Stimuli-Sensitive Microhydrogels

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Abstract Microhydrogels have become a very interesting and important material in hydrogels bioapplications. New techniques for the design, synthesis, characterization, function, and application of microhydrogels are providing exciting new possibilities in the micronized science. Hydrogels are a soft material with sizes and shapes that are subject to change depending on environmental conditions such as temperature, pH, coexisting materials, and light. Hydrogels that respond to these environmental stimuli and cause swelling changes in aqueous media are known as "stimuli-sensitive hydrogels."

Introduction

Hydrogels are classified according to their size: bulk gels, macrogel, microgel, and nanogel. The microgels range from submicron to millimeter, whereas the size of nanogel is less than 100 nm. The size of materials is a crucial factor that determines their properties. The dependence of physical properties (x) on diameter (D) of spherical materials is presented in (1):

$$x = kD^n \tag{1}$$

The specific surface area of a spherical particle is inversely proportional to the diameter. The diffusion rate is also inversely proportional to the diameter. The time needed for the gels to transfer stimuli to its center was proportional to the square of the diameter of the gels (Table 1) [1]. Therefore, smaller gels provide much quicker and more efficient performance. If the particles are too small then they can cause problems; this makes microgels, in some cases, preferable to nanogels. Microgels have an additional merit, in that their size is in the same range as the wavelength of visible light. This unique feature enables the microgels to be applied for optically functionalized devices.

Stimuli-Sensitive Microgels

There are many kinds of thermosensitive hydrogels that include synthetic polymers, such as poly(acrylamide) derivatives, poly(methacrylamide) derivatives, poly(butyl vinyl ether), poly(ε-caprolactam), and derivatives of naturally occurring polymers, such as hydroxypropylcellulose and methylcellulose [2, 3].

Preparation of Microhydrogels

Polymerizations, such as inverse emulsion polymerization, precipitation polymerization, and dispersion polymerization, are the main methods for preparing polymer particles. Other routes include polymer molecule assembling in water, spray drying of polymer solutions,

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Table 1. Parameters determing the gels size

x	n
Volume	3
Specific surface area	−1
Period for stimuli to reach the center	2
Diffusion rate	−1
Sedimentation rate	2
Interparticle distance[a]	1

[a]At a constant volume fraction

evaporation or extraction of solvent from oil-in-water (O/W) emulsions in which polymer is added in the oil phase.

Microgel Preparation by Particle-Forming Polymerization

In an aqueous polymerization of *N*-isopropylacrylamide (NIPAM) at 70°C, the reaction system is homogeneous. Once polymerization is initiated, the polymer molecules are phase separated to give a condensed poly(*N*-isopropylacrylamide) (PNIPAM) phase of PNIPAM nanoaggregates [4]. The nanoaggregates grow with increasing conversion and finally become microhydrogels. Precipitation polymerization of acrylamide in aqueous alcohol forms monodispersed microgels [5, 6]. In this system, the number of nanoaggregates or nanogels is fixed at an early stage of polymerization; as a result, the size distribution of final microgels is quite narrow. The size of microgels is controlled by the composition of polymerization medium and the addition of surfactant to the aqueous polymerization of NIPAM in order to form smaller microgels. The addition of a hydrophilic comonomer, such as acrylic acid (AAc), makes smaller microgel particles.

Copolymerization of NIPAM and other monomers causes not only a change in microgel size, but also a change in thermosensitivity. For these microgels, depending on the crosslinking density of the shell, compression or shrink-wrapping of the core was observed [7]. The significance of the crosslinker used was shown in the study of *N*-vinylcaprolactam (VCL)-based microgels using two kinds of crosslinkers [8]. The compatibility between VCL and the crosslinker is the most important factor for well-structured temperature-sensitive microgels.

