Polym. Bull. (2011) 67:677–692
DOI 10.1007/s00289-011-0458-3

ORIGINAL PAPER

Behaviour of stereoblock poly(*N*-isopropyl acrylamide) in acetone–water mixtures

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Received: 16 July 2010 / Revised: 15 December 2010 / Accepted: 11 February 2011 /
Published online: 19 February 2011

Abstract The purpose of this study was to investigate the usability of poly(*N*-isopropyl acrylamide) (PNIPAM) as an additive for crystallization of a model drug, nitrofurantoin (NF), and utilizing the thermoresponsivity of the polymer to enable control of the viscosity during the crystallization process. Crystallization of NF in the presence of PNIPAM resulted in dendritic crystal growth and the originally observed growth of needle-shaped crystals was prohibited. The effect of acetone, a cosolvent used for the crystallization, on thermosensitivity of PNIPAM was studied and the properties of atactic PNIPAM and triblock PNIPAM polymers containing atactic and isotactic rich blocks were compared. The investigated PNIPAMs were all soluble in the acetone–water mixtures leading to phase separation at lower temperatures with increasing acetone content, up to approximately 50 vol% (0.20 mol fraction). At higher acetone contents no phase separation was observed on heating. The presence of acetone altered the viscosity of the solutions prior to the phase separation depending on the polymer architecture. The PNIPAM polymers induced smaller and potentially more easily processable crystals, however, the viscosity increase in the presence of acetone occurred only 1–3 °C prior to phase separation complicating the practical use of this approach.

Keywords Poly(*N*-isopropyl acrylamide) · Phase separation · Rheology · Turbidity · Solvent mixtures · Crystallization

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Introduction

In the recent years, there has been an increasing interest in polymers with thermosensitive properties. These materials have been used for various applications, such as for wound healing, viscosity adjustment and excipients in pharmaceutical formulations with controlled release of active pharmaceutical substances [1, 2]. Another attractive application of thermally sensitive polymer would be the use as additives in crystallization processes to be able to control and modify the properties of the crystallization outcome. For the pharmaceutical industry controlled crystallization is of great interest as it represents a possible way to improve the solid state properties of materials in order to overcome technical difficulties during processing and to improve the solubility of especially poorly water soluble drug molecules [3–5]. Crystal size and shape have great influence on powder flowability, compressibility and on mixing ability with excipients used in drug formulation. The majority of new active pharmaceutical ingredients (API) are poorly soluble in water but permeate well over the intestinal membrane (Biopharmaceutics Classification System, BCS class II compounds). The bioavailability of BCS class II compounds can be improved, e.g. by minimizing the crystal size and thus increasing the surface area and thereby the dissolution rate. Crystallization processes in pharmaceutical industry are typically batch cooling operations. The use of thermally sensitive polymers would enable maximized nucleation rate at higher temperatures due to the high viscosity that restrains the diffusion of the drug molecules and thereby nucleation dominates over growth of already existing nuclei. Furthermore, the thermoresponsive polymers enable optimal crystal separation at low temperatures with lower viscosity in a given system. However, crystallization of pharmaceuticals often involves the use of organic cosolvent in aqueous solution and therefore evaluation of the functionality of the polymer in water–organic solvent mixtures needed.

Atactic (a) poly(*N*-isopropyl acrylamide) (PNIPAM) is a thermosensitive polymer in aqueous solutions. At temperatures below a specific temperature ($\sim$31 °C) atactic PNIPAM is water soluble, but phase separates on heating [6, 7]. The phase separation takes place in a narrow temperature range almost independently of the polymer concentration. At low concentrations colloidally stable aggregates (mesoglobules) may be formed [8], while at higher concentrations macroscopic precipitation often occurs. By modifying the structure of the polymer, for instance, by incorporating different hydrophobic side groups, PNIPAM-based materials are able to form micelles at temperatures below the phase transition. A similar effect has been achieved by introducing isotactic (i) rich blocks in the PNIPAM resulting in triblock structures having either isotactic or atactic end blocks and atactic or isotactic centre block, respectively [9–11].

Water, small alcohols and aprotic polar organic solvents like acetone, DMSO and THF are all good solvents for the atactic PNIPAM [12, 13]. However, at certain ratios of water and organic solvent PNIPAM becomes poorly soluble, a phenomena known as cononsolvency [13]. Cononsolvency has previously been observed for mixtures of water with methanol [14], THF and DMSO [13]. In addition, the

presence of organic solvent has been found to lead to lowering of the phase-transition temperature as compared to an aqueous solution.

The hydration and dehydration of PNIPAM is assumed to take place through the recently introduced concept of cooperative hydration [15–17]. When a hydrogen bond between a water molecule and an amide group in the polymer chain is formed, the polymer chain changes conformation, facilitating hydrogen bonding to the next monomer and so forth. The concept of cooperative hydration explains the instant hydration/dehydration behaviour of PNIPAM in a narrow temperature range almost independently of concentration.

