New carrier for protein and drug delivery based on injectable Poly(ethylene glycol)-Poly(ε- caprolactone)-Poly(β-amino ester) (PAE-PCL-PEG-PCL-PAE) pH/temperature hydrogel

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ABSTRACTS

We prepared PAE-PCL-PEG-PCL-PAE pentablock copolymers and evaluated their sol-gel transition behaviors. The sol-gel phase transition of aqueous media of the copolymers was mainly affected by the following factors; PEG molecular weight, the PCL/PEG mol ratios and β-amino ester block molecular weight.

Keywords: injectable, biodegradable, pH/temperature-sensitive, hydrogel

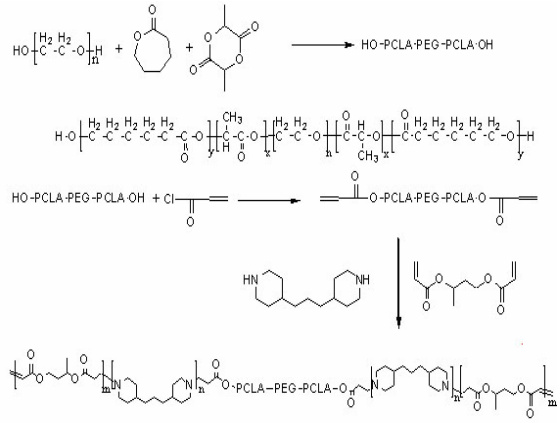
INTRODUCTION

The stimuli-sensitive phenomena of polymer hydrogels, especially the thermo-reversible gels and pH-reversible gels have been developed for polymeric drug carriers, implantation, and other medical devices over the past few years[1-2]. The term of stimuli-sensitive hydrogels is that they can change their structure by themselves to respond to environmental stimuli. Recently, temperature-sensitive hydrogels[3] have been attracted because they can be injected subcutaneously through a needle into animals. But, despite their biodegradability, it is too difficult to be injected into deep position of animals due to the phenomena of clogging ,which is that gelation occurs inside the needle during injection by temperature change due to the body heat transfer. Therefore, we introduced the β-aminoester component(PAE) as a pH sensitive moiety to temperature sensitive block copolymers consisting of Poly(ε-Caprolactone)-Poly(EthyleneGlycol)- Poly(ε -Caprolactone)(PCL-PEG-PCL). The block copolymer synthesized can be responsive to both temperature and pH. As you know, Poly (β-amino ester)(PAE) was known as a pH-responsive and biodegradable polymer[4-6]. In this paper, we used PAE as a pH-sensitive block to design pH/temperature-sensitive pentablock copolymers. And then, the sol-gel transition behaviors of aqueous solutions of pentablock copolymers were investigated. The factors which can control the shift of the sol-gel transition phase diagram of aqueous solution of pentablock copolymers also were investigated.

EXPERIMENTAL

PCL-PEG-PCL triblock copolymers are synthesized by ring opening polymerization from PEG and ε –caprolactone(CL) in the presence of stannous octate as a catalyst. The composition and molecular weight of triblock copolymer to control the balance of hydrophobic/ hydrophilic of PEG/PCL was adjusted by the feed ratios of PEG and CL. And then, the triblock copolymer synthesized was acrylated by using acryloyl chloride and then pentablock copolymer(PAE-PCL-PEG-PCL-PAE) is synthesized by additional polymerization from acrylated triblock copolymer, 1,4-butandiol diacrylate(BDA), and 4,4-trimethylene dipiperadine(TMDP). The chain length of pH-sensitive block of poly (β-amino ester) was controlled by the amount of BDA and TMDP. And the molecular structure and composition of triblock, pantablock copolymers

were characterized by ^{1}H-NMR. And the number-average molecular weight (M_n) and molecular distribution (MWD) of these block copolymers were determined by gel permeation chromatography. The detailed synthesis process for triblock copolymer(PCL-PEG-PCL), acrylated triblock copolymer, pentablock copolymer (PAE-PCL-PEG-PCL-PAE) was described at Scheme.1 And then the synthesized block copolymers were dissolved at a given concentration in buffer solution. The sol-gel transition at each temperature was determined by investing the vial horizontally after keeping for 10 min at a constant temperature as described in our previous paper[7-8]



