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ORIGINAL PAPER

Synthesis and thermo-sensitive property of star poly(*N*-isopropylacrylamide) with α -D-glucose-based group

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Abstract Polymers containing functional biological activity groups have potential biological application. A new type of initiator (Glu-Br) synthesized by α-D-glucose and excessive 2-bromo-isobutyrlbromide was used to initiate NIPAM polymerization by atom transfer radical polymerization in DMF/Water mixture solvent, HMTETA as ligand and CuCl as catalyst. A star polymer was obtained with the reaction molar ratio of $[NIPAM]_0$:$[Glu\text{-}Br]_0$:$[CuCl]_0$: $[HMTETA]_0$ = 100:1:5:1. The polymerization reached a low polydispersity (PDI = 1.15–1.47) with the linearity plot of the $M_{n,GPC}$ against conversion, and the reaction time revealed the well-controlled polymerization by ATRP. The LCST(lower critical solution temperature) of the star polymer was increased with the molecular weight increasing. Used fluorescein dye molecules as model drug to loaded in the star polymer to measure its envelope ability. The results indicated that the polymer has a promising application in the field of drug controlled release system.

Keywords α -D-glucose · Atom transfer radical polymerization (ATRP) · N-isopropylacrylamide · Lower critical solution temperature (LCST)

PNIPAM has a lower critical solution temperature (about 32 °C) in water solution. When the solution temperature is higher than the LCST, the polymer molecules in aqueous solution transforms from linear to agglomerate make the solution changes from clarification into turbid. The unique properties of PNIPAM are very interest to make researchers do many works about a variety of copolymer and block copolymers synthesized by NIPAM, which are applied to various fields, including drug controlled release of nano science and technology [1–6].

At present, atom transfer radical polymerization (ATRP) is the most important technology in the field of polymer chemistry, which is a prime method to control molecular weight and structure of polymer with specific performance. In recent years, more and more reports about the synthesis of polymers containing biological activity functional groups by ATRP technique. David M. Haddleton [7] successfully used cholesterol derivatives as macromolecular initiator to initiate methyl methacrylate polymerization to obtain block copolymers with biological function groups in tail. Debora Bontempo [8] used ATRP technology to obtain low dispersion and biotinylated PNIPAM by step polymerization. Since the polymer chain does not hinder between antibiotics and protein, and biotinylated PNIPAM is also very ease to bond with streptavidin. Dong Jin Kim et al. [9] prepared thermo-sensitive mixture particles with PNIPAM/dextran by ATRP polymerization with the diameter about 100 μm, the thermo-sensitive particles will be used as micro carrier in biomedical field.

Also, the star polymers have unique shape and potential superior performance due to their complex structure. Regular star polymers have simple point for grafting with the branch of relative uniform molecular weight and polydispersion index. Compared with linear polymer, star polymers possess particular special structure, lower viscosity and higher functional groups on the end of the chain. So, star shape polymer is always used as substance to evaluate solution property and rheological behavior of polymer [10, 11]. More and more people are interested in

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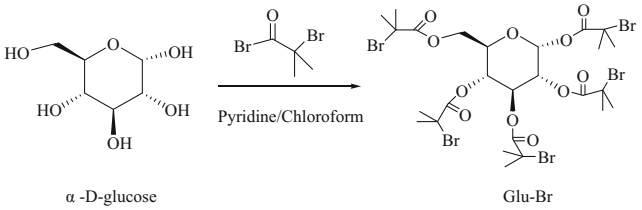
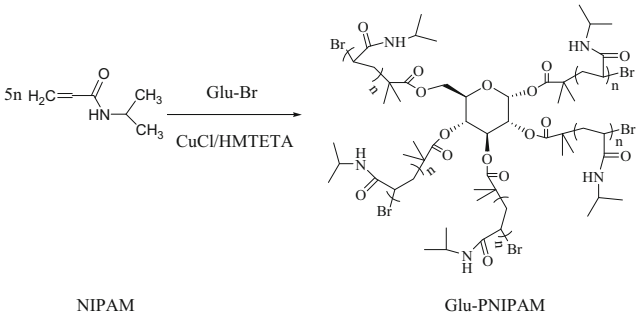
studying them. Star polymers with regular structure can be prepared by living polymerization with three modes including active core first arm, arm first core and node coupling [12]. Tao He et al [13] prepared star amphiphilic ABC epsilon-caprolactone-methyl methacrylate-styrene copolymer by combination method of ATRP, ring-opening polymerizationand and nitroxide-mediated polymerization, and characterized its structure. Haifeng Gao et al. [14] accepted the core first order, add two kinds of initiator and crosslinking agent in the ATRP polymerization, get the star Miktoarm butyl acrylate - methyl methacrylate copolymer finally. Shuping Jin et al. [15] synthesized two component block copolymer $PAANa_{75}$-b-$PNIPAM_m$ using ATRP and reverse ATRP combination technology, this copolymer was not only sensitive to temperature and pH, but also sensitive to salt. When the concentration of NaCl in solution reached to a certain value, the block polymer will form a spherical star micelle with PNIPAM core and PAANa shell. Krishnan Ranganathan et al. [16] accepted dobby polyglycerol (HPG) as the core, using RAFT and ATRP combined method, synthesized thermosensitive Miktoarm Star Polymer HPG-g-PDMA/PNIPAM, when this polymer reached the phase transition temperature, micelle colloid with PNIPAM core and PDMA shell can be formed, colloidal stability was concerned with star polymer arm length and the content of monomer component ratio in polymer system.

