거대상분리에 의한 PEO-PLGA-PEO 삼중블록공중합체의 새로운 젤 형성 메커니즘에 관한 유변학적 연구

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A Rheological Study on the New Gelation Mechanism of PEO-PLGA-PEO Triblock Copolymers Induced by the Macroscopic Phase Separation

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Introduction

Recently, the synthesis of poly(ethylene oxide-b-(DL-lactic acid-co-glycolic acid)-b-ethylene oxide) (PEO-PLGA-PEO) triblock copolymers with properties of nontoxicity and biodegradability was reported.[1,2] Aqueous solutions of these new biodegradable triblock copolymers have shown to undergo the sol-to-gel transition with the increase in temperature.[1-3] Moreover, it has been found that the PEO-PLGA-PEO with low molecular weights remains as a gel in-vivo for more than a month while the gel phase of a PEO-PPO-PEO (typically, Pluronic® F127) dissolves in-vivo at short time upon dilution.[3-5] This implies that the gelation mechanisms of these two block copolymers are quite different. Most recently, we investigated two gel states of a PEO-PPO-PEO (Pluronic P103) triblock copolymer and two different gelation mechanisms were proposed: the gel at lower temperature is caused by the close-packing of micelles while the turbid gel at higher temperature is driven by the macroscopic liquid-liquid phase separation.[6] This result clearly represents the effect of the length of hydrophilic PEO end blocks on gelation. In present study, the phase diagram of a PEO-PLGA-PEO (750-3.5K-750) is presented compared with that of Pluronic P103 because they contain almost the same molecular weight and same composition. This approach enables us to find clues on the effect of type of hydrophobic middle blocks on the gelation since the relative hydrophobicity of different types of hydrophobic units has been placed in the order of LGA: PO as 3:1.[7] We employed dynamic light scattering, small angle X-ray scattering, and rheology and based on the experimental results, a new gelation mechanism of aqueous solutions of amphiphilic triblock copolymers containing short hydrophilic PEO end blocks is suggested.

Experimental

The PEO-PLGA-PEO (750-3.5K-750) triblock copolymer was synthesized by ring opening polymerization in our laboratory and the molecular characteristics were summarized in Table 1. Tube inversion method and

turbidity measurement were employed to construct for phase diagram of PEO-PLGA-PEO aqueous solution and dynamic light scattering (BI-9000AT) equipped with a digital autocorrelator and a light source of He-Ne laser with λ = 632.8 nm was used to investigate the size distribution. Rheometer (RMS-800) in a coni-cylinder geometry (cup diameter, 52 mm; bob diameter, 50 mm; bottom gap length, 20 mm; gap size, 0.2 mm) was used to measure the moduli of solutions as a function of temperature. Small strain was applied (2.7 %) to ensure linear viscoelasticity and frequency was 0.5 rad/s. Small angle X-ray scattering (Synchrotron SAXS, PALS) was also used to investigate the change of structure upon increase in temperature.

Results and Discussion

Phase diagrams of aqueous Pluronic P103 and PEO-PLGA-PEO (750-3.5K-750) solutions are represented in Figs. 1(a) and (b). The Pluronic P103 undergoes two different sol-to-gel transitions at two different temperature regions while PEO-PLGA-PEO (750-3.5K-750) shows only soft gel states at higher temperature. Turbidity depending only on temperature not on concentration is observed and as a result, the temperature range of the turbidity change can be classified into four distinct regions as indicated in figure. The first gel state of Pluronic P103 turns out to be the hexagonal microphase while the second gel state showing turbidity change with four distinct regions is somewhat disrupted as shown in Fig 2. Moreover, the second gel is not thermoreversible as evidenced by rheology (Fig 3). For PEO-PLGA-PEO (750-3.5K-750) triblock copolymer, the correlation function as confirmed by DLS shows quite slow decay, which dominates the correlation function, at the temperature of maximum turbidity (Table 2). In rheological measurements, the local maximum in the G' is observed at the temperature of maximum turbidity, however, the G' values do not change abruptly at the sol-to-soft gel boundary as shown in Fig 4(a). We further found that $G'' > G'$ and G' is highly dependent on the frequency at the soft gel state implying viscoelastic characteristics, which is quite different from general concepts of gels (Fig 4(b)). Unlike Pluronic F127, the micelles of PEO-PLGA-PEO (750-3.5K-750) in aqueous solution can not pack through the entanglement of the PEO corona chains because of the small molecular weight of PEO chains much below the entanglement molecular weight (Me) of about 1,600.[8] It is believed that the extensive aggregation of the copolymer due to the macroscopic liquid-liquid phase separation causes the turbidity. With increasing the temperature of the copolymer solution, the aggregation of micelles is triggered by the hydrophobic attraction and then the formation of cluster is dominant up to the maximum in turbidity. In the regions III and IV the micelle clusters are in more separated from water because PEO chains are no longer in favor of water over a certain temperature range and chains eventually collapsed from water upon further increase in temperature.

References

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Table 1. Characteristics of the triblock copolymer used in present study

Triblock copolymers used	^{1}H-NMR		GPC		
	M_n	DLLA/GA (mole ratio)	M_n	M_w	PDI
PEO-PLGA-PEO	750-3,500-750	80/20	5,360	7,200	1.33

Table 2. Hydrodynamic radii of a 24 wt% aqueous solution of PEO-PLGA-PEO (750-3.5K-750) triblock copolymer at different temperatures.