In this study, the working hypothesis is that chemical properties of the PNIPAM polymer favourably affect the morphology of the poorly soluble nitrofurantoin (NF) monohydrate crystals giving increased surface area and thereby increase the bioavailability; whereas the thermoresponsive properties of the PNIPAM is used to control the viscosity of the system, giving high viscosity during crystallization thus minimizing the size of the obtained crystals, and low viscosity during separation of the crystals from the system, thus easing the filtration or other separation processes. For this purpose, the crystallization of NF is studied in the presence of three different PNIPAM polymers, atactic, triblock with atactic end blocks and isotactic centre block (a–i–a), and tri-block with atactic centre block and isotactic ends (i–a–i). Furthermore, as the crystallization medium often includes both the organic solvent (e.g. acetone) and water, the thermal behaviour of aqueous solutions of the three PNIPAMs is scrutinized in the presence of various amounts of acetone.

Materials and methods

Materials and sample preparation

Three different PNIPAM polymers are investigated, a24.3 which is atactic and two PNIPAM triblock polymers composed of atactic and isotactic rich blocks, a12–i10–a12 and i5–a70–i5. The structure of the polymers is identified with its abbreviation, e.g. a12–i10–a12 stands for a polymer where the isotactic rich block is in the middle with the atactic blocks placed at the ends of the polymer chain, while the numbers denote the block size in kg/mol. The isotactic content of isotactic block is approximately 70% [11]. The molecular weight of the polymers was investigated previously with SEC against PMMA standards [11] to be 24,300 ($M_w/M_n = 1.22$), 34,500 ($M_w/M_n = 1.37$) and 64,700 ($M_w/M_n = 1.31$) for a24.3, a12–i10–a12 and i5–a70–i5, respectively. The synthesis and characterization of the polymers has been described in detail in a previous publication [11].

For the use in the experiments, 50 mg/mL stock solutions of each polymer in deionized water were prepared. Appropriate amounts of stock solution, deionized water and acetone (Sigma-Aldrich, HPLC grade) was mixed to achieve to the desired acetone content (vol%) and a final polymer concentration of 10 mg/mL. All PNIPAM solutions were allowed to stand for minimum 5 days at 5 °C to ensure a complete dissolution of the polymers.

Crystallization

For the crystallization experiments solution containing 10 mg/mL PNIPAM in 67 vol% acetone was prepared and NF anhydrate (Unikem, Denmark, Ph.Eur. grade) added until to a final concentration of 2.5 mg/mL. 20 μL drops of the prepared solution were then placed on glass slides and solvent was allowed to evaporate freely at a controlled temperature (27 °C) on a Krüss G12 hot stage. The temperature of the glass slide was equilibrated and checked with an IR-thermometer before a drop of the NF solution was placed on the slide, and the evaporation of the solvents consequently led to the crystallization of the drug.

Light microscopy

A Zeiss Axiolab microscope (Carl Zeiss) was used to observe the size and the morphology of the final crystals. The microscope was equipped with a DeltaPix digital camera with a resolution of 1280 × 1024 pixels (Maaloev, Denmark). DeltaPix software version 1.6 (Maaloev, Denmark) was used to acquire detailed pictures of the crystals. The size of the view field was 1.1 × 0.7 mm.

Turbidity measurements

The phase-transition temperatures of the solutions were determined by turbidity measurement on a Thermo Scientific Evolution 300 UV/VIS spectrophotometer. The turbidity of the polymer solutions (10 mg/mL) was measured at 500 nm using a 1 cm quartz cuvette with magnetic stirring. The temperature range measured went from 5 to 40 °C with a temperature increase of 0.5 °C/min. The cuvettes were covered with a lid to minimize evaporation. The phase-transition temperature was obtained from the intercept of the baseline and a straight line fitted to the steep increase of the turbidity.

Thermal analysis

Enthalpy changes of PNIPAM solutions were studied using a TA NanoDSC (TA Instruments). Solutions with 1 and 10 mg/mL PNIPAM in 0, 20, 33, 42 vol% (0, 0.06, 0.11, 0.15 mol fraction) acetone were loaded into 0.33 mL capillary cells. Thermal analysis was performed in the range of 5–60 °C with a temperature increase of 1 °C/min under a pressure of three atmospheres, after which data were analysed using NanoAnalyze software version 2.0.1 (TA Instruments). The phase-transition temperature was determined as the intercept of the baseline before the first endothermic event and the up-going slope of the first endothermic event. After filling the capillary tube, the chamber was closed with a lit. The pressure in this chamber will change during heating due to changed gas pressure of the solvents. By using pre-compression, the pressure was kept constant.

