

Phase Transition and Micellization of Temperature Responsive Dextran-graft-poly (*N*-isopropylacrylamide) Polymers

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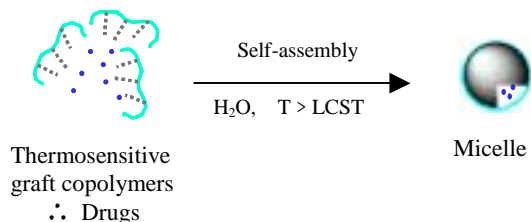
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Abstract: Phase behavior and micellization of dextran-graft-poly (*N*-isopropylacrylamide) (PNIPAAm) polymers in aqueous solution are investigated in this paper using DSC and AFM methods. It is found that with the increase of grafting (G%) of the copolymers the endothermic enthalpy during the phase transition increases significantly and the transition temperature decreases slightly. The phase transition behavior of the copolymers is scanning rate dependent. Micelles are formed whenever the solution temperature is raised above the LCST of the copolymers. It is proposed that by using this thermal responsive property of the copolymers, drugs could be incorporated into the micelles without employing any organic solvent.

Keywords: Dextran, graft copolymers, thermosensitive, LCST.

Polymeric micelles formed from amphiphilic copolymers have received a lot of attention as drug delivery systems¹. Pharmaceutical research on polymeric micelles has been mainly focused on hydrophilic-hydrophobic block copolymers². Drugs, especially poorly water-soluble drugs can be incorporated in the core of the micelles by physical entrapment through dialysis or emulsification techniques. In both processes, one cannot avoid using organic solvents in order to prevent the formation of large aggregates and to achieve relatively high loading level of drugs. Recently, we proposed to prepare stimuli-sensitive dextran graft copolymers, which might be used as micelle carriers for drug delivery avoiding the use of organic solvents during incorporation of the drugs

Figure 1 Schematic illustration of using thermosensitive graft copolymers to incorporate drugs into the micelles for controlled delivery

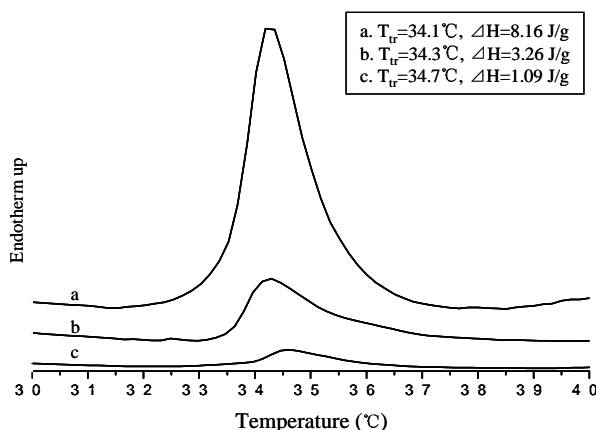


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(Figure 1). In fact, there is some recent work on the use of thermosensitive polymers in block copolymers. Poly (N-isopropylacrylamide) (PNIPAAm) was used as thermo-sensitive polymer and combined with hydrophilic polymers^{3,4}. PNIPAAm exhibits a reversible phase transition in aqueous solution at about 32°C, which is the lower critical solution temperature (LCST). Micelles can be constructed when the temperature is raised above the LCST of the block copolymer containing PNIPAAm, where PNIPAAm forms the hydrophobic core. In this paper the phase transition of the dextran grafted with PNIPAAm in aqueous solution is reported.

The synthesis of dextran graft copolymers with PNIPAAm was reported elsewhere⁵. The phase transition temperature of the graft copolymers in water was determined by differential scanning calorimetry (DSC) using a Perkin-Elmer Pyris 1 instrument with heating rates varying from 0.5 to 10°C/min. The sample size was about 20 mg of an aqueous solution (0.5 g/L). Distilled water was used as the reference. The thermosensitive behavior of the copolymers in water was also examined by the changes of light transmittance ($\lambda=500$ nm) at various temperatures with a Bio810 UV-Vis spectrometer. The sample and the reference cell were thermostated with a temperature controlled circulation system. The values of the LCST of the polymer solution were determined as the temperature of 50% decrease in optical transmittance. The morphologies of micelles were taken with an atomic force microscope (SPA 300HV/SPI 3800N, Seiko Co.) in the tapping mode. The micelle solution of the copolymers (0.1 g/L) was cast onto a freshly prepared polystyrene coated glass plate and dried at the temperature above the LCST of the copolymers.

