Colloid Polym Sci (2009) 287:627–643
DOI 10.1007/s00396-009-2028-x

INVITED REVIEW

Thermoresponsive copolymers: from fundamental studies to applications

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Received: 9 February 2009 / Revised: 17 March 2009 / Accepted: 27 March 2009 / Published online: 18 April 2009

Abstract Thermoresponsive copolymers have attracted considerable interest in both the polymer and biomaterial literature. They show interesting fundamental behaviour (thermally triggered contraction and aggregation) as well as potentially useful properties (reversible gelation). Biocompatible thermoresponsive copolymers are being developed for application in drug delivery and regenerative medicine. This review focuses on the fundamental aspects of thermally triggered conformational changes with an emphasis on copolymer design. Also, the ability to use these copolymers to produce thermoresponsive colloidal dispersions is discussed. Recent examples from within our group and elsewhere are considered in order to illustrate structure–property relationships. The review focuses on copolymers involving *N*-isopropylacrylamide. However, non-acrylamide thermoresponsive copolymers are also considered in detail. Emerging areas that appear likely to be actively pursued in the future are also discussed.

Keywords Thermoresponsive copolymer · NIPAm · LCST · Thermogelation

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Thermoresponsive homopolymers: a brief review

Thermoresponsive homopolymers show major changes in conformation in response to modest temperature changes. Two general types of behaviours occur. Polymers that become miscible with the solvent as the temperature increases exhibit upper critical solution temperatures [1, 2]. Those that become insoluble with temperature increase exhibit lower critical solution temperature (LCST) behaviour and are the subject of this review. The LCST is manifested in a coil-to-globule transition. The LCST is specific to both the polymer and the solvent. In this review, we focus on thermoresponsive polymers in aqueous solutions. Thermoresponsive homopolymers have attracted much research interest because of their potential applications, which include rheological control additives, thermal affinity separation [3–5], controlled drug release [3, 6] and gene therapy [7–9]. Most of the polymers that are being developed for these applications are copolymers, although responsive microgel particles have also attracted considerable interest [10–12]. The aim of this article is to review recent work concerning thermoresponsive copolymers and illustrate the underlying structure–property relationships with a view to facilitating improvements in their design.

Thermoresponsive homopolymers have a repeat unit that contains hydrophilic and hydrophobic moieties. One of the best known examples of a synthetic thermoresponsive polymer is poly(*N*-isopropylacrylamide) (PNIPAm). Its structure is shown in Fig. 1 (**H1(a)**). The repeat unit consists of hydrophilic (amide) and hydrophobic (isopropyl) groups. The LCST for PNIPAm is about 32°C [13, 14]. This is a convenient temperature from the context of biomedical applications because it is below body temperature. At temperatures below the LCST, water is a good solvent, and the polymer chains exist as coils. At temper-

atures above the LCST, the hydrogen bonding of water with the amide groups is disrupted. Attractive inter-segment interactions between the isopropyl groups dominate, and the chains collapse to globules.

The LCST is determined by a balance between attractive segment–water interactions and segment–segment interactions. Structural factors that increase segment–segment attractive interactions decrease the LCST; those that increase attractive segment–water interactions increase the LCST. The LCST for PNIPAm is affected by the nature of substituent groups, molar mass [14, 15], co-solvent [16, 17], salts [14, 18, 19] and surfactants [20]. For example, added NaCl decreases the LCST, while added sodium dodecylsulfate increases it. The relative effectiveness of salts in increasing or decreasing the solubility (and hence LCST) of synthetic polymers and biopolymers in aqueous solution generally follows the Hofmeister series [18]. Ions with a high charge-to-volume ratio (e.g. SO_4^{2-}) compete with the polymer chains for water molecules and effectively dehydrate them, promoting hydrophobic segment–segment interactions [19]. The LCST increases with added surfactant due to the association of surfactant micelles with polymer chain segments which results in increased inter-segment repulsion [21].

The structures of the most widely studied thermoresponsive homopolymers are shown in Fig. 1. Table 1 gives a list of abbreviations for a wide range of thermoresponsive homopolymers and their LCST values. The repeat units shown in Table 1 form the basis for the majority of the copolymers considered later. The repeat units contain amide groups, hydroxyl groups or ether groups which form hydrogen bonds with water.

N-alkyl-substituted polyacrylamides (**H1**, Fig. 1) are an important family of thermoresponsive polymers [15–24]. The *N*-substituted groups determine the LCSTs of the homopolymers. The LCSTs decrease with increasing of number of carbon atoms on the alkyl group or the number of alkyl groups present. When the *N*-alkyl-substituted group is longer than a propyl group, attractive inter-segment interactions (hydrophobic association) between alkyl groups become dominant, and the polymers are insoluble in water at room temperature [22, 23]. The presence of hydroxyl or ether groups on the *N*-substituted group can increase the segment–water interactions (via hydrogen bonding) and, hence, the LCST [25–27]. For example, PHIPAm (**H1(c)**) has an LCST which exceeded the temperatures that could be measured [27].

Alkyl-substituted celluloses (**H5**) are potentially important for biomaterial applications because they are modified natural polymers. They can dissolve in water at reasonably low temperatures because they contain both hydroxyl groups and ether bonds in the repeat unit. The alkyl-substituted celluloses, such as methylcellulose (MC) [28], ethyl(hydroxyethyl)cellulose (EHEC) [28] or hydroxypropylcellulose (HPC) [14], have LCSTs at 50, 65 and 42°C, respectively (Table 1).

Synthetic thermoresponsive polymers that do not contain acrylamide-based repeat units have also attracted considerable interest. Poly(2-dimethylamino)ethyl methacrylate) (PDMA; **H6(a)**) [29], poly(vinyl methyl ether) (PVME; **H4**) [28], Poly(*N*-vinylcaprolactam) (PVCL; **H2**) [15] and poly(proprylene oxide) (PPO; **H3**) [30] are important classes of non-acrylamide-containing thermoresponsive homopolymers. The T_{cp} of PPO is rather broad and smeared-out between 10 and 20°C. The poly(2-alkyl-2-oxazoline)s (**H7**) are structurally comparable to poly(*N*-alkyl acrylamide)s; however, the main chain contains N. They show similar structure–property relationships to the *N*-alkyl-substituted polyacrylamides. For example, their LCSTs decrease with increasing the number of carbon atom of alkyl substitution; poly(2-methyl-2-oxazoline) (PMOZ) has no cloud point [31]; whereas poly(2-ethyl-2-oxazoline) (PEOZ) has a T_{cp} of 62°C, while that of poly(2-isopropyl-2-oxazoline) (PIPOZ) is about 36°C [32]. The relationships between copolymer architecture and LCST for this class of polymers has been considered in detail by Huber et al. [33, 34]

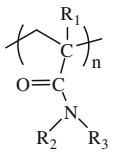
Thermoresponsive copolymers

Thermoresponsive copolymers combine two or more co-monomers where at least one of these would give a thermoresponsive homopolymer. As will be shown below, they enable convenient tuning of the LCST as well as incorporation of additional functionality. For example, they can incorporate charge or biodegradability within a thermoresponsive chain. They can also enable grafting of the copolymers to surfaces and particles. It is through copolymerization that the properties of thermoresponsiveness can be transferred to other systems. A number of copolymer architectures can be prepared (Fig. 2), and these are discussed in turn below.

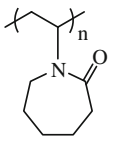
Synthetic methods used for preparation

Among the synthetic methods used to prepare thermoresponsive copolymers, the most popular methods are, in order, conventional free-radical polymerization (FRP), atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer polymerization (RAFT). FRP can also be applied to the preparation of comb copolymers as well as graft copolymers. In the latter case, the "grafting to" approach is used. In this method, preformed side chains are covalently bonded onto the main chain. Although FRP is a simple method for the synthesis

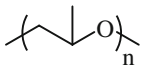
Fig. 1 Structures of selected thermoresponsive homopolymers



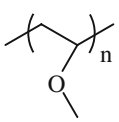
H1. *N*-alkyl-substituted polyacrylamides
(a) PNIPAm: R_1 = H and R_2 = R_3 = CH_3
(b) PAAm: R_1 = R_2 = R_3 = H
(c) PHIPAm: R_1 = H, R_2 = H, R_3 = $CH(CH_3)CH_2OH$



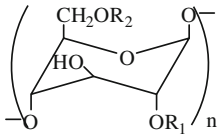
H2. PVCL



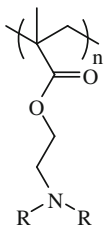
H3. PPO



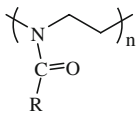
H4. PVME



H5. celluloses
(a) MC: R_1 = R_2 = CH_3
(b) MHEC: R_1 = CH_3, R_2 = CH_2CH_2OH



H6. PDMA
(a) PDMA: R = CH_3
(b) PDEA: R = CH_2CH_3



H7. Poly(2-alkyl-2-oxazolines)
(a) PMOZ: R = CH_3
(b) PEOZ: R = CH_2CH_3
(c) PIPOZ: R = $CH(CH_3)_2$

