Synthesis of Thermoresponsive Polymeric Micelles of PNIPAAm-*b*-OMMA as a Drug Carrier for Loading and Controlled Release of Prednisolone

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ABSTRACT: We synthesized a drug delivery system of poly(*N*-isopropylacrylamide)-*b*-oligo(methyl methacrylate) (PNIPAAm-*b*-OMMA) via polycondensation of two homopolymers in 1,4-dioxane. The products are characterized by FT-IR and ^{1}H-NMR spectra and TEM. The PNIPAAm-*b*-OMMA copolymer micelles in aqueous solution present the same lower critical solution temperature (LCST) as the unmodified PNIPAAm, owing to the formation of a core–shell micellar structure that the hydrophilic shell shields the hydrophobic inner OMMA core from interacting with water. The micelle carriers exhibit two heterogeneous microdomains: a hydrophobic inner core capable of highly solubilizing hydrophobic prednisolone molecules, plus a hydrated outer shell that stabilizes this micellar structure below its LCST. Moreover, the micelle carriers show reversible thermoresponsive aggregation/dispersion in response to temperature cycles through the LCST. By using the antiinflammation drug prednisolone as model drug, it is found that the PNIPAAm-*b*-OMMA drug carrier could prolong the release time and control the release amount by changing the temperature. Accordingly, this copolymer micelle may provide as an effective drug carrier for drug control and release. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 111: 701–708, 2009

Key words: thermoresponsive polymeric micelles; PNIPAAm-*b*-OMMA; drug carrier; controlled release

INTRODUCTION

During last decade, polymeric micelles self-assembled by amphiphilic copolymers have attracted much attention because of their intrinsic scientific interests and technological significance.[1–3] In particular, the synthesis of stimuli-responsive polymers has increasingly attracted much more interest for biologic and materials scientists.

The stimuli-responsive polymers have the ability to respond to these changes in their external environment. They can exhibit dramatic changes in their swelling behavior, network structure, permeability, or mechanical strength in response to external stimuli, and have potential applications in many fields. For example, electrical fields,[4–6] magnetic fields,[7] pharmaceutical fields,[8–10] catalysis,[11–13] and so on.[14–17] Nowadays, the most commonly studied polymers having environmental sensitivity are thermoresponsive[18] polymers and pH-responsive[19–22] polymers. Especially, the thermoresponsive polymers have gained considerable attention in the pharmaceutical field, because of the ability of the hydrogels to swell or deswell in response to the change of the temperature of surrounding fluids. These polymers are usually formed by the amphiphilic di- and triblock copolymers. In an aqueous environment, the hydrophobic segments of the copolymer aggregate together while the hydrophilic segments stretch. In this way, the micelles form a core–shell structure, where the hydrophilic blocks like a shell protect the interior hydrophobic core, avoiding the interaction of the core with the external environment.

Since Tanaka found that *N*-isopropylacrylamide gel underwent a phase transition by changing temperature in 1984, the number of the reports on aqueous micelles increased dramatically.[23–26] PNIPAAm has become one of the most common materials

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investigated by researchers. PNIPAAm is water soluble and hydrophilic at the environmental temperature below 32°C, the lower critical solution temperature (LCST) of the linear polymer.[27–29] As the temperature exceeds the LCST, PNIPAAm becomes insoluble and aggregates to precipitate. This phase transition is reversible and occurs within a narrow temperature range.[30] When PNIPAAm is terminal-modified by hydrophobic homopolymers, the terminal-located hydrophobic groups are able to form hydrophobic microdomains that can be clearly isolated from PNIPAAm chains in aqueous media by the aggregation of hydrophobic segments. This property of hydrophobically modified PNIPAAm gel has been investigated in many fields.[6,23,31–35] Because the polymers possess high drug loading capacity of inner core as well as unique disposition characteristics in the body, they are used as novel drug carriers in the field of drug targeting.[36,37] The advantageous properties of polymeric micelles as drug carriers are associated with solubilization of low-solubility drugs and potentials for tumor targeting and controlled drug release. The simplicity of micelle formation by self-assembly of amphiphilic block copolymers and drug encapsulation by physical mixing rather than chemical conjugation are extremely attractive features of polymeric micelles.[38]

