**Summary:** Solutions of poly(N-isopropylacrylamide) (PNIPA) with added sodium dodecyl sulfate (SDS) were investigated by light scattering methods at temperatures of 15–40 °C. The formation of well-defined nanoparticles of PNIPA was observed on heating at low SDS additions. The effects of PNIPA and SDS concentrations and the molecular weight of PNIPA on nanoparticle parameters were investigated. An interpretation based on stabilization of PNIPA nuclei by SDS was suggested.

The proposed mechanism of nanoparticle formation.
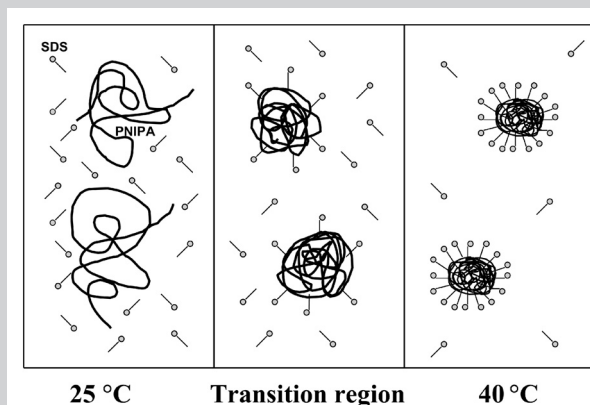
# Thermoresponsive Polymeric Nanoemulsions

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## Introduction

In the past decade stimuli-responsive polymers responding in a desired way to a change in temperature, pH, electric or magnetic field, or other parameters attracted much attention.[1−6] In an aqueous environment, some of the polymers undergo fast, reversible changes in microstructure from a hydrophilic to hydrophobic state triggered by small changes in the environment, which manifest themselves by a precipitate formation. These macroscopic changes are typically reversible and the system returns to its initial state when the trigger is removed. Such highly nonlinear responses make stimuli-responsive polymers ideal candidates for use in biotechnology or medicine.[2−6]

Probably the most often studied systems are those based on poly(N-isopropylacrylamide) (PNIPA).[7−9] PNIPA undergoes the coil-to-globule transition at 32 °C [lower critical solution temperature (LCST)[8]], a property which is the result of rather complex polarity of this molecule. Below the LCST, the amide functionality binds water molecules via hydrogen bonding, thus imparting water solubility to the polymer; above the transition temperature, the hydrogen bonds break and the polymer expels water and precipitates. Its LCST close to physiological temperature makes the polymer an especially good candidate for applications in biotechnology and in medicine.[3,6,10]

In the 1990s several papers dealt with the investigation of the surfactant effect on conformations of thermosensitive macromolecules (mainly PNIPA).[11−19] The main effect obtained is a strong influence of the addition of ionic surfactants on solubilization of PNIPA. The solubilization of PNIPA ($\overline{M}_w = 7 \times 10^6$, $c_{PNIPA} = 5 \times 10^{-5}$ g · mL$^{-1}$) by sodium dodecyl sulfate (SDS) above the LCST proceeds in two distinct steps. At SDS concentrations of only $2.5 \times 10^{-4}$ g · mL$^{-1}$, the aggregation of PNIPA is completely prevented (intermolecular solubilization) and the behavior of isolated polymer molecules in the globule state can be studied above the LCST. Increasing SDS concentration above $3 \times 10^{-4}$ g · mL$^{-1}$ induces the globule-coil transition (intramolecular solubilization) above the LCST. Below the LCST, the surfactant causes expansion of polymer coils.[16] The effects were explained by the formation of polymer surfactant aggregates.

In contrast to previous studies, the formation and properties of PNIPA nanoparticles stabilized by SDS are investigated. The formation of monodisperse nanoparticles

was observed in SDS-PNIPA solutions at SDS concentrations from $2 \times 10^{-5}$ to $5 \times 10^{-4}$ g · mL$^{-1}$ (0.069–$1.75 \times 10^{-3}$ M) in a broad range of PNIPA concentrations $(2 \times 10^{-5} - 1 \times 10^{-3}$ g · mL$^{-1})$ above the LCST. The nanoparticles are assumed to be PNIPA nuclei, which form at the early stage of phase separation, stabilized with SDS. Since the structure of nanoparticles is similar to emulsions, we call the resulting nanoparticles as polymeric nanoemulsions in the title of this paper.