Table 1 LCSTs of thermoresponsive homopolymers

Abbreviation		LCST[a] (°C)	No.[b]	Reference
PNIPAm	Poly(*N*-isopropylacrylamide)	32	H1(a)	[22]
PAAm	Poly(acrylamide)	Soluble	H1(b)	[24]
PHIPAm	Poly(*N*-2-hydroxyisopropylacrylamide)	Soluble	H1(c)	[27]
PVCL	Poly(*N*-vinylcaprolactam)	31	H2	[15]
PPO	Poly(proprylene oxide)	10–20	H3	[30]
PVME	Poly(vinyl methyl ether)	33.8	H4	[28]
MC	Methylcellulose	50	H5(a)	[28]
EHEC	Ethyl(hydroxyethyl)cellulose	65	H5(b)	[28]
PDMA	Poly(2-dimethylamino)ethyl methacrylate)	50	H6(a)	[29]
PMOZ	Poly(2-methyl-2-oxazoline)	Soluble	H7(a)	[31]
PEOZ	Poly(2-ethyl-2-oxazoline)	~62	H7(b)	[31]
PIPOZ	Poly(2-isopropyl-2-oxazoline)	~36	H7(c)	[32]
PDMAm	Poly(*N*,*N*-dimethylacrylamide)	Soluble		[24]
PEA	Poly(*N*-ethylacrylamide)	82		[24]
PEMA	Poly(*N*,*N*-ethylmethylacrylamide)	70		[23]
PNPAm	Poly(*N*-*n*-propylacrylamide)	25		[23]
PTBA	Poly(*N*-*tert*-butylacrylamide)	Insoluble		[23]
PNBA	Poly(*N*-*n*-butylacrylamide)	Insoluble		[23]
PBMEAm	Poly(*N*,*N*-bis(2-methoxyethyl) acrylamide)	49		[26]
PMPAm	Poly(*N*-(3-methoxypropyl)acrylamide)	>60		[26]
PEPA	Poly(ethoxypropylacrylamide)	~32		[25]
HPC	Hydroxypropylcellulose	42		[14]

[a] It has been assumed that the LCST is equivalent to T_{cp} values reported in the original papers. Soluble implies that no LCST could be determined

[b] The numbers refer to the structures shown in Fig. 1

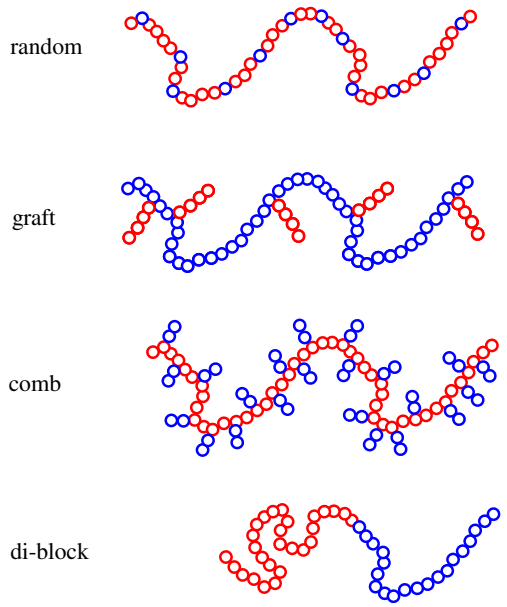


Fig. 2 Thermoresponsive copolymer architectures. The copolymers are depicted at below the LCST. The *red segments* are thermoresponsive

of thermoresponsive copolymers, the polydispersity (PD), which is often in the vicinity of 2.0 to 2.5, is large compared with what can be achieved using ATRP or RAFT.

ATRP [35] is a valuable tool for preparing well-defined copolymers. Thermoresponsive block copolymers with low PDs have been prepared using this method [36]. ATRP was used in the preparation of $PDMA^+$-*g*-PNIPAm graft copolymers (DMA^+ is quarternarised *N*,*N*-dimethylaminoethyl methacrylate) using the "grafting from" approach. In this method, polymer side chains are grown from the main chain. That method enabled convenient control of the molar mass of the grafted chains [37]. A limitation of ATRP is that acidic monomers and some monomers with low intrinsic reactivity cannot be polymerised using this method. Additionally, the final product contains a significant amount of transition metal complex, which must be removed prior to use. That can often be achieved using dialysis or filtration.

RAFT is also an important method for preparing low PD thermoresponsive copolymers. It is generally accomplished by performing a radical polymerisation in the presence of the thiocarbonylthio compounds. These act as reversible chain transfer agents (CTAs) [38]. The use of thiocarbonylthio CTAs yields polymers terminated with a dithioester, which enables block or graft copolymerization. For example, CTA-modified poly(ethylene oxide (PEO) was used as the macro-chain transfer agent enabling preparation of well-defined PEO-*b*-PNIPAm [39]. Also, PNIPAm-*b*-PAMPS was prepared by ATRP and compared with RAFT polymerizations [40]. A drawback of RAFT is that many of the thiocarbonylthio CTAs are coloured. This can provide an obstacle for potential applications where optical transparency is important.

Characterisation

The LCST, being a thermodynamic quantity, has a precisely determined value that is not dependent on the measurement technique. Experimentally, the LCST can be estimated from the cloud point using variable-temperature turbidity measurements or visual observations. The method used is based on cloud point measurements for alcohol ethoxylate surfactants. A dilute copolymer solution (often 1 wt.%) is heated, and the temperature at which the turbidity abruptly increases is determined. Figure 3 shows variable-temperature turbidity data for linear PNIPAm and $PDMA^+$-*g*-PNIPAm copolymers [37]. Collapse of individual polymer chains results in aggregation and a strong increase in turbidity [41]. The point of inflection of the turbidity vs. temperature data is often used to determine the cloud point temperature (T_{cp}). However, the onset of the turbidity increase may also be used. For a sharp transition, there is not a great deal of difference in the values. It should be noted, however, that T_{cp} is an experimental value that is dependent on the conditions used for its measurement. It is commonly assumed that the T_{cp} value is equal to the LCST, and this approximation is used here.

Thermoresponsive copolymers can form macromolecular micelles or aggregates. Whether or not micelles or micellar aggregates exist depends on the temperature with respect to the LCST and the copolymer structure. In some cases, stable macromolecular micelles may exist above the LCST. In other cases, these may associate to give colloidally stable aggregates. In dilute solutions, the macromolecular micelle or aggregate size can be determined using light scattering. Copolymer solutions of $PDMA^+$-*g*-PNIPAm have been investigated using variable temperature hydrodynamic diameter measurements

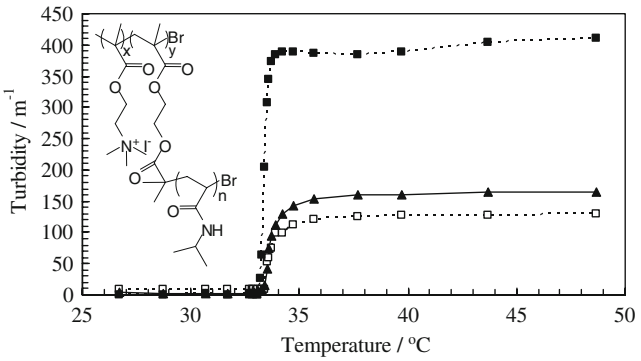


Fig. 3 Variation of turbidity with temperature for PNIPAm (*closed squares*), $PDMA_{30}^+$-*g*-$(PNIPAm_{210})_{14}$ (*open squares*) and $PDMA_{37}^+$-*g*-$(PNIPAm_{195})_{12}$. Data taken from [37]. DMA^+ is quaternarised *N*,*N*-dimethylaminoethyl methacrylate

(Fig. 4a). The copolymer chains aggregate at temperatures greater than the LCST (ca. 33.5°C) and form colloidally stable aggregates. These contract as the temperature is increased. Electrophoretic mobility measurements (Fig. 4b) as a function of temperature provide useful information concerning electrostatic interactions. For $PDMA_{37}^{+}$-*g*-$(PNIPAm_{195})_{12}$, the positive surface charge density increased with temperature. The data suggested that aggregate contraction and structural rearrangement occurred that increased the surface concentration of the cationic copolymer backbone [37].