	R_h (fast mode)	R_h (slow mode)
30 ℃	9.5 nm	47.9 nm
45 ℃	24.8 nm	283.1 nm
50 ℃	1,170 nm	> 5 μm

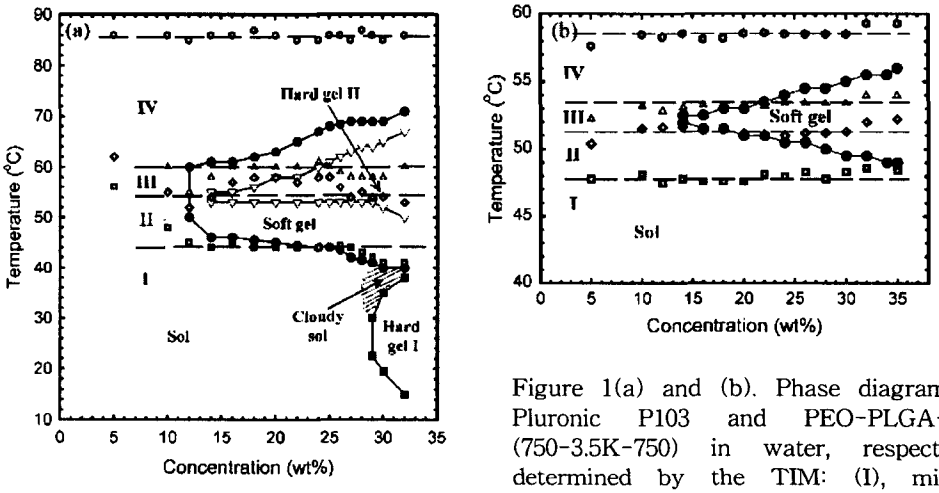

Figure 1(a) and (b). Phase diagrams of Pluronic P103 and PEO-PLGA-PEO (750-3.5K-750) in water, respectively, determined by the TIM: (I), minimal turbidity region; (II), turbidity-increase region; (III), turbidity-decrease region; (IV), constant turbidity region before chain collapse state.

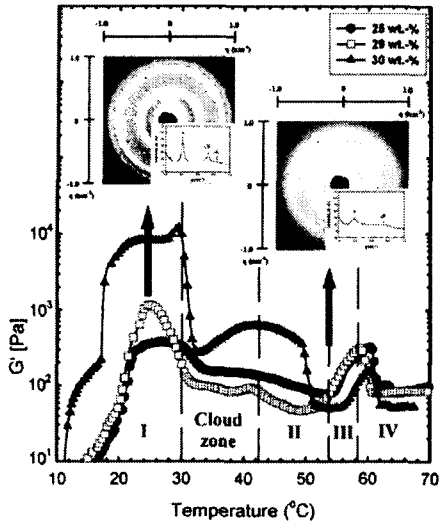

Figure 2. Change of storage modulus (G′) as a function of temperature for aqueous solutions of Pluronic P103 with different concentrations as indicated in the figure. The 2D SAXS patterns and circular averaged 1D SAXS profiles of a 29 wt% aqueous solution of Pluronic P103 at 25 ℃ corresponding to the hard gel I state (left) and at 55 ℃ related to the hard gel II state (right) are also included in the figure. A relative ratio between the positions of first three diffraction peaks of 1: $(3)^{\frac{1}{2}}$: $(4)^{\frac{1}{2}}$ for the scattering profile obtained at 25 ℃ demonstrates the hexagonal microphase.

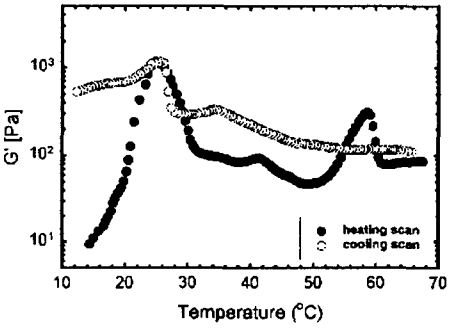

Figure 3. Change of storage modulus (G′) as a function of temperature during heating and cooling scans of a 29 wt% aqueous solution of Pluronic P103. The heating scan is initially performed and followed by the cooling scan.

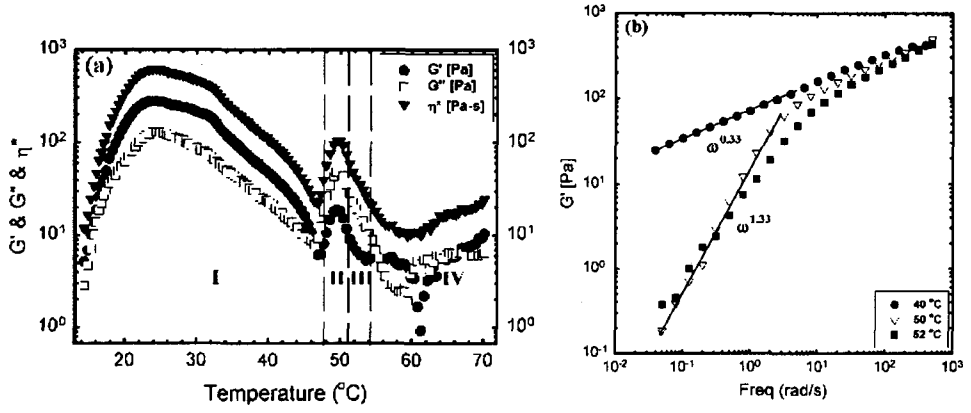

Figure 4.(a) Change of storage modulus (G′), loss modulus (G″), and complex viscosity (η*) as a function of temperature and (b) change of storage modulus (G′) as a function of frequency for a 24 wt% aqueous solution of PEO-PLGA-PEO (750-3.5K-750) triblock copolymer. The temperatures chosen were 40 ℃ (a sol in region I), 50 ℃ (a sol in region II), and 52 ℃ (a soft gel in region III).