Micellization and Thermogelation of Poly(ether urethane)s Comprising Poly(ethylene glycol) and Poly(propylene glycol)

Xian Jun Loh,[*1] *Lim Wan Ian Cheng,*[1] *Jun Li*[*1,2]

Summary: A series of multiblock poly(ether urethane)s comprising poly(ethylene glycol) (PEG), and poly(propylene glycol) (PPG) segments were synthesized. Their aqueous solutions exhibited thermogelling behavior at critical gelation concentrations (CGC) ranging from 8 to 12 wt%. The composition and structural information of the copolymers were studied by GPC and ^{1}H NMR. The critical micellization concentration (CMC) and thermodynamic parameters for micelle formation were determined at different temperatures. The temperature response of the copolymer solutions were studied and found to be associated with the composition of the copolymers.

Keywords: micelles; poly(ethylene glycol); poly(propylene glycol); thermogelling polymers

Introduction

There has been great interest in the development of thermogelling copolymers over the past decade.[1] These injectable materials have potential applications in the areas of sustained drug delivery, gene delivery and tissue engineering. The most popular thermogelling copolymers are poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*- poly(ethylene glycol) (PEG-PPG-PEG) triblock copolymers, or Pluronics. These copolymers have been widely investigated for controlled drug delivery, [1–3] wound covering, [4] and chemosensitizing for cancer therapy.[5] However, its intrinsic properties such as non-biodegradability, quick release of bioactive agents, high gelation concentration and *in vivo* gel instability have limited its use in biomedical applications.[6–7] In this work, we designed and synthesized thermogelling copolymers with a random block structure. The synthesis of these polymers can be performed via a simple one-step coupling reaction of commercially available products and should be easily reproduced by any laboratory. These gels required lower aqueous concentrations to exhibit the thermogelling effect as compared with Pluronics copolymers. The compositional effect of poly(PEG/PPG urethane)s were studied. The critical micellization concentrations and the critical gelation concentrations can be fine-tuned by adjusting the PEG:PPG ratio. Thermodynamic analysis of the process of micellization yields insight into the balance between the packing of the copolymer chains and the association of water molecules with the polymer. This provides valuable information on the design of thermogelling copolymers based on the adjustment of the composition of the block copolymer during the synthesis process.

[1] Institute of Materials Research and Engineering, A*STAR (Agency for Science, Technology and Research), 3 Research Link, Singapore 117602, Singapore
E-mail: XianJun_Loh@scholars.a-star.edu.sg; bielj@nus.edu.sg
[2] Division of Bioengineering, Faculty of Engineering, National University of Singapore, 9 Engineering Drive 1, Singapore 117576, Singapore

Experimental Part

Materials

Poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG) was purchased

from Aldrich. The M_n and M_w of PEG were found to be 1890 and 2060, respectively. The M_n and M_w of PPG were found to be 2180 and 2290, respectively. Dibutyltin dilaurate (95%) 1,6-hexamethylene diisocyanate (HMDI) (98%), methanol, diethyl ether, 1,2-dichloroethane (99.8%) and 1,6-diphenyl-1,3,5-hexatriene (DPH) were purchased from Aldrich. 1,2-dichloroethane was distilled over CaH_2 before use.