The structure of thermoresponsive copolymers in solution can be investigated using small-angle neutron scattering (SANS) [42, 43]. SANS involves the scattering of neutrons by nuclei [44] and provides insightful information about the internal structure of macromolecular micelles or aggregates. Scattering profiles for solutions of P(NIPAm-*co*-PEGMA) (PEGMA is polyethylene glycol methacrylate) are shown as a function of temperature in Fig. 5 [43, 45–47]. P(NIPAm-*co*-PEGMA) is a thermoresponsive comb copolymer with a thermally responsive backbone (Fig. 2). The SANS data enabled calculation of the aggregation number, N_{agg}, for the micelles as a function of temperature. At room temperature, single copolymer chains were evident. Above the LCST (which was 36.5°C), the gradient in the low q region increased (Fig. 5) [43, 45–47]. The N_{agg} value increased from unity (at 25°C) to 27 at 50°C. SANS data have been used to describe the local structure of

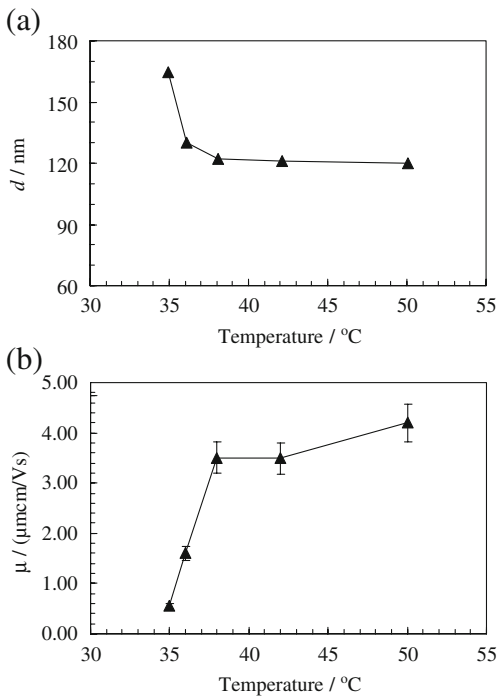


Fig. 4 Variation of **a** hydrodynamic diameter and **b** electrophoretic mobility with temperature for $PDMA_{37}^{+}$-*g*-$(PNIPAm_{195})_{12}$. The data were taken from [37]

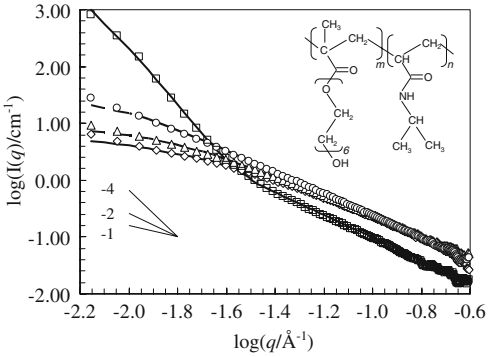


Fig. 5 SANS profiles as a function of temperature for solutions of P(NIPAm-*co*-PEGMA) (*inset*) in D_2O. The temperatures were 25 (*diamond*), 32 (*triangle*), 36 (*circle*) and 50 (*square*) °C. Data taken from [43, 45–47]

thermoresponsive PAAc-*g*-PNIPAm copolymer solutions as a function of temperature [42]. The scattering profiles were fitted using a model for polydisperse spherical micelles with hard sphere interactions. At temperatures above the LCST, the PNIPAm segments assembled into aggregates with a hard-sphere equivalent diameter of about 35 nm. The aggregate size was independent of polymer concentration.

Semi-dilute or concentrated thermoresponsive copolymer solutions invariably exhibit thermally triggered coagulation, viscosity (η) increases or gelation depending on copolymer architecture and concentration. Static rheology measurements are an ideal method for studying η changes. Data for PAAc-*g*-PNIPAm are shown in Fig. 6 [48]. The data show a thermally triggered increase in η, i.e. thermothickening. This occurred when the temperature increased beyond the respective LCST values. The associ-

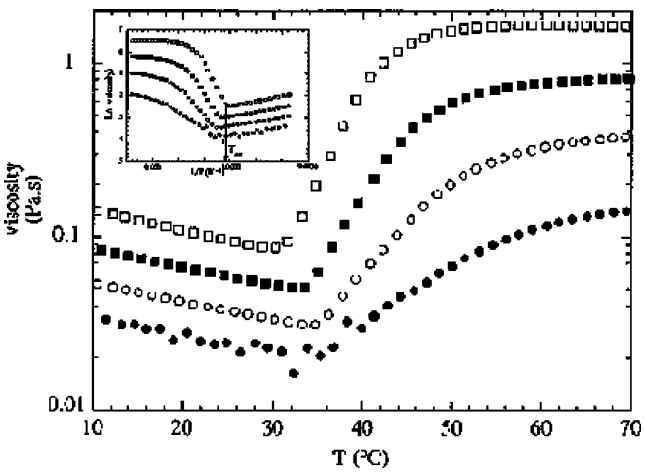


Fig. 6 Variation of viscosity with temperature for copolymer solutions of PAAc-*g*-PNIPAm. The concentrations of polymer used were 0.8% (*closed circles*), 1.5% (*open circles*), 3% (*closed squares*) and 6% (*open squares*). The association temperature was determined by plotting the data using an Arrhenius type plot (*inset*). Figure taken from [48]

ation temperatures, T_{assoc}, were estimated by plotting the data in an Arrenhius style ($\ln\eta$ vs. $1/T$)—see inset of Fig. 6. The value for T_{assoc} was taken as the point of intersection of lines drawn through the data.

For copolymer solutions that gel upon heating, dynamic rheology measurements are an ideal method to non-destructively probe the elastic properties. The most important parameters are the gelation temperatures (T_{gel}), elastic modulus (G') and tanδ (=G''/G', where G' is the loss modulus). The value for T_{gel} can be estimated using tube-inversion measurements. T_{gel} is the temperature at which flow does not occur when the tube is (gently) inverted. Tube inversion is an efficient method for estimating gel boundaries prior to rheology measurements. Figure 7a shows gelation phase diagrams for PDMA$^+$-*g*-PNIPAm solutions [49]. The phase diagrams were used to guide subsequent rheological studies (See Fig. 7b, c). Generally, if the G' values is less than about 100 Pa, the gel is weak and may not support its own weight during a tube inversion experiment. This is because tube inversion applies shear. The variation of G' and G'' with temperature is a more sensitive method for determining T_{gel}. At the gel point, tanδ=1, and this point should be independent of oscillation frequency (ω). The latter is a Winter–Chambon criterion for gelation [50, 51]. It can be seen from Fig. 7b that T_{gel} is about 35°C, which was close to the LCST (33.5°C).

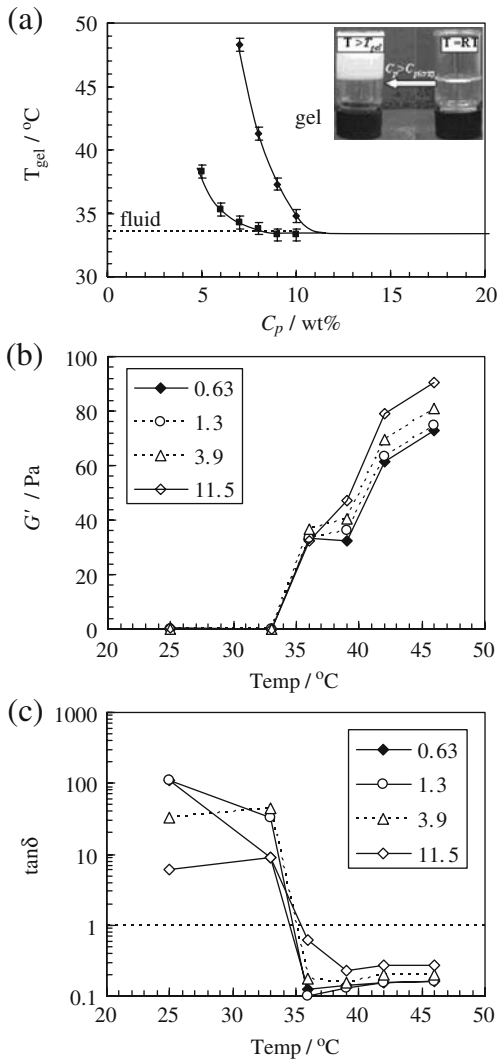


Fig. 7 **a** Gelation phase diagram for PDMA$_{30}^+$-*g*-(PNIPAm$_{210}$)$_{14}$ and PDMA$_{37}^+$-*g*-(PNIPAm$_{195}$)$_{12}$ solutions. T_{gel} and C_p, are the gelation temperature and copolymer concentration, respectively. Variation of **b** G' and **c** tanδ with temperature. The concentrations used for **b** and **c** were 5 wt.%, and this line is shown in **a**. The legends for **b** and **c** show the oscillation frequencies. Data taken from [49]

Literature review

Researchers have mostly focused on PNIPAm copolymers because the solutions undergo a sharp, well-defined, coil-to-globule transition. Furthermore, the copolymer can be prepared using a variety of methods. The structures of the B moieties for P(NIPAm-*co*-B) are shown in Fig. 8. The LCST values of the copolymers are given in Table 2. The LCST of a thermoresponsive copolymer can be conveniently tuned by the mole ratio of the co-monomers used for preparation. A number of studies have considered NIPAm copolymerised with co-monomers that are more hydrophilic. The LCSTs of corresponding copolymers are higher than that of PNIPAm, e.g. P(NIPAm-*co*-HIPAm) (**R16**) or P(NIPAm-*co*-VP) (**R9**). NIPAm has also been copolymerised with hydrophobic co-monomers, such as vinyl laurate (VL, **R8**) [52] or benzo-15-crown-5-acrylamide (BCAA, **R19**) [52]. In both cases, the LCSTs were lower than 32°C. P(NIPAm-*co*-BCAA) is a thermoresponsive copolymer with pendent crown ether groups. Once alkali metal cations such as K^+ are added to the solution, the BCAA groups complex K^+, which disrupts hydrogen bonding between the oxygen atoms in the crown ether and water. As a result, the hydrophobicity of the polymer increases, and the LCST shifts to lower values.

