



## Feature Article

## Tuning the gelation of thermoresponsive gels



Anna P. Constantinou, Theoni K. Georgiou\*

Department of Materials, Imperial College London, Exhibition Road, London SW7 2AZ, United Kingdom

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## ABSTRACT

Thermoresponsive gels are exciting polymeric materials with many biomedical applications in medical devices, drug delivery, tissue engineering and bio-printing. Also, they have great potential to be used in 3-D printing and thus in the fabrication of many different devices and materials. As it is crucial for the application of these gels to be able to control and tailor the gelation temperature and concentration this was the main focus and point of discussion of this feature article. Thus, it is discussed in detail how by varying the molar mass, composition, stereochemistry and architecture the thermoresponsive properties of these gels are altered.

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**Abbreviations:** 3-D, 3-dimensional; AA, acrylic acid; Bipolymer, a polymer that is based on two different monomers; BMSiVE, 2-(*tert*-butyldimethylsilyloxy)ethyl vinyl ether; BnLA, 3-benzoyloxymethyl lactide; BO, butylene oxide; BuMA, *n*-butyl methacrylate; CGC, critical gelation concentration; CL, caprolactone; Copolymer, a polymer that is based on more than one monomers;  $\bar{D}$ , dispersity (see MMD); DAAC, 2-carboxyethyl acrylate (DAA); DL-Ala, D,L-Alanine; DLLA, D,L-lactide; DMA, *N,N*-dimethylacrylamide; DMAEA, 2-(dimethylamino)ethyl acrylate; DMAEMA, 2-(dimethylamino)ethyl methacrylate; EA, ethylene adipate; EG, ethylene glycol; EO, ethylene oxide (same as EG); EOEOVE, 2-(2-ethoxy)ethoxyethyl vinyl ether; EOVE, 2-ethoxyethyl vinyl ether; ES, ethylene succinate; EtMA, ethyl methacrylate; GA, glycolide; GTP, group transfer polymerisation; HA, hexamethylene adipate; HEMA, 2-hydroxyethylmethacrylate; HMA, *n*-hexyl methacrylate; L-Ala, L-alanine; LA, lactide; LCST, Lower Critical Solution Temperature; LLA, L-lactide; MM, molar mass (same as molecular mass); MMD, molar mass distribution; MOVE, 2-methoxyethyl vinyl ether; MPEG, methoxypoly(ethylene glycol); NIPAm, *N*-isopropylacrylamide; PDMAEMA, poly[(2-dimethylamino)ethyl methacrylate]; PEG, poly(ethylene glycol); PEGMA, methoxy poly(ethylene glycol) methacrylate; PNIPAAm, poly(*N*-isopropylacrylamide); PO, propylene oxide; PVME, poly(vinyl methyl ether); SO, styrene oxide; Terpolymer, a polymer that is based on three different monomers;  $T_g$ , glass transition temperature;  $T_{gel}$ , gelation temperature; TRG, thermoresponsive gels.

\* Corresponding author.

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## 1. Introduction

Thermoresponsive polymers are polymers that exhibit a drastic change in their physical properties in response to temperature and hence they are also called temperature-responsive polymers. In solution this discontinuous change in physical properties manifests as a change in solubility and with a change in temperature the polymer becomes insoluble and precipitates out from solution. Polymers that become hydrophobic when increasing temperature demonstrate a Lower Critical Solution Temperature (LCST) behaviour that can be clearly observed visually since the solution becomes cloudy. The phase diagram of this behaviour is shown in Fig. 1(a). Each of the points on the curve is a cloud point while the minimum of the curve corresponds to the LCST. The most common thermoresponsive polymers that exhibit LCST behaviour are poly(*N*-isopropylacrylamide) (PNIPAAm) [1–4], poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) [5], poly(vinyl methyl ether) (PVME) [1], and poly(ethylene glycol) (PEG) [6,7]. The chemical structures of their repeating units are shown in Fig. 2. However, one has to be careful when quoting a transition temperature (the LCST or a cloud point) as this is influenced not just by the solvent (or solvent mixtures) and the ionic strength of the solution, but also by the molar mass (MM) and the molar mass distribution (MMD, dispersity,  $\bar{D}$ ) of the polymer [4–7]. In certain conditions and usually when the thermoresponsive polymers are combined with other comonomers their aqueous solutions can form physical gels when increasing the temperature. A physical gel is a 3-dimensional (3-D) polymer network that is held together via physical entanglements, hydrogen bonds and/or hydrophobic interactions [8,9]. The phase diagram of these aqueous based systems of thermoresponsive gels is shown in Fig. 1(b).

This solution–gel (sol–gel) transition is thermo-reversible and thus these gels are also often called thermally-reversible gels as well as thermoresponsive gels (TRGs). This transition can be observed visually via the formation of a gel (the solution no longer flows, see Fig. 3) and phase diagrams like the one shown in Fig. 1(b) can be constructed where the points on the green curve are gelation points. The gelation point can more accurately be determined via rheological measurements and it is taken as the point where elastic modulus,  $G'$  exceeds the viscous modulus  $G''$  (i.e. the solid phase becomes dominant) [10] as shown in Fig. 3. When increasing the temperature syneresis is often observed where liquid is also present with the gel, a phenomenon that was first reported by Graham in 1864 when observing gelatine solutions [11].

TRGs have many biomedical applications [12] including drug delivery [13–21] and tissue engineering as in-situ forming gels [22–27] and in 3-D bioprinting [28–31]. Furthermore with the increasing recent interest in 3-D printable materials and the need to control the rheology of the solution while printing [32,33] the areas of potential usage of TRGs has increased since 3-D printing is applied to the manufacture of materials in various industries besides the medical industry, like aerospace, automotive, building and construction, marine, food industry and in manufacturing electronic and optical devices [34–36].

In TRGs applications it is highly important to be able to control the gelation point, i.e. the temperature that the polymer solution becomes a gel,  $T_{gel}$ . Ideally this transition should be clear and sharp and not be happening over a range of temperatures. The latter can be improved by using well-defined polymers of narrow MMD. Since the control and tailor-ability of the gelation temperature is crucial it is also the focus of this feature article and specifically how the polymer characteristics

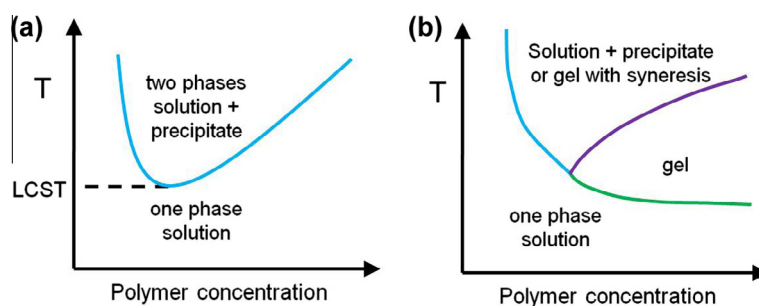


Fig. 1. Phase diagram (a) of a thermoresponsive homo- and co-polymer that exhibits a LCST behaviour and (b) a thermoresponsive copolymer that is able to form reversible gels.

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