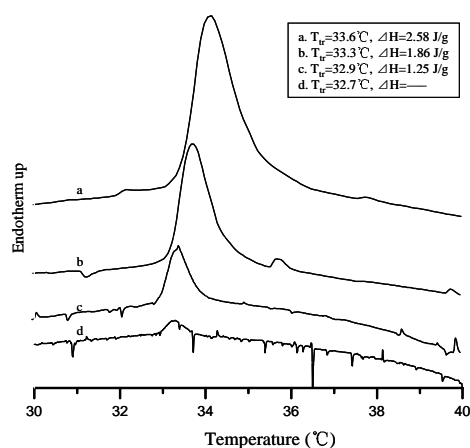
Figure 2 DSC thermograms of dextran-*graft*-PNIPAAm copolymers with grafting (G%) of (a) 33.8 (b) 27.9 and (c) 17.2. The scanning rate is 10°C/min



The mechanism of the phase transition of PNIPAAm homopolymer in water has been extensively studied and it is generally accepted that the destruction of the hydrogen bonding between PNIPAAm and water, and the hydrophobic interaction of PNIPAAm molecules result in the phase transition of PNIPAAm in aqueous medium at about 32°C. The endotherm of the phase transition can be detected by DSC⁶. It is seen in **Figure 2**

that during the phase transition with the increase of grafting (G%) the endothermic enthalpy increases significantly and the transition temperature decreases slightly. The DSC thermograms in **Figure 3** show that the phase transition behavior of the copolymers

Figure 3 Dependence of the phase transition of dextran-graft-PNIPAAm copolymer (G%=33.8) on the DSC scanning rate at (a) 5°C /min, (b) 3°C /min, (c) 1°C /min and (d) 0.5°C/min



is scanning rate dependent. The transition temperature of the copolymers decreases when the scanning rate is decreased. It is also observed during the phase transition that the endothermic enthalpy decreases significantly when the scanning rate is decreased, though many large fluctuations present in the DSC thermograms.

Figure 4 Light transmittance changes of the graft copolymers with different grafting in aqueous solution as the function of temperature

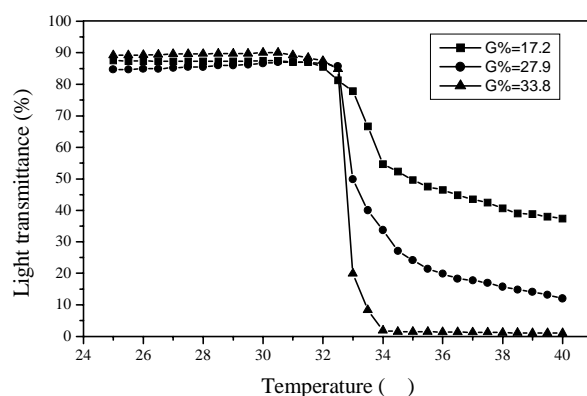
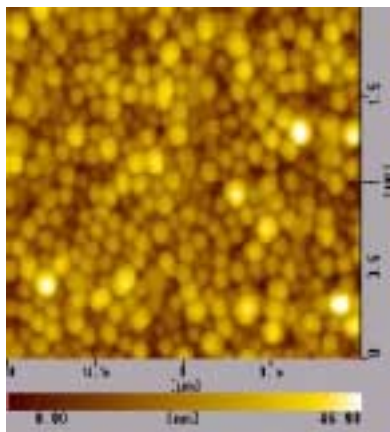


Figure 4 shows the optical transmittance of the aqueous copolymer solution at various temperatures. The phase transition range becomes narrower with the increase of the G % of the copolymers, and the transition points of the graft copolymers move slightly to higher temperature when G % of the copolymer decreases. The results are consistent with the results of DSC measurements in this study and it was observed that

incorporation of hydrophilic or hydrophobic groups into PNIPAAm chains changes the LCST of the PNIPAAm copolymers^{3, 7}.

It was found that the micellization of the graft copolymers in aqueous solution at 37°C is time dependent, and the final average mean diameter of the micelles is less than 30 nm for the copolymer with grafting (G%) of 33.8%. The AFM shows clearly that the morphology of the constructed micelles at the temperature above the LCST of the copolymer is in spherical shape and the average size of the dried micelles is about 80 nm in diameter (**Figure 5**).

Figure 5 AFM image of the micelles formed on freshly prepared polystyrene coated glass plate



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