Rheological characterization

Oscillatory experiments were conducted with a TA AR-G2 rheometer (TA Instruments) using a stainless steel cone and plate geometry with a diameter of 60 mm and 1° cone angle. A cover was used to reduce the evaporation of acetone during the measurement. During the measurement, the temperature was controlled with a Peltier element in the plate. The linear viscoelastic regime was established by oscillatory strain experiments at 0.316 rad/s which showed viscoelastic linearity of all samples at 0.01 strain and consequently strain was set to 0.01 in the frequency sweeps. The frequency sweeps were conducted from 0.1 to 100 rad/s at temperatures ranging 10–40 °C with either 1 or 5 °C intervals for both 10 and 50 mg/mL solutions. The dynamic moduli (G' and G'') were monitored as function of frequency and temperature. As the storage modulus (G') does not contribute much to the profile of such dilute system the complex viscosity (η^*) (Eq. 1) was used for the evaluation of the overall temperature profile of the samples as it takes into account both the storage modulus (G') and the loss modulus (G''), where ω is the angular frequency:

$$|\eta^*(\omega)| = \frac{\sqrt{G'(\omega)^2 + G''(\omega)^2}}{\omega} \tag{1}$$

Results and discussion

In this study, PNIPAM triblock polymers consisting of atactic (a) and isotactic (i) blocks (i5–a70–i5, a12–i10–a12) are investigated and compared to atactic reference materials (a24.3). The chemical structure is shown in Fig. 1a. At room temperature, the atactic block is water soluble, whereas the isotactic block is not [18, 19]. Nuopponen et al. have shown that in dilute conditions triblock PNIPAMs form "flower-like" or "branched" micelles below the phase-transition temperature depending on the order of atactic and isotactic blocks (Fig. 1b, c) [10]. The triblock PNIPAM chains form micelles with a hydrophobic core and a hydrophilic outer shell [10], rich in isotactic blocks and atactic blocks, respectively. At higher concentrations (>45 mg/mL) interconnections between micelles has been observed for the i–a–i polymer leading to gelling at room temperature [9]. This difference in architecture of the polymers allows investigation of the effect of this parameter alone on the crystallization process, as the polymers are chemically similar.

Crystallization of nitrofurantoin monohydrate

The presence of PNIPAM polymer during crystallization of NF monohydrate leads to an obvious change in the morphology of the achieved crystals. When NF is crystallized from acetone–water solutions with no polymer present, needle-shaped crystals are obtained as shown in Fig. 2a. All crystallization experiments resulted in the same NF solid state, confirmed by X-ray powder diffraction and Raman microscope as preformed in previous study [20]. Crystallization of NF in the

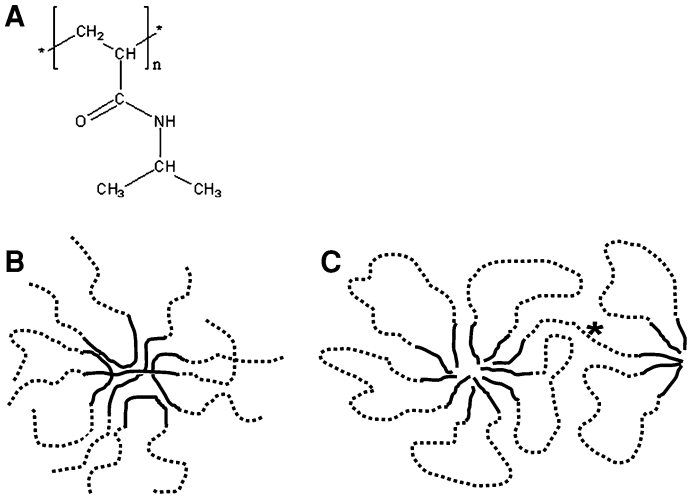

Fig. 1 Chemical structure of PNIPAM (**a**) and schematic illustration of branched a–i–a (**b**) and flowerlike i–a–i (**c**) micelles in dilute aqueous solution. Atactic part: *Dashed line*. Isotactic part: *Solid line*. At sufficient high concentration the flower-like micelles (**c**) can be interconnected with polymer chains an example is marked with *asterisks*

presence of <3.3 mg/mL of PNIPAM in 67 vol% acetone in aqueous solution, does not influence the morphology of the obtained NF crystals. However, in the presence of 10 or 20 mg/mL PNIPAM the shape of the obtained NF crystals is triangular and no needle growth can be observed, as shown in Fig. 2b–d. The same overall crystal morphology is achieved with all studied PNIPAM polymer solutions. The architectural difference between the a12i10a12 and the i5a70i5 PNIPAM appears to influence the size of the achieved crystals. The crystals grown in the presence of i5a70i5 are smaller compared to those crystals grown in the presence of a24.3 and a12i10a12. The differences in crystal size could be attributed to the larger viscosity rise of i5a70i5 with increasing polymer concentration as compared to a24.3 and a12i10a12 (Fig. 6a, b), further discussed below. The level of interactions between the NF and the polymer, the possible incorporation of polymer in the crystal, as well as the performance of modified NF in pharmaceutical formulations needs further investigation. However, the observed morphology change preventing formation of needle-shaped crystals is desired as the following downstream processing, e.g. mixing and compression, of needle-shaped crystals is generally known to be a challenge. Therefore, the thermoresponsive properties of the PNIPAM for the use as a viscosity control of the system were scrutinized further.

