

## 온도민감성 블록 공중합체의 합성과 물리화학적 특성

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### Synthesis of Thermosensitive Block Copolymers and Theirs Physicochemical Properties

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#### Introduction

Many types of drug carriers have been investigated and demonstrate some potential for targeted drug delivery[1]. Polymeric micelles have some interesting characters as described below. AB-type block copolymers having both hydrophilic and hydrophobic segments are known to form micellar structures in aqueous media due to their amphiphilic character. Highly hydrated outer shells of polymeric micelles can inhibit intermicellar aggregation of hydrophobic inner cores. Consequently, polymeric micelles maintain their satisfactory aqueous stability irrespective of the high content of hydrophobic drug bound within the micelle inner core[2].

Poly(N-isopropylacrylamide)(PNIPAAm) is a well-known water-soluble polymer showing reversible hydration-dehydration changes in response to small solution temperature changes. A temperature showing hydration-dehydration changes is called the lower critical solution temperature (LCST). The LCST of PNIPAAm in water is known to be 32°C. Poly( $\epsilon$ -caprolactone) (PCL), as the hydrophobic segment, has been well known as a biodegradable polymer, so we predict that polymeric micelles will dissociate into block copolymers when the hydrophobic segments are degraded[3,4].

In this study, the well-defined PNIPAAm/PCL diblock copolymers were synthesized through combining radical polymerization of N-isopropylacrylamide and the ring-opening polymerization of  $\epsilon$ -caprolactone. Polymeric micelles composed of PCL as a hydrophobic core and PNIPAAm as a hydrophilic shell were prepared by a diafiltration method.

#### Experimental method

N-isopropylacrylamide(NIPAAm)(Aldrich) was purified by recrystallization from n-hexane.  $\epsilon$ -caprolactone(Fluka) was dried over calcium hydride for 48h at room

temperature and distilled under reduced pressure. 2-mercaptoethanol(ME)(Aldrich) was used further purification. 2,2-azoisobutyronitrile(AIBN)(WAKO) was purified by precipitation into ice water from an acetone solution and dried under vacuum. The dialysis tubes(Spectrum) were used for micelle preparation.

#### ***Synthesis of hydroxy-terminated PNIPAAm(PNIPAAm-OH)***

The PNIPAAm-OH was synthesized in bulk or in methanol solution by the radical polymerization of NIPAAm monomer using ME as a chain transfer agent. NIPAAm, ME, and AIBN as a initiator were dissolved in methanol. The ratios of NIPAAm/ME are shown in **Table 1**. Polymerization was carried out at 70°C for 24h. The polymer dialyzed against methanol for 3h and then distilled water exchange at intervals of 30min during 24h. The resultant solution was freeze-dried.

#### ***Synthesis of PNIPAAm/PCL diblock copolymer***

PNIPAAm/PCL diblock copolymers were obtained by ring-opening polymerization of  $\epsilon$ -caprolactone using terminal hydroxyl group of the PNIPAAm with Sn(II)Oct as a catalyst. Polymerization proceeded at 130°C for 24h. The copolymer products were dissolved in dichloromethane and precipitated in an excess of diethyl ether and then dried in vacuum. Chemical ratios of PNIPAAm/PCL copolymer is shown **Table 1**.

Table 1. Characterization of PNP/PCL diblock copolymers

	molecular weight	Mol % of PNP	Mol % of PCL
PN30	5520 <sup>a</sup>	100	0
PNC3066	11477 <sup>b</sup>	48	52
PNC3088	21629 <sup>b</sup>	26	74
PN40	7000 <sup>a</sup>	100	0
PNC4066	13083 <sup>b</sup>	54	46
PNC4088	14350 <sup>b</sup>	49	51
PN50	11790 <sup>a</sup>	100	0
PNC5066	20048 <sup>b</sup>	59	41
PNC5088	25053 <sup>b</sup>	47	53

<sup>a</sup> Measured from GPC analysis

<sup>b</sup> Calculated from <sup>1</sup>H-NMR spectra in CDCl<sub>3</sub>

#### ***Characterization of PNIPAAm/PCL diblock copolymer***

Molecular characterization of PNIPAAm/PCL diblock copolymers was confirmed through <sup>1</sup>H-NMR spectrophotometer, FT-IR spectrophotometer, differential scanning calorimeter(DSC) and gel permeation chromatograph analysis(GPC).

