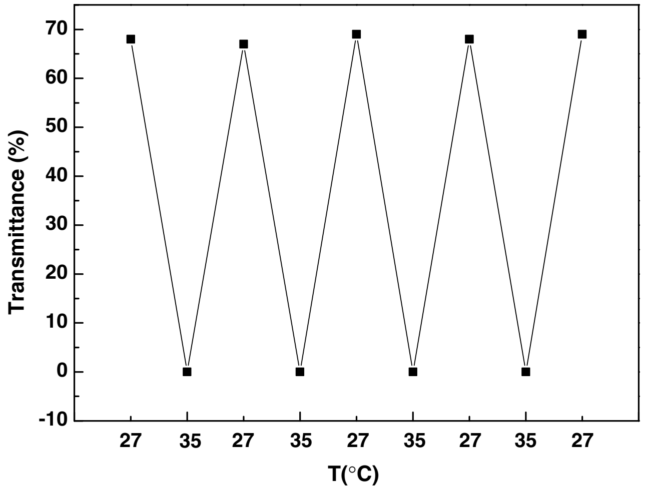


Fig. 4 Reversible changes of the optical transmittance of the polymeric vesicles in water against temperature fluctuation, [polymer] = 0.25 wt%

above the CAC at different temperatures. A plot of solution transmittance (*T*%) as a function of temperature is shown in Fig. 3. It can be seen from Fig. 3 that PNIPAAm-b-PPG-b-PNIPAAm solution transmittance(*T*%) decreases sharply when the solution is heated above a critical temperature of 32 °C, which is consistent with the LCST of pure PNIPAAm solution. In general, the LCST of PNIPAAm random copolymers can be increased or reduced by incorporating hydrophilic or hydrophobic comonomers [13, 14]. In our work, however, the LCST of the copolymers were not affected with the incorporating of hydrophobic chains, PPG. This may be due to the fact that strong interaction of the hydrophobic chains formed clearly phase-separated micellar structures [15–17].

Reversible structural changes of PNIPAAm-b-PPG-b-PNIPAAm vesicles were characterized by measuring the changes of the optical transmittance of the aggregates in water. The results are shown in Fig.4. The optical transmittance of the aggregates is modified by temperature fluctuation. This figure shows that PNIPAAm-b-PPG-b-PNIPAAm aggregates can change the structure quickly from the hydrated state below the LCST to the dehydrated state above the LCST and that the structural change of the PNIPAAm-b-PPG-b-PNIPAAm vesicles in the heating and cooling circle is reversible.

Conclusion

In summary, PNIPAAm-b-PPG-b-PNIPAAm triblock copolymers were synthesized by redox polymerization. They can form polymeric vesicles by self-assembly in aqueous solution. The hollow structure of PNIPAAm-b-PPG-b-PNIPAAm aggregates in combination with the temperature-sensitive property may make the vesicles especially useful as intelligent capsules for drug delivery systems.

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