Synthesis of Poly(PEG/PPG urethane)s

Poly(PEG/PPG urethane)s were synthesized from PEG and PPG using HMDI as a coupling reagent similar to previous reports.[8–13] The amount of HMDI added was equivalent to the reactive hydroxyl groups in the solution. Typically, 1.8 g of PEG and 0.9 g of PPG were dried in a 250-ml two-neck flask at 50 °C under high vacuum overnight. Then, 20 ml of anhydrous 1,2-dichloroethane was added to the flask. Following that, an equimolar of HMDI and two drops of dibutyltin dilaurate ($\sim 8 \times 10^{-3}$ g) were added sequentially. The reaction mixture was stirred at 75 °C under a nitrogen atmosphere for 48 hrs. The resultant copolymer was precipitated in hexane. A series of poly(PEG/PPG urethane)s with different PEG/PPG ratios were prepared, and their number-average molecular weight and polydispersity values are given in Table 1. The yield was 80% and above after isolation and purification. ^{1}H NMR ($CDCl_3$) of poly(PEG/PPG urethane)s EP(1:1): δ (ppm) 1.11 (-O(C***H***$_3$)CHCH$_2$O-), 1.32 (-OOCNHCH$_2$-CH$_2$C***H$_2$C H$_2$***CH$_2$CH$_2$NHCOO-), 1.47 (-OO-CNHCH$_2$C***H$_2$***CH$_2$CH$_2$C***H$_2$***CH$_2$NHCOO-), 3.14 (-OOCNHC***H$_2$***CH$_2$CH$_2$CH$_2$CH$_2$C***H$_2$***-NHCOO-), 3.38 (-O(CH$_3$)C***H***CH$_2$O-), 3.45 (-O(CH$_3$)CHC***H$_2$***O-), 3.63 (-OC***H$_2$C H$_2$***O-), 4.19 (-OOCN***H***CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-N***H***COO-).

Molecular Characterization

Gel permeation chromatography (GPC) analysis was carried out with a Shimadzu SCL-10A and LC-8A system equipped with two Phenogel 5μ 50 and 1000 Å columns (size: 300 × 7.8 mm) in series and a Shimadzu RID-10A refractive index detector. THF was used as eluent at a flow rate of 1 ml/min at 45 °C. Monodispersed poly(ethylene glycol) standards were used to obtain a calibration curve. The ^{1}H NMR (400 MHz) spectra were recorded on a Bruker AV-400 NMR spectrometer at room temperature. The ^{1}H NMR measurements were carried out with an acquisition time of 3.2 s, a pulse repetition time of 2.0 s, a 30° pulse width, 5208 Hz spectral width, and 32K data points. Chemical shift was referred to the solvent peaks ($\delta = 7.3$ ppm for $CHCl_3$).

Critical Micellization Concentration (CMC) Determination

The CMC values were determined by using the dye solubilization method. [8,10] The hydrophobic dye 1,6-diphenyl-1,3,5-hexatriene (DPH) was dissolved in methanol with a concentration of 0.6 mM. 40 μL of this solution was mixed with 4.0 mL of copolymer aqueous solution with concentrations ranging from 0.0000305 to 0.5 wt % and equilibrated overnight at 4 °C. A UV-Vis spectrophotometer was used to obtain the UV-Vis spectra in the range of 330–430 nm at 20^{v}C, 30 °C, 40 °C and 50 °C. The CMC value was determined by the plot of the difference in absorbance at 378 nm and

Table 1.
Molecular characteristics of poly(PEG/PPG urethane)s.

Copolymer[a]	Feed ratio(wt %)		Actual Composition (wt %)[c]		Copolymer characteristics		
	PEG	PPG	PEG	PPG	M_n[b] ($\times 10^3$)	M_w/M_n[b]	cmc[d] $\times 10^4$ (g/mL)
EP1-1	50.0	50.0	52.2	47.8	32.0	1.65	1.29
EP2-1	66.7	33.3	71.9	28.1	39.3	1.39	3.58
EP3-1	75.0	25.0	78.3	21.7	30.4	1.58	5.65

[a]Poly(PEG/PPG urethane)s are denoted EP, E for P**E**G and P for P**P**G. The M_n of PEG and PPG used for the copolymer synthesis was 1890 and 2180 g mol^{-1}, respectively.[b]Determined by GPC.[c]Calculated from ^{1}H NMR results.[d]Critical micellization concentration (cmc) in water determined by the dye solubilization technique at 30 °C.

at 400 nm ($A_{378} - A_{400}$) versus logarithmic concentration.

Micelle Size Variation with Temperature

The particle size of the micelles were measured at various temperatures using the dynamic light scattering analyser (Brookhaven Instruments Corporation, Holtsville, NY, 15 mW laser, incident beam = 676 nm).

Lower Critical Solution Temperature Determination

Cloud points were measured with a UV-vis spectrophotometer similar to previous reports.[14–17] Aqueous copolymer solutions (1 wt%) were heated at 2 °C/min while both the transmittance at 650 nm (1 cm path length) and the solution temperature were monitored.

