Colloids and Surfaces A: Physicochem. Eng. Aspects 489 (2016) 122–127

Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

journal homepage: www.elsevier.com/locate/colsurfa

Tailor-made microgel particles: Synthesis and characterization

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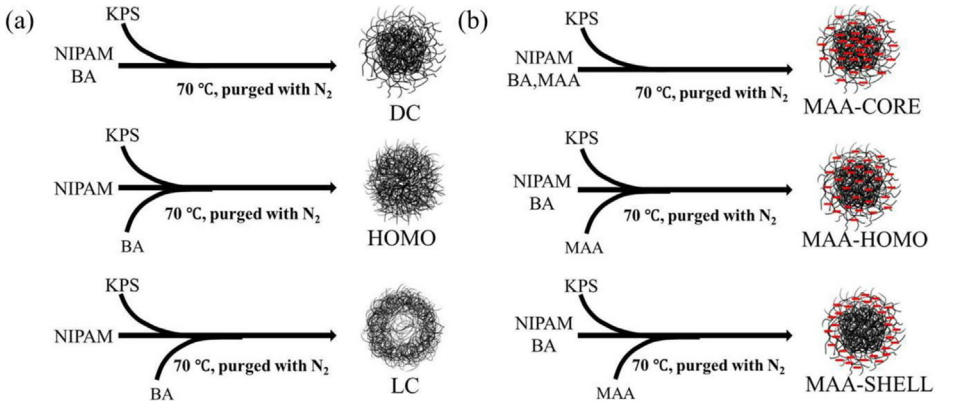
HIGHLIGHTS

- PNIPAM-based microgels with controlled crosslink distributions were synthesized.
- PNIPAM-*co*-PMAA microgels with controlled charge distributions were synthesized.
- Crosslink distribution influences temperature-dependent deswelling of microgels.
- Charge distribution influences microgel swelling in response to pH.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 15 July 2015
Received in revised form 16 October 2015
Accepted 23 October 2015
Available online 28 October 2015

Keywords:
Microgels
PNIPAM
Crosslink distribution
Charge distribution

ABSTRACT

Microgels are soft particles that consist of chemically cross-linked three-dimensional polymer networks. They are usually synthesized by precipitation polymerization. However, this method often leads to an inhomogeneous spatial distribution of crosslinks and functional groups within the microgel particles caused by differences in the reactivity ratios of the applied monomers, co-monomers, and crosslinkers. This lack of control of the structure has a profound effect on the properties of microgels, which in turn significantly limits their applications. In this work, poly(*N*-isopropylacrylamide) (PNIPAM)-based microgels with controlled distribution of crosslinks and charges were synthesized by batch polymerization or starve-feeding semi-batch polymerization. The structures of microgels with different crosslink distributions were characterized by laser light scattering (LLS). Our results show that the distributions of crosslinks influence the deswelling behaviors of microgels in response to temperature. When organic acid like methacrylic acid (MAA) was incorporated into the microgel, the resulting microgel particles added responsiveness to pH. The charge distributions, namely the spatial distribution of the functional MMA groups in the microgels were verified by potentiometric titration and electrophoresis. These microgels exhibit different swelling properties in response to pH. The developed approach for improving control of functional group distribution in microgels is essential for the design of more advanced microgel structures for specific applications.

1. Introduction

Microgels are soft particles that consist of chemically crosslinked three-dimensional polymer networks [1]. "Micro" concerns the size of microgel. Typically, its diameter ranges between

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http://dx.doi.org/10.1016/j.colsurfa.2015.10.042
0927-7757/

50 nm to 5 μm[2]. Therefore, on a macroscopic level microgels behave like colloids. "Gel" refers to its ability to swell in aqueous or organic solvents [3]. On a microscopic level, microgels also behave like macrogels. When the solvent quality changes from good to poor, the microgels will collapse as a result of the escape of solvent from the gel network. Microgels have often been termed "smart" since the size, physical properties and interaction forces between microgels are tunable by control of solvent quality [4,5]. Among the stimuli-responsive microgels, those based on poly(*N*-isopropylacrylamide) (PNIPAM) have received most attention. PNIPAM is a thermo-responsive polymer with a repeating unit consisting of hydrophilic (amide) and hydrophobic (isopropyl) groups. PNIPAM chains undergo a coil-to-globule transition in aqueous media around 31 °C, a so-called "lower critical solution temperature" (LCST) [6]. For PNIPAM microgels, the critical temperature is often referred to as volume phase transition temperature (VPTT) [7]. Below the VPTT, water behaves as a good solvent through hydrogen bonding with the amide groups. This hydrogen bonding with water is disrupted upon heating, causing water to act as a poor solvent, resulting in the collapse of microgels. It is this unique feature that makes them very attractive in the study of physics and chemistry of soft matter [8,9] as well as in applied fields such as drug delivery [10–12], biosensors [13,14] and tissue engineering [15,16].

