Poly(N-isopropylacrylamide-*b*-ε-caprolactone) 과 Poly(ethylene glycol-*b*-ε-caprolactone)를 이용한 온도민감성 나노입자의 응용

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Application of Thermosensitive Nanoparticles using Poly(N-isopropylacrylamide-*b*-ε-caprolactone) and Poly(ethylene glycol-*b*-ε-caprolactone)

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Introduction

Polymeric amphiphiles, containing hydrophilic and hydrophobic components, have been extensively studied in biotechnology and pharmaceutical fields due to their unique properties of micelle or micelle-like self-aggregate formation in aqueous milieu [1]. Among various hydrophilic and hydrophobic segments, hydrophilic polymers of PNIPAAm and PEG, and hydrophobic PCL have unique characteristics such as thermosensitivity, biocompatibility, and biodegradation. PNIPAAm is a well-known water-soluble thermosensitive polymer showing reversible hydrated extended coil to globule transition by increasing temperature over the lower critical solution temperature (LCST)[2]. PEG, another hydrophilic block, has been frequently employed for preparation of polymeric amphiphiles due to its unique biocompatibility and solubility. PCL, as the hydrophobic segment, is well known biodegradable hydrophobic polymer [3]. In this study, the well-defined PNIPAAm-PCL and PEG-PCL block copolymers were synthesized by ring-opening polymerization of ε-caprolactone using mPEG-OH and PNIPAAm-OH, prepared by telomerization of NIPAAm, as initiators. Thermosensitive nanaparticles according to various ratios of PNIPAAm-PCL and PEG-PCL were prepared by a dialysis method. And then, we investigated physicochemical properties of the formed thermosensitive nanoparticles by ^{1}H NMR, DSC, DLS and fluorescence spectroscopy.

Experimental method

Materials

N-isopropylacrylamide (NIPAAm, Aldrich) was purified by recrystallization from n-hexane. The ε-caprolactone (Fluka) was dried over calcium hydride for 48hr at room temperature and distilled under reduced pressure. Metoxy PEG (mPEG) with molecular weight of 2000 was purchased from Sigma-Aldrich co. and purified by recrystallization on dichloromethane/diethyl ether system. 2-mercaptoethanol (ME, Aldrich) was used without further purification. 2,2-azoisobutyronitrile (AIBN, WAKO) was purified by precipitation into ice water from an acetone solution and dried under vacuum.

Synthesis and characterization of PNIPAAm-OH, PNIPAAm-PCL and PEG-PCL diblock copolymer

The PNIPAAm-OH was synthesized in methanol by temomerization of NIPAAm using ME as a chain transfer agent. PNIPAAm-PCL and PEG-PCL diblock copolymer were synthesized by ring opening polymerization of ε-caprolactone mPEG-OH and PNIPAAm-OH as initiators with trace amount of stannous octate (SnOct) as a catalyst. The polymerization was performed at 140℃ for 24h in xylene. After reaction, the copolymers were dissolved in dichloromethane and precipitated in an excess amount of diethyl ether and dried *in vacuo* for 48h. The synthesis of PNIPAAm-PCL and PEG-PCL diblock copolymers were confirmed by ^{1}H-NMR and GPC.

Preparation and characterization of thermosensitive nanoparticles

Thermosensitive nanaparticles according to various ratios of PNIPAAm-PCL and PEG-PCL were prepared by a solvent evaporation method. The particle sizes and size distribution, morphology of nanoparticles, aggregation behavior in aqueous environment, and microscopic physicochemical properties of the aggregates were investigated by DLS, AFM, ^{1}H NMR, and fluorescence spectroscopy, respectively.

Result and discussion

The ^{1}H NMR spectra and shifted chromatogram to higher MW range obtained by GPC of the copolymers clearly reveled that the block copolymers were successfully synthesized (Table 1).

Table1. Characterizations of the block copolymers

Samples	HPL MW	PCL Mw[a)]	PCL wt %	Mn[a)]	Mn[b)]	PDI[b)]
mPEG	2K	-	-	2000	1690	1.20
PEG-PCL	PEG, 2K	1900	48.8	3900	4840	1.37
PNP-OH	11K	-	-	11000	11400	2.10
PNP-PCL	PNP, 11K	1700	13.4	12700	15200	1.99

[a)] Calculated from 1H-NMR data
[b)] Measurement of GPC

The formed self-aggregates, with different compositions, showed different physicochemical properties such as particle size, LCST . The thermosensitive properties were critically affected by compositions of PNIPAAm block (Fig. 1 and Table 2). The introduction of PNIPAAm-PCL into the self-aggregates endowed the unique characters, originated from thermosensitive PNIPAAm block, such as LCST, decrease of particle size by increasing temperature, and micropolarity changes. The results of aggregation behavior and microscopic characterization of the aggregates were listed in Table 1. The particle size and CAC decreased with increment of PEG-PCL component due to increased PCL content and reduced bulky PNIPAAm block (Fig. 2). The obtained aggregation numbers of PCL blocks in a hydrophobic microdomain, measured by fluorescence quenching method, were in the range of 7 ~ 14 with increasing the values by increasing PEG-PCL content. The results revealed that M1, containing bulky hydrophilic block, required relatively smaller number of PCL block to form a hydrophobic microdomain than M5.

