

Thesis of Ph.D. Dissertation

Preparation and characterization of hierarchically structured soft nano- and microgels

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Eötvös Loránd University
Budapest, 2019

1. Introduction and Objectives

Hydrogels are water swollen polymer networks, which are key components not only in all living organisms but also in many rapidly developing applied and future technologies. One of the most important classes of hydrogels is the smart or stimuli responsive hydrogels, which are able to reversibly respond to physical or chemical changes of their environment. A prominent representative of smart hydrogels is crosslinked poly(*N*-isopropylacrylamide) or pNIPAm, which attracted a considerable attention in the last few decades due to its temperature-dependent swelling. pNIPAm gels are synthesized by the copolymerization of *N*-isopropylacrylamide (NIPAm) and *N,N'*-Methylenebis(acrylamide) (BA), which is the most commonly used crosslinker. First, it was reported by Pelton *et al.* in 1986 that highly monodisperse pNIPAm microgel particles can be prepared from NIPAm monomers in a simple precipitation polymerization reaction. [1] The main advantage of precipitation polymerization is that while highly monodisperse particles are produced their size and composition can be easily controlled. There are many studies about copolymerizing *N*-isopropylacrylamide with either ionic or non-ionic comonomers. However, pNIPAm microgels, consisting of NIPAm and BA, have a core-shell character. In their early work, Wu *et al.* showed that the crosslinker has a higher reaction rate compared to the reaction rate of NIPAm. [2] The larger reaction rate of the crosslinker monomer (BA) results in the inhomogeneous distribution of crosslinking inside the polymer beads. In their work, Acciaro *et al.* showed that by keeping the reaction rate of NIPAm and BA monomers constant during the synthesis, homogeneously crosslinked pNIPAm particles can be prepared. [3] The homogeneous crosslinker density has several effects on the properties of the prepared particles. The most importantly the homogeneous crosslinker density gave rise to much higher swelling ratio. Additionally, it was also found that the monomer feeding to the reaction mixture has a large effect on the timescale of the polymer network formation. While the crosslinked microgel particles form practically immediately in a batch synthesis due to the accumulation of the crosslinker in the particle core, in the case of the fed synthesis the crosslinker concentration in the growing polymer chain is kept low in the initial stage of the polymerization and as a consequence significant time is required (~90 minutes) to form the crosslinked microgel particles. This implies that the size of the smallest homogeneously crosslinked microgel particles is limited by the time required for the formation of the

crosslinked polymer network allowing the preparation of only relatively large (> 400 nm) swollen microgel particles. Though, several applications require not only the precise control of the microgel size and its internal structure but as small particles as possible [4], Acciaro *et al.* did not investigate if it is possible to decrease the size of the homogeneously crosslinked microgel particles. In the case of the classical batch polymerization the size of the pNIPAm microgel particles has been traditionally controlled by the addition of ionic surfactants (mostly sodium dodecyl sulfate, SDS) to the reaction mixture. Thus, I set my first goal to identify how small homogeneous pNIPAm microgel particles can be prepared by the feeding method with increasing the SDS concentration in the reaction mixture. Additionally, I used both classical batch precipitation polymerization (at 60, 70 and 80°C) and monomer-feeding precipitation polymerization (at 80°C) to determine how the collapsed particle size varies with the total surfactant concentration.

There is also a great demand for the preparation of pNIPAm microgel particles with well-defined core/shell structure. To prepare microgel particles with different composition in their core and shell, typically the method of Jones *et al.* was used in the last few decades. [5] Although this method was successfully used to prepare such microgels, it also has some serious drawbacks: e.g. there is a strong limitation regarding the quality and quantity of the monomers used to prepare the particle shell, and the preparation of the core-shell particles takes a lot of effort both in work and time.

Since homogeneously crosslinked microgel particles could be prepared by controlling the composition of the reaction mixture during the growth of the microgel particles, I aimed at developing a new synthetic method for the preparation of core-shell pNIPAm microgels based on the precise control of the composition of the reaction mixture. The application of this synthetic approach indeed gave rise to the formation of a shell with different composition on the growing pNIPAm microgel core.

