Transition Behavior of Hydrogels Consisting of Enantiomeric Block Copolymers of Polylactides (PLLA or PDLA) and Poly(ethylene glycol) (PEG)

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Statement of Purpose: Preformed scaffolds will be impregnated with cells in gel-precursor solutions. The cell suspension will thereby become entrapped in the hydrogel following gelation. In addition, bioactive molecules such as protein-based growth-factors would also be introduced during the gelation. The authors have developed several classes of hydrogels formed by stereo-complexation of enantiomeric block copolymer micelles from polylactides (PLLA or PDLA) and poly(ethylene glycol) (PEG) for use as injectable drug carrier and implantable scaffold for tissue engineering.[1,2] A novel thermo-sensitive formation of hydrogel was demonstrated by mixing micellar solutions of enantiomeric block copolymers. The hydrogels from ABA, BAB, and AB type copolymers indicated different sol-gel mechanisms. The mechanistic study of these novel hydrogels gives a significant benefit toward the clinical use of PLA-PEG hydrogels.

Methods: L-Lactide and D-lactide were supplied by Purac Biochem and Shimadzu Crop., respectively. PEG with a number average molecular weight (*M*n) of 4600 Da and monomethoxy-poly(ethylene glycol) (MePEG) with an *M*n of 2000 Da were purchased from Aldrich. Tin octoate ($SnOct_2$) was purchased from Nacalai Tesque, purified by distillation, and used as a polymerization catalyst. The ordinary ring-opening polymerization of L- or D-lactide initiated with PEG and MePEG gave the ABA and AB block copolymers, respectively, in high yields.[1,2] The BAB triblock copolymers were obtained by the coupling of the AB diblock copolymers with hexamethylene diisocyanate.[3]

Table I. Typical block copolymers

type	*Copolymers*	*PLA block (M_n)*	*PEG block (M_n)*	*total (M_n)*	*PLA/ PEG*
ABA	PLLA-PEG-PLLA	1300	4600	7200	0.56
	PDLA-PEG-PDLA	1100	4600	6800	0.48
BAB	PEG-PLLA-PEG	2000	2000	6000	0.50
	PEG-PDLA-PEG	2000	2000	6000	0.50
AB	PLLA-PEG	1100	2000	3100	0.55
	PDLA-PEG	900	2000	2900	0.45

Table I summarizes a set of copolymers of ABA, BAB, and AB types that have been demonstrated to induce thermo-sensitive gelation when L- and D-copolymers are mixed. These copolymers readily formed the core-shell type amphiphilic micelles in water. The average hydrodynamic diameters of the micelles measured by DLS were in the range of 20-30 nm for 1 wt% solutions of all these copolymers. To obtain sol-to-gel or gel-to-sol transition, micellar solutions were prepared at various concentrations, and both solutions of L- and D-copolymers were mixed together at low temperature (typically at 4°C). Then the temperature increased up to 75 °C to observe the sol-gel behavior.

Results / Discussion: PLLA or PDLA forms a 10/3 helix crystal, while the mixture of them creates stereocomplex, a 3/1 helix crystal which have different chemical and physical properties. The enantiomeric mixture of ABA type copolymers is characterized by an interesting thermo-responsive sol-to-gel transition that is induced around 37°C as increased temperature. The gel formation was successfully monitored, and the responsibility of the stereocomplex formation on the gelation was confirmed by temperature dependent X-ray measurement (Fig 1). For the BAB type copolymers, the hydrogel was formed immediately after the L- and D-solutions are mixed at room temperature. 35wt% concentration of the mixed solution is in gel and sol states at 37 and 75°C, respectively, while the single solution (PEG-PLLA-PEG) remained fluid irrespective of the temperature. This enantiomeric hydrogel returned to gel after cooling to room temperature, that is, showed reversible sol-gel transformation. The X-ray analysis of this gel revealed negligible stereocomplex formation after heating in contrast to ABA hydrogel. The AB type enantio-mixed hydrogel showed similar behavior with BAB, but irreversible gel-to-sol transition.

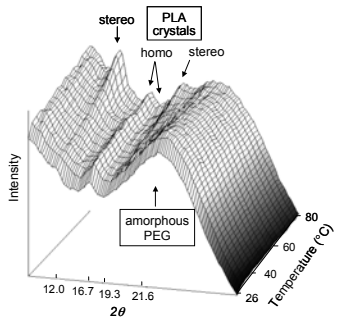

Fig 1. WAXS data of ABA gel.

Conclusions: Hydrogel formation of block copolymers consisting enantiomeric PLA and PEG was demonstrated. The thermally reversible gel-sol transition occurred in the mixed micellar solution of the enantiomeric BAB triblock copolymers. Since the stereocomplexation of the PLLA and PDLA is not responsible for the gelation, coagulation of micelles ought to be induced by the interaction of the PEG chains to which the helix formation of the PLLA and PDLA is transmitted. The PEG helices with opposite helical senses may interdigitate to lead the crosslinking of the system. The hydrogel of the mixed solution from enantiomeric AB copolymers also supported the PEG-crosslinking mechanism.

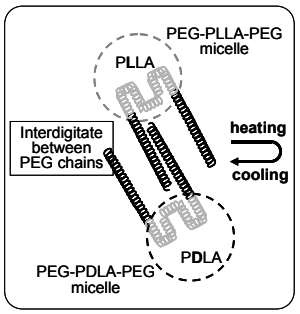

Fig 2. Schematic of BAB gel.

References: (1) Fujiwara, T.; Mukose, T.; Yamaoka, T. et al. *Macromol. Biosci.* **2001**, *1*, 204. (2) Mukose, T.; Fujiwara, T.; Nakano, J. et al. *Macromol. Biosci.* **2004**, *4*, 361. (3) Jeong, B.; Bae, Y. H.; Lee, D. S.; Kim, S. W. *Nature* **1997**, *388*, 860.