Sol-Gel Transition

The sol-gel transition was determined by a test tube inverting method with temperature increments of 2 °C per step. Each sample of a given concentration was prepared by dissolving the polymer in distilled water in a 2-mL vial. After equilibration at 4 °C for 24 h, the vials containing samples were immersed in a water bath at a constant designated temperature for 15 min. The gelation temperature was characterized by the formation of a firm gel that remained intact for 1 minute when the tube was inverted by 180°. The critical gelation concentration (CGC) is defined as the minimum copolymer concentration in aqueous solution at which the gelation behavior could be observed.

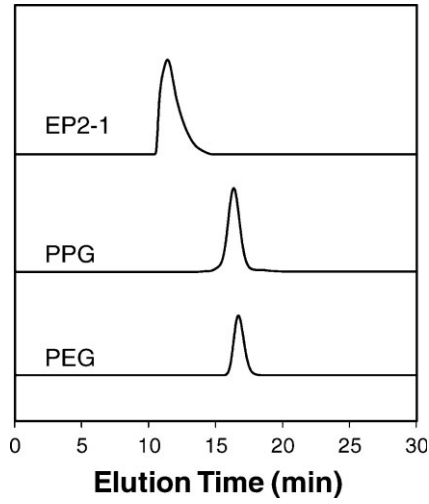
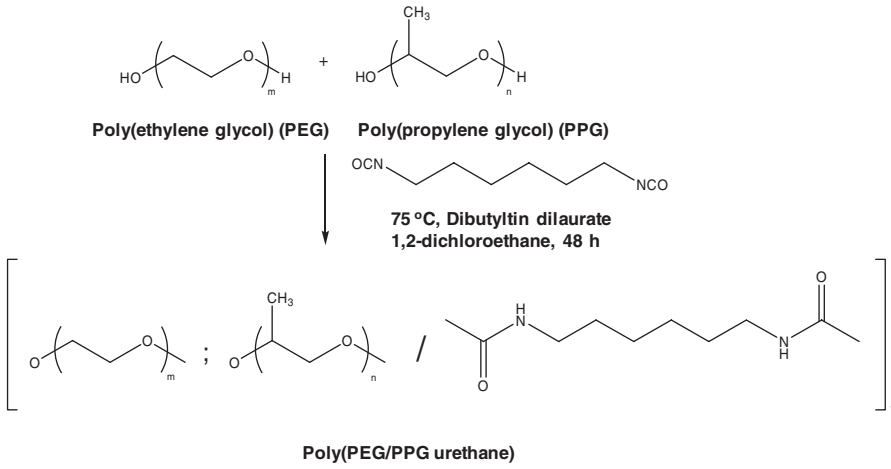


Figure 1.
GPC diagrams of EP2-1 and its PEG and PPG precursors.

Results and Discussion

Synthesis and Characterization of Poly(PEG/PPG urethane)s

Poly(PEG/PPG urethane)s were prepared by the randomly coupling PEG and PPG



Scheme 1.
Synthesis of poly(PEG/PPG urethane)s.

segment blocks using the isocyanate of 1,6-hexamethlyene diisocyanate (HMDI) in the presence of dibutyltin dilaurate. We found that dibutyltin dilaurate is most suitable for the synthesis of the poly(PEG/PPG urethane)s, allowing us to obtain the appropriate molecular weight of about 30,000 mol.g^{-1} within 2 days. The synthesis of the poly(PEG/PPG urethane)s is presented in Scheme 1b. Solution-based synthesis of the poly(ether urethane)s is preferred over the bulk synthesis method as the latter method often led an incomplete reaction or the formation of allophane crosslinked polymers. When solution polymerization is used, we observed that the reaction can be carried out to completion and the crosslinking effects of the polymer can be controlled.