## Experimental Part

### Materials

Linear PNIPA polymers were purchased from Polymer Source Inc. Polymers with viscosity-average molecular weight $M_\eta = 67\,000$, $122\,000$, and $220\,000$ were used for investigation.

Sodium dodecyl sulfate was obtained from Sigma. Q-water was used as a solvent. The critical micelization concentration (CMC) was $2.3 \times 10^{-3}$ g · mL$^{-1}$ ($8.1 \times 10^{-3}$ M).[20]

### Preparation of Nanoparticles

Nanoparticles were prepared by heating SDS-PNIPA solutions above LCST temperature.

Two procedures were used:

(**a**) Fast temperature jump from 25 to 40 °C realized by inserting square (10 mm × 10 mm) or cylindrical (diameter 10 mm) measuring cells with 1 mL of the solution into stirred water bath at 40 °C. The PNIPA transition region ($\approx$32 °C) was reached in 40 s. The cell was then transferred to a preheated sample holder for measurements.

(**b**) Cell with the solution was inserted into Zetasizer at room temperature and heated in 1 °C steps up to 45 °C. On every temperature change, the measurements were performed after reaching the steady conditions, typically after 20 min in the phase separation region.

On cooling, the light scattering data were taken after a fixed waiting time of 20 min.

### Static Light Scattering (SLS)

Static light scattering measurements were carried out with a homemade goniometer with vertically polarized light at wavelength $\lambda_o = 632.8$ nm, using the angular range of 30–140°, and temperatures from 25 to 40 °C. To obtain weight-average molecular weight $\overline{M}_w$ and radius of gyration $R_g$, scattering curves in the Zimm plot were extrapolated to zero angle.

Since the concentrations of the solutions used for measurements were very low (below $5 \times 10^{-4}$ g · mL$^{-1}$), the measured apparent molecular weights $M_{wa}$ well approximate the $\overline{M}_w$ values at infinite dilution.

The refractive index increment (d$n$/d$c$) of PNIPA (0.194 mL · g$^{-1}$) was measured in water with a Brice-Phoenix refractometer at the wavelength of 633 nm.[21]

### Dynamic Light Scattering (DLS)

Polarized DLS measurements were made in the angular range of 30–135° using the same homemade goniometer equipped with an ALV 5000, multibit, multi-tau autocorrelator covering approximately 10 decades in delay times, $\tau$.

The time autocorrelation functions were fitted assuming the Pearson distribution of characteristic relaxation times, $\tau_c$:[22,23]

$$z(\tau_c) = \tau_o^p \tau_c^{-p-1} \exp(-\tau_c/\tau_o)/\Gamma(p) \qquad (1)$$

where $\tau_o$ and $p$ are parameters, and $\Gamma(p)$ is the gamma function of parameter $p$. The average hydrodynamic radius, $R_h$, was calculated from the diffusion coefficient, using the Stokes-Einstein equation.

The static and dynamic light scattering was also measured at an angle of 173° on a Nano-ZS, Model ZEN3600 (Malvern, UK) zetasizer. The apparatus was used mainly for automated measurement of temperature dependences of particle size ($R_h$) and scattering intensity ($I_s$). For evaluation of data, the DTS(Nano) program was used. The mean positions of the peaks in intensity-hydrodynamic radius ($R_h$) distribution were taken for data representation. The temperature dependences of $I_s$ were only used for the determination of the transition temperature, $T_{tr}$.