2. Background and Methods

The size of the pNIPAm microgel particles has been traditionally controlled by the addition of ionic surfactants (mostly sodium dodecyl sulfate, SDS) to the reaction mixture. It was already shown by McPhee *et al.* that the addition of SDS in low concentration gave rise to more

monodisperse microgel particles and by increasing the SDS concentration the size of the microgel particles could be decreased [6]. It was also found that above 2.0 mmol/dm³ SDS concentration no further decrease in the particle size could be obtained. Later, the effect of higher amount of SDS on the pNIPAm microgel size was investigated by several research groups. Finally, Andersson *et al.* used SDS concentration as high as 6.7 mmol/dm³ and reported 38 nm final collapsed pNIPAm microgel size [7]. However, the effect of larger SDS concentrations on the microgel size has not been investigated systematically, yet.

Several applications of pNIPAm homo- and copolymer microgel particles require the precise control of the structure and composition of microgels. Hence, in the early 2000s Jones and Lyon developed a two-stage synthetic method for the preparation of core-shell microgel particles. [5] However, this method was successfully used for the synthesis of pNIPAm-shell-pNIPAm-co-10%AAc and pNIPAm-co-10%AAc-shell-pNIPAm microgels there had been a strong limitation regarding the quality and quantity of the monomers used to prepare the particle shell. Further, the preparation of the core-shell particles took a lot of effort both in work and time. Later, Brendt and Richtering presented the preparation of a dually temperature-sensitive core-shell pNIPAm microgel particles. [8] In 2012 Hoare *et al* developed a semi-batch synthetic method. The method was used for the preparation of pNIPAm-co-MeAAc microgel particles with different radial MeAAc distribution in the particle network. [9] Although the above-mentioned methods were successfully used for the preparation of core-shell microgel particles with different composition in their core and shell, these methods are restricted both in quantity and quality of the used monomers.

During my PhD work I used three types of synthesis techniques for the preparation of pNIPAm based microgel particles with different structure. All three techniques were based on the principles of the classical precipitation polymerization developed by Pelton *et al.* In the first case I used the classical batch synthesis method for the preparation of pNIPAm or pNIPAm-co-10%AAc microgel particles. For the preparation of homogeneously crosslinked microgel particles I used the method of Acciaro *et al.* The method is based on the continuous addition of a monomer stock solution to reaction mixture to keep the monomer concentrations and hence the composition of the growing particles constant during the synthesis.

Two types of synthesis methods were used for the preparation of core-shell microgel particles. On the one hand, the method of Jones *et al* was used to prepare core-shell microgel particles

with different composition in their core and shell (pNIPAm-shell-pNIPAm-co-10%AAc or pNIPAm-co-10%AAc-shell-pNIPAm). The microgel particles, which were prepared with this method were used as reference systems during my researches. On the other hand, I developed a new synthetic method, which was based on the precise control of the composition of the reaction mixture during the synthesis. The synthesis was started with the preparation of the core particles, and when the conversion of the monomers reached a given value (>90-98%) a second shot of a monomer solution was added. This way, the added monomers were incorporated onto the surface of the already grown particle core. I demonstrated the effectiveness of this method with the preparation of pure hydrophilic polymer shells.

During the synthesis of pNIPAm microgel particles 3 mL samples were taken from the reaction vessel regularly. The samples were taken with a syringe filled with 3 mL of 10 mmol/dm³ solution of hydroquinone monomethyl ether to ensure immediate inhibition of the polymerization reaction. The unreacted monomers were separated from the polymer by centrifugal filters. The monomer concentration in the purified samples were determined by *HPLC-UV* and were used for the calculation of monomer conversion curves. To obtain core-shell microgel particles, the addition times of the second shot of monomers were determined by analyzing the calculated monomer conversion curves.

The size and temperature dependent swelling properties of the prepared microgel particles were measured by dynamic light scattering, which provided indirect information about the core-shell nature of the microgel particles.

3. Scientific results

Based on my investigations the following scientific results could be obtained:

1. **The size of pNIPAm microgel particles prepared by precipitation polymerization is controlled by two key parameters: the underlying adsorption isotherm of surfactant adsorption on the collapsed microgel particles and the effective initiator concentrate (that is the amount of initiator fragments providing surface charge for the precursor particles in unit volume of reaction mixture). While the latter parameter is determined by the reaction temperature, the surfactant surface**

excess on the precursor particle is controlled by the surfactant concentration in the reaction mixture.