Scheme.1 The synthesis of pentablock copolymers

RESULT AND DISCUSSION

The various PCL-PEG-PCL triblock copolymers were obtained from the ring opening polymerization. The molecular structure, Mn of the triblock copolymers synthesized and the average number of acrylate groups in the end of acrylated PCL-PEG-PCL block copolymer obtained from the acrylation reaction can be calculated by the ^{1}H-NMR spectrum with the known PEG molecular weight(Figure.1). We also checked the structure of the pentablock copolymer synthesized using ^{1}H-NMR spectroscopy.(Figure.2)

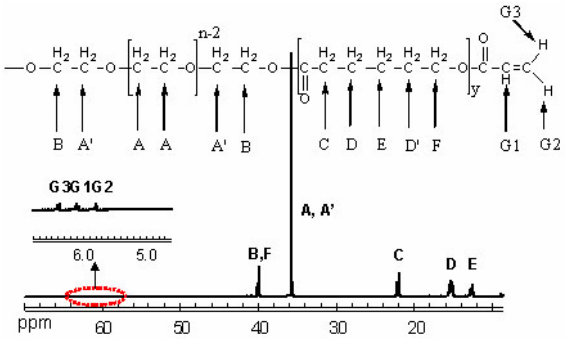


Figure 1. ^{1}H-NMR spectroscopy of the acrylated triblock copolymer

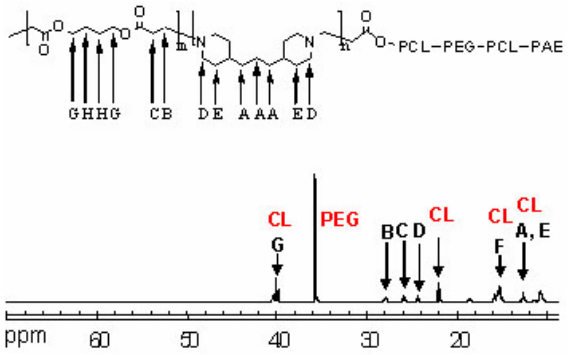


Figure 2. ^{1}H-NMR spectroscopy of pentablock copolymers (PAE-PCL-PEG-PCL-PAE)

Moreover, as can be seen in Figure. 3, the GPC curves of PCL-PEG-PCL and PAE-PCL-PEG-PCL-PAE show unimodal peaks with a narrow molecular weight distribution of M_w/M_n. Therefore, we can conclude that these block copolymers were successfully synthesized.

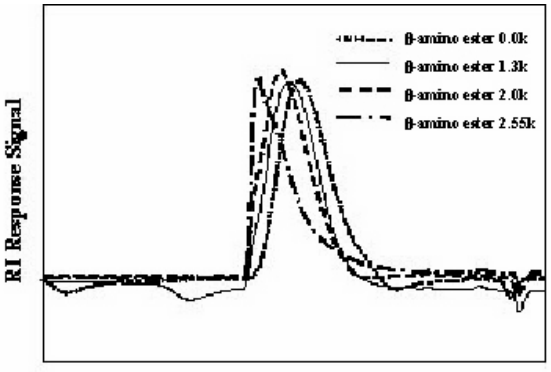


Figure 3. GPC trace of various length of poly (β-amino ester)s

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Fig. 4 shows the phase diagrams of PAE-PCL-PEG-PCL-PAE pentablock copolymer with various PEG molecular weights; a) at pH 7.4 and b) at concentration 20 wt% of pentablock copolymer in aqueous solution and Fig. 5 shows the phase diagrams of PAE-PCL-PEG-PCL-PAE pentablock copolymer with various hydrophobic/hydrophilic chain length and concentration at pH 7.4 and various hydrophobic/hydrophilic chain length and pH at concentration 20 wt%.

The results of the Fig. 4.a and 5.a indicate that the concentration of copolymers also influences directly on critical gel concentration(CGC), critical gel pH(CGpH) and critical gel temperature(CGT). When the concentration increased, micelles density in aqueous solution is increased up as a proportional rule. And the interlocking density between micelles increased. As a result that the CGC is decreased, the CGpH is increased and the range of CGT is increased. In conclusion, the gel phase areas in the phase diagrams of PAE-PCL-PEG-PCL-PAE pentablock copolymer can be controlled with the hydrophobic/hydrophilic chain length ratios and the concentration of the solution in water as variable. The Figure 4.b and 5.b showed that, following the increasing of pH, the lower CGT decreased and the range between lower and upper CGT increased. As pH increased up, ionization of amino groups increased. More ionic binding connections between micelles produce matrix in the copolymer aqueous solution, including sol to gel phase transition at lower CGT and gel to sol transition at higher CGT. As a result that the lower CGT is decrease and the upper CGT is increase.