PNIPAm copolymers can be rendered cationic or anionic, respectively, by inclusion of basic or acidic co-monomers. This approach combines pH and thermal responsiveness within one macromolecule and illustrates the advantage offered by copolymerisation. The pH at which half of the ionisable groups are charged is the pK_a of the co-monomer. In the case of a basic co-monomer, the pK_a applies to the conjugate acid. Copolymers containing acid co-monomers are anionic when the pH approaches the pK_a; whereas those containing basic co-monomers are cationic when the pH approaches the pK_a. The LCST values increase with degree of charge on the copolymer backbones. This is because electrostatic repulsion between neighbouring segments opposes chain collapse.

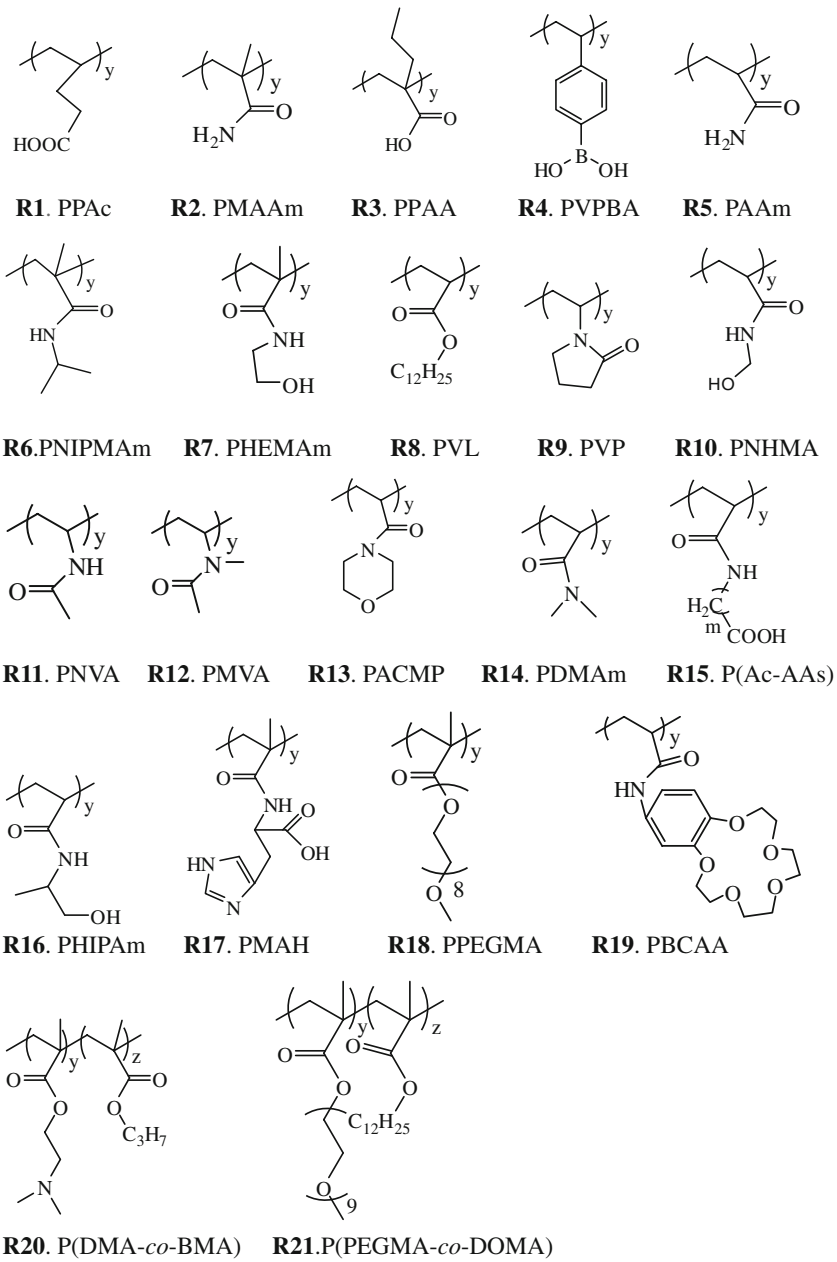


Fig. 8 Selected structures of the co-monomers (B) incorporated within random P(NIPAm-*co*-B) random copolymers

The LCST for P(NIPAm-*co*-PAA) (**R3**) decreased with increasing PAA content when the pH was decreased to below 5.5, whilst it increased between pH values of 6.0–7.0 [53]. The decrease in LCST was probably due to hydrogen bonding between the amide and RCOOH groups. In contrast, the alternating copolymer, P(NIPAm-co-VP), had an LCST that increased from 30 to 60°C with VP content [54]. Because VP has a basic character, it caused an increase in LCST temperature at pH 4.0 compared to that at pH=7.4.

Thermoresponsive *di-block* copolymers enable combination of distinct polymer properties. They are, however, more challenging to prepare than random copolymers, and living polymerisation methods are used (e.g. ATRP or RAFT). The structures of the B blocks within PNIPAm-*b*-PB copolymers are shown in Fig. 9. The respective LCSTs are given in Table 3. It can be seen from comparison with Table 2 that the LCST variation with co-monomer type for PNIPAm block copolymers is smaller than that for random copolymers. The LCST of PNIPAm block copolymers is usually similar to that of PNIPAm homopolymer. This is because of the greater spatial separation between the two co-monomer types within block copolymers. For example, the LCSTs for PNIPAm–*b*-PLA **(B6)**, a biodegradable block copolymer, were ca. 32°C [55]. Interestingly, PNIPAm-*b*-PEO **(B4)** had slightly increased LCST values (ca. 36°C) [39, 56]. When the temperature was higher than LCST, PNIPAm-*b*-PEO formed macromolecular micelles or vesicles depending upon the ratio of block lengths and copolymer concentration.

Table 2 P(NIPAm-*co*-B) random copolymers and their LCST

Abbreviation	Co-monomer	LCST[a] (°C)	No.[b]	Reference
P(NIPAAm-*co*-PAc)	4-Pentenoic acid	19.2–36.5	R1	[103]
P(NIPAm-*co*-MAAm)	Methacrylamide	32.4–43.2	R2	[104]
P(NIPAAm-*co*-PAA)	Propylacrylic acid	Insoluble to Soluble	R3	[53]
P(NIPAm-*co*-VPBA)	Vinylphenylboronic acid	20–40	R4	[55]
P(NIPAm-*co*-AAm)	Acrylamide	34.7–100	R5	[105]
P(NIPAm-co-NIPMAm)	*N*-Isopropylmethacrylamide	34–45.6	R6	[106]
P(NIPAm-*co*-HEMAm)	2-Hydroxyethylmethacrylamide	21.4–30.3	R7	[107]
P(NIPAm-*co*-VL)	Vinyl laurate	<16	R8	[52]
P(NIPAm-*co*-VP)	*N*-Vinyl-2-pyrrolidinone	32.2–39.6	R9	[104]
P(NIPAm-*co*-NHMA)	*N*-Hydroxylmethylacrylamide	32–80	R10	[72]
P(NIPAm-*co*-NVA)	*N*-Vinylacetamide	30–60	R11	[104]
P(NIPAm-co-MVA)	*N*-Methyl-*N*-vinylacetamide	33.2–39.1	R12	[104]
P(NIPAm-*co*-ACMP)	4-Acryloylmorpholine	31.1–35.3	R13	[104]
P(NIPAm-*co*-DMAm)	*N*,*N*-Dimethylacrylamide	32–72	R14	[108]
P(NIPAm-co-(Ac-AAs))	*N*-Acryloyl amino-alkylacides	23–36	R15	[109]
P(NIPAm-*co*-HIPAm)	2-Hydroxyisopropylacrylamide	32–80	R16	[27]
P(NIPAm-*co*-MAH)	2-Methacryloamidohistidine	31–35	R17	[110]
P(NIPAm-*co*-PEGMA)	Poly(ethylene glycol) methacrylate	34–39.5	R18	[45–47]
P(NIPAm-*co*-BCAA)	Benzo-15-crown-5-acrylamide	22–32	R19	[52]
P(NIPAm-*co*-DMA-*co*-BMA)	2-(Diethylamino)ethyl methacrylate butylmethacrylate	20.3–28.4	R20	[111]
P(NIPAm-*co*-PEGMA-*co*-DOMA)	Poly(ethylene glycol) methacrylate dodecyl methacrylate	17–52	R21	[112]

[a] It has been assumed that the LCST is equivalent to T_{cp} values reported in the original papers

[b] The numbers refer to the structures shown in Fig. 8

The LCST of PNIPAm block copolymers containing pH-responsive blocks are also affected by pH. A block copolymer of PNIPAm-*b*-P4VP **(B7)** had a conformation that changed with temperature and pH [57]. In aqueous solution at 25°C, the copolymer existed as unimers when the pH was 2.8. When the temperature was increased to 50°C, the copolymer associated into macromolecular micelles with PNIPAm core and P4VP shell. Alternatively, at 25°C when the pH was increased to 6.5, the macromicelles existed as P4VP cores and PNIPAm shell. The core-shell structures were reversible with pH and temperature.