Smart polymer material synthesis with biological compatibility and topological structure based on ATRP technology is a novelty of this paper, because a-D-glucose as the star type thermo- sensitive polymer core (Glu-PNIPAM) synthesis has not been reported. α-D-glucose is annular biological monosaccharide with 5 terminal hydroxyl groups. Because glucose is the nutrient substances of metabolism in the body, it has good biological compatibility. In this paper, in accordance with the order of the core first, α-D-glucose macromolecular initiator with multi functional groups synthesized, and then initiated the NIPAM monomer ATRP to obtained star polymer with regular structure and narrow molecular weight distribution. The polymerization kinetics and properties of polymer were also studied.



Scheme 1 The process of α-D-glucose macromolecule initiator (Glu-Br) synthesis. ^{1}H NMR($CDCl_3$,400 MHz) δ:6.43(d,J3.76,1 H), 5.70 (t,J9.85,1 H), 5.25–5.35(dd,2 H), 4.39 (m,J3.58,3.58,4.46,3 H), 1.90(m,30 H); ^{13}C NMR($CDCl_3$,100 MHz) δ:171.1–169.2(5CO), 89.4.



Scheme 2 NIPAM was initiated by Glu-Br to polymerized into Glu-PNIPAM

Experiment

Experimental materials

Hexane/toluene mixed solvent (10/1, *v*/*v*) was used to recrystallize NIPAM (99 + %, Aldrich); pyridine and chloroform (analytical pure) has been drying with CaH_2 before use; DMF (high quality pure, Fine Chemical Research Institute of Tianjin); HMTETA (99 %, Belgium); α-D-glucose(99 %, Belgium); 2-bromide isobutyl bromide(98 %, Belgium); Cuprous chloride (99 %, Sinopharm Chemical Reagent Co., Ltd.); Neutral alumina (100–200 mesh, Sinopharm Chemical Reagent Co., Ltd.); Dialysis bag (M_W = 1000).

Instrument and equipment

The molecular weight and distribution of the star polymer was measured by Water 410 gel permeation chromatography with narrow distribution polystyrene samples as standard in tetrahydrofuran as the mobile phase; the monomer conversion rate is calculated by weight difference method; ^{1}H NMR and ^{13}C NMR were performed with $CDCl_3$ as solvent by the JEOL JNM-A400 II (400 MHz) nuclear magnetic resonance