Phase-transition characteristics

As discussed earlier, the crystallization of NF involves the organic solvent acetone, in order to improve the yield. Therefore, the influence of the presence of acetone on the thermal characteristics is studied in detail. Although the aqueous solution properties of PNIPAM have been widely studied, most of the studies are limited

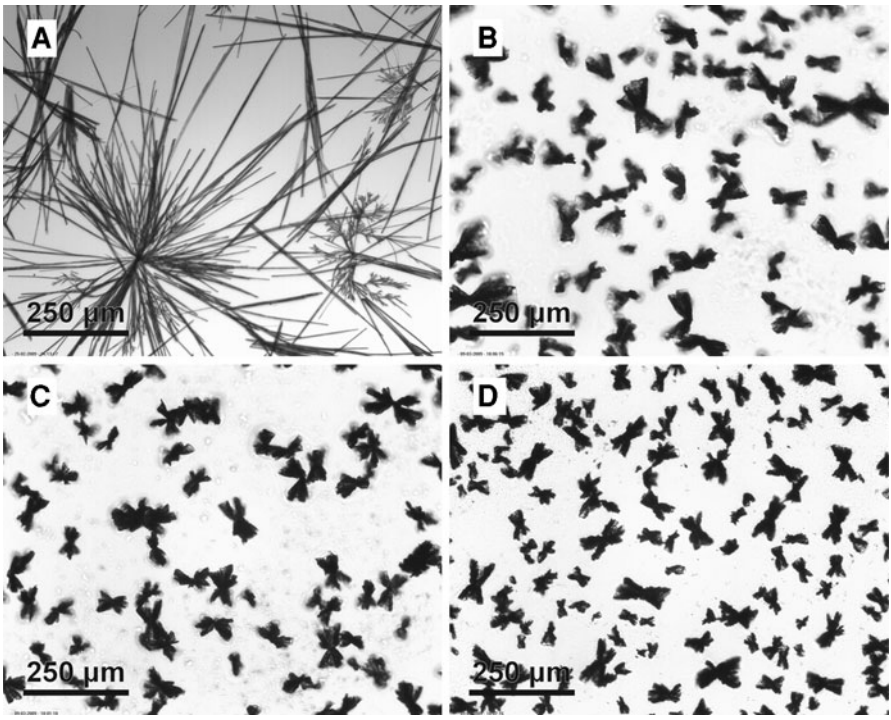

Fig. 2 Nitrofurantoin monohydrate crystallized at 27 °C with initial condition of 67 vol% acetone with **a** no addition of polymer, **b** 10 mg/mL w/v a24.3, **c** 10 mg/mL w/v a12i10a12 and **d** 10 mg/mL w/v i5a70i5

solely to atactic PNIPAM. In addition, the thermosensitive properties of PNIPAM change with varied solvent composition, as previously shown for water/methanol [21] and other water–organic solvent mixtures [22].

The phase separation temperatures (PST) of the different PNIPAMs (10 mg/mL) in aqueous solutions containing acetone are investigated by turbidity measurements. The PSTs are highly dependent on both the acetone content and the composition of PNIPAM triblock polymer (Fig. 3). With increasing acetone content in the polymer solution, the PST decreases to a minimum at an acetone content around 33–50 vol% depending on the structure of PNIPAM polymer. A sharp transition in a narrow temperature range is observed for a24.3 and a12–i10–a12 at all solvent compositions, with the a24.3 showing a slightly sharper transition than that of a12–i10–a12. In contrast, the i5–a70–i5 shows a broad phase transition that becomes even broader with increasing acetone content. The lowering of the PST and the broadening of the phase separation indicate that the stability of the hydrogen bonds between PNIPAM and water is lowered due to decreased water content and dynamic complex formation between water and acetone.

The conversion between one-phase and two-phase system in the cononsolvency area is fully reversible at temperatures from 5 to 40 °C. The PST decreases with increasing acetone content for the studied polymers up to $\sim$35 vol% acetone after