Biodegradable block copolymers of PNIPAm have also been prepared. One example is **B3** (Table 3) which contained a block that was itself a random copolymer chain of P(GA-*co*-BLG) [58]. The LCST changed from 15 to 32°C depending on BLG content and pH. At the same pH value, increasing BLG content in P(GA-*co*-BLG) led to a slight decrease in LCST. Another example of a biodegradable PNIPAm block copolymer is PNIPAm-*b*-PLA (**B6**). The LCST for this copolymer was also ca. 32°C.

A range of thermoresponsive *graft* copolymer have also been prepared (Fig. 10 and Table 4). Graft copolymers are well suited to the preparation of thermothickening or thermogelling solutions. PNIPAm graft copolymers also usually have a similar LCST to that of PNIPAm [37, 59, 60]. Some of the copolymers have LCSTs which vary with the composition and graft length [61]. When short PNIPAm chains are grafted onto a polyacids, the LCST is dependent on pH [62]. An example of this was the copolymer formed by grafting PNIPAm oligomer onto a PAAc backbone **(G6)** [63]. At pH=7.4, where the carboxyl groups of PAAc were neutralised, the LCST of the copolymer was almost the same as that of PNIPAm. However, the LCST of the graft copolymer decreased to ca. 16°C when the pH value decreased to 4.0. This was presumably due to association of graft-backbone segments caused by hydrogen bonds between –COOH groups on the backbone and NIPAm amide groups.

Some thermoresponsive graft copolymers contain a PNIPAm backbone and hydrophilic side chains [64, 65]. A well-studied example is P(NIPAm-*co*-PEGMa (Fig. 5) [43, 45–47]. This copolymer is also thermogelling. It has also been reported that PNIPAm-g-PEO-C_8F_{17} (**G10**) in semi-dilute aqueous solution was thermogelling [64]. This was due to collapsed PNIPAm chains and C_8F_{17} groups bridged by soluble PEO chains. Table 4 shows that some thermoresponsive graft copolymers contain natural polymer backbones, e.g. poly(L-lysine) (**G1**), chitosan or dextran (**G3**). In each case, PNIPAm has been grafted onto side chains which render the solutions thermoresponsive. The

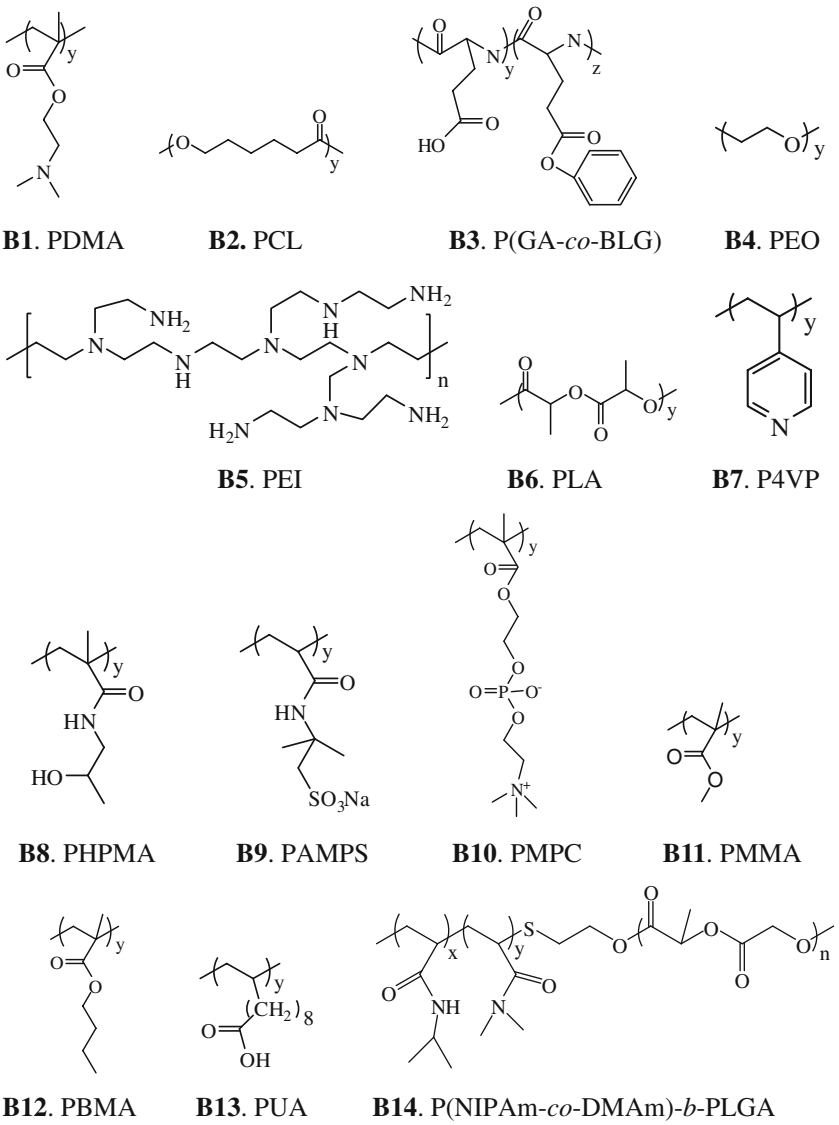


Fig. 9 The structures of the B block for diblock PNIPAm-*b*-PB copolymers

semi-dilute aqueous solutions of chitosan-*g*-PNIPAm have also been reported to show thermogelling behaviour.

Thermoresponsive copolymers that do not contain *N*-alkyl substituted poly(acrylamide)s are also of interest. These include PEO copolymers [66–70], PMVE block copolymers [71] and PVCL graft copolymers [68] (Fig. 11 and Table 5). The random copolymers of P(MAA-*co*-PEGMA) **(E6)** were reported to have thermoresponsive properties, and the LCSTs depended on the co-monomer ratio, pH and PEG chain length. P(NIPAm-*co*-NHMA) copolymers have also been studied [72]. Wang et al. investigated a series of P(PPGMA-*co*-PEGMA) **(E8)** copolymers and showed that the LCST could be controlled over a wide temperature range, which included 37°C, by varying the co-monomer mole ratio during synthesis [73]. This copolymer can also be considered as a comb copolymer.

P(MEO_2MA-*co*-OEGMA) copolymers [70] **(E1)** have also been prepared that exhibit LCST values between 26 and 90°C, which were precisely adjusted by varying the OEGMA content in the copolymer. For example, LCST values of 32, 37 or 39°C were observed for copolymers possessing on average 5, 8 or 10 mol.% MeO_2MA, respectively. The MEO_2MA block is relatively hydrophobic (cf. OEGMA) because it has a short EO chain length and a methoxy end group.

For the block copolymers of PMVE and PIBVE **(E5)**, the LCSTs are the same as that of PMVE (ca. 40°C) [71]. However, the LCSTs of the PVCL graft copolymers (**E3**) were sensitive to the grafting density of PTHF chains [68]. The responsiveness decreased with an increasing PTHF grafting degree. This indicated that the PVCL aggregation above the LCST was hampered by the PTHF side chains. Importantly, the general trends observed for the control of the LCST for PNIPAm copolymers also apply for the non-acrylamide thermoresponsive copolymers.

