Thermosensitive Copolymers of *N*-(2-Hydroxypropyl)methacrylamide and Alkyl Methacrylates

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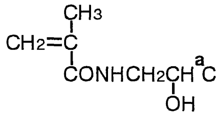
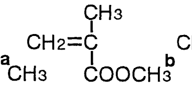
The aqueous solution of copolymers of *N*-(2-hydroxypropyl)methacrylamide (HPMA) and alkyl methacrylate (RMA, alkyl : methyl or butyl) with molar ratio of RMA more than 0.08 was found to exhibit the LCST though no phase transition occurred for the case of the homopolymer of HPMA.

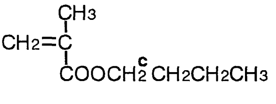
A kind of aqueous polymer solutions such as poly(ethylene oxide)[1] and poly(*N*-isopropylacrylamide)[2] exhibit phase separation at elevated temperature which is called the lower critical solution temperature (LCST). Considerable attention has been paid towards thermosensitive hydrogel showing a reversible swelling change in response to temperature. Particularly, crosslinked copolymers containing *N*-isopropylacrylamide have a potential in the design of drug delivery systems (DDS).[3-6] On the other hand, Kopeček et al. have been concentrated on poly[*N*-(2-hydroxypropyl)methacrylamide] [poly(HPMA)] for possible application in biomedical field, for instanse, the copolymer of HPMA being used for infusion solution,[7] DDS[8] and protein carrier.[9-11] In the course of our study on biomedical materials with a hydrogel structure,[12-13] we found the phase separation of aqueous solution of copolymers containing the HPMA moiety in response to change in temperature.


$CH_2=C(CH_3)-CONHCH_2\overset{a}{C}H(OH)CH_3$

HPMA


$CH_2=C(CH_3)-COOCH_3^{\,b}$

MMA


$CH_2=C(CH_3)-COO\overset{c}{C}H_2CH_2CH_2CH_3$

BMA

HPMA was prepared according to the method of Strohalm and Kopeček.[14] A series of copolymer as written by poly(HPMA-co-RMA)I-VII (R = methyl and butyl) were obtained by radical copolymerization of HPMA with methyl methacrylate (MMA) or butyl methacrylate (BMA) initiated with 2,2'-azobisisobutyronitrile (AIBN) as an initiator in ethanol, by changing the molar ratio of RMA from 0 to 0.38. The results are summarized in Table 1. The molar ratio of RMA in poly(HPMA-co-RMA) was determined by ^{1}H-NMR spectroscopy, measuring the areas at 3.67 ppm, 3.51 ppm, and 3.86 ppm assigned to H^a in HPMA, H^b in MMA, and H^c in BMA, respectively. The transmittance of aqueous poly(HPMA-co-RMA) solution (C = 1 gdL^{-1}, pH 5.55 or C = 0.5 gdL^{-1}) was measured for each 2 ℃ rise in temperature from 10 to 70 ℃ by spectrophotometry, measuring the absorption at 600 nm with a Shimadzu UV-160A, as shown in Figures 1, 2. The aqueous solution of the poly(HPMA-co-RMA) with molar ratio of RMA more than 0.08 exhibits remarkable phase change in response to the change of temperature within 10 ℃ and 70 ℃. The poly(HPMA-co-MMA)IV shows, for instance, transparency at below 34 ℃ and it sharply turns opaque when the temperature is raised to 38 ℃. On the other hand, no phase transition occurred for poly(HPMA) and poly(HPMA-co-RMA) with molar ratio of RMA less than 0.05. The introduction of hydrophobic monomer (hydrophobicity : BMA > MMA) and an increase in the molar ratio of the RMA moiety in poly(HPMA-co-RMA) result in a lowering the phase transition temperature (LCST) as shown in

Table 1. Results of copolymerization of HPMA and RMA[a]

poly(HPMA-co-RMA)	RMA	Yield	$[\eta]^b$	Molar ratio c) in copolymer		LCST
	mmol	%	dLg^{-1}	HPMA	: RMA	℃
poly(HPMA)	—	77.89	0.33	1.00	0.00	—
poly(HPMA-co-MMA) I	1.05	89.96	0.34	0.95	0.05	—
poly(HPMA-co-MMA) II	2.10	91.12	0.35	0.92	0.08	54
poly(HPMA-co-MMA) III	4.20	89.85	0.37	0.86	0.14	50
poly(HPMA-co-MMA) IV	6.29	89.39	0.41	0.79	0.21	34
poly(HPMA-co-MMA) V	8.40	81.03	0.39	0.71	0.29	24
poly(HPMA-co-MMA) VI	10.50	91.88	0.50	0.69	0.31	20
poly(HPMA-co-MMA) VII	12.60	93.39	0.46	0.64	0.36	19
poly(HPMA-co-BMA) I	1.05	90.12	0.37	0.96	0.04	—
poly(HPMA-co-BMA) II	2.10	90.24	0.56	0.91	0.09	48
poly(HPMA-co-BMA) III	4.20	89.89	0.58	0.84	0.16	28
poly(HPMA-co-BMA) IV	6.29	63.37	0.62	0.74	0.26	26

[a] Reaction condition : HPMA, 20.95 mmol ; AIBN, 0.2 mmol ; ethanol, 10 mL ; 60 ℃, 8 h.
[b] Measured at 1.0 g dL^{-1}in ethanol at 25 ℃.
[c] Calculated from ^{1}H-NMR spectroscopy with a Jeol EX-400.