## Results

In contrast to previous studies,[15–18] where a high-molecular-weight PNIPA was used, lower molecular weight polymers were used in the present study. The SDS concentrations $c_{SDS} \leq 5 \times 10^{-4}$ g · mL$^{-1}$ are not able to prevent intermolecular aggregation; hence, PNIPA aggregates form well-defined nanoparticles. This is demonstrated in Figure 1 where the temperature dependence of light scattering intensity, $I_s$, measured at $\theta = 173°$ is shown for polymer concentration $c_{PNIPA} = 5 \times 10^{-4}$ g · mL$^{-1}$ and SDS concentration $c_{SDS} = 5 \times 10^{-5}$ g · mL$^{-1}$. $M_\eta$ of the PNIPA used was $122\,000$.

The parameters of nanoparticles at 40 °C [procedure (**a**)] are as follows: $M_{wa} = 1.3 \times 10^7$, $R_h = 25.2$ nm, and $\Delta R_h/R_h$ ($\Delta R_h$ is the halfwidth at the halfheight of the $R_h$ distribution) = 0.15 and the particle density $\rho_p = 0.32$ g · mL$^{-1}$. The nanoparticles are stable for at least 24 h. The particle density was calculated using the hydrodrodynamic volume of particles $V_h$ ($V_h = 4\pi R_h^3/3$) and $M_{wa}$ of nanoparticles. The parameters are practically the same for both the preparation methods. The only difference between the results is the presence of a small amount of large aggregates in solution prepared by the slow heating. While steady values of $I_s$ obtained on heating were used for plotting in Figure 1, the $I_s$ values measured on cooling were obtained after a fixed waiting time of 20 min. Since dissolution of nanoparticles on cooling is a slow process, 20 min was not sufficient for reaching steady conditions. Therefore, the observed hysteresis in Figure 1 is mostly due to kinetics of nanoparticle dissolution. The particle residues are detected
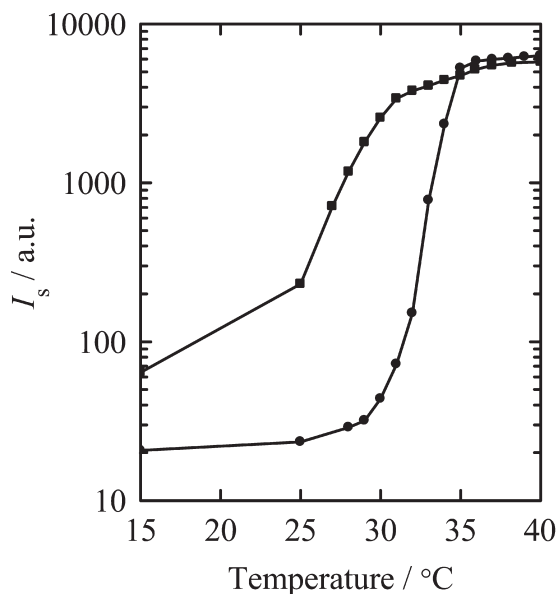
Figure 1. Temperature dependence of the scattered light intensity $I_s$ at $\theta = 173°$; ($\bullet$) measured on heating [procedure (**b**)]; ($\blacksquare$) slow stepwise cooling [procedure (**b**)] after fast heating of solution to $40\,°C$ [procedure (**a**)]; $M_\eta = 122\,000$, $c_{PNIPA} = 5 \times 10^{-4}$, and $c_{SDS} = 5 \times 10^{-5}\,g \cdot mL^{-1}$.
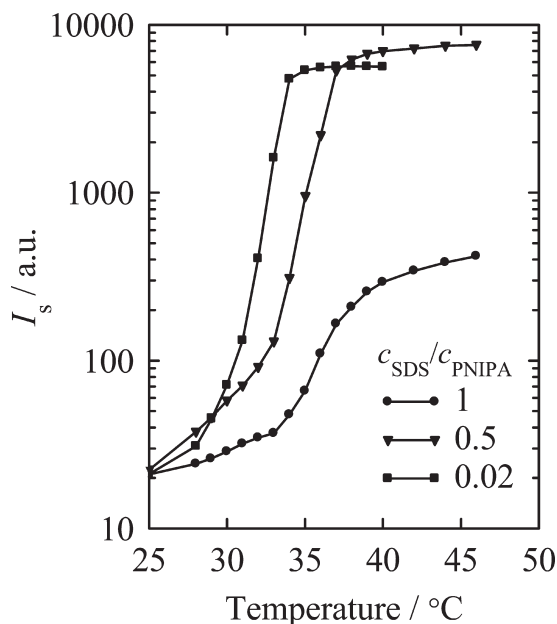