Oligo(methyl methacrylate) (oligo-MMA) is a kind of relatively inexpensive amorphous glassy oligomer that has good biocompatibility. OMMA used in the medical environment has been advocated in the past years by many authors.[39] Zhang and coworkers[40] have used a similar copolymer to load prednisone acetate and studied its release behavior. Herein, we use low aqueous solubility drug prednisolone as a model drug to investigate its release performance *in vitro*. Prednisolone is a kind of glucocorticoids, which are widely used for the clinical treatment of allergic disorders.[41] Unmodified prednisolone shows high initial encapsulation efficiency and is usually used by intravenous injection. However, experiments have shown that this kind of unmodified prednisolone was rapidly released from the liposomes upon intravenous injection.[42] To get satisfactory effectives, more doses are needed. On the other hand, too many doses could cause side effects, such as acne, osteoporosis, and bone fracture. To delay release time of prednisolone, many prednisolone drug systems are synthesized. However, most of these drug systems are formed by chemical conjugations,[43] and few studies were reported on physical methods. In this work, our goal is to design a temperature-responsive amphiphilic block copolymer of PNIPAAm-*b*-OMMA that can be used as a drug carrier and to investigate the delivery properties of prednisolone in the polymer carrier via dialysis method, which is much simpler than chemical reactions.[38]

EXPERIMENTAL

Materials

N-isopropylacrylamide (ACROS Organics, Morris Plains, NJ) was recrystallized from hexane and dried in vacuum at room temperature before use. 2,2′-Azoisobutyronitrile (AIBN) was purified by recrystallization in ethanol. 2-Amino ethanethiol hydrochloride (AET-HCl), 3-mercaptopropionic acid, and *N*-hydroxy succinimide were purchased from Alfa Aesar (Heysham, Lancs, UK) and used without further purification. Methyl methacrylate (MMA) from Bodi Chemical Co. (Tianjin, China), *N*,*N*-dimethyl acetamide (DMAc) from Fuchen Chemical Co. (Tianjin, China), and *N*,*N*′-dimethyl formamide (DMF) and 1,4-dioxane from Beijing Chemical Works were purified under reduced pressure distillation prior to use. Unless specially stated, otherwise, all reagents and solvents were of commercial grade and were dried just before use.

Synthesis of amino-terminated poly(*N*-isopropylacrylamide) (PNIPAAm)

Here we use AET-HCl as a chain-transfer agent to introduce $-NH_2$.[36] The amino-terminated PNIPAAm was prepared by radical polymerization. NIPAAm (8×10^{-3} mol), AIBN (1.6×10^{-5} mol), and AET-HCl (1.2×10^{-4} mol) were added into a 100-mL three-necked flask and dissolved by 10 mL DMAc. The solution was degassed by bubbling with nitrogen for 1 h. Polymerization was carried out at 70°C for 10 h. After the polymerization, the product was condensed under reduced pressure to evaporate most DMAc. The product was precipitated several times by an excess of diethyl ether and dried in vacuum. An excess of triethanolamine was added dropwise to this polymer solution in tetrahydrofuran (THF) at room temperature to convert PNIPAAm-NH_2-HCl into PNIPAAm-NH_2. The obtained polymer solution was repeatedly precipitated in an excess of diethyl ether and filtered using a 0.22-μm pore-size percolation film. Finally, the product was dried in vacuum at 30°C.

Synthesis of carboxyl-terminated oligo-MMA

Oligo-MMA with a terminal carboxyl group was synthesized by the free-radical oligomerization of MMA (4.8×10^{-2} mol) in DMAc (10 mL) using AIBN (2.4×10^{-4} mol) and 3-mercaptopropionic acid (MPA) (1.70×10^{-3} mol) as initiator and chain transfer reagent, respectively.[40] The solution was degassed by bubbling with nitrogen for 30 min. The polymerization reaction was performed at 60°C for 6 h followed by precipitation with addition of water and filtration with Buchner funnel. Then the

polymer was dried in vacuum at 50°C to obtain a white powder.

Synthesis of PNIPAAm-*b*-OMMA diblock copolymers

To obtain PNIPAAm-*b*-OMMA, OMMA-COOH (2.1×10^{-4} mol), PNIPAAm-NH_2 (2.4×10^{-5} mol), and *N*-hydroxysuccinimide (NHS, 2.1×10^{-4} mol) were dissolved in dioxane (10 mL). Dicyclohexylcarbodiimide (2.1×10^{-4} mol) in dioxane (2 mL) was added dropwise to the polymer solution. All procedures were carried out at room temperature under a nitrogen atmosphere. Twenty-four hours after this reaction, the product was precipitated in an excess of diethyl ether. The obtained polymer was dried in vacuum after filtration.