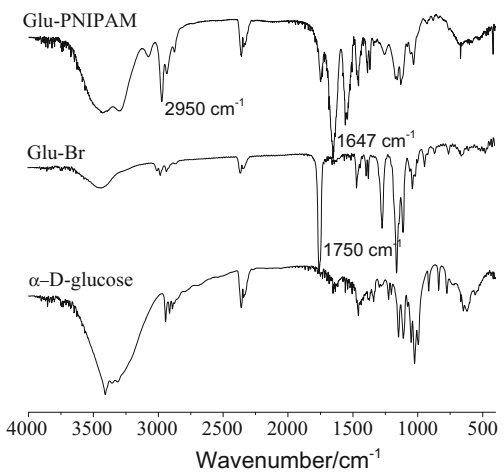


Fig. 1 IR spectra of α-D-glucose, Glu-Br and Glu-PNIPAM

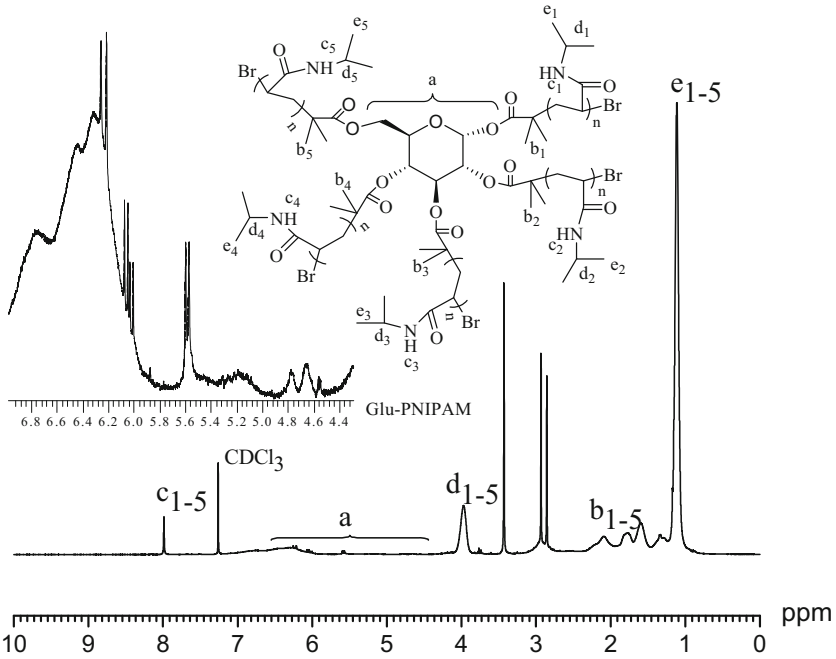


Fig. 2 ^{1}H NMR spectra of Glu-PNIPAM in $CDCl_3$

instrument; infrared spectrum was tested by FTIR-8400S (Japan) infrared spectrometer; LCST was calculated by the results of UV Mini 1240 ultraviolet spectrophotometer measurement; fluorescence spectra was tested by RF-5301PC fluorescence spectrophotometer.

Synthesis of the initiator Glu-Br

The process of α-D-glucose macromolecule initiator (Glu-Br) synthesis was shown in Scheme 1. α-D-glucose (1 g, 0.0056 mol) was dissolved in anhydrous pyridine (6 mL) and anhydrous chloroform (20 mL) mixed solvent in the 100 ml three-necked flask. The solution was stirred for 1 h at room temperature and then arranged in the ice bath. 2-bromide isobutyl bromide (7.72 g, 0.034 mol) was added in drop by drop until excess, then the mixture was refluxed in oil bath for 3 h at 80 °C, followed with reaction at room temperature for 3 days. The products was obtained by ether extraction, and washing with ice water and 0.1 M sodium bicarbonate solution, and then drying the washing crude product with anhydrous magnesium sulfate to extract, the pale yellow crude product was obtained by vacuum distillation, finally, 1.52 g white solid product (yield was 28.8 %) was obtained by methanol recrystallization.

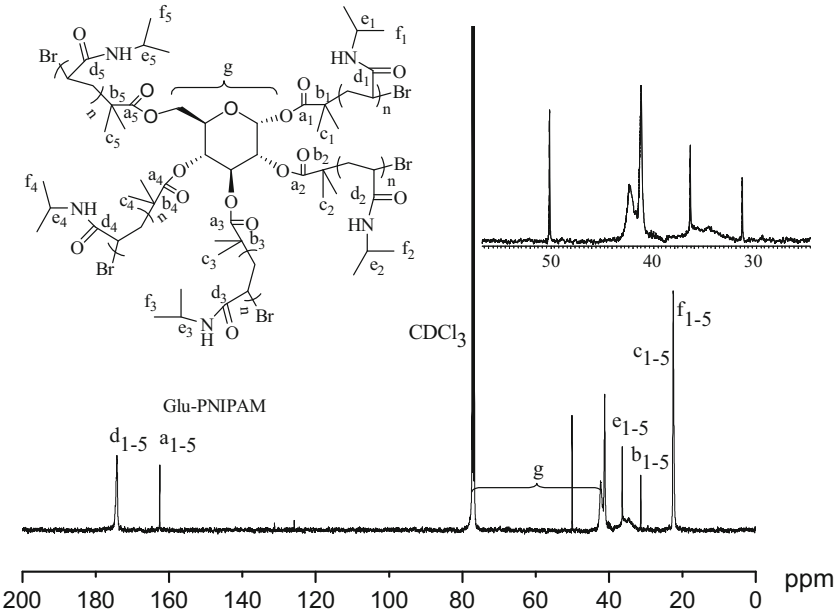


Fig. 3 ^{13}C NMR spectra of Glu-PNIPAM in $CDCl_3$

(CH), 70.6–68.2(4CH),62.6(CH_2), 55.3–54.9[5C$(CH_3)_2$Br],30.7–30.1[10$(CH_3)_2$Br]。.