A series of random multiblock poly-(PEG/PPG urethane)s were synthesized, and their molecular weights and molecular weight distributions were determined by GPC (Table 1). A typical GPC chromatograph of one of the poly(PEG/PPG urethane)s, EP2-1, shows a unimodal peak in GPC chromatograph of the poly-(PEG/PPG urethane) (Figure 1). The non-overlapping nature of the plot with those

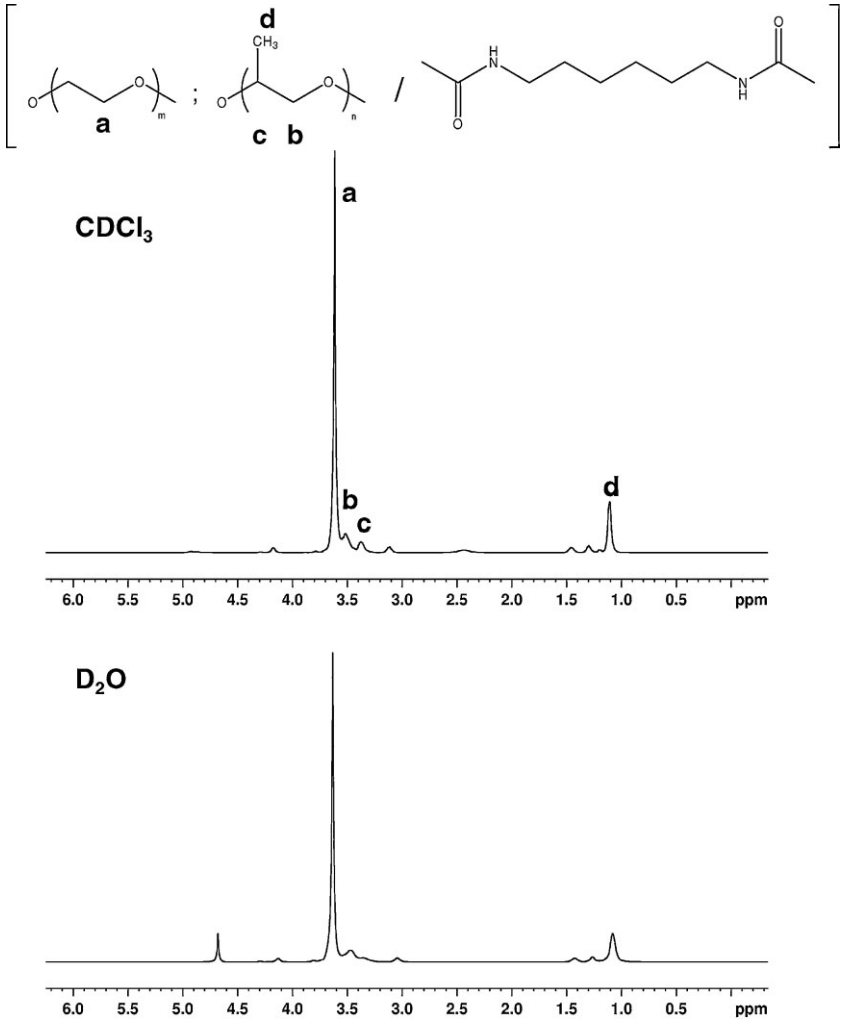


Figure 2.
400 MHz ^{1}H NMR of EP2-1 in $CDCl_3$ and D_2O.

of corresponding precursors indicates that a complete reaction took place with no unreacted precursor remained.[8–13] The molecular weights of the poly(PEG/PPG urethane)s and their polydispersities are tabulated in Table 1.