Figure 2. Effect of SDS concentration ($c_{SDS}/c_{PNIPA}$) on the phase transition tested by scattered light intensity $I_s$ [procedure (**b**)]; $M_\eta = 122\,000$, $c_{PNIPA} = 5 \times 10^{-4}\,g \cdot mL^{-1}$.

even after 5 h of stepwise cooling at 15 °C where $I_s$ obtained after cooling [procedure (**b**)] is distinctly higher than $I_s$ of the starting polymer solution. The aggregates are fully dissolved after 24 h at 3 °C and the solution can be used for further experiments.

The effect of SDS concentration on the temperature dependence of the light scattering intensity, $I_s$, measured at $\theta = 173°$ is shown for solutions with polymer concentration $c_{PNIPA} = 5 \times 10^{-4}\,g \cdot mL^{-1}$ in Figure 2.

$I_s$ values at temperatures above the LCST are for the solution with $c_{SDS}/c_{PNIPA} = 1$ distinctly smaller than $I_s$ for solutions with lower SDS contents, where only small differences on the level of measurement reproducibility were observed. The effect can be explained in accord with previously published results. Solubilization of PNIPA increases with increasing content of SDS, which manifests itself in the suppression of intermolecular aggregation. Other parameters of the PNIPA-SDS solution are also influenced by the SDS content. Transition temperature $T_{tr}$ increases upon increasing the $c_{SDS}/c_{PNIPA}$ ratio (Figure 3).

$M_{wa}$ and $R_h$ values of resulting nanoparticles (at 40 °C) decrease with increasing $c_{SDS}/c_{PNIPA}$ ratio reflecting again the effect of increasing solubilization of PNIPA with SDS (Figure 3). Polydispersity $\Delta R_h/R_h$ of nanoparticles changes with $c_{SDS}/c_{PNIPA}$ in a more complex way (see Figure 3). The best nanoparticles with a polydispersity comparable with micelles were observed at $c_{SDS}/c_{PNIPA} = 0.02$ or 1.

The parameters of nanoparticles are also dependent on concentration of PNIPA in solution. The $c_{PNIPA}$-dependences of $M_{wa}$, $R_h$, and the polydispersity $\Delta R_h/R_h$ are shown
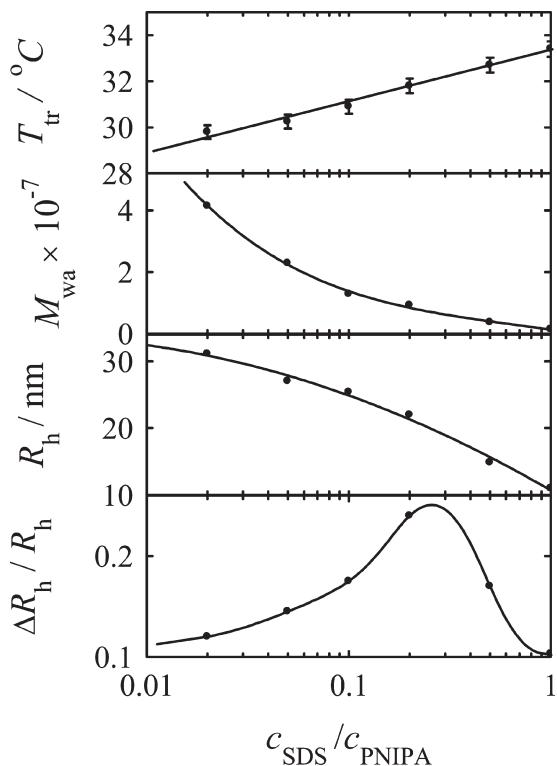