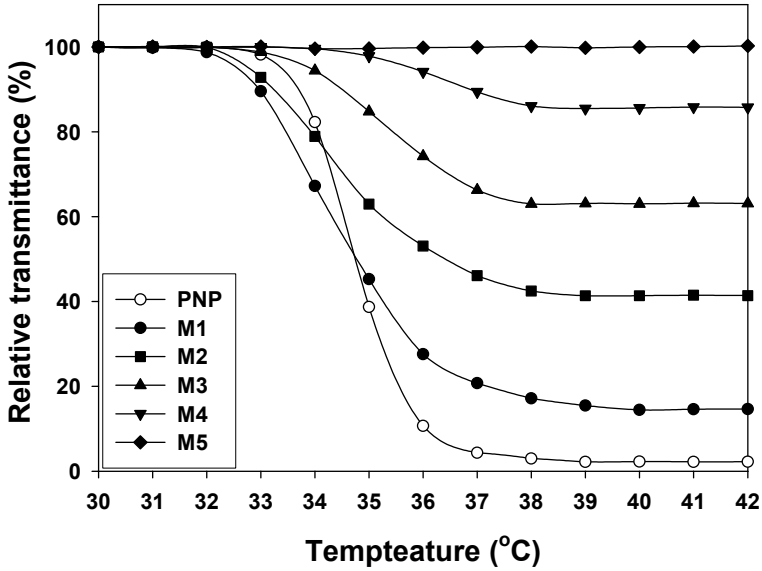

Fig. 1. Temperature sensitivities of PNIPAAm and mixed micelles

Table 2. Characterizations of the thermosensitive nanoparticles

	PEG/PCL (Wt%)	LCST (°C)	D (nm)	CAC (mg/mL)	K_v ($\times 10^{-5}$)	N_{PCL}
M1	0	34.5	259	5.33	5.00	7.84
M2	25	34.6	231	3.02	5.14	8.07
M3	50	35.3	230	2.71	5.38	8.46
M4	75	36.1	204	2.10	5.94	10.55
M5	100	-	191	1.43	6.60	13.99

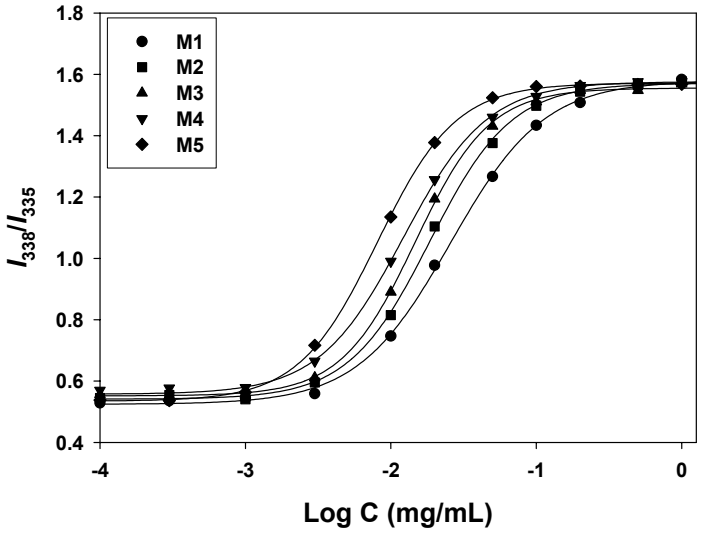

Fig. 2. CAC of PNIPAAm and mixed micelles

Conclusion

The present study demonstrated synthesis and self-aggregation behavior of the mixed micelles of PNIPAAm-PCL and PEG-PCL diblock copolymers in an aqueous environment. With introduction of various technical procedures such as ^{1}H-NMR, DSC, GPC, DLS, and fluorescence spectroscopy, the physicochemical characteristics of thermosensitive nanaparticles according to various ratios of PNIPAAm-PCL and PEG-PCL were closely related to the hydrophobic/hydrophilic balance and PNIPAAm content. Based on these results, the thermosensitive self-aggregates may be a potential candidate for biomedical and pharmaceutical applications such as drug delivery and imaging.

References

1. Kataoka K. et al. *ADDR* 2001, 47, 113
2. Feil H. et al. *Macromolecules* 1993, 26, 2496
3. Savic R. et al. *Science* 2003, 300, 615