The chemical structure of poly(PEG/PPG urethane)s was verified by ^{1}H NMR (Figure 2). The ^{1}H NMR spectrum of EP2-1 in $CDCl_3$ shows all proton signals belonging to PEG and PPG segments. Signals corresponding to methylene protons in repeated units of PEG segments are observed at 3.63 ppm, the signals at 1.11 ppm are assigned to the methyl protons of PPG. As the content of HMDI among the starting materials is below 1 wt%, the compositions of the poly(PEG/PPG urethane)s could be determined from the integration ratio of resonances at 1.11 and 3.63 ppm within the limits of ^{1}H NMR precision, and the results are shown in Table 1. NMR spectroscopy was used to investigate the effect of solvent on the micelle structure.[8,18,19] $CDCl_3$ is a good nonselective solvent for PEG and PPG while water is a good selective solvent for PEG but poor for PPG. As shown in Figure 2, in $CDCl_3$, the peaks due to the PEG and PPG segments were sharp and well defined. In D_2O, PEG is shown as a sharp peak but PPG peaks are collapsed and broadened. In Figure 3, the NMR spectrum of the region corresponding to the methyl group of PPG is shown in D_2O and $CDCl_3$. In $CDCl_3$, the peak width at half length of this peak ($\omega 1$) is 14.140 Hz. When the copolymer is dissolved in D_2O, the peak width at half length of this peak ($\omega 2$) increased to 21.836 Hz. This shows that the molecular motion of PPG is slower in D_2O than in $CDCl_3$, indicating a hydrophobic core structure made up of PPG with the hydrophilic PEG as the outer corona structure, confirming the core-corona structure of the micelle.[8,18,19]

Micelle Properties

The micelle properties of the water-soluble poly(PEG/PPG urethane)s were studied. The critical micelle concentration of amphiphilic copolymers can be determined by surface tension measurements, dynamic light scattering and dye solubilization methods using dyes such as pyrene and DPH. In this work, the CMC of the poly(PEG/PPG urethane)s were determined using the DPH solubilization method. The CMC determination was carried out for these copolymers at 20, 30, 40 and 50 °C at aqueous polymer

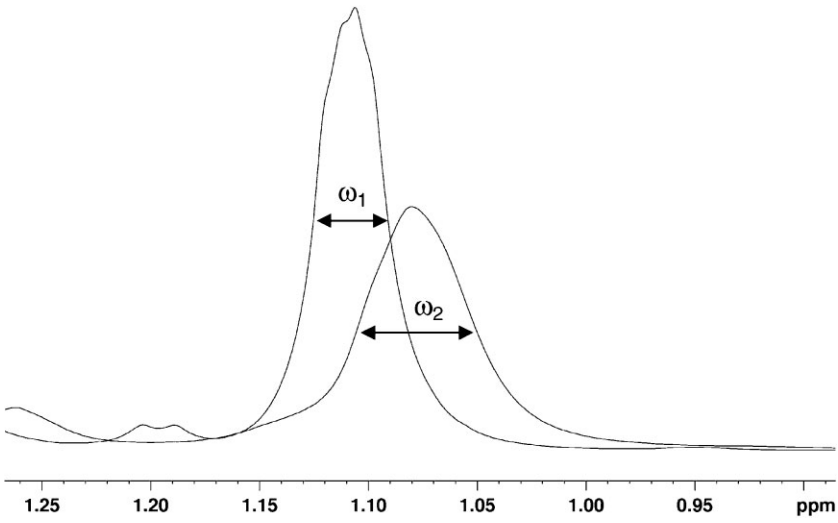


Figure 3.
Comparison of ^{1}H NMR of EP2-1 in $CDCl_3$ and D_2O in the $-CH_3$ of PPG region.

concentrations of 0.0000305 to 0.5 wt %. DPH shows a higher absorption coefficient in a hydrophobic environment than in water. During the formation of the micelle, the dye is encapsulated in the hydrophobic core of PPG, leading to an increase in the absorbances at 344, 358 and 378 nm (Figure 4a).[8,10,18] The point where the absorbance suddenly increases corresponds to the concentration at which micelles are formed. The CMC was determined by extrapolating the absorbance at 378 nm minus the absorbance at 400 nm ($A_{378} - A_{400}$) versus logarithmic concentration (Figure 4b). The CMC values for the water-soluble copolymers at 30 °C are tabulated in Table 1.