Figure 3. Dependences of the transition temperature, $T_{tr}$, molecular weight, $M_{wa}$, hydrodynamic radius, $R_h$, and size polydispersity, $\Delta R_h/R_h$ of nanoparticles on $c_{SDS}/c_{PNIPA}$ at 40 °C [procedure (**a**)]; $M_\eta = 122\,000$, $c_{PNIPA} = 5 \times 10^{-4}\,g \cdot mL^{-1}$.
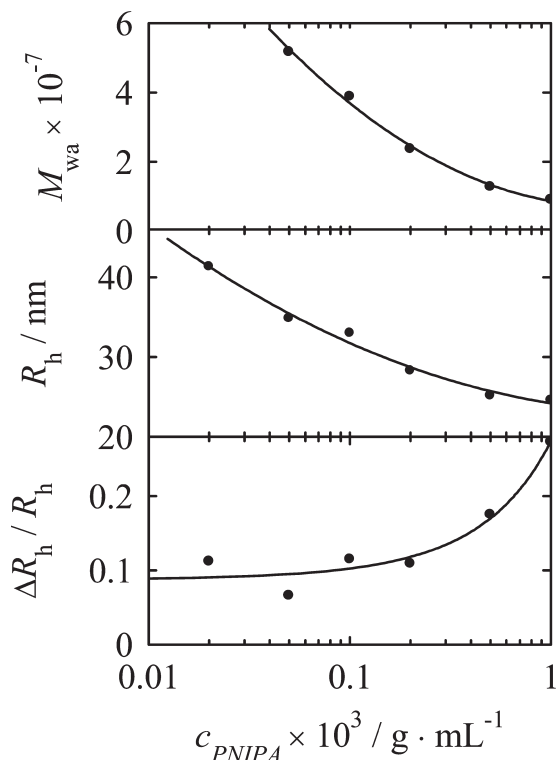
Figure 4.  Concentration dependence of the molecular weight, $M_{wa}$, hydrodynamic radius, $R_h$, and size polydispersitty, $\Delta R_h/R_h$ of nanoparticles at 40 °C [procedure (**a**)]; $M_\eta = 122\,000$, $c_{SDS}/c_{PNIPA} = 0.1$.

for solutions with the fixed $c_{SDS}/c_{PNIPA} = 0.1$ in Figure 4. $M_{wa}$ and $R_h$ values decrease with increasing $c_{PNIPA}$.

In contrast, $\Delta R_h/R_h$ increases upon increasing $c_{PNIPA}$. Thus, the best monodisperse nanoparticles ($\Delta R_h/R_h < 0.1$) can be prepared at low values of $c_{PNIPA}$. As to the transition temperature, $T_{tr}$ decreases with increasing $c_{PNIPA}$ but only little by 1 °C in the $c_{PNIPA}$ range of $2 \times 10^{-5}$–$5 \times 10^{-4}$ g·mL$^{-1}$.

The parameters of nanoparticles are strongly dependent on molecular weight of PNIPA. The characteristics of nanoparticles obtained for three molecular weights of PNIPA at $c_{PNIPA} = 5 \times 10^{-4}$ and $c_{SDS} = 5 \times 10^{-5}$ g·mL$^{-1}$ are given in Table 1.

$M_{wa}$ and $R_h$ of nanoparticles decrease with increasing $M_\eta$. This behavior is explained in the *Discussion*.

Table 1.  Characteristics of nanoparticles for three molecular weights of PNIPA at 40 °C [procedure (**a**)]; $c_{PNIPA} = 5 \times 10^{-4}$ and $c_{SDS} = 5 \times 10^{-5}$ g·mL$^{-1}$.

| PNIPA $M_\eta \times 10^{-3}$ | Nanoparticles $M_{wa} \times 10^{-6}$ | $R_h$ nm | $\Delta R_h/R_h$ |
|---|---|---|---|
| 67 | 78 | 46.0 | 0.09 |
| 122 | 13 | 25.2 | 0.15 |
| 220 | 5.0 | 21.0 | 0.13 |

## Discussion

The observed formation of well-defined thermosensitive nanoparticles can be qualitatively explained as follows. It is well known that nuclei of a new phase formed after passing of the system through the phase transition point are monodisperse at the early stage of phase separation.[24,25] In the particular case, we speak about the phase transition from single-phase regime (solution) to two-phase regime (precipitated PNIPA and solution) on heating above the transition temperature. The nuclei of PNIPA are hydrophobic and, therefore, they attract SDS molecules. If the adsorbed SDS reaches a critical surface concentration, the nanoparticles are sufficiently solubilized and the growth of nanoparticles stops. The nanoparticles covered with SDS are protected against aggregation by repulsive electrostatic interactions.