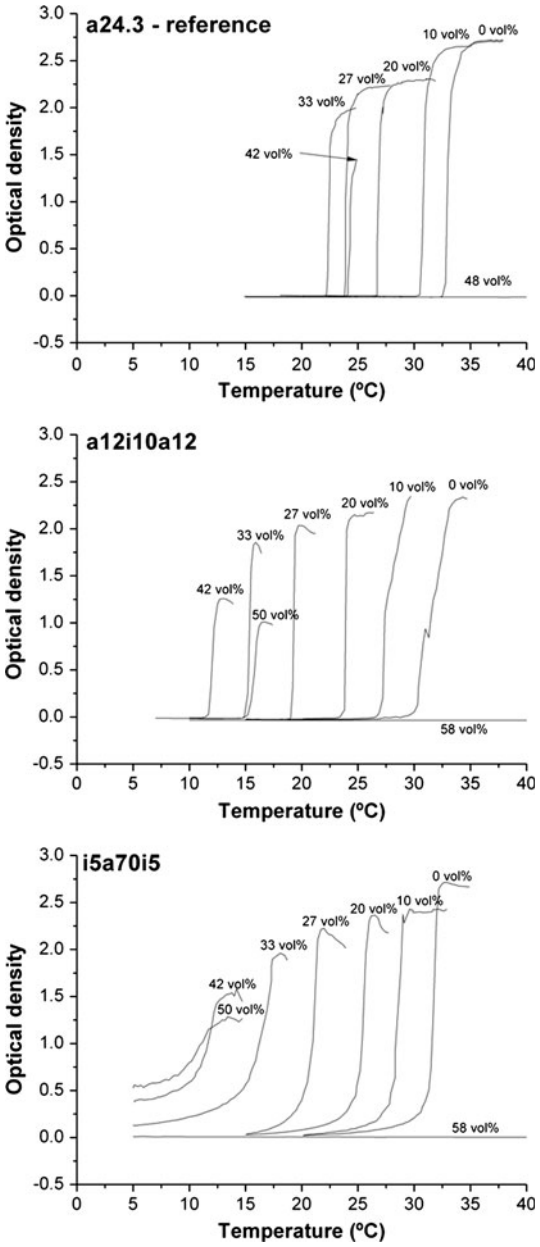

Fig. 3 Turbidity measurements of a24.3, a12i10a12 and i5a70i5 (10 mg/mL) PNIPAM in different composition of acetone and water for determination of the phase separation temperature. The acetone content is indicated in vol% at each curve

which there is a slight increase for a24.3 and a12i10a12 before disappearance of the PST at 48 and 58 vol% for the a24.3 and the modified polymers, respectively (Fig. 4). The PST for atactic PNIPAM in different water–organic solvent mixtures has previously been investigated by several authors, and similar cononsolvency behaviour was observed [12, 13, 21, 23–26]. In general, the studies showed that the

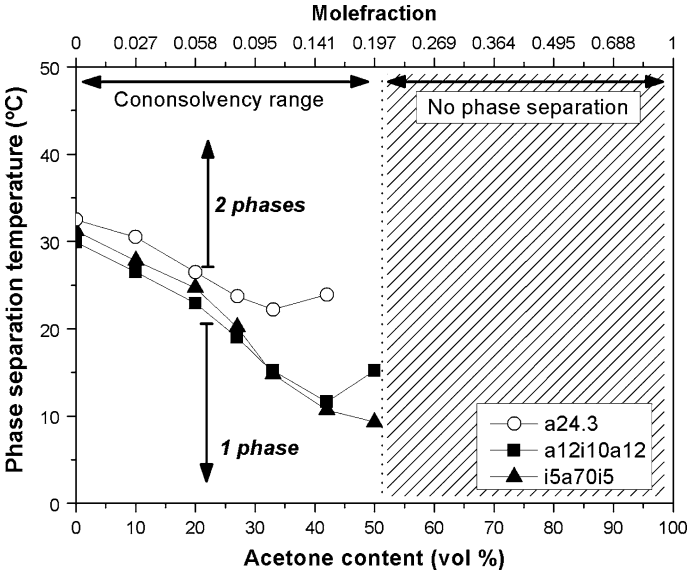

Fig. 4 Phase diagram for a24.3, a12i10a12 and i5a70i5 PNIPAM polymer (10 mg/mL) in different acetone–water mixtures

addition of organic solvents decreases the PST of PNIPAM. In water–methanol mixtures, cononsolvency has been observed between 10 and 65 vol% methanol (0.05–0.45 mol fraction); the phenomenon being explained by complexation between methanol and water molecules and, thereby, a decrease in the ability of water to hydrate the PNIPAM polymer [21, 25, 26]. In the methanol–water mixtures, the phase separation was no longer observed when the mole fraction of methanol was above 0.45 [21, 22], above this concentration uncomplexed methanol in the solvent dissolved the PNIPAM polymer [25–29]. This behaviour is similar to current observations in the acetone–water system. In a binary mixture, acetone and water can form at least three different complexes, where one acetone molecule makes complex with one, four or ten water molecules [30–32]. The acetone–$(H_2O)_4$ complex is the most stable of the three observed complexes [31, 32]. Above 50 vol% acetone content (0.20 mol fraction) not all the acetone molecules can be occupied in the form of the most stable acetone–$(H_2O)_4$ complex, and increased amounts of free acetone molecules will be present in the solution. The excess acetone changes the thermal behaviour of the system preventing the phase separation by dissolving the polymer. In the present case, it is noteworthy when comparing the behaviour of atactic PNIPAM and the hydrophobic modified triblock PNIPAMs that both the phase-transition temperatures and the cononsolvency range polymers differs. The triblock polymers do not undergo phase transition at acetone contents above 50 vol% at any temperatures, while no phase separation is observed for the atactic PNIPAM already at acetone contents above 42 vol%. It is therefore assumed that the aggregation induced by the isotactic rich blocks leads to different phase-transition behaviour than the atactic PNIPAM. In addition, the assumed