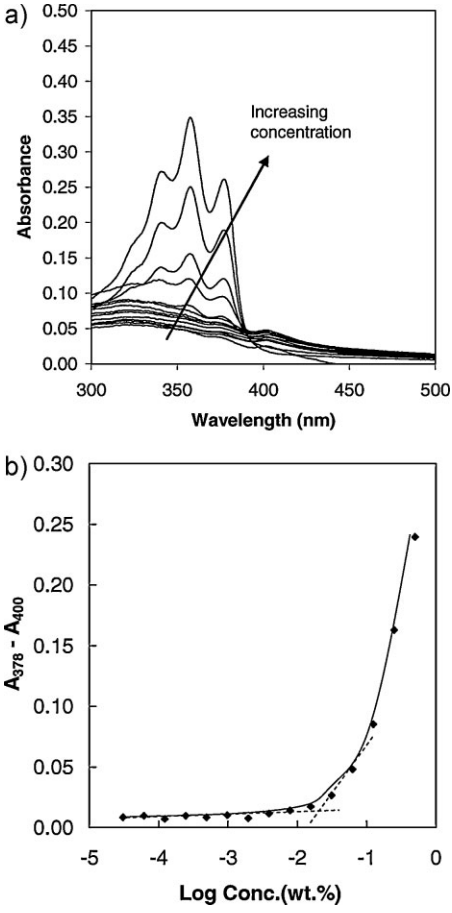


Figure 4.
a) UV-vis spectra changes of DPH with increasing EP2-1 copolymer concentration in water at 30 °C. DPH concentration was fixed at 6 mM and the polymer concentration varied between 0.0000305 and 0.5 wt %. The increase in the absorbance band at 378 nm indicates the formation of a hydrophobic environment in water. b) CMC determination by extrapolation of the difference in absorbance at 378 nm and 400 nm.

Assuming a closed association of unimers into micelles, thermodynamic functions such as the molar standard enthalpy, ΔH°, and the entropy, ΔS°, and free energy, ΔG°, for micelle formation can be extracted from the studies of the CMC dependence on temperature.[10,20] The free energy of micellization ΔG°, can be calculated by

$$\Delta G^\circ = RT \ln(X_{cmc})$$

where R is the gas law constant, T is the temperature in K and X_{cmc} is the CMC in mole fraction of polymer in the aqueous solution at temperature T. The values of ΔG° are negative, indicating the spontaneity of the micellization process. These values are temperature-dependent, becoming more negative at higher temperatures. These values indicate that the formation of micelles is favoured at higher temperatures. The values are tabulated in Table 2.

Further, the values of the standard enthalpy of micellization, ΔH°, and the standard entropy of micellization, ΔS°, can be extracted from the Arrhenius plot of $\ln(X_{cmc})$ versus 1/T.

$$\Delta H^\circ = R(d \ln X_{cmc}/d T^{-1})$$

$$\Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)/T$$

Figure 5 shows the plot of $\ln X_{cmc}$ *versus* T^{-1}. ΔH° can be calculated from the slope of the linear plot. In all the solutions studied, enthalpy of micellization was shown to be an endothermic process, similar to aqueous solutions of Pluronic block copolymers. [20] The enthalpy values became less positive with increasing PEG content. On the other hand, the entropy contribution is positive with the value becoming less positive with increasing PEG content. The micellization process is entropy-driven. At low temperatures, when the polymer chains are soluble in water, water molecules interacted closely with the main polymer backbone. Upon raising the

Table 2.
Thermodynamic Parameters of the Micellization Process of Poly(PEG/PPG urethane)s.

Copolymer	Temperature (°C)	cmc $\times 10^4$ (g/mL)	ΔG (kJ/mole)	ΔS (kJ/mole/K)	ΔH (kJ/mole)
EP1-1	20	2.27	−38.7	0.339	
	30	1.29	−41.4	0.337	60.8
	40	0.64	−44.6	0.337	
	50	0.22	−49.0	0.340	
EP2-1	20	5.97	−36.8	0.282	
	30	3.58	−39.4	0.281	45.7
	40	2.95	−41.6	0.279	
	50	0.97	−45.5	0.282	
EP3-1	20	6.37	−36.0	0.247	
	30	5.65	−37.9	0.244	36.1
	40	2.31	−40.4	0.244	
	50	1.09	−43.4	0.246	

temperature of the solution, the interaction between the water molecules and the polymer backbone becomes less favourable. The result is an expulsion of water molecules from the polymer backbone, leading to an overall entropy gain of the system due to the free water molecules.[10]