Preparation of polymeric micelles

Polymeric micelles of PNIPAAm-*b*-OMMA copolymers were prepared by dissolving the copolymer (50 mg) in DMAc (10 mL), followed by dialysis against distilled water. The dialysis bag was used with 7000 molecular weight cutoff at 10°C for 24 h. PNIPAAm-*b*-OMMA micelles were purified by a 0.45-μm pore-size filtration membrane, and lyophilized to leave a white powder of micelles.

Characterization of polymers

The molecular weights and polydispersity index of PNIPAAm-NH_2, OMMA-COOH, and PNIPAAm-*b*-OMMA were determined using gel permeation chromatography (GPC) consisting of a Waters 515 HPLC Pump and a Waters 2410 refractive index detector. THF was used as the solvent with a flow rate of 1.0 mL/min at 30°C, using narrow dispersive polystyrene as calibration standards. Proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy (600 MHz) measurements were performed on Bruker AV 600 spectrometer in $CDCl_3$ at 45°C. Fourier-transform infrared (FT-IR) spectra of the block copolymer and corresponding homopolymers of PNIPAAm and OMMA were measured in the range of 4000–500 cm^{-1} with a Nexus 8700 (Thermofisher Co.) using KBr pellets.

Characterization of micelles

Transmission electron microscopy (TEM) images were obtained from a JEM 3010 instrument operated at an accelerating voltage of 150 keV. TEM sample was prepared by placing a drop of micelle dispersion on a copper grid, with carbon film and staining with 2% (w/v) phosphotungstic acid aqueous solution. The hydrodynamic particle sizes and size distribution of micelles were measured with quasi-elastic light scattering on a model ZETA-SIZER 3000HSA nanoinstrument.

Absorbance measurements

Temperature-responsive behavior of PNIPAAm-NH_2 and amphiphilic block copolymer micelles were measured by a turbidity method. The aqueous polymer solutions (500 mg/L of PNIPAAm-NH_2 and 300 mg/L of PNIPAAm-*b*-OMMA) at various temperatures were measured at 500 nm and 542, respectively, by a UV–vis spectrometer (UV–vis 2501 PC, Shimadzu). The sample was thermostated in a refrigerated circulator baths at a different temperature from 22 to 44°C. Values for the LCSTs of polymer solutions were determined at a temperature showing the onset of turbidity.

Drug loading and release

Low aqueous solubility drug prednisolone was used as a model drug for investigating the loading and release properties of drug in the polymer carrier. The dry copolymers (15 mg) and prednisolone (15 mg) were dissolved in 3 mL DMF and stirred for 1 h. Water is then added at a slow rate, and then the solutions were dialyzed in a dialysis tube (molecular weight cut off: 3500 g/mol) against 900 mL distilled water.[44]

After dialysis, the dialysis tube was directly immersed into 500 mL distilled water. At various time intervals, 5 mL of drug solution was taken to measure drug concentration by using Shimadzu UV–vis spectrophotometer (based on standard curve: C (μg/mL) = $A/0.0543$, where A is the UV absorbance at 243 nm)) and refreshed by 5 mL of distilled water each time (according to Chinese pharmacopoeia standard method). The amount of percentage release of prednisolone was calculated from the following equation:

$$\%\text{Release} = \frac{W_t}{W_{\text{total}}} \times 100 \quad (1)$$

where W_t is the weight of released prednisolone at time t and W_{total} is the total absorbed prednisolone in the polymeric micelle structure. W_{total} was calculated by the free drug amount (i.e., the total drug amount used in this work, here it is 15 mg) minus the amount of unloaded drug. The amount of unloaded drug was analyzed by measuring the absorbance at 243 nm of dialyzate after drug loading. It was found that around 7.18 wt % of the free drug prednisolone was loaded into PNIPAAm-*b*-OMMA micelles ($W_{\text{total}} = 10.77$ mg).