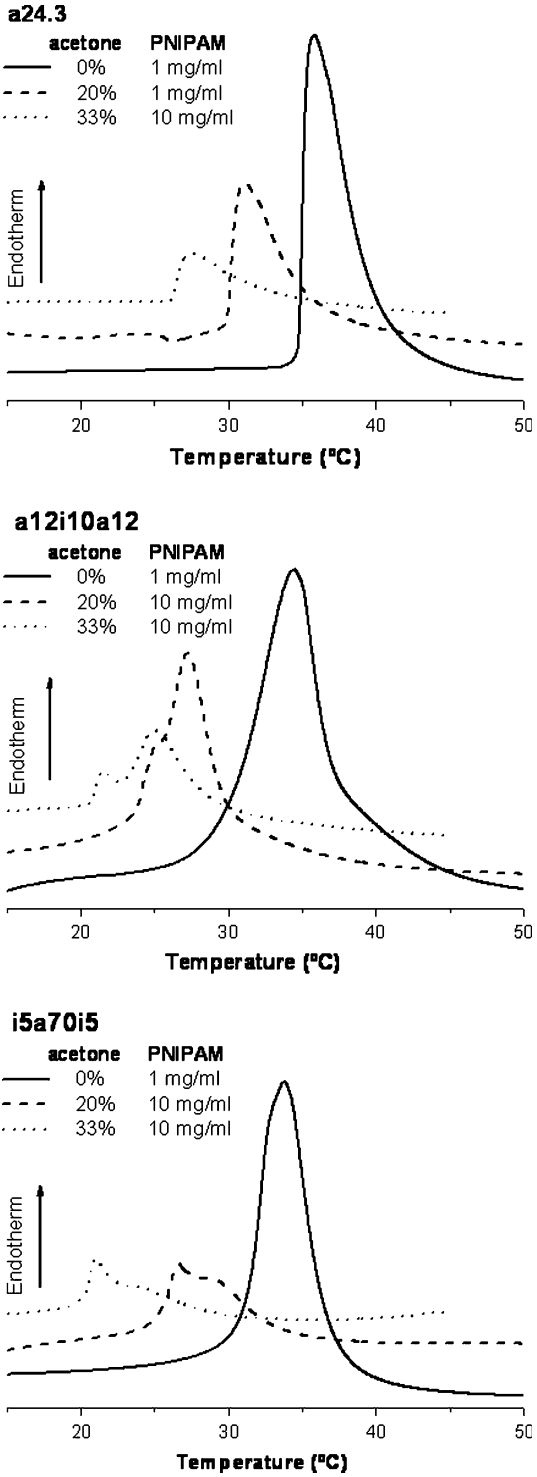

Fig. 5 Thermograms of a24.3, a12i10a12 and i5a70i5 PNIPAM in solutions with three different acetone and water compositions. The acetone content is indicated at each curve in vol%. As the enthalpy change decreased with increasing amount of acetone added the measurements were conducted at different PNIPAM concentrations, which are indicated in the figure

Table 1 Comparison of phase separation temperatures (PST) determined by turbidity and calorimetry

Acetone content	PST determined by turbidity			PST determined by calorimetry		
	0 vol%	20 vol%	33 vol%	0 vol%	20 vol%	33 vol%
a24.3	32.5 °C	26.5 °C	22.2 °C	34.5 °C	29.5 °C	26.5 °C
a12i10a12	29.9 °C	22.9 °C	15 °C	30 °C	25 °C	20.5 °C
i5a70i5	31.2 °C	24.7 °C	14.8 °C	31 °C	25 °C	20 °C

flowerlike micelle structure of i5–a70–i5 leads to broader phase-transition behaviour compared to the a24.3 and a12–i10–a12. To enable crystal modification by the PNIPAMs the two-phase area in the phase diagram should be avoided and thereby, either acetone of more then 42 or 50 vol%, depending on the architecture of the polymer, is needed or the temperature should be kept lower than the phase-transition temperature.

Thermal analysis

The phase separation of PNIPAMs was investigated with differential scanning calorimetry (DSC) shown in Fig. 5. Similar to the cloud point measurements, the onset and maximum temperature of the thermal event during phase separation is shifted to lower temperatures with increasing acetone content in the PNIPAM solutions. The PST determined by calorimetric method shows the same tendency as the PST determined by the turbidity method, Table 1. However, slightly higher values are obtained when determined by DSC. In addition, the enthalpy change significantly decreases with increasing acetone content, the same effect has been previously observed for addition of methanol [13]. The decrease in the enthalpy change and the lowering of the onset temperature with increasing acetone content can be attributed to the decreased water activity and disturbance of the water cage formed around the dissolved PNIPAM molecules. With decreased water activity less energy is required to break the hydrogen bonds. In the absence of acetone a single endothermic transition upon the phase separation is observed for a24.3, where the up-going slope is very step supporting the concept of cooperative hydration/dehydration of the chain. Likewise, in mixtures of water and acetone the phase transition of the a24.3 solution also shows a single-step endotherm. The endothermic event during phase transition of a12i10a12 and i5a70i5 in aqueous solution is much broader than for the a24.3. In the case of i5a70i5, a shoulder is observed close to event maximum. The broadening of thermal events during phase separation of a12i10a12 and i5a70i5 indicates that dehydration of the whole polymer chain does not take place in one single step, but possibly in two steps with a large temperature overlap preventing the separation of the individual signals. The different solubility of atactic and isotactic PNIPAM supports the two-step phase separation indicated in the thermograms. By addition of acetone to the a12–i10–a12 and i5–a70–i5 solutions the two-step phase separation is revealed clearly as two endothermic peaks in the thermogram. This change in thermal behaviour of the triblock PNIAM is most likely related to the aggregated structure of the triblock