Synthesis of star polymers

The ATRP of NIPAM was occurred in the DMF/Water (20/3, *v*/*v*) mixed solvent at 25 °C, the reaction process can be seen in Scheme 2.

First, CuCl (0.088 g) was added to the end of the tube with "H″ shape (H tube), the initiator of Glu-Br dissolved in DMF (3 mL) and deionized water (1.2 mL) mixed solvent and added to the other end of the H tube with the process of freeze-vacuum-unfreeze for three cycles, then under the protection of nitrogen, the ligand HMTETA (0.05 mL) and DMF (2 mL) were added to the end of CuCl in H tube by micro syringe, after a while, the solution mixed with dissolved NIPAM (2 g) in DMF (3 mL), then sealed the tube. The reaction was performed for 2–12 h in water bath at 25 °C. After the reaction, liquid nitrogen was used to cool the reaction mixture rapidly to terminate reaction before contact with air. The mixture was diluted by DMF and copper ion was removed with alumina columns, then colorless and transparent solution was obtained. Finally, unreacted monomer was removed by dialysis bag with Mw = 1000, followed with vacuum distillation to remove the solvent to obtain Glu-PNIPAM after 4 days later, then the Glu-PNIPAM was vacuum drying at 50 °C for 24 h to obtain final product.

LCST measurement

LCST of the star polymer was obtained by the cloud point curve test with UV Mini 1240 ultraviolet spectrophotometer. Firstly, a certain concentration (2 mg/mL) polymer aqueous solution is prepared to load into 10 mm quartz cuvette, then the cuvette is placed in temperature controlled water-bath with 0.1 °C/min heating rate. As the temperature increases, the transparent rate of polymer aqueous solution will change to turbid at a certain temperature, the LCST value will be obtained by drafting the cloud point curve.

Results and discussion

Characterization of star polymers

Because DMF not only can be dissolved monomer and initiator, but also has good stability, DMF and water are selected as mixed solvent to synthesis star PNIPAM. Moderate amounts of water can accelerate the polymerization reaction mainly due to the amide group of water molecule, monomer and polymer are combined together through interaction of hydrogen bond, thus weakened the polymer catalyst and radicals at the end of chain.

Table 1 Synthesis[a], Characterization and LCST of different samples of Glu-PNIPAM

Time(h)	$M_{n,th}$[b]	M_n[c]	M_w	M_w/M_n	Conv(%)[d]	LCST(°C)
2	8400	7700	10,400	1.35	13.2	23.9
4	13,000	10,200	15,000	1.47	21.4	24.3
8	20,900	18,400	21,200	1.15	35.3	24.8
10	26,000	20,400	24,600	1.20	44.3	25.2
12	30,000	23,500	28,200	1.19	51.4	25.8

[a] Solvent, DMF/water(*v*/*v*,20/3);temp.,25 °C;$[NIPAM]_0/[Glu\text{-}Br]_0/[CuCl]_0/[HMTETA]_0$ = 100/1/5/1

[b] $M_{n,th} = 5*M_{NIPAM}[NIPAM]_0 conv/100[Glu\text{-}Br]_0 + M_{Glu\text{-}Br}$

[c] Determined by Waters 410 GPC

[d] Determined by gravimetric measurement

Figure 1 gave the FTIR spectra of α-D-glucose, Glu-Br initiator and Glu-PNIPAM polymer. α-D-glucose had a great absorption peak in the vicinity of 3500–3400 cm^{-1}, it was mainly caused by the -OH stretching vibration. For Glu-Br, the absorption peak near 3500–3400 cm^{-1} almost disappeared, at the same time a strong absorption peak caused by the C = O stretching vibration appeared at 1750 cm^{-1}. When the Glu-Br trigger NIPAM polymerization to obtain Glu-PNIPAM, contrasted with Glu-Br infrared spectrum, the absorption peaks of Glu-PNIPAM at 3400 cm^{-1} ($\nu_{N\text{-}H}$) and 2950 cm^{-1} ($\nu_{C\text{-}H}$) were enhanced greatly, at the same time the absorption peak of C = O stretching vibration was occurred blue shift, moved from the original 1750 cm^{-1} to 1647 cm^{-1}, it was mainly due to the C = O group of induced PNIPAM conjugated with the C = O group of original initiator Glu-Br.