PNIPAM microgels can be prepared by emulsion polymerization both in the presence and absence of surfactants [17,18]. The reaction should be conducted above the LCST of PNIPAM so that the water soluble monomer NIPAM will polymerize and the resultant PNIPAM chains will be able to precipitate out from the aqueous phase. Therefore, the polymerization is also called precipitation polymerization [19]. By copolymerization with *N*,*N*′-methylenebisacrylamide (BA), PNIPAM chains are chemically crosslinked and form colloidal particles. However, this crosslinking is not uniform throughout the microgels. Wu et al. investigated the kinetics of PNIPAM microgel formation and found that BA polymerized substantially faster than NIPAM [20]. Thus, the crosslinker density is higher in the first formed polymer than in the last. In other words, the microgel periphery will be less crosslinked and more swollen than the microgel core. This heterogeneous internal structure of microgel particles was proven by small angle neutron scattering (SANS) [21] and further confirmed by atomic force microscopy (AFM) [22]. The inhomogeneous crosslink distribution influences the subchain length, mesh size, swelling behaviors of microgels [23], and limits their applications in drug delivery [24], and emulsion preparation [25]. In addition, functional monomers are often copolymerized into PNIPAM microgels to make them more intelligent, such as pH-sensitive [26], glucose-sensitive [27], light-sensitive [28], *etc*. However, the same problem arises for those comonomers—the comonomers have a spatial distribution within the microgel interior as a result of the different reactivity ratio relative to NIPAM [29]. This lack of control of the functional group distribution of microgels will have uncontrollable effects on the application. For example, microgels whose functional groups are localized near the surface are more readily accessible for bioconjugation, while microgels whose functional groups are localized in the core are able to bind more drugs.

Therefore, prior to successfully exploiting widespread applications of microgels, a better method to synthesize microgels with tailored structure is required. In this work, we aim to synthesize PNIPAM microgels with controlled distributions of crosslinks and charges. A combination of semi-batch and starve-feeding was developed to localize the crosslinks and charges in the core, in the shell or homogenously within the microgels. And the resultant microgels were fully characterized, and their properties were compared to shed some light on the structures of the microgels.

2. Materials and methods

2.1. Materials

N-Isopropylacrylamide (NIPAM, J&K SCIENTIFIC) was recrystallized from a toluene-*n*-hexane mixture. Potassium persulfate (KPS, Merck) was purified by recrystallization from water. *N*,*N*′-Methylenebisacrylamide (BA, Fluka) was used without any purification. Methacrylic acid (MAA, Sigma–Aldrich) was purified by vacuum distillation. Deionized water was used in all experiments.

2.2. Synthesis of PNIPAM microgel particles with controlled crosslink distributions

Generally, PNIPAM microgel particles were synthesized using surfactant-free emulsion polymerization (SFEP). Microgels with a dense core (DC) structure were synthesized by batch polymerization. First, NIPAM (1613.1 mg) and BA (115.6 mg) were dissolved in deionized water (145 mL) in a 250 mL two-neck reactor fitted with a nitrogen bubbling inlet and outlet and a reflux condenser and stirred with a magnetic stir bar. After stirring the solution for 40 min at 70 °C under nitrogen bubbling, the polymerization was initiated by addition of KPS (81.1 mg) dissolved in deionized water (10 mL). The reaction mixture was kept at 70 °C for 4 h. Microgels with homogeneous crosslink distribution (HOMO) and microgels with a loose core (LC) structure were prepared by semi-batch polymerization while keeping the same amounts of monomers as that of DC microgels. For HOMO microgels, the crosslinker BA in 5 mL water was added immediately upon KPS initiation with a syringe pump at a speed 10 mL/h for 30 min. In the case of LC microgels, BA in 5 mL water was added 15 min after KPS initiation at a speed of 20 mL for 15 min. The three kinds of microgels were purified by centrifugation to remove the lower molar mass polymer and unreacted reagents. The synthesized microgels were deposited onto clean silicon wafers for SEM observation. Images were taken by a FEI Quanta 400 FEG microscope operating at 10 kV.

2.3. Synthesis of PNIPAM-co-PMAA microgel particles with controlled charge distributions

PNIPAM-*co*-PMAA Microgels were synthesized also using SFEP with MAA as the comonomer. Microgels with a MAA-rich core (MAA-CORE) were synthesized by batch polymerization. NIPAM (1613.1 mg), BA (115.6 mg) and MAA (129.2 mg) were dissolved in deionized water (145 mL) in a 250 mL two-neck reactor fitted with a nitrogen bubbling inlet and outlet and a reflux condenser and stirred with a magnetic stir bar. After stirring the solution for 40 min at 70 °C under nitrogen bubbling, the polymerization was initiated by addition of KPS (81.1 mg) dissolved in deionized water (10 mL). The reaction mixture was kept at 70 °C for 4 h. Microgels with a homogeneous MAA distribution (MAA-HOMO) and microgels with a MAA-rich shell (MAA-SHELL) were prepared by semi-batch polymerization while keeping the same amounts of monomers as that of MAA-CORE microgels. For MAA-HOMO microgels, MAA in 5 mL water was added immediately upon KPS initiation with a syringe pump at a speed 10 mL/h for 30 min. In the case of MAA-SHELL microgels, MAA in 5 mL water was added 15 min after KPS initiation at a speed of 20 mL for 15 min. The three kinds of microgels were purified by centrifugation to remove the lower molar mass polymer and unreacted reagents. The synthesized microgels were deposited onto clean silicon wafers for SEM observation. Images were taken by a FEI Quanta 400 FEG microscope operating at 10 kV.