Figure 3. Consequently, it can be said that an appropriate hydrophobic-hydrophilic balance of the copolymer is considered an important factor in controlling LCST.[6] A series of poly(HPMA-co-RMA) were thus found to be thermosensitive copolymers ; they form a hydrated and extended conformation at low temperature and form extensively dehydrated and compact chain conformation at high temperature.[3,5,6] These copolymers are expected as a novel thermosensitive carrier which can be controlled on - off switches for drug release.

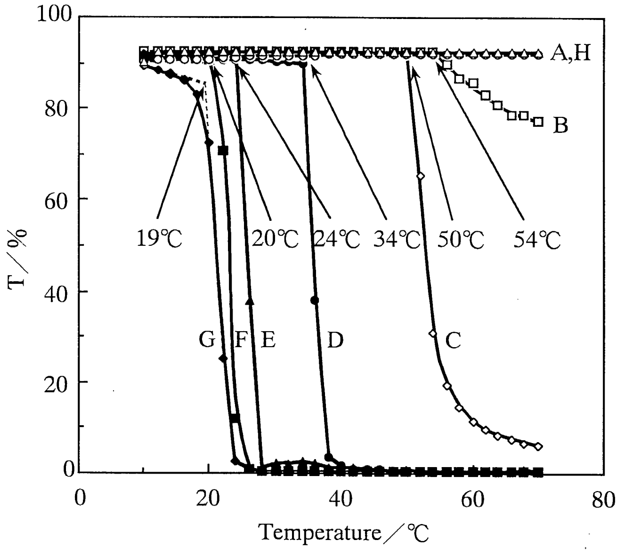


Figure 1. Effect of temperature on the transmittance (T) of aqueous poly(HPMA-co-MMA) solution. A, B, C, D, E, F, and H are 1.0 gdL^{-1}of aqueous poly(HPMA-co-MMA)I, poly-(HPMA-co-MMA)II, poly(HPMA-co-MMA)III, poly(HPMA-co-MMA)IV, poly(HPMA-co-MMA)V, poly(HPMA-co-MMA)VI, and poly(HPMA) solution, respectively. G is 0.62 gdL^{-1} of aqueous poly(HPMA-co-MMA)VII solution, respectively.

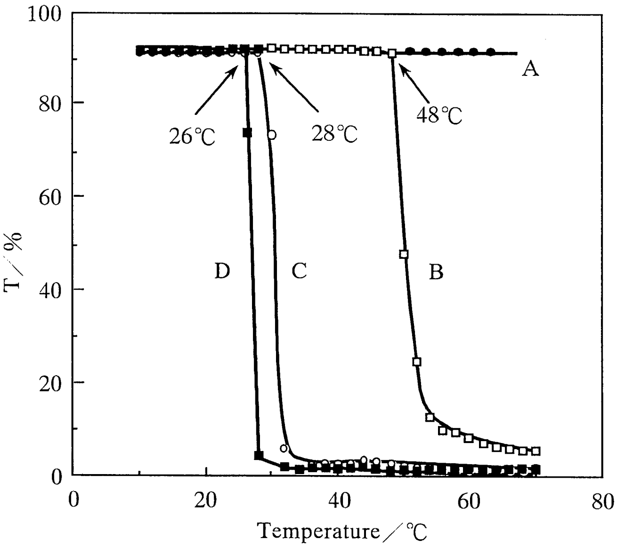


Figure 2. Effect of temperature on the transmittance (T) of aqueous poly(HPMA-co-BMA) solution. A, B, and C are 0.5 gdL^{-1}of aqueous poly(HPMA-co-BMA)I, poly(HPMA-co-BMA)II, and poly(HPMA- co-BMA)III, respectively. D is 0.15 gdL^{-1}of aqueous poly(HPMA-co-BMA)IV solution.

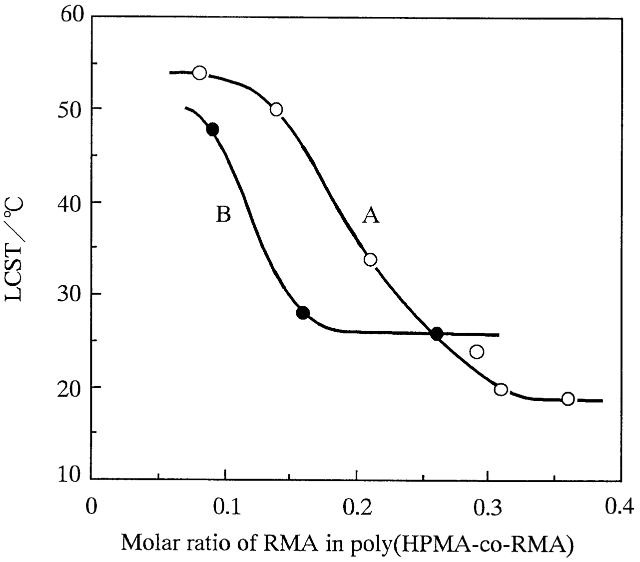


Figure 3. Effect of molar ratio of RMA on the LCST of poly -(HPMA-co-RMA). A and B are poly(HPMA-co-MMA) and poly(HPMA-co-BMA), respectively.

References and Notes

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14 J. Strohalm and J. Kopeček, *Angew. Makromol. Chem.*, **70**, 109 (1978) : HPMA, mp 67～68 ℃. Found : C, 58.37 % ; H, 9.03 % ; N, 9.58 %. Calcd for $C_7H_{13}NO_2$ = 143.186 : C, 58.72 % ; H, 9.15 % ; N, 9.78%.