Microgel Preparation by Surface Modification of Core Particle

Core-shell microspheres, with the shell being composed of a hydrogel, are regarded as microgels. The core-shell particles are made by seeded polymerization and graft polymerization, although some core-shell particles are prepared by molecular assembly of amphiphilic block copolymers. When grafting reactions are carried out without using a crosslinker, “hairy-like” particles are obtained. Hairy PNIPAM particles are prepared using core particles with iniferters on the surface. The polymerization is carried out by UV irradiation at a temperature lower than the LCST of PNIPAM [9–11]. This controlled radical polymerization produces hairy-like PNIPAM particles with controlled chain lengths. When the dispersion is dried on a substrate, these PNIPAM particles form two-dimensional colloidal arrays. The inter particle distance of the colloidal array usually corresponds to twice the thickness of hairy layers.

Microgel Preparation by Assembling Polymer Molecules in Solution

Some polymer molecules dissolved in aqueous medium can be assembled by using stimuli. For example, PNIPAM microgels are obtained from an aqueous solution of PNIPAM by increasing the temperature which causes phase separation. The suitable temperature, for PNIPAM microgels to form from a solution, is well above the LCST of PNIPAM, and is usually, around 70°C [12]. Hydroxypropyl cellulose (HPC) is an amphiphilic cellulose derivative and its amphiphilicity depends on temperature with an LCST of ~41°C [13]. Thus, the HPC in aqueous solution can be converted to microaggregates by warming the solution above 41°C [14].

Amphiphilic block copolymers, for example, block copolymer of polyethyleneoxide (PEO) and PNIPAM, form micelles when the aqueous solution is warmed above the LCST of PNIPAM. On cooling, the micelles disappear and polymers dissolve to avoid this break down, the core (PNIPAM) or shell (PEO) must be crosslinked. Poly(glycerol methacrylate) (PGLM)-block-PNIPAM can actually form two types of micelles [15]; one is with a PNIPAM core and a PGLM micellar shell and the other is a PGLM core with a PNIPAM micellar shell. The first one is formed by warming the polymer as described earlier. Another technique is as follows: a methanol solution of the two polymer systems is made and then tetrahydrofuran (THF) is slowly added to the solution under stirring. This method is based on the principle that methanol is a common solvent for both of PGLM and PNIPAM blocks but THF is a nonsolvent of PGLM.

Polyelectrolytes in aqueous solution assemble as microaggregates by adding molecules with opposite charges; the electrostatic interactions between them facilitate particle formation. For example, carboxymethylcellulose (CMC) molecules dissolved in water assemble when a cationic surfactant, polycation or multivalent metal ion are added [16]. Similarly, CMC is converted to a microgel by assembling with chitosan.

Stimuli Responsiveness of Microhydrogels

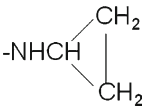
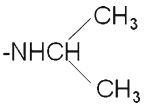
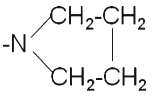
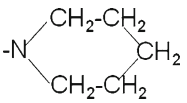
Temperature Responsiveness of Microhydrogels

Acrylamide derivative polymers (LCSTs in Table 2, poly(vinyl methylether) (LCST: 36°C), poly(*N*-vinylcaprolactam) (LCST: 26°C), PEO-block-polypropyreneoxide-block-REO, Pluronics, and hydroxypropyl cellulose (LCST: 41°C) are well known thermo-sensitive polymers. The LCST can be changed by copolymerizing hydrophilic and hydrophobic comonomers that made the LCST of copolymers higher or lower, respectively. For example, microgels composed of poly(NIPAM-*co*-butyl acrylate) has a lower LCST and poly(NIPAM-*co*-AAc) has a higher LCST than 32°C. The combination of two acrylamide derivatives, *N*-acryloylpyrrolidine (LCST: 5°C) and *N*-acryloyl piperidine (LCST: 55°C), forms microgels with predictable LCST based on the molar fraction of two components [17].