#### ***Preparation and characterization of PNIPAAm/PCL polymeric micelles***

Polymeric micelles composed of PCL as a hydrophobic core and PNIPAAm as a hydrophilic shell were prepared by a diafiltration method. The sizes and shapes of the thermosensitive micelles were investigated with a atomic-force microscope(AFM).

Fluorescence spectra for CMC of PNIPAAm/PCL diblock copolymer were recorded with a spectrofluorimeter.

### **Result and discussion**

**Table 1** shows a series of PNIPAAm/PCL diblock copolymers prepared. The molecular weight of the corresponding PNIPAAm-OH was fixed at 5520, 7000, and 11790 g/mol, while the PCL segments were controlled through adjusting molar ratio of CL monomer to PNIPAAm-OH. The block copolymers were characterized by GPC and their composition determined by  $^1\text{H-NMR}$  from the signal intensities of the PNIPAAm methyl group ( $\delta=1.1$  ppm) and the PCL methylene ester group ( $\delta=4.06$  ppm).

From the results FT-IR, PCL was found to exhibit characteristic absorptions at  $1720\text{ cm}^{-1}$  which were attributed to the C=O stretching band. In particular, absorption of C=O stretching band at  $1720\text{ cm}^{-1}$  apparently increased as length of PCL chain increased.

DSC was used to analyze thermal characteristics of PNIPAAm/PCL diblock copolymers. **Table 2** shows thermal properices of PNIPAAm/PCL diblock copolymers. The mobility of PCL chains in PNIPAAm/PCL diblock copolymers was suppressed by the bulky PNIPAAm chains, which leads to the decrease in  $T_m$  of PCL blocks. The LCST of PNIPAAm/PCL diblock copolymers might be dpected to be lower than  $32^\circ\text{C}$  because of the presence of hydrophobic PCL chain in place of formerly hydrophilic terminal hydroxyl group.

Table 2. Thermal properties of PNP/PCL diblock copolymers

	Mol % of PCL	$T_m(^{\circ}\text{C})^a$	LCST( $^{\circ}\text{C})^b$	$T_m(^{\circ}\text{C})^b$
PN30	0	-	31.16	-
PNC3066	52	55.88	30.10	52.97
PNC3088	74	57.58	30.64	54.80
PN40	0	-	30.26	-
PNC4066	46	53.10	29.01	49.09
PNC4088	51	54.26	29.79	52.35
PN50	0	-	29.50	-
PNC5066	41	55.34	29.00	52.02
PNC5088	53	56.37	29.40	54.01

a Measured solid samples by micro-DSC

b Measured samples in PBS7.4 by micro-DSC

The AFM image clearly indicated the presence of spherical particles with nanoscopic dimensions. As shown in **table 3**, the average sizes ranged from 100 to 280nm. The

sizes increased with increasing the length of PCL segments. The suggested that aggregation numbers of PNIPAAm/PCL diblock copolymer in micelles increased through more strong hydrophobic interactions as the hydrophobic/hydrophilic increased. The CMC decreased with increasing the length of PCL segments.

Table 3. Characterization of PNP/PCL polymeric micelles

	Mol % of PCL	micelle size (nm)	CMC(mg/L)
PNC3066	52	100~160	5.623
PNC3088	74	130~200	3.981
PNC4066	46	150~220	8.318
PNC4088	51	180~240	6.6761
PNC5066	41	190~230	7.586
PNC5088	53	220~280	4.266

### Conclusion

The PNIPAAm/PCL diblock copolymers were synthesized through combining the radical polymerization of NIPAAm and ring-opening polymerization of CL. The well-defined PNIPAAm/PCL diblock copolymers were confirmed through <sup>1</sup>H-NMR, FT-IR, and GPC analysis. The thermal properties and crystallinity of the PNIPAAm/PCL diblock copolymers depended on the composition of two blocks. From the results AFM, the sizes of the micelles from 100 to 280nm and shapes were spherical. The CMC decreased with increasing the length of PCL segments.

### References

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