TABLE I
Preparation and Analysis of PNIPAAm

Code	[S]/[M][a]	M_n[b]	M_w	M_w/M_n
PNIPAAm1	0.06	3,078	4,573	1.49
PNIPAAm2	0.05	6,949	11,425	1.64
PNIPAAm3	0.04	10,573	15,217	1.44
PNIPAAm4	0.03	12,269	20,249	1.65
PNIPAAm5	0.02	13,001	20,803	1.60
PNIPAAm6	0.01	15,320	23,979	1.57

[a] Mole ratio of monomer [M] (NIPAAm) and chain transfer agent [S] 2-amino ethanethiol hydrochloride.
[b] The molecular number (M_n) and molecular weight (M_w) of the polymer were determined by GPC.

RESULTS AND DISCUSSION

Polymer synthesis

Thiol compounds are well known to participate actively in the telomerization of vinyl monomers.[45] NIPAAm is considered to be easily telomerized with thiol compounds.[46,47] Herein, amino end group was introduced to one terminal end of the formed PNIPAAm during telomerization, with AET-HCl as a chain-transfer agent. By adjusting the amount of AET-HCl, PNIPAAm-NH_2 was obtained with molecular weights ranging from 4500 to 20,000. Table I lists the results of PNIPAAm obtained in different concentrations of AET-HCl. It is found that chain length of the polymer can be controlled by varying the ratio of AET to the monomer. Apparently, short chain-length polymers were obtained using large amounts of AET. This method allows the synthesis of fairly small ($M_n < 20{,}000$ g/mol) homogeneous (polydispersity < 2.0) molecules with a clearly defined ligand-coupling site in terminal position by a form of controlled radical polymerization.[46,48]

OMMA-COOH was also prepared by radical polymerization using MPA as a chain transfer agent. End groups of OMMA-COOH were changed to activate ester groups by reacting with NHS. PNIPAAm-*b*-OMMA copolymers were synthesized by a condensation reaction between the amino end groups of PNIPAAm and the activated terminal end groups of OMMA. The GPC data for PNIPAAm-NH_2, OMMA-COOH, and PNIPAAm-*b*-OMMA are given in Table II with acceptable polydispersities.

TABLE II
GPC Data of PNIPAm-NH_2, OMMA-COOH, and Block Copolymer of PNIPAm-*b*-OMMA

Polymer	M_n	M_w	Polydispersity (M_w/M_n)
PNIPAAm-NH_2	12,269	20,249	1.65
OMMA-COOH	3,483	6,583	1.89
PNIPAAm-*b*-OMMA	15,197	34,652	2.28

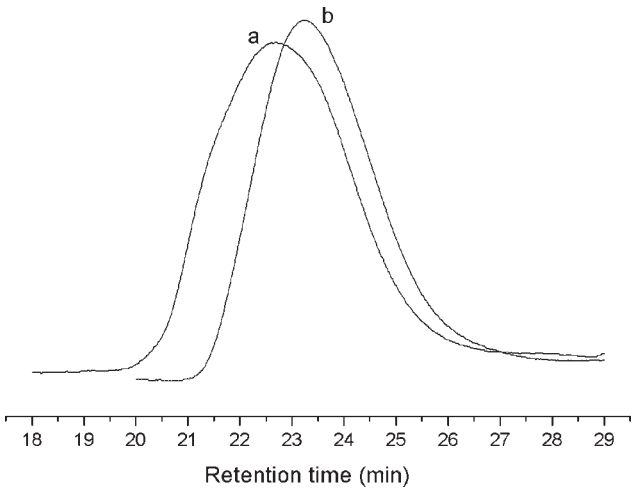

Figure 1 GPC traces of (a) PNIPAAm-*b*-OMMA block copolymer and (b) PNIPAAm-NH_2.

In this work, we chose PNIPAAm4 to synthesize the copolymer because of its longer chain and good symmetry of GPC trace. Longer hydrophilic chain may be more helpful for loading drugs.[49] Typical molecular weight distributions for the homopolymer of PNIPAm-NH_2 and block copolymer PNIPAAm-*b*-OMMA are shown in Figure 1. GPC traces clearly show that the elution peak of homopolymer shifts to a higher molecular weight after copolymerization. The block copolymer elution peak is relatively symmetric and shows no appreciable tailing at the lower molecular weight side, indicating that the product is not a mixture but a copolymer.