Lower Critical Solution Temperature (LCST) Behaviour of the Aqueous Copolymer Solutions

The dilute aqueous solutions of these poly(PEG/PPG urethane)s exhibit a LCST behavior very similar to the PNIPAM solutions.[14–17] The LCST point is defined as the point where there is a sudden drop in transmittance at a certain critical temperature. Figure 6 shows a plot which illustrates the dependence of the transmittance of the aqueous polymer solution on temperature. The concentration of the aqueous polymer solution was 1 wt%. This value is lower than the CGCs of the copolymers. This was to ensure that the aqueous solution remained in a sol state throughout the experiment. For all the polymers, there was a sudden drop in transmittance at the LCST. The LCST decreases with increasing PPG content in the polymer. This is consistent with other studies regarding LCST behavior. In general, it was found that a higher hydrophobic component in the polymer reduced the LCST of the copolymer solution. At the concentrations tested, the copolymers self-assemble into micelles in the aqueous

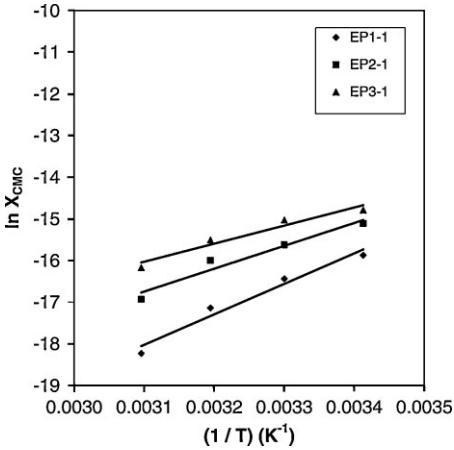


Figure 5.
Determination of $\Delta H_{micellization}$ of EP series of copolymers.

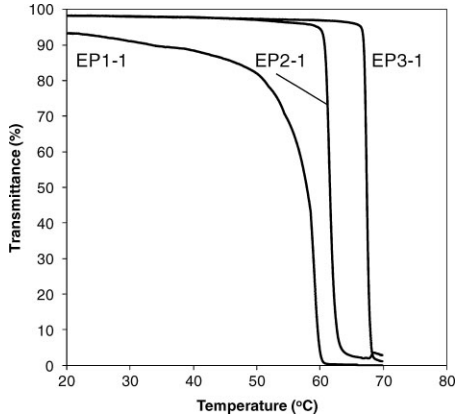


Figure 6.
Temperature-induced changes in transmittance of 1 wt% aqueous copolymer solutions.

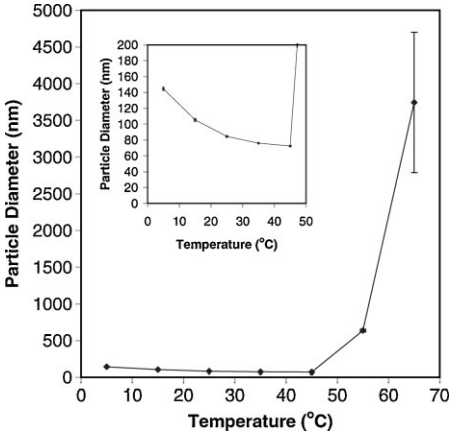


Figure 7.
Variation of micelle size at different temperatures. (Sample: 1 wt% aqueous EP1-1 solution).

solutions. From the earlier discussion on the thermodynamics of micellization, water expulsion takes place upon micellization. This process probably takes places continuously as the temperature was raised, up to the critical temperature, LCST. At the LCST, the polymer molecules collapse into each other, leading to the formation of particulate matter. From our macroscopic observations, we can see that the solution undergoes a transition from clear solution to turbid solution. The changes in the micelle size were also monitored at different temperatures (Figure 7). The micelle size decreases as the temperature is heated up to the LCST where the formation of large sub-micron particles (> 400 nm) was detected. When the temperature is increased, the PPG segment becomes more hydrophobic and the micelle core starts to shrink. This occurs up to a certain point where the entire micelle becomes very hydrophobic and the micelle starts to aggregate to form particles. The complete particle size variations of the micelles are tabulated in Table 3.