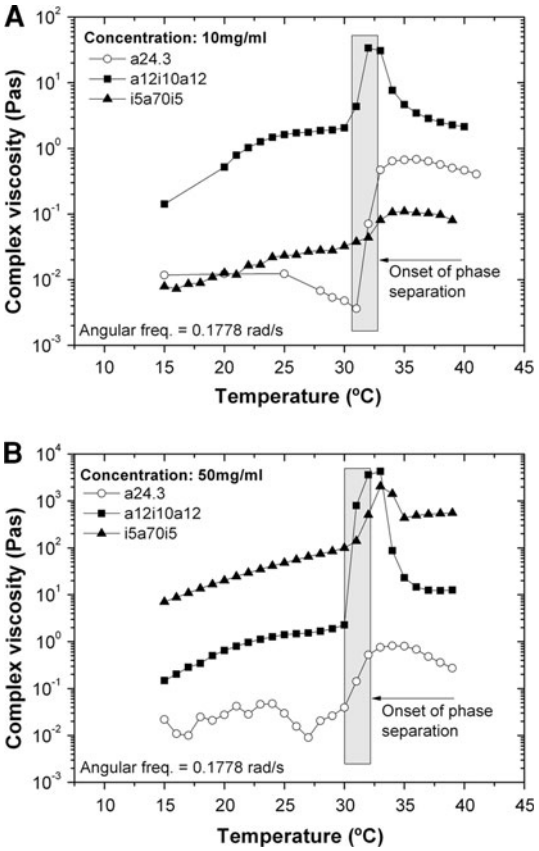

Fig. 6 Complex viscosity (Pas) as a function of temperature investigated for the a24.3, a12i10a12 and i5a70i5 PNIPAM polymers in water. **a** Concentration of polymer solution: 10 mg/mL. **b** Concentration of polymer solution: 50 mg/mL. Angular frequency = 0.1778 rad/s

PNIPAM solutions, where the isotactic polymer part closest to the hydrophobic core undergoes phase transition at lower temperatures than the atactic polymer part closest to the shell. Similar two-step phase-transition behaviour has been observed for PNIPAM covalently bound to surfaces of gold nanoparticles [33] and hydrophobic hyperbranched polyester [34].

Rheological characterization

The phase-transition behaviour may also be addressed by monitoring the viscosity of the solutions. It has earlier been found that concentrated (>45 mg/mL) solutions of i5–a70–i5 PNIPAM are thermoassociating below their phase-transition temperature forming gels, while a24.3 PNIPAM shows decreasing viscosity from 5 °C up to the phase transition [9, 35]. Similar results are obtained in the present case at more dilute (10 mg/mL) conditions. The aqueous PNIPAM solutions containing isotactic blocks shows different temperature dependency of the complex viscosity upon heating compared with the atactic polymer (Fig. 6a). The a12–i10–a12 polymer has the highest viscosity at low temperatures, whereas the viscosity of i5–a70–i5 and the a24.3 is similar, and lower than for a12–i10–a12. The viscosity of

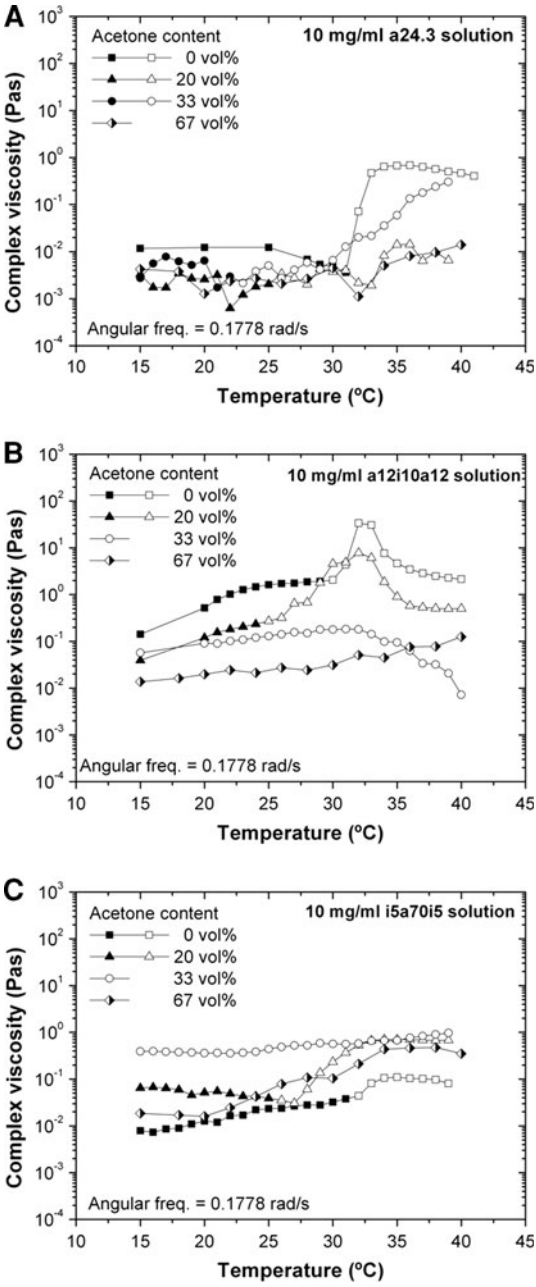

Fig. 7 Complex viscosity (Pas) of PNIPAM solutions as a function of temperature in different acetone–water mixtures. **a** a24.3, **b** a12i10a12 and **c** i5a70i5. *Closed symbols* indicates that the PNIPAM solutions are not phase separated (one-phase system), *open symbols* indicates that the PNIPAM solutions has phase separated (two-phase system), *half-open symbols* indicates no phase separation observed