Now, the effect of SDS concentration on parameters of nanoparticles can be understood. The higher the SDS concentration, the faster is the reaching of the critical concentration of SDS on the nuclei surface and nucleation stops earlier at smaller values of $M_{wa}$ and $R_h$.

As to the effect of polymer concentration on $M_{wa}$ and $R_h$ of nanoparticles at the constant ratio $c_{SDS}/c_{PNIPA} = 0.1$, the situation is more complicated. Both the phase transition kinetics and transport properties of SDS are slowed down simultaneously on dilution. Therefore, a detailed explanation of the obtained results is impossible at the interpretation level used. The partial solubilization of PNIPA on molecular level by SDS, which should be more effective at higher concentrations, could be responsible for the observed decrease in $M_{wa}$ and $R_h$ with increasing concentration.

Since the growth rate of nuclei is among others controlled by polymer diffusion,[24,25] the effect of molecular weight of PNIPA ($M_\eta$) on $M_{wa}$ and $R_h$ of nanoparticles can be explained. While the transport of SDS is independent of $M_\eta$, the growth rate of nuclei slows down with increasing $M_\eta$. As a consequence, the growth of PNIPA nuclei stops with SDS sorption earlier at smaller sizes for high $M_\eta$ than at low ones. Therefore, $M_{wa}$ and $R_h$ of nanoparticles decrease with increasing $M_\eta$.

The formation of the nanoparticles is generally a very complex process based on the phase transition kinetics and transport properties of species. Therefore, a detailed interpretation of the obtained results is impossible at this state of knowledge.

## Conclusion

Solutions of PNIPA and SDS mixtures were investigated by light scattering in the temperature region of 15–40 °C. In contrast to previous studies, where surfactants were used in excess, lower concentrations of SDS were used. Under such conditions, PNIPA forms well-defined nanoparticles

(e.g., $M_{wa} = 1.3 \times 10^7$, $R_h = 25.2$ nm at $c_{PNIPA} = 5 \times 10^{-4}$ g·mL$^{-1}$, $c_{SDS} = 5 \times 10^{-5}$ g·mL$^{-1}$ and at 40 °C). The effect of PNIPA and SDS concentration and of molecular weight of PNIPA on the $M_{wa}$, $R_h$, and $T_{tr}$ of thermosensitive nanoparticles was investigated. The following properties of nanoparticles were observed:

(1) Transition temperature $T_{tr}$ of PNIPA phase separation increases with increasing value of $c_{SDS}/c_{PNIPA}$. $M_{wa}$ and $R_h$ values of resulting thermosensitive nanoparticles (at 40 °C) decreases with increasing $c_{SDS}/c_{PNIPA}$ ratio.

(2) Parameters of nanoparticles are also dependent on the concentration of PNIPA in solution. $M_{wa}$ and $R_h$ decrease with increasing $c_{PNIPA}$. In contrast, $\Delta R_h/R_h$ increases with increasing $c_{PNIPA}$.

(3) $M_{wa}$ and $R_h$ of nanoparticles decrease with increasing $M_\eta$ of PNIPA.

The observed formation of well-defined thermosensitive nanoparticles can be qualitatively explained by stabilization of monodisperse nuclei of PNIPA with SDS in the transition region of phase separation of PNIPA. The adsorbed SDS hydrophilizes the nanoparticle surface. If the amount of adsorbed SDS reaches the critical surface concentration, the nanoparticles are sufficiently solubilized and the growth of nanoparticles stops. Since the structure of nanoparticles is similar to emulsions, we suggest calling them thermoresponsive polymeric nanoemulsions. Further experiments with various surfactants are in progress.

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