To identify the structure of Glu-PNIPAM star polymer, ^1H NMR and ^{13}C NMR were used to characterize the structure.

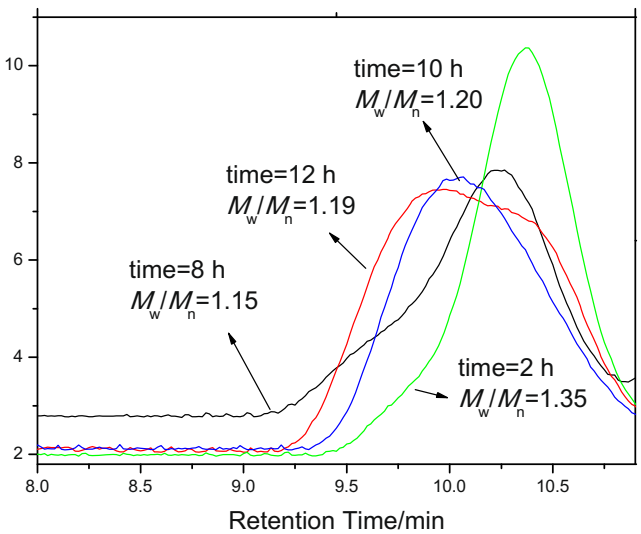


Fig. 4 GPC traces of the products obtained through ATRP at 25 °C. $[NIPAM]_0/[Glu\text{-}Br]_0/[CuCl]_0/[HMTETA]_0$ = 100/1/5/1 in DMF/H_2O(*v*/*v*, 20/3)

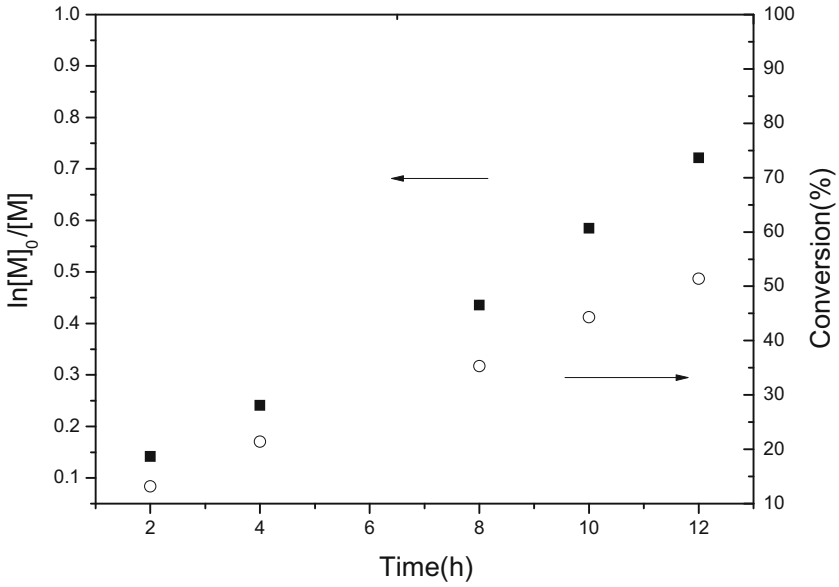


Fig. 5 Monomer consumption $\ln([M]_0/[M])$ and conversion as a function of time

Figure 2 was ^{1}H NMR spectra of Glu-PNIPAM star polymer tested in $CDCl_3$, as we can see, signals produced by $H(CHMe_2)$ of monomer's isopropyl groups were located nearby δ=1.11(e_{1-5}) and δ=3.97(d_{1-5}), respectively; signals produced by $H(CHMe_2)$ of NH groups were located nearby δ=7.99(c_{1-5}); signals produced by $H(CHMe_2)$ of CH_3CCO were located nearby δ=2.09(b_{1-5});H of α-D-glucose core was near δ=4.40–6.60 (a) (The weight of the polymer molecular was relatively large, the signal reflected H of α-D-glucose core was relatively weak).