Structure of the block copolymer

FT-IR spectra of the block copolymer and the corresponding two homopolymers of PNIPAAm-NH_2 and OMMA-COOH are shown in Figure 2. In the

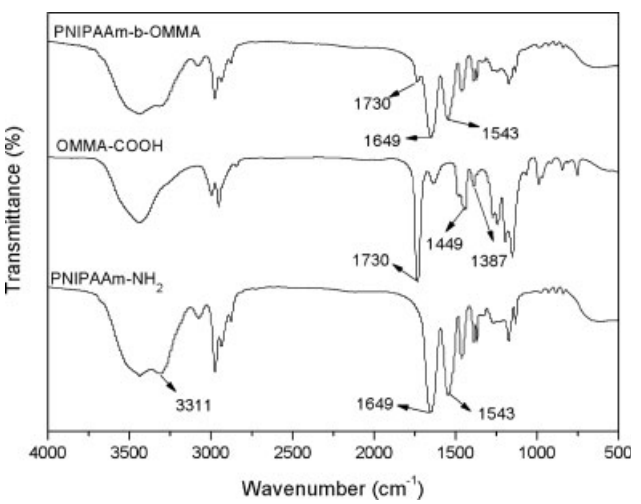

Figure 2 FT-IR spectra of PNIPAAm-NH_2, OMMA-COOH, and PNIPAAm-*b*-OMMA.

spectrum of the PNIPAAm-NH_2, the two peaks at 3311 and 1543 cm^{-1} are assigned to the vibration of the N—H bond, and the obvious peak at 1649 cm^{-1} is attributed to the vibration of amide carbonyl group.[50] As for the OMMA-COOH, the characteristic band of C=O in carbonyl groups of OMMA at 1730 cm^{-1} is clear. The peaks at 1449 and 1387cm^{-1} are attributed to the bend vibration of —CH_2 or —CH_3 group.[51] All the bonds mentioned earlier are found in the spectrum of PNIPAAm-*b*-OMMA copolymer, but the peak at 1730 cm^{-1} assigning to C=O in carbonyl groups of OMMA decreases compared with that of OMMA because of polymerization. The results testify the occurrence of the copolymerization.

The ^{1}H-NMR spectrum of the block copolymer is shown in Figure 3. The copolymers are linear shapes in $CDCl_3$, so all ^{1}H-NMR resonances attributed to NIPAAm and MMA units are detected. Using NIPAAm and MMA as reference compounds, assignment of the spectrum was carried out and results are depicted in Figure 3. Characteristic signals at 4.0, 1.6, and 1.2 ppm because of PNIPAAm could be clearly observed. Comparing the peak intensity of methine in the NIPAAm unit (2.3 ppm) to that of methylene in the MMA unit (1.8 ppm), the results are in excellent accordance with the GPC results that M_n of PNIPAAm-NH_2 (12,269) is larger than that (3483) of OMMA-COOH. Assignments of one methine proton (4.0 ppm) for the PNIPAAm and three methyl protons (3.7 ppm) for the OMMA segments also prove the successful formation of the diblock copolymer.

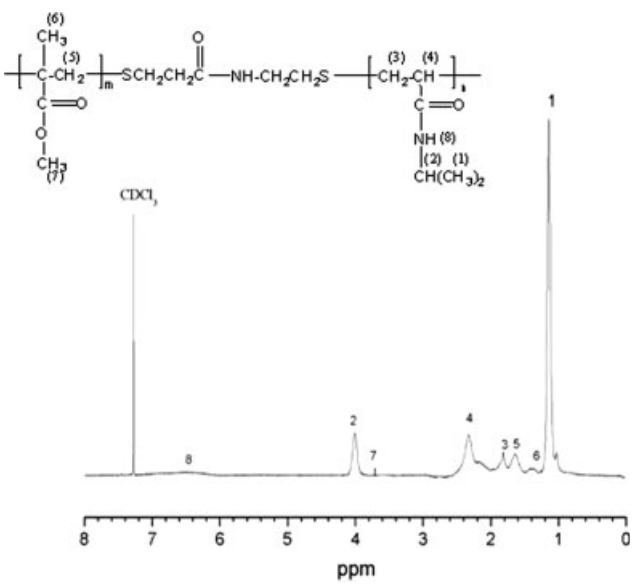

Figure 3 ^{1}H-NMR spectra of PNIPAAm-*b*-OMMA in $CDCl_3$ and peak assignment of the synthesized copolymer.