Thermo-Reversible Sol-Gel Transition of the Copolymers

The phase diagrams of the poly(PEG/PPG urethane)s in aqueous solutions were determined by the test tube inverting method (Figure 8). The lower soluble

Table 3.
Particle size of poly(PEG/PPG urethane) micelles at different temperatures. Numbers in brackets indicate polydispersity.

Temperature (°C)	EP1-1/nm	EP2-1/nm	EP3-1/nm
5	144.6 ± 2.2 (0.233)	155.9 ± 2.9 (0.237)	184.0 ± 15.2 (0.343)
15	105.4 ± 1.9 (0.220)	161.3 ± 2.4 (0.266)	177.4 ± 2.4 (0.262)
25	84.5 ± 1.1 (0.200)	134.5 ± 3.3 (0.300)	123.5 ± 3.0 (0.271)
35	76.0 ± 0.3 (0.142)	86.6 ± 1.7 (0.320)	84.8 ± 1.4 (0.238)
45	72.4 ± 0.6 (0.149)	78.2 ± 0.8 (0.312)	67.6 ± 1.1 (0.253)
55	637.7 ± 18.2 (0.256)	96.4 ± 3.5 (0.313)	87.5 ± 3.1 (0.240)
65	3744.2 ± 956.2 (0.484)	576.6 ± 107.5 (0.496)	627.2 ± 262.5 (0.405)

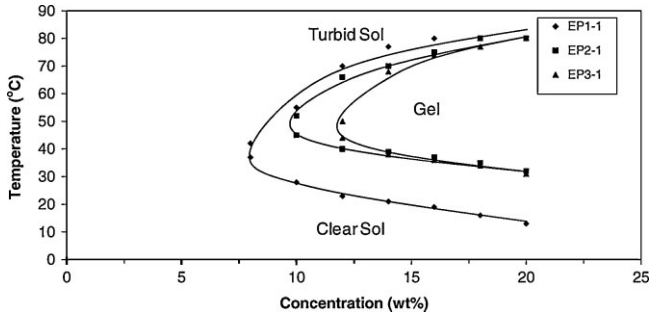


Figure 8.
Sol-gel phase diagrams of poly(PEG/PPG urethane)s in aqueous solutions.

region, gel region and the upper soluble region can be observed in the diagram. As the temperature increased monotonically from 4 to 80 °C, the aqueous polymer solution underwent a sol-gel-sol transition. The reversible change also took place upon cooling from 80 to 4 °C. The critical gelation concentration (CGC) is defined as the minimum copolymer concentration in aqueous solution at which the gelation behavior could be observed. The CGCs of the copolymers in this work were found to be between 8 and 12 wt%. The CGCs increased with increasing PEG content. We also found that the gelation window increased with increasing PPG content. Therefore, from this experiment, we learnt that the amount of PPG in the copolymer plays a critical part in the determination of the CGC of the copolymer.

Conclusion

Thermogelling poly(PEG/PPG urethane)s were synthesized using HMDI as a coupling agent. The CMC values of the water-soluble copolymers were determined by DPH solubilization method. Additionally, the CMC of the copolymers was determined at different temperatures. From these data, ΔG, ΔH and ΔS of micellization were extracted. The thermodynamic parameters of micellization were related with the gelation of the copolymer in solution. The sol-to-gel transitions of the aqueous copolymers were studied, and phase diagrams showing the various sol and gel regions as a function of temperature and concentration of the solution was generated. The critical gelation concentration of the copolymers in this work ranged from 8–12 wt%. In addition to the sol-to-gel phase transition, the solution thermo-response was also evaluated by studying the LCST behavior in dilute aqueous copolymer solutions. The critical gelation concentrations of the copolymers were found to be finely intertwined with the composition of the copolymer.

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Dedication

This paper is dedicated to the memory of S. L. Lim (1914-2009) for his inspiration and words of encouragement for one of the authors, X. J. Loh, whenever needed. He will be deeply missed.

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