Figure 3 was ^{13}C NMR spectra of Glu-PNIPAM, the peak signals at δ=22.46(f_{1-5}) and δ=36.60 (e_{1-5}) were caused by tertiary carbon(CH) and primary carbon(CH_3) atoms of $NHCH(CH_3)_2$, the signal produced by C = O of monomer was near δ=174.15 (d_{1-5}), the signal produced by C = O of initiator was located at δ=162.48 (a_{1-5}); the peak signals of quaternary carbon(C) and primary carbon(CH_3) atoms in $C(CH_3)_2CO$ were located at δ=31.33(b_{1-5}) and δ=23.59(c_{1-5}), respectively; the peak signal of quaternary carbon(C) in α-D-glucose core was located in δ=42.31–77.32(g) region(parts of signal were overlapping with the solvent peak).

Polymerization kinetics

Because the Cu(I) is easy to lose an electron into Cu(II) and has a great affinity with halogen atoms, and can form stable complexes (four coordination) with HMTETA polyamine ligand, even water is present in the reaction solvent, Cu(I) also does not easily occur disproportionation, CuCl was as catalyst and HMTETA as ligand in this paper.

Table 1 lists the experimental data of Glu-PNIPAM synthesis and characterization, including molecular weight, conversion and LCST.

As can be seen from Table 1, the polymerization used DMF/water as mixed solvent at 25 °C, the initial ratio of the polymerization system was $[NIPAM]_0/[Glu\text{-}Br]_0/[CuCl]_0/[HMTETA]_0$ = 100/1/5/1, the polymerization time was 2,4, 8, 10, 12 h, whose molecular weight were 7700, 10,200, 18, 400, 20,400 and 23,500, the conversion rate of corresponding reaction monomer were 13.2 %, 21.4 %, 35.3 %, 44.3 % and 51.4 %, respectively.

The GPC traces of the products were shown in Fig. 4. With the prolongation of the polymerization time, the retention time of products in gel permeable chromatographic column was shorter, and the result indicated molecular weight of polymer increased gradually. Reaction time of 2, 8, 10 and 12 h corresponded to 10.38, 10.20, 10.07 and 9.97 min respectively. In the whole process of polymerization, the molecular weight of the products retain to lower lever. The PDI calculate by Mw/Mn was 1.35, 1.15,1.20 and 1.19 respectively.

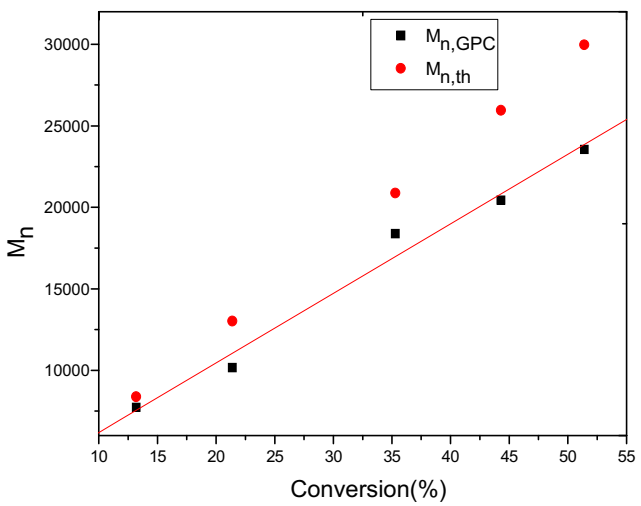


Fig. 6 Glu-PNIPAN molecular weight as a function of conversion

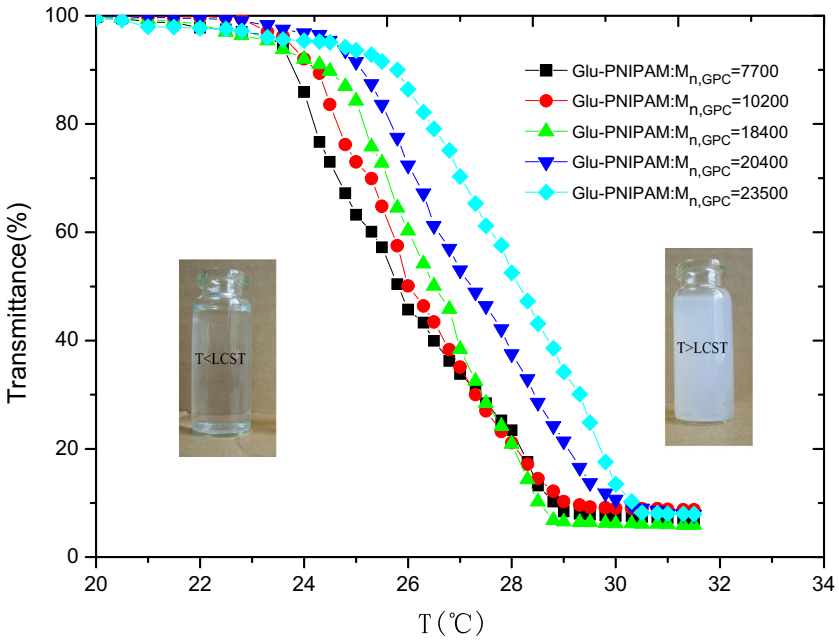


Fig. 7 Dertermination of the LCST of the aqueous Glu-PNIPAM solutions (2 mg/mL, heating rate = 0.1 °C/2 min)

