# Copolymers of *N*-Alkylacrylamides as Thermosensitive Hydrogels

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**Summary**: Many of the N-alkyl substituted acrylamide polymers can manifest a lower critical solution temperature (LCST) in aqueous solutions. The LCST of such polymers can be easily varied by a free radical copolymerization of the appropriate comonomers. Natural compounds such as bile acids can be introduced into such polymers to modify the LCST and aggregation behavior and to render the material both thermo- and pH-sensitivity.

## Introduction

Some polymers can manifest a drastic change in water solubility at a certain temperature, which is known as the lower critical solution temperature (LCST). The behavior is associated with the temperature dependence of hydrogen bonding and hydrophobic interactions. This property of the polymers can be very useful because of the rheological and technological implications and potential biomedical and industrial applications. The thermosensitivity of poly(*N*-isopropylacrylamide) (PNIPAM, which has a LCST at ca. 32 °C) has been extensively studied [1,2]. The variation of the LCST of the thermosensitive polymers can be achieved by copolymerization, chemical modification of the polymer, or the addition of salts or surfactants in the aqueous solutions [2,3]. LCST was also observed for aqueous solutions of other *N*-substituted polyacrylamides [4-7], but these polymers have not drawn as much attention as PNIPAM.

It is interesting and important to tune predictably the LCST of the polymers for the different applications. The thermosensitivity of the polymers can be controlled by the relative hydrophilicity of the copolymers, hence the chemical structure and composition of the constituent monomers. It is also useful to introduce natural compounds for the biological applications of the polymers, which, at the same time, can modify the thermosensitivity and aggregation behavior of such materials. Therefore, different copolymers of N-alkylacrylamides and bile acid derivatives have been prepared to improve and modify the biocompatibility, solution property and aggregation behavior of such materials.

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## Copolymers of *N*-substituted acrylamide monomers

In the case of *N*-substituted acrylamides, the hydrophilicity of the *N*-alkyl substitution group should be important in the determination of the LCST and the properties of the polymers. We have selected a number of *N*-substituted acrylamide monomers, including acrylamide (AA), *N,N*-dimethylacrylamide (DMA), *N*-ethylacrylamide (EA), *N,N*-diethylacrylamide (DEA), *N*-tert-butylacrylamide (TBA), in the preparation of several series of copolymers to vary the LCST of the polymers in a systematic fashion. We have found that the LCSTs of the copolymers are quite sharp and can be varied between the LCST values of the corresponding homopolymers. The results are shown in Figure 1 for the copolymers made. The LCST was found to vary as a function of the chemical composition of the copolymers according to the following equation:

$$T = \frac{\mu_1 T_1 + K\mu_2 T_2}{\mu_1 + K\mu_2} \tag{1}$$

where $\mu$ is the molar fraction of a given monomer (note that $\mu_1 + \mu_2 = 1$), $T$ is the LCST of the corresponding homopolymers 1 and 2, and $K$ is a weighting parameter inferior to 1 ranging from 0.51 for poly(TBA-co-EA) to 0.13 for poly(TBA-co-DMA) (Figure 1).

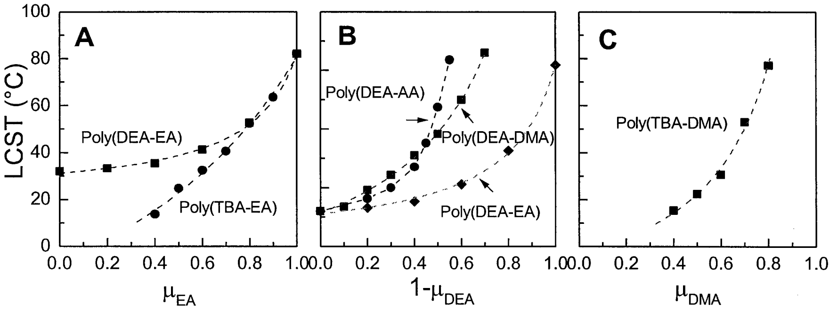

Figure 1. Tuning LCST by copolymerization of N-alkyl substituted acrylamide

## Copolymers of *N*-alkylacrylamides with bile acid derivatives

Bile acids are natural amphiphilic compounds with interesting properties. Methacrylic and acrylic derivatives of bile acids have been prepared by attaching a polymerizable double bond to one of the functional groups of the bile acid molecule. We have made copolymers of *N*-substituted acrylamides with the (meth)acrylamide derivatives of cholic acid (Figure 2, top, where the content of cholic acid residues ranged from 0 to 5 mol%) by free radical copolymerization in solution [8] and studied the LCST and aggregation behavior of the copolymers [9]. In general, the LCST of the acrylamide copolymers can be lowered by the presence of the bile acid residues, as observed clearly by turbidimetry shown in Figure 3A. The lowering of the LCST by the the presence of bile acid in the copolymers shows a linear relationship with the molar content of the methacrylamide derivatives of cholic acid (Figure 3B).