2. With increasing surfactant concentration, the surface excess of the surfactant molecules adsorbed on the precursor particles increases until it reaches saturation. Once saturation is reached the size of the precursor particles do not decrease further with increasing surfactant concentration. Thus, the smallest collapsed pNIPAm microgel size that could be achieved using sodium dodecyl sulfate as a surfactant was 60.0 ± 0.5 nm in the case of a homogenous microgel particles prepared by the monomer feeding method at 80 °C and $29,3 \pm 0,3$ nm in the case of the microgels prepared by the classical batch polymerization method at 70 °C.
3. During the synthesis of pNIPAm microgel particles the growth of the microgel particles can be maintained for more than ten hours when appropriate reaction conditions are ensured (e.g. radical scavengers are excluded from the reaction mixture).
4. pNIPAm microgel particles with controlled core/shell structure can be prepared in a single pot precipitation polymerization reaction by controlling the monomer composition of reaction mixture, which in turn controls the composition of the growing polymer chain ends at the surface of the microgel particles.
5. pNIPAm microgel particles bearing a hydrophilic shell (e.g. pNIPAm-shell-100%pAAc) or hydrophilic double shells (pNIPAm-shell-100%pAAc-shell-PEO) can be prepared in a single pot precipitation polymerization reaction by the addition of the shell monomers to the growing microgel particles in the final state of core (or core/shell₁) growth.
6. pNIPAm microgel particles bearing a polyvinyl alcohol shell with controlled thickness can be prepared using vinyl acetate as the shell monomer in a one pot semi-batch precipitation polymerization reaction then hydrolyzing the vinyl acetate after the polymerization reaction. Due to the low boiling point of vinyl acetate (71 °C) a key step of the polymerization reaction is that the reaction temperature has to be decreased to 60 °C (below the boiling point of vinyl acetate) before the addition of shell monomer to the reaction mixture and the reaction has to be performed in a closed reaction vessel.

4. References

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5. Publications

A. Journal articles:

The thesis based on the following publications:

A1. How small can poly(N-isopropylacrylamide) nanogels be prepared by controlling the size with surfactant? Kardos, A., Gilányi, T., Varga, I., *Journal of Colloid and Interface Science* 2019, 557, 793. DOI: 10.1016/j.jcis.2019.09.053 (Impact Factor=6.361; 2018)

A2. Effect of internal charge distribution on the electrophoretic mobility of poly(N-isopropyl acrylamide) based core-shell microgel particles., Varga, I., Kardos, A. Borsos, A. Gilányi, T.,

Journal of Molecular Liquids 2019, 111979. DOI: 10.1016/j.molliq.2019.111979, In press, (Impact Factor=6.361; 2018)

A3. Preparation of poly(N-isopropylacrylamide) microgel beads with double hydrophilic shells in a single pot reaction, Kardos, A., Lów, P., Varga, I., (In preparation)

Other publication:

A4. Effects of Ionic Strength on the Surface Tension and Nonequilibrium Interfacial Characteristics of Poly(sodium styrenesulfonate)/Dodecyltrimethylammonium Bromide Mixtures., Ábrahám, Á.; Kardos, A.; Mezei, A.; Campbell, R.A.; Varga, I. Langmuir 2014, 30, 4970. DOI: 10.1021/la500637v

A5. Supramolecular Hydrogel Based on pNIPAm Microgels Connected via Host/Guest Interactions., Antoniuk, I.; Kaczmarek, D.; Kardos, A.; Varga, I.; Amiel, C. Polymers 2018, 10, 566. DOI:10.3390/polym10060566

A6. Effect of Dilution on the Nonequilibrium Polyelectrolyte/Surfactant Association., Bali, K.; Varga, Zs.; Kardos, A.; Varga, I.; Gilányi, T.; Domján, A.; Wacha, A.; Bóta, A.; Mihály, J.; Mészáros, R. Langmuir 2018., 34, 14652. DOI: 10.1021/acs.langmuir.8b03255

A7. Impact of local inhomogeneities on the complexation between poly(diallyldimethylammoniumchloride) and sodium dodecyl sulfate., Bali, K., Varga Zs., Kardos A., Mészáros R., Colloids and Surfaces A 574, 21. DOI: 10.1016/j.colsurfa.2019.04.052

B. Conference presentations

B1. Preparation of Core/Shell Soft, Responsive Nanogel Particles Kardos, A.; Varga, I. Poszter prezentáció, 18th International Symposium and Summer School on Bioanalysis, június 25-30 (2018), Komarno, Slovakia