The initial kinetic curve can be seen from Fig. 5, $\ln[M]_0/[M]$ and conversion rate was a linear relation with time basically, but the conversion rate of whole polymerization process was only 51.4 % after reacting for 12 h, which was associated with the ligand we selected. Giancarlo Masci [17] reported that HMTETA wasn't the most effective ligand compared with Me_6TREN. In Fig. 6, the molecular weight of the polymer was equal to the theory in initial stage, but with the reaction continuously carrying on, especially in the later stage, the molecular weight had a certain deviation from theory value. The result measured here was only the relative molecular weight, and one of the main reasons was that free radical chain termination reaction was occasionally occurred as the reaction progress, resulting in the conversion rate of single body reducing, the molecular weight became lower. The conversion rate increased with the molecular weight, the line was basically linear. The molecular weight distribution maintained lower along the whole polymerization process, which demonstrated that the whole polymerization process had great property of control.

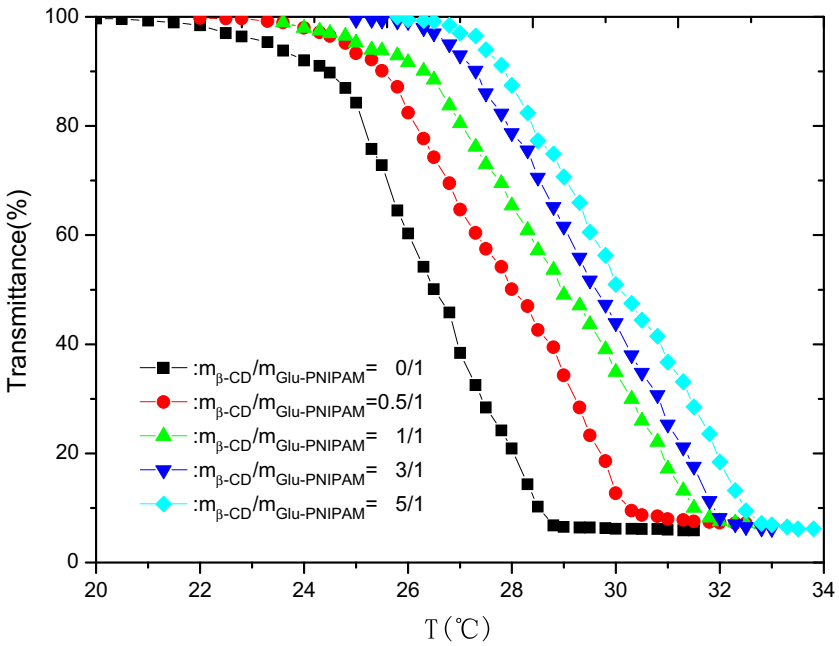


Fig. 8 Cloud point curves of the aqueous Glu-PNIPAM solution (2 mg/ml) with different amounts of β-CD