Table 3 PNIPAm-*b*-B di-block copolymers and their LCSTs

Abbreviation	B block identity	LCST[a] (°C)	No.[b]	Reference
PNIPAm-*b*-PDMA	Poly(2-(diethylamino)ethyl methacrylate)	25–35	B1	[113]
PNIPAm-*b*-PCL	Poly(ε-caprolactone)	29.5–32.2	B2	[88]
PNIPAm-*b*-(PGA-*co*-BLG)	Poly[(L-glutamic acid)-co-(*g*-benzyl L-glutamate)]	15–32	B3	[58]
PNIPAm-*b*-PEO	Poly(ethylene oxide)	34–36	B4	[39, 56]
PNIPAm-*b*-PEI	Polyethyleneimine	31–39	B5	[114]
PNIPAm–*b*-PLA	Poly(D,L-lactide)	~32	B6	[55]
PNIPAm-*b*-P4VP	Poly(4-vinylpyridine)	36	B7	[57]
PNIPAm-*b*-PHPMA	Poly[*N*-(2-hydroxypropyl) methacrylamide]	~33	B8	[115]
PNIPAm-*b*-PAMPS	Sodium poly(2-acrylamido-2-methylpropanesulfonate)	32.5–36.5	B9	[40]
PNIPAm-*b*-PMPC-*b*-PNIPAm	Poly(2-methacryloyloxyethyl phosphorylcholine)	~33	B10	[116]
PNIPAm-*b*-PMMA	Poly(methyl methacrylate)	~33	B11	[86]
PNIPAm-*b*-PBMA	Poly(butyl methacrylate)	~32.5	B12	[87]
PNIPAm-*b*-PUA	Poly(10-undecenoic acid)	30.8	B13	[117]
P(NIPAm-*co*-DMAm)-*b*-PLGA	Poly(*N*-isopropylacrylamide-*co*-*N,N*-dimethylacrylamide)-*b*-poly (D,L-lactide-*co*-glycolide)	39	B14	[94]

[a] It has been assumed that the LCST is equivalent to T_{cp} values reported in the original papers

[b] The numbers refer to the structures shown in Fig. 9

Rheological properties

Thermoassociation and thermothickening

When the temperature of a copolymer solution approaches the LCST, the chains collapse. Provided interchain repulsion is not dominant, macromolecular micelles spontaneously form. At sufficiently high copolymer concentrations (e.g. in the semi-dilute regime or concentrated regimes), this can lead to thermothickening [74]. The seminal work in this area was conducted by Hourdet et al. [42, 48, 75–78]. Thermothickening arises from reversible intermolecular associations of hydrophobic segments that form hydrophobic microdomains. These act as physical (transient) cross-links between neighbouring copolymer chains. This is depicted in Fig. 12 for a graft copolymer consisting of a hydrophilic backbone and thermoresponsive side chains [74]. The current interpretation of thermothickening beha-

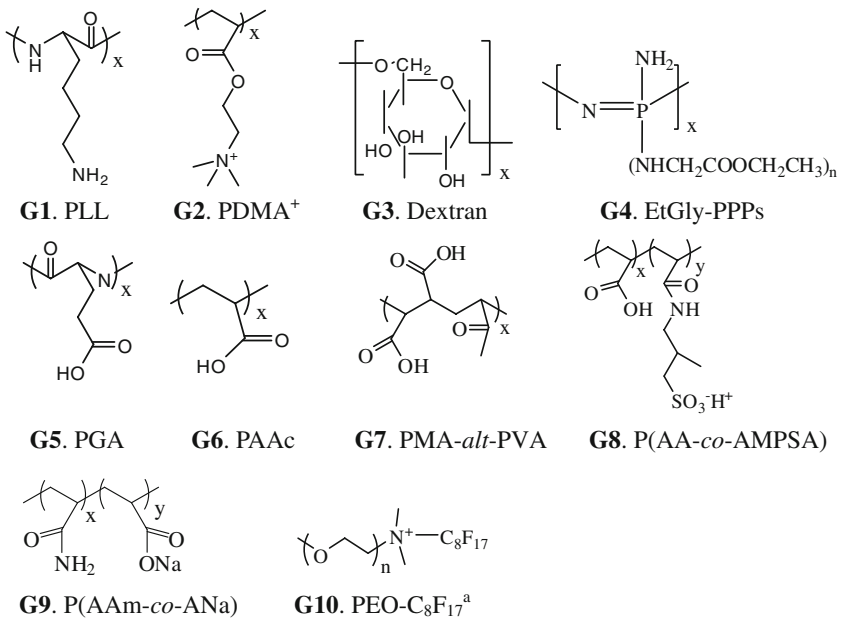


Fig. 10 The structures of the backbone or graft chains for PNIPAm graft copolymers. [a.] PEO-C_8F_{17} grafted onto the PNIPAm backbone

Table 4 Graft copolymer of PNIPAm and their LCSTs

Abbreviation	Backbone (or graft chains)	LCST[a] (°C)	No.[b]	Reference
PLL-*g*-PNIPAm	Poly(L-lysine)	~32	G1	[59]
$PDMA^{+}$-*g*-PNIPAm	Poly(2-(*N*,*N*,*N*-dimethylamino) ethyl methacrylate)	~33.5	G2	[37]
Dextran-*g*-PNIPAm	Dextran	~32	G3	[60]
EtGly-PPPs-*g*-PNIPAm	Ethyl glycinate polyphosphazenes	18.5–33	G4	[118]
PGA-*g*-PNIPAm	Poly(L-glutamic acid)	23–33	G5	[62]
PAAc-*g*-PNIPAm	Poly(acrylic acid)	16–32	G6	[119]
P(MA-*alt*-VA)-*g*-PNIPAm	Poly(maleic acid-*alt*-vinyl acetate)	~33	G7	[120]
P(AAc-*co*-AMPSA)-*g*-PNIPAm	Poly(acrylic acid-*co*- 2-acrylamido-2-methyl propane sulfonic acid)	~33	G8	[121]
P(AAm-*co*-ANa)-*g*-PNIPAm	Poly(acrylamide-*co*-sodium acrylate)	~33	G9	[83]
PNIPAm-*g*-PEO-C_8F_{17}[c]	End-perfluoroalkyl modified PEO	~32	G10	[64]
Chitosan-*g*-PNIPAm	Chitosan	30–32		[122]

[a] It has been assumed that the LCST is equivalent to T_{cp} values reported in the original papers

[b] The numbers refer to Fig. 10

[c] PEO-C_8F_{17} grafted onto the PNIPAm backbone

viour draws upon transient network theory. [79] Green and Tobolsky considered the elasticity of (non-thermally responsive) associative thickeners [79]. A transient network was formed by junctions that continually break and recombine. A long-lived transient network formed when the lifetime of the hydrophobic segments within the junctions (microdomains) was significantly greater than the time between successive detachments. The latter was a function of the shear rate. The original theory assumed that the energy for detachment of chains from junctions was not temperature dependent [79]. However, this assumption will not be valid for thermoresponsive copolymers because the detachment energy for the segments within junctions should abruptly increase at the LCST. Therefore, transient network theory requires modification in order to be applied to the problem of thermothickening.

The ability of a copolymer solution to exhibit thermothickening is dependent on the copolymer structure and concentration. Copolymer chains that are highly charged tend to exhibit strong interchain repulsion which prevents

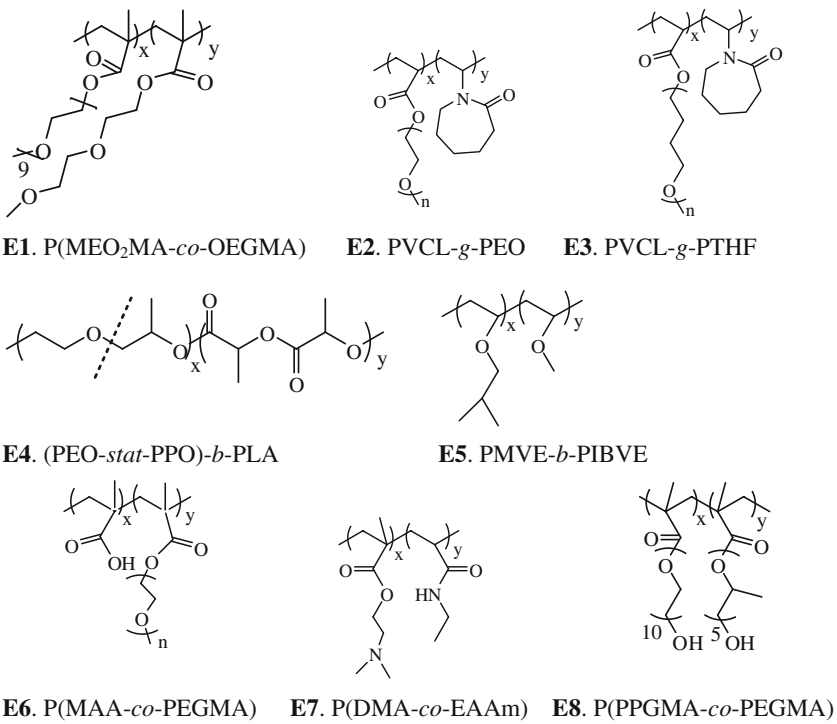


Fig. 11 The structures of selected non-acrylamide containing thermoresponsive copolymers