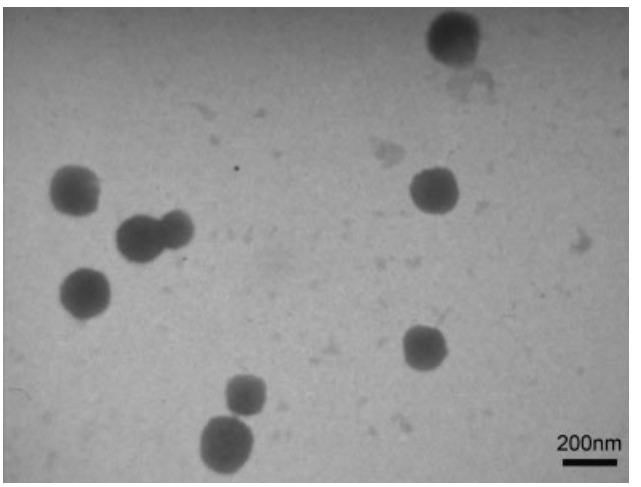

Figure 4 TEM image of the block copolymer of PNIPAAm-*b*-OMMA.

Micelle formation

Both the particle size and size distribution affect the efficiency of their utilization in a given application. They are determined by two independent methods: TEM and quasi-elastic light scattering. The morphology of the polymeric micelles in aqueous solution is observed with TEM after transferring the aqueous solution to the carbon-coated copper grids. PNIPAAm homopolymer is soluble in water, while OMMA homopolymer is water insoluble. So, in aqueous solution, PNIPAAm-*b*-OMMA block copolymers self-assembled into micelles, with OMMA as the core and PNIPAAm as the shell.

It could be seen from Figure 4 that the block copolymers mainly form spherical micelles with an average diameter of about 200 nm. The quasi-elastic light scattering measured the hydrodynamic diameter (geometrical diameter for hard spheres) of the particles in water. The corresponding results are shown in Figure 5. The PNIPAAm-*b*-OMMA micelles exhibit a narrow size distribution with an average diameter of around 323 nm. Because such particles are highly water swollen at room temperature, the hydrodynamic particle size is large than the particle size measured by TEM.

Thermoresponsive structural changes of the polymers

As shown in Figure 6(a), the amino-terminated PNIPAAm, which is soluble, gives a clear solution in cold water below the LCST, and becomes cloudy as the temperature exceeds the LCST. As expected, the PNIPAAm-*b*-OMMA shows a similar phenomenon. The copolymer is also well dispersed in aqueous solution after ultrasonic vibration. When the temperature exceeds the LCST, the solution becomes turbid, as shown in Figure 6(b). This phenomenon should

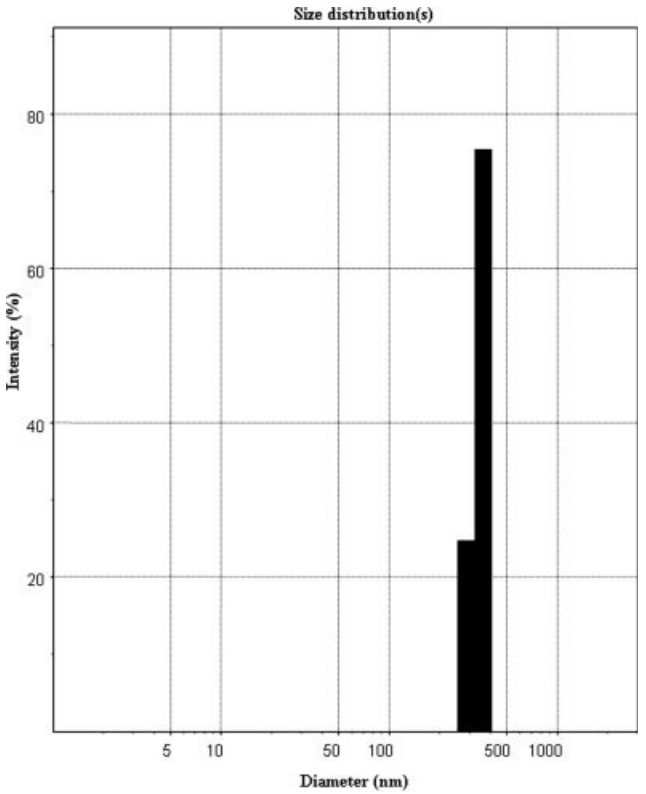

Figure 5 Size distribution of PNIPAAm-*b*-OMMA micelles in aqueous media.

be due to the aggregation of hybrid nanoparticles. The collapse of the PNIPAAm brush leads to the attractive interaction between hybrid nanoparticles, because the hybrid nanoparticles become hydrophobic in the case. This kind of interaction will surely contribute to the aggregation between hybrid nanoparticles, since the PNIPAAm corona becomes "sticky" above their LCST.