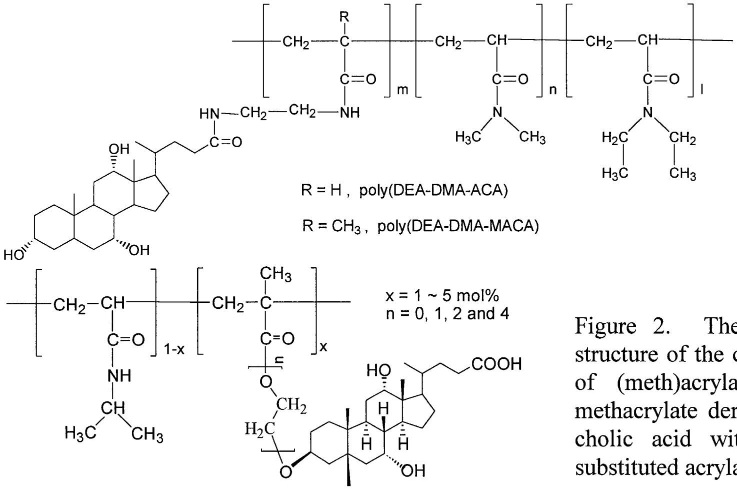

Figure 2. The chemical structure of the copolymers of (meth)acrylamide and methacrylate derivatives of cholic acid with N-alkyl substituted acrylamides.

Alternatively, a double bond can also be attached to one of the OH groups of cholic acid through a short poly(ethylene glycol) (PEG) spacer [10] (Figure 2, bottom structure). The PEG spacer makes the copolymers more hydrophilic and the free carboxylic acid group of the bile acid renders the copolymers with N-alkylacrylamide both thermo- and pH-sensitive [11]. As shown in Figure 4, the LCST of the copolymer is much higher in its ionized form (at higher pH values). The decrease in the LCST at lower pH values is certainly related to the protonation of the carboxylic acid group of the cholic acid moiety in the copolymers, which makes the polymer less hydrophilic.

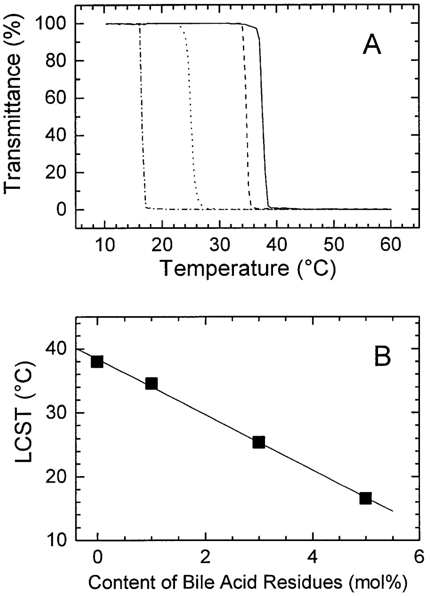

Figure 3. The variation of LCST of poly(DEA-co-DMA-co-MACA) with the molar percentage of MACA. (A) Light transmittance of the 1 wt% polymer solutions at a wavelength of 500 nm with a heating rate of 0.5°C/min. (B) Linear dependence of the LCST of the copolymers on the content of MACA.

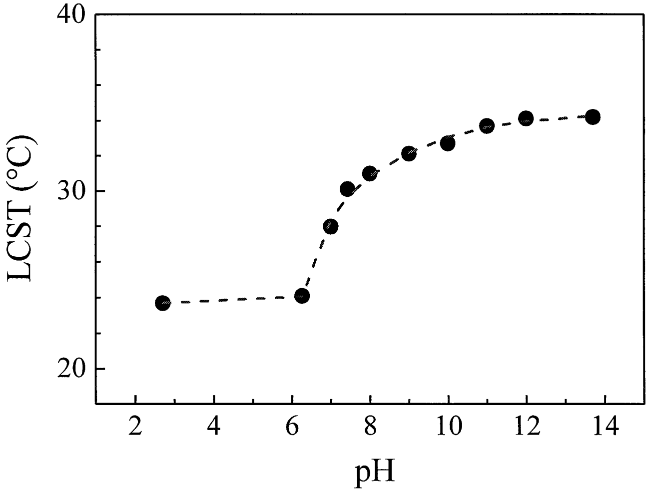

Figure 4. The variation of the LCST as a function of temperature for a copolymer of NIPAM with 3 mol% of methacrylate derivative of cholic acid with a tetra(ethylene glycol) spacer.

## Conclusion

The LCST of the N-alkylacrylamide polymers in water can be modified easily and predictably by copolymerization of the appropriate monomers. Natural compounds such as bile acids can be introduced into such copolymers to modify the aggregation behavior of the linear copolymers and to make new hydrogels. The change of the LCST of such copolymers has been shown to be directly related to the content of the bile acid residues in the materials. The free carboxylic acid group of bile acid makes such polymers sensitive to both temperature and pH changes in the aqueous environment. These properties should be interesting for the potential biomedical applications of such materials.

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