Table 5 The non-acrylamide containing thermoresponsive copolymers and their LCSTs

Abbreviation		LCST[a] (°C)	No.[b]	Reference
$PMEO_2MA$-*co*-POEGMA	Poly[2-(2-methoxyethoxy)ethyl methacrylate)-*co*-oligo (ethylene glycol) methacrylate)]	26–90	E1	[70]
PVCL-*g*-PEO	Poly(*N*-vinylcaprolactam)-*g*-poly(ethylene oxide)	30.7–35.2	E2	[68]
PVCL-*g*-PTHF	Poly(*N*-vinylcaprolactam)-*g*-poly(tetrahydrofuran)	35–50	E3	[68]
(PEO-*stat*-PPO)-*b*-PLA	Poly(ethylene oxide-*stat*-propylene oxide)-*b*-poly(D,L-lactide)	36–46	E4	[67]
PMVE-*b*-PIBVE	Poly(methyl vinyl ether)-*b*-poly(isobutyl vinyl ether)	40	E5	[71]
P(MAA-*co*-PEGMA)	Poly(methacrylic–*co*-poly(ethylene glycol) methyl ether methacrylate	0–90	E6	[66]
P(DMA-*co*-EAAm)	Poly((*N*,*N*-dimethylamino)ethyl methacrylate-*co*-ethylacrylamide)	12~76	E7	[29]
P(PPGMA-*co*-PEGMA)	Poly(propyleneglycol methacylate – co-polyethyleneglycol methacrylate)	20–79	E8	[73]

[a] It has been assumed that the LCST is equivalent to T_{cp} values reported in the original papers

[b] The numbers refer to Fig. 11

microdomain formation and thermothicknening. Durand and Hourdet investigated thermoassociation of a range of P(NIPAm-*co*-AAc) copolymer solutions (AAc is acrylic acid). As discussed earlier (Fig. 6), the key parameter is T_{assoc} [48, 80].

Thermogelation of copolymer solutions and dispersions

Thermoassociation can result in gel formation if the hydrophilic portions of backbone do not allow macroscopic phase-separation, and the lifetimes of the hydrophobic segments within the junctions are long compared to the detachment time. Furthermore, the energies for detachment must also be relatively large compared to the thermal and mechanical energies. The architecture of thermogelling copolymers must restrict phase separation at higher temperatures. In order for an extended network to occur the polymer chain segments between the (microdomains) crosslinks must be expanded. This implies a good solvency environment, and/or strong inter-segment repulsion must exist for those units. This can be achieved in a number of ways. We have used a cationic copolymer, $PDMA_x^+$-*g*-$P(PNIPAm_n)_y$ (inset of Fig. 3), which has a cationic backbone and PNIPAm side chains to give an extended structure. The gels form at reasonably low copolymer concentrations (ca. 4 wt.%). The ratio of hydrophilic polymer segments to the thermoresponsive polymer segments (i.e. *x*/*y*) and the effective lengths of these segments (*n*) control the gelation behaviour (Fig. 7). Increasing the proportion of charged ($PDMA^+$) segments (increasing *x*/*y*) increased electrostatic repulsions between the hydrophilic polymer segments and T_{gel} (See Fig. 7a). As mentioned above, there are a number of other copolymers that are also thermogelling. The best examples appear to be graft copolymers, which include $PDMA_x^+$-*g*-$P(PNIPAm_n)_y$ and PAAc-*g*-PNIPAm [42].

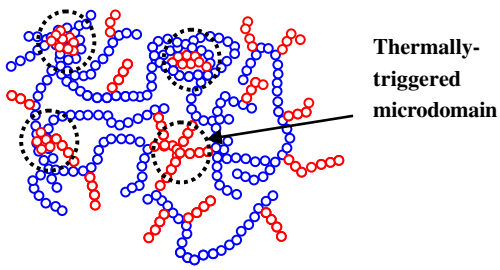


Fig. 12 Depiction of thermoassociative microdomain formation for a thermoresponsive graft copolymer. The *red segments* are thermally responsive

The values for G' will increase with the number density of elastically effective chains and the junction detachment energy. The key structural requirements for the design of thermogelling copolymer that form gels at low copolymer concentrations are graft copolymer architecture with thermoresponsive side chains that are relatively long and a highly charged polymer backbone. The chain lengths of the side chains must be large compared to the Debye length of the solution if the backbone is charged. The condition of an extended backbone could in principle be met without the use of electrostatic repulsion if the backbone segments were hydrophilic and highly hydrated or the expanded structure was sterically favourable.

Thermoresponsive copolymers can be used as thermoresponsive stabilisers for emulsions [45], latexes [47] and inorganic dispersions [81]. This requires a significant attraction between the thermoresponsive copolymer chains and the dispersed phase. When this is operative, the dispersion can be rendered thermogelling. The Saunders group has used P(NIPAm-*co*-PEGMA), P(DEAm-*co*-PEGMA) and $P(DMA^+$-*g*-NIPAm) as thermoresponsive stabilisers. $PDMA_{30}^+$-*g*-$(PNIPAm_{210})_{14}$ appears to be a versatile stabiliser [82]. The copolymer confers responsive-

ness to a range of anionic dispersions including laponite, Ludox or poly(lactide-*co*-glycolide) (PLGA) nanoparticles (See Fig. 13) [82]. It is effective because there is a strong attractive interaction between the cationic copolymer and the dispersed (anionic) nanoparticles. Importantly, the copolymer solutions do not form gels without the dispersed particles at the same copolymer concentrations. This shows that the particles increase the crosslink density and are intimately involved in the network.

The thermogelled laponite/P(DMA_{30}^{+}-*g*-($PNIPAm_{210}$)$_{14}$) dispersions were remarkable in that the presence of only a very small quantity of laponite (0.7 wt.%) enabled thermogelation to occur at lower copolymer concentrations (e.g. 1 wt.%) [81]. The minimum total volume fraction of laponite and copolymer required to form a gel was only 0.01. The Saunders group also showed that P(NIPAm-*co*-PEGMA) (Fig. 6) could be used to prepare thermogelling emulsions and latex dispersions [45–47]. That work was the first example of thermally triggered emulsion gelation using a synthetic copolymer. When the temperature was above the LCST, the copolymer chains at the oil–water interface collapsed upon heating and became adhesive. SANS studies [45] showed that the gelled emulsions consisted of oil droplets with an encapsulating layer of collapsed polymer. The addition of anionic surfactant was shown to obstruct gelation due to electrostatic repulsion. Similarly, addition of P(NIPAm-*co*-PEGMA) to butadiene–acrylonitrile latex also resulted in thermogelation [47]. For the P(NIPAm-*co*-PEGMA) system, it was the hydrophobic attraction between the copolymer backbone segments and the particles that was responsible for the thermogelation properties of the dispersions.

Petit et al. reported that addition of the thermoassociative copolymer P(AAm-*co*-ANa)-*g*-PNIPAm (**G9**) to silica particle dispersions resulted in formation of composite networks due to the strong affinity of PNIPAm side chains for silica particles [83]. The thermogelation was due to the interaction of hybrid (silica/PNIPAm) network and copolymer, probably by hydrogen bonding between the amide groups and the Si-OH groups. The viscoelastic properties of those networks were controlled by the concentration of silica and the fraction of PNIPAm grafts participating in bridges between particles.

Thermoresponsive copolymers as biomaterials

Delivery

There are two general drug delivery strategies: passive and active targeting [84, 85]. Both delivery mechanisms rely upon the particles resisting adsorption of proteins within the body. The ability of the delivery vehicles to circulate within the body (e.g. plasma) depends on a number of factors, including particle size. Larger particles are detected by the reticuloendothelial system. Particles which are much less than 100 nm have an advantage in this regard. Macromolecular micelles formed by thermoresponsive copolymers have sizes that are well within this range.

Thermoresponsive macromicelles can solubilise hydrophobic compounds and enable triggered release at target sites within the body. Amphiphilic PNIPAm block copolymers self-assemble into macromolecular micelles in aqueous solutions [86–89]. Hydrophobic polymer chains, such as PMMA [86] or PCL [88], can form the core, and the PNIPAm chains **(B11** and **B2)** compose a responsive hydrophilic shell. During the process of the formation of the micelles, hydrophobic drug molecules can be absorbed within the hydrophobic cores. The macromolecular micelles **(B11** and **B2)** were stable to aggregation at room temperature but collapsed at the PNIPAm LCST, triggering drug release. The process is depicted in Fig. 14.