LCST of the polymers

The LCSTs of the aqueous solutions of PNIPAAm and PNIPAAm-*b*-OMMA were measured by turbidimetry. The absorbance at 500 nm (for PNIPAAm-NH_2) and 542 nm (for PNIPAAm-*b*-OMMA)

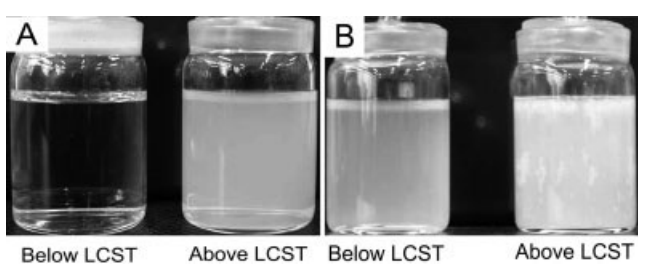

Figure 6 The structural changes of (a) the PNIPAAm-NH_2 and (b) PNIPAAm-*b*-OMMA as the temperature increased above LCST.

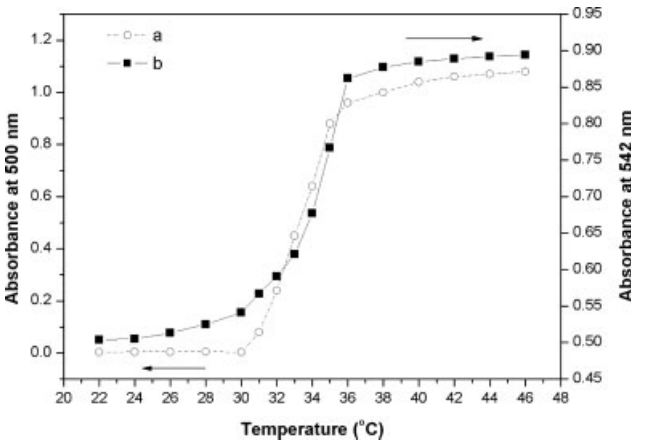

Figure 7 Absorbency of (a) PNIPAAm-NH_2 and (b) PNIPAAm-*b*-OMMA in aqueous at 500 and 542 nm and the temperature range from 22 to 44°C.

was measured as a function of temperature. Figure 7 demonstrates the variation in turbidity of PNIPAAm and copolymer solutions. The LCSTs are defined as the transferring points of the optical density. As shown in Figure 7, the LCSTs of PNIPAAm and copolymer solutions are located around 33 and 34°C, respectively. In these two cases, both solutions show sharp transitions within merely 5°C.

The micelles undergo changes in their structures along with the temperature change. When the temperature increases, the copolymer itself exhibits a sharp phase transition at 34°C, and a complete transition occurs within a very narrow temperature range. In general, the incorporation of hydrophobic moieties into PNIPAAm promoted the LCST shift to a lower temperature than the corresponding pure PNIPAAm, because the incorporation of the hydrophobic comonomer facilitated chain aggregation.[52,53] Here, we get similar results with Zhang and coworkers,[40] i.e., the PNIPAAm-*b*-OMMA copolymers exhibit nearly the same LCST as that of pure PNIPAAm. That is to say, OMMA shows little hydrophobic contribution to LCST. This indicates that the hydrophobic terminals of the copolymers self-assemble into a phase-separated inner core under hydrophobic affinity. Hydrated PNIPAAm chains remain dispersed surrounding the aggregated hydrophobic OMMA inner core. This core–shell micellar structure isolates the hydrophobic inner core from the aqueous media and therefore did not influence the LCST of the PNIPAAm outer shell.