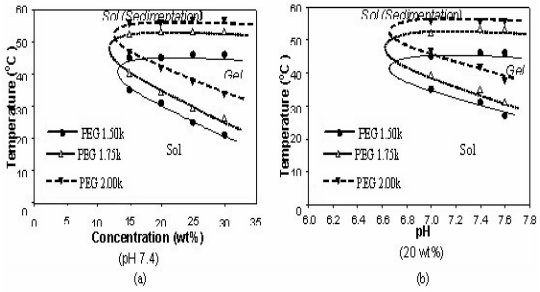

Figure 4. Phase diagrams of poly (PAE-PCL-PEG-PCL-PAE)s at β-aminoester 1.3k, PCL/PEG=2.0/1 with various PEG molecular weight, a) at pH 7.4; b) at concentration 20wt%.

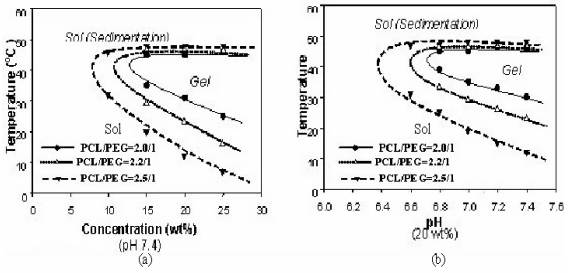

Figure 5. Phase diagrams of poly (PAE-PCL-PEG-PCL-PAE)s at PEG 1.5k, β-aminoester 1.3k with various hydrophobic/hydrophilic (PCL/PEG) ratios. a) at pH 7.4; b) at concentration 20wt%.

Fig. 6 shows the phase diagrams of PAE-PCL-PEG-PCL-PAE pentablock copolymer with various pH-sensitive chain length and pH at concentration 20 wt%. When the chain length of the pH-sensitive block is increased, amino group density is augmentative, ionic interlocking between micelles to form gel as a semi-interpenetrating networks structure increased up[9-10]. As a result, the CGpH in phase diagrams of pentablock copolymer aqueous solution decreased. However, when β-amino ester block length is increased up to 2.0k, ionic density obtained from the ionization of amino groups is very high. The hydrophilicity of the copolymer raise up and the solubility of PAE-PCL-PEG-PCL-PAE pentablock copolymer in polar solvent increased. As a result, the copolymer could be dissolved in PBS buffer easily at low temperature, and the pentablock aqueous solution just change to gel structure when the copolymer become more hydrophobic at higher temperature.

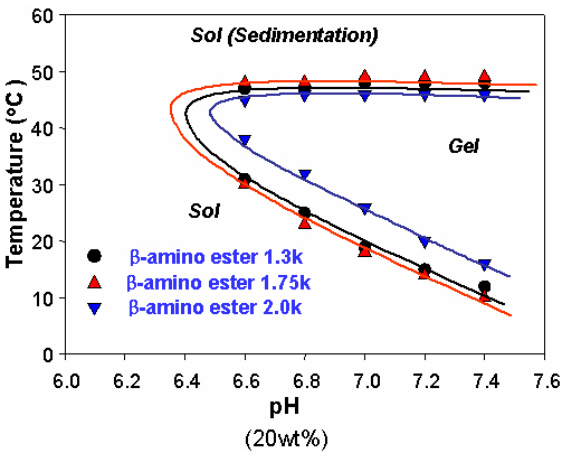

Figure 6. Phase diagrams of poly (PAE-PCL-PEG-PCL-PAE)s at PEG 1.5k, PCL/PEG=2.5/1 with various β-aminoester block length, concentration 20wt%.

CONCLUSION

PAE-PCL-PEG-PCL-PAE pentablock copolymers were synthesized and sol-gel phase transition of aqueous media of the copolymers was investigated. The copolymer aqueous solution in PBS buffer changed from a sol phase to a gel phase with increasing temperature and pH. Through various experiments, the gel phase domain of PAE-PCL-PEG-PCL-PAE pentablock copolymer can be adjusted by the PEG molecular weight, the PCL/PEG mol ratios and β-amino ester block. The result of the experiment demonstrated that the pentablock copolymers can be used as a biomaterial for drug, protein delivery.

ACKNOWLEDGEMENTS

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