For thermoresponsive delivery systems, a trigger that is being pursued is hyperthermia. Hyperthermia is localised

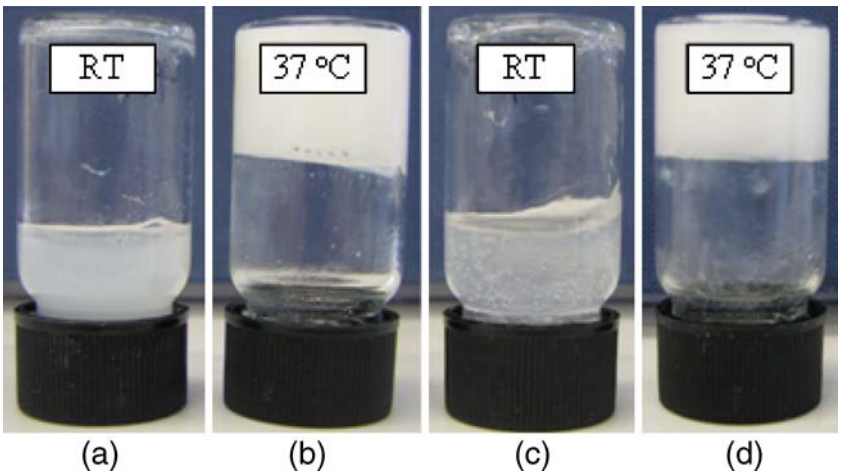


Fig. 13 Thermogelation of PLGA (0.5 wt.%)/$PDMA_{30}^{+}$-*g*-($PNIPAm_{210}$)$_{14}$ (2.5 wt.%) (**a**, **b**) and laponite (0.5 wt.%)/$PDMA_{30}^{+}$-*g*-($PNIPAm_{210}$)$_{14}$ (2.5 wt.%; **c**, **d**) dispersions. The PLGA nanoparticles had a size of ca. 200 nm and were prepared using nanoprecipitation [69]). The laponite (Laponite RD) had an average diameter and thickness of 20 and 1 nm, respectively

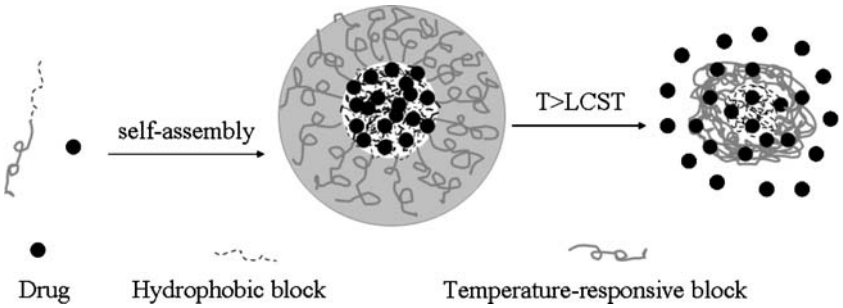


Fig. 14 Depiction of thermoresponsive amphiphilic copolymer used for drug delivery and controlled release

heating for thermally targeted drug delivery [86, 90, 91]. Triggered release of antitumor drugs by hyperthermia has significant advantages in clinical applications, since it is relatively straightforward to implement. Furthermore, side effects can be reduced because the systemic drug concentration is decreased, whilst the local concentration resides within the therapeutic window. To release drugs site-specifically upon local heating requires the drugs to be loaded by using thermoresponsive polymer matrix with an LCST between 37 and 42°C. This can be achieved using a number of copolymers because LCST tuning is straightforward (discussed above). For example, P(NIPAm-*co*-AAm)-*b*-PLA self-assembled micelles can load up to 27% Docetaxel (a chemotherapeutical drug) [92]. When the temperature was above the LCST, e.g. 41°C, the hydrophilic shell of the micelle collapsed, and drug release occurred from the micellar core. Thermoresponsive block copolymers, such as poly(*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide-*co*-2-aminoethyl methacrylate)-*b*-poly (10-undecenoic acid), P(NIPAm-*co*-DMAm)-*b*-PLA [93], and P(NIPAm-*co*-DMAm)-*b*-PLGA [94] have tunable LCSTs in the range of 39°C and have also been investigated for triggered drug release.

Thermoresponsive block copolymers can also be used for protein delivery [95]. PNIPAm-*b*-PLA **(B6)** microspheres containing bovine serum albumin (a model protein) were prepared using a water-in-oil-in-water double emulsion method which involved solvent evaporation. The microspheres provided sustained release of BSA over 3 weeks in PBS at 37°C. An advantage of this system is that the PLA block is biodegradable.

Thermoresponsive copolymers have also been investigated for transfection. The latter is the uptake of plasmid DNA molecules by the cells and then expression into the cells. In order to increase transfection efficiency and decrease the cytotoxicity, synthetic cationic copolymers based on PEIs [96, 97] or other cationic polymers [98, 99] were investigated as nonviral gene for human gene therapy. The aim was to introduce genes into target cells to be transfected and produce therapeutic proteins. Poly (*N*-isopropylacrylamide-*co*-*N*-(3-(dimethylamino)propyl) methacryl amide)-*b*-polyethyleneimine P(NIPAm-*co*-NDAPM)-*b*-PEI) was used as a nonviral gene vector and exhibited lower cytotoxicity than that of PEI [96]. This copolymer was able to effectively bind plasmid DNA. Importantly, the transfection efficiency of P(NIPAm-*co*-NDAPM)-*b*-PEI/DNA complexes could be adjusted by altering the temperature, suggesting that the copolymer had potential as a thermoresponsive nonviral gene vector.

Regenerative medicine

The field of regenerative medicine is attracting considerable interest and relies on materials that combine cell delivery with the ability to support cell growth. Cell delivery vehicles that can be mixed with cells at room temperature and form aggregates when co-injected with the cells into the body are being actively studied. Ideally, they should form a porous gel that will protect the cells and promote tissue growth. Recently, Wang et al. have shown that P(PPGMA-*co*-PEGMA) copolymers can be used as thermoresponsive stabilisers for PLGA or PCL microparticle dispersions [73]. The particle dispersions exhibited thermally triggered formation of gels. Furthermore, incorporation of C2C12 cells within the aggregates exhibited good cell viability and proliferation. Thus, it was demonstrated that an injectable, biodegradable, dispersion containing cells could produce a viable scaffold for cell growth under physiological conditions. That work has excellent potential to provide a general purpose cell delivery system for regenerative medicine applications.

A biodegradable thermoresponsive graft copolymer, gelatin-*g*-PNIPAm, was also investigated as an injectable scaffold [100]. It had an LCST of approximately 34°C and served as an in situ scaffold on which fibroblasts proliferated. Gelatin-*g*-PNIPAm biodegraded over time without excessive inflammatory reactions. The experiments of the subcutaneous tissue of Wistar rats showed that after injection a white, opaque cell-incorporated gel immediately formed. Fibroblasts formed spherical shape and homogeneously distributed in the gel and proliferated in the native tissue. The study showed that thermoresponsive systems have considerable potential for use as injectable cell

composite delivery systems. It is the combination of biodegradability with thermoresponsiveness that offers the greatest potential for regenerative medicine applications. Ideally, all parts of the copolymer should biodegrade. The rates of biodegradation will need to be balanced by the rates of cell growth etc.

Conclusion and future directions

Thermoresponsive copolymers have been extensively investigated in recent years and have become fairly well understood. The copolymers provide excellent opportunity to finely tune the LCST and thermoassociative properties. Self-assembled structures, such as macromolecular micelles, vesicles or aggregates, can be designed to take up a range of actives. Biodegradability can be readily incorporated. Their ability to form reversible gels on their own or with other dispersions provides potential applications as injectable soft biomaterials. PNIPAm and its derivatives have been the most widely studied in delivery applications. This is due to the sharpness of the LCST and its versatility in terms of copolymer architecture variation as well as the LCST of PNIPAm being close to body temperature. A major limitation for PNIPAm is that the unreacted NIPAm monomer has shown evidence of neurotoxicity [101]. Thus, in the future, the thermoresponsive copolymers that do not contain acrylamides are likely to gain increasing attention, and this would appear to be a very promising area for research. The challenge is to prepare thermoresponsive copolymers with structures that are as close as possible to systems that are already approved for use in medical devices but with superior properties.

The discussion has shown that a wide range of LCST behaviour can be engineered through control of thermoresponsive copolymer architecture. The application of thermoresponsive polymers within the coatings industry has, so far, been limited. Applications in that area require robust systems where the responsiveness is not affected by additives. An interesting aspect that is only beginning to be explored is the combination of enzyme responsiveness with thermoresponsive behaviour. It has been shown that incorporation of peptide sequences within crosslinked copolymers can provide enzyme responsive behaviour [102]. The combination of the two attributes within one copolymer system could provide enhanced applications for delivery and regenerative medicine applications. This is another area in which the potential for application of thermoresponsive copolymers is promising.

Acknowledgments The authors gratefully acknowledge the EPSRC for funding the work performed on thermoresponsive copolymers at Manchester. We are grateful to the referees for their helpful comments.

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