atactic PNIPAM decreases with increasing temperature whereas the polymers having isotactic rich blocks show a continuous increase in viscosity. Approaching the phase-transition temperature, which is similar for all the systems depicted, the PNIPAMs dehydrate to form a temporary network which can be observed as an

increase in the viscosity. When the temperature is further increased above ~31–33 °C, the a12–i10–a12 polymer shows a decrease in viscosity due to phase transition and the formation of a two-phase system. The same decrease is not detected for the other two polymer types at concentration of 10 mg/mL. Similar tendencies are observed as the concentration of the polymer is increased to 50 mg/mL (Fig. 6b). The a24.3 has the lowest viscosity at 15 °C which stays nearly constant up to phase separation. At 50 mg/mL concentration, the i5–a70–i5 shows the highest viscosity and thus is seen to be the most concentration dependent of the polymers studied, which is in accordance with earlier obtained results [9]. For both of the isotactic block containing PNIPAMs an increase in viscosity is detected upon heating prior to the PST. During the phase transition, a drastic increase followed by a distinct decrease in viscosity is observed. Similarly, as in with case of a12–i10–a12 at concentration of 10 mg/mL, this is due to the temporary networking in the phase-transition process followed by the formation of a two-phase system.

The effect of increased acetone concentration on the polymer solutions for the different polymers at 10 mg/mL concentration is shown in Fig. 7. In general, for all polymers, when phase separation of PNIPAM takes place the complex viscosity increases slightly, similar to observations in pure water. However, the increased acetone content does not result in as drastic change in the rheological property of solutions as observed by turbidity measurements or thermal analysis. Increasing acetone content in the a24.3 PNIPAM decreases the viscosity below the PST slightly (Fig. 7a) and the sharp increase in viscosity during phase separation of a24.3 is diminished at higher acetone content. This is most probably due to the altered solvent structure around the polymer preventing network formation when acetone is present. In the case of a12i10a12 polymer increased acetone content also decreases viscosity significantly below PST. Chen et al. have investigated the effect of methanol on aqueous atactic PNIPAM solutions and found that increased methanol content decreased the intrinsic viscosity of the polymer up to a methanol content of 0.2 mol fraction [36]. This was assumed to be caused by changes in the water cage around the hydrated polymer. In the case of acetone–water system, similar observations can be made with a24.3 and a12i10a12. In contrast, the complex viscosity of the i5a70i5 solution increases with increasing amount of acetone present, until the cononsolvency region is exceeded, and phase separation is prevented.

Conclusions

Crystallization of NF monohydrate from polymer solutions results in smaller crystals with triangular morphology compared to crystallization from pure solvent, where needle-shaped crystals are obtained. The solvent composition of water acetone mixtures induces a great influence on the solution properties of atactic PNIPAM and triblock polymers containing atactic (a) and isotactic (i) rich blocks PNIPAM. The architecture of the polymer and the viscosity of the crystallization solution thus appear to influence the achieved crystal size. Turbidity measurements and thermal analysis reveal decrease in phase-transition temperature with increasing

acetone content up to 50 vol%, after which phase transition is no longer detected. The introduction of acetone complicates the phase separation by broadening and lowering the temperature range during which the phase transition takes place. This is indicated by the lowering of the enthalpy change of the phase separation and the creation of a two-step phase transformation for the a–i–a and i–a–i type PNIPAM. The complex viscosity of aqueous solutions changes before and as well as during phase transition depending on the polymer. Heating of the atactic PNIPAM results in a decrease in viscosity below the phase transition, where an increase in viscosity is observed for a–i–a and i–a–i PNIPAM. The viscosity of a–i–a PNIPAM at low temperatures decreases upon increasing acetone content, and a slight increase in viscosity is detected for the i–a–i type, while the increased acetone content in atactic PNIPAM solution only appeared to have a minor effect on viscosity.

The chemical properties of the PNIPAM polymers favourably affects the morphology of the NF crystals changing the shape into more processable crystals and decreasing the crystal size, increasing the surface area and thereby influencing the bioavailability. However, the thermoresponsive properties of the PNIPAM, in the presence of acetone, cannot be utilized for the control of the viscosity as the gelation and phase separation occurs in too narrow temperature regime and thereby the viscosity change obtained is minimal.

Acknowledgments Advanced Technology Foundation and the Ministry of Science, Technology and Innovation (Denmark) is acknowledged for funding the NanoDSC equipment.

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