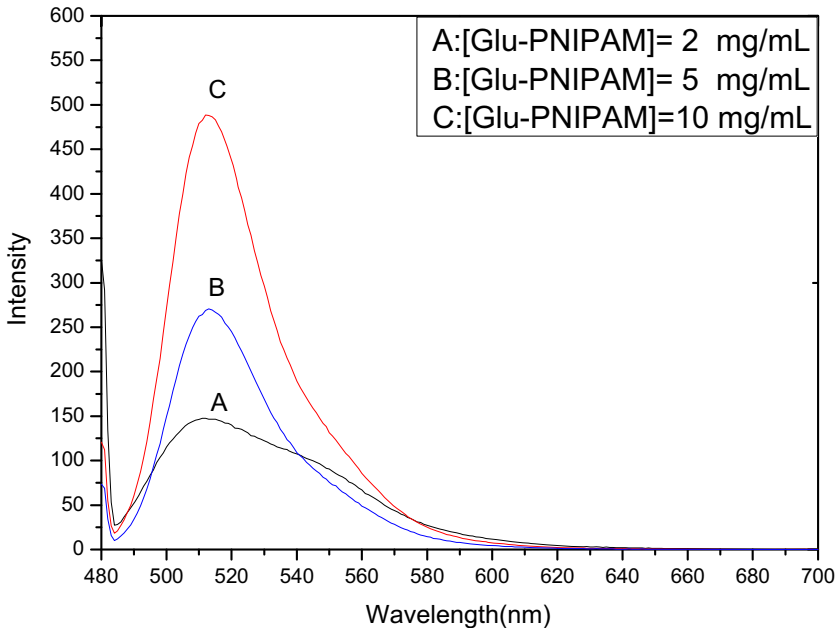


Fig. 9 Fluorescence spectra of aqueous Glu-PNIPAM solution of A, B and C

Thermo-sensitive analysis

When the temperature reached a certain value, an obvious transformation from clear to turbid was observed in Glu-PNIPAM aqueous solution, it can be seen from fig. 7. In order to confirm the LCST, we adopted UV Mini 1240 ultraviolet spectrophotometer to obtained the cloud point curve via measuring the transmittance of Glu-PNIPAM water solution under different temperature (heating rate: 0.1 °C/min). In Fig. 6, we choose the temperature as LCST which was corresponding to the 90 % transmittance of the solution, the LCST value were 23.9, 24.3, 24.8, 25.2 and 25.8 °C with molecular weight are 7700,10, 200,18,400,20,400,23,500, respectively. As can be seen, the LCST increased with molecular weight increasing in lower molecular weight. It was consistent to the effects of molecular weight and terminal groups on thermosensitive polymers reported by Steven and Furyk et al. [18]

β-cyclodextrin(β-CD) is cyclic oligosaccharides which are composed of 7 glucose units, molecular structure is slightly conical ring. It has outer hydrophilic and hydrophobic cavity that provide a hydrophobic binding site like enzyme. As the main host, β-CD can envelope various appropriate guest [19, 20]. Different amount of β-CD (until reached saturation at 0 °C) were added into 10 mL Glu-PNIPAM aqueous solution ($M_{n,GPC}$ = 18,400, 2 mg/mL) stirring 2 h in ice bath firstly, and then placing at 3 °C for 4 days to measure the LCST of Glu-PNIPAM aqueous solution. It was found that the phase transformation temperature of Glu-PNIPAM increased with β-CD content as shown in Fig. 8. The LCST of Glu-PNIPAM increased from 24.8 to 28 °C, and with β-CD content gradually increased to saturation, LCST tended to change slowly.

Fluorescence analysis of Glu-PNIPAM carried fluorescein

In order to test the wrapped-capacity of Glu-PNIPAM polymer, we prepared aqueous Glu-PNIPAM solution A, B and C with the same molecular weight and three different concentrations of 2 mg/mL, 5 mg/mL and 10 mg/mL, respectively. Then a certain amount fluorescein was added into the solution, stirring in ice bath for 2 h, placing the solutions at 3 °C for 5 days, using Mw = 1000 dialysate bag to dialysis filtrated solution for 10 days (small fluorescein molecule unwrapped will be filtered out).

Figure 9 showed the fluorescence emission spectra of A, B and C solution. They showed strong fluorescence emission at the 515 nm, fluorescence intensity increased from A to C. The results showed the star Glu-PNIPAM polymer had better ability of carrying fluorescein molecular. With the Glu-PNIPAM concentration increasing, the more fluorescein molecule was loaded in, as seen in fig. 8 stronger fluorescence emission spectra.

Conclusion

Thermo-sensitive star polymer (Glu-PNIPAM) with α-D-glucose core was successfully synthesized using the Glu-Br as initiator by ATRP. The star Glu-PNIPAM polymer had narrow molecular weight distribution with LCST of 23.9–25.8 °C. The molecular size had a certain influence on LCST within a certain range, the higher molecular weight was, and the bigger LCST value was. Compared with PNIPAM (LCST value is 32 °C), the LCST of Glu-PNIPAM reduced to 23.9 °C, this was because the hydrophobic interaction of

polymer terminal groups with α-D-glucose core. When adding different amounts β-CD into Glu-PNIPAM polymer aqueous solution with certain concentration (2 mg/ml), the formation of complex with Glu-PNIPAM and β-CD made the phase transition temperature of Glu-PNIPAM had a great degree of increasing (increasing from 24.8 to 28 °C). At the same time, the star Glu-PNIPAM polymer had ability of wrapped small fluorescein molecular, which had a great prospect application in the field of drug controlled release.

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