Loading and *in vitro* release of drug encapsulated in copolymer carrier

Dialysis is one of the most extensive methods for drug loading. The block copolymer and prednisolone are dissolved in DMF followed by dialysis of the solution against water. In fact, hydrophobic

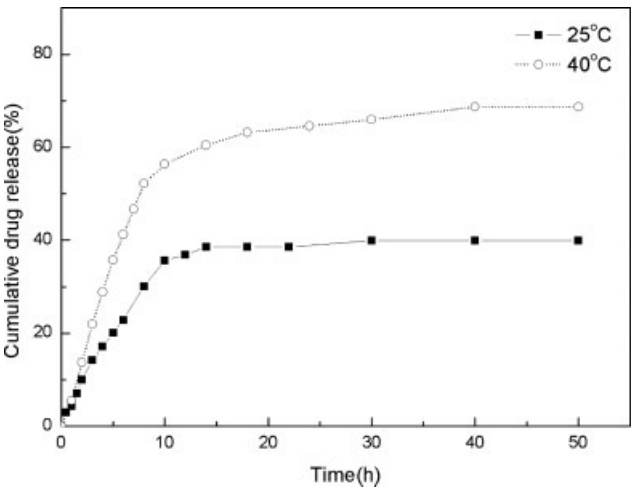

Figure 8 Prednisolone release from PNIPAm-*b*-OMMA micelles at different temperature.

drugs can be incorporated in micelle cores by direct mixing of the drug powder and micellar solution. However, this simple method cannot get acceptable drug loading amount for OMMA. The reason is that this technique may be only used for micelles with soft cores (i.e., those with glass transition temperature T_g below the drug loading temperature), like pluronic micelles. However, for the loading drugs in micelles with solid cores (having T_g above the drug loading temperature) like OMMA, we chose a more complex technique.[38] A gradual replacement of the organic solvent with water, which was a nonsolvent for the core-forming block, triggered self-assembly of hydrophobic blocks accompanied by the entrapment of drug in the micelle cores. The semipermeable membrane prevents micelle diffusion out of the dialysis tube but allows removal of unloaded free drug.

Use the loading method mentioned earlier, we get copolymer micelle loading with prednisolone. The micelle could be lyophilized and made into tablet. This new drug system can be applied in oral delivery.

The release of prednisolone from the copolymer carriers at different temperature is shown in Figure 8. It can be observed that the total prednisolone release is 40% during the 50-h study, when the temperature is 25°C, i.e., below the LCST. One of the most attractive features of PNIPAAm-based micelles as drug carriers is their intelligent property to external temperature changes. When the temperature is raised to 40°C, i.e., above LCST, the total prednisolone release increases to 70%. The increased release of prednisolone might be due to the structural deformation of the PNIPAAm segments at $T = 40$°C, i.e., above the LCST. The outer shell disappeared with the hydrophilic PNIPAAm transforming into hydrophobicity. As water was squeezed out of the micelles, the drug was released along with the water molecules. Moreover, the results in Figure 8 indicate that the fractional release did not reach 100%. Because water pockets were formed in the collapsed micelle and drug was entrapped in the micelle and could not be completely released. The release pattern of the model drug prednisolone in response to pulsatile temperature change is almost the same as the pattern of the copolymer (see Fig. 7). So it is not presented here.

Many drug delivery systems were developed to control the release of prednisolone; however, the prednisolone release amount of these drug carriers reached their maximums in less than 6 h.[54,55] The PNIPAAm-*b*-OMMA drug carrier could prolong the release time and control the release amount by changing the temperature. So this copolymer is an effective drug carrier for drug control and release. These results will also permit a deeper understanding for the design of the thermoresponsive polymeric micelle as a feasible multifunctionalized drug carrier.

CONCLUSIONS

The diblock copolymer PNIPAAm-*b*-OMMA and its physical properties were investigated. The thermoresponsive polymeric micelles comprising PNIPAAm outer shells and OMMA inner cores were synthesized. The polymeric micelles had the same LCST with unmodified PNIPAAm because of the completely core–shell structure. The PNIPAAm-*b*-OMMA with the loaded hydrophobic drug prednisolone in their inner cores was stable below the LCST. The release of the drug loaded in the polymeric micelles could be controlled by changing the temperature of the aqueous solution. The PNIPAAm-*b*-OMMA/prednisolone micelle could selectively release prednisolone upon heating above the LCST. The sensitive thermoresponse indicates that this polymer is an excellent carrier for controlling drug delivery.

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