Microgel Volume Phase Transition Temperature

Temperature responsiveness of microhydrogels is usually discussed by the microgel size change at their LCST at which the polymer molecule dehydrates and the gels collapses with a drastic decrease in volume. The temperature responsiveness of a microgel can also be volume phase transition temperature (VPTT) responsive instead of LCST [18]. The size of interest is not that of the dried microgel but that of the hydrodynamic form which is the effective size of the swollen hydrogels in an aqueous medium. The hydrodynamic size is commonly

Table 2. LCST of poly(acrylamide) derivatives

	$-CH_2-C(CH_3)(C=O)-$	$-CH_2-CH(C=O)-$
	61	47
	45	31
$-NH-CH_2-CH_2-CH_3$	27	23
		55
		05

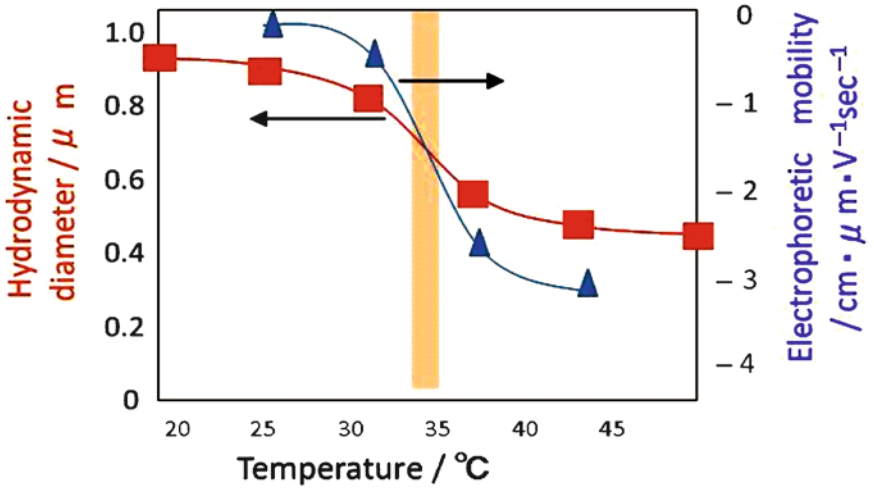


Fig. 1. Hydrodynamic size and electrophoretic mobility of poly(*N*-isopropylacrylamide) (PNIPAM) microgels as functions of temperature.

measured by dynamic light scattering (Fig. 1). Careful use of this data must be taken since the correlation function obtained by the dynamic light scattering measurements gives the diffusion constant of the particles, from which, the hydrodynamic diameter of particles is calculated; however, the swollen particles have an unclear interface. The real amount of water held in PNIPAM microgel is determined by DSC or other analyses.

Volume phase transitions cause changes in the electrophoretic mobility of the microgels because the charges, which remain buried in the gels at low temperatures, are concentrated at the surface layer of the shrunken gels at temperatures >LCST. However, the electrophoretic mobility does not serve for ζ potential determination because the ζ potential is not related to microgels that have no clear interface [19]. Measurements by force microscopy and incoherent elastic scattering reveal the elastic modulus of microgel. A difference of two orders in the elastic modulus has been seen between the temperatures above and below VPTT [20].

Temperature Dependent Hydrophilicity–Hydrophobicity of Microgel

The reversible swelling–deswelling of PNIPAM microgel reflects the reversible change in hydrophilicity–hydrophobicity of the gels. PNIPAM molecule dissolved in water is amphiphilic based on surface tension measurements. The surface tension of an aqueous solution of PNIPAM decreases with increasing temperature; this also occurs for dispersions of PNIPAM microgel. This property is utilized in the preparation of thermoreversible Pickering emulsions. PNIPAM microgels form micelle-like assemblies in organic solvent/water systems to give an O/W or W/O emulsion. Several aliphatic and aromatic solvents are mixed with aqueous dispersion of PNIPAM microgel. The mixture is stirred for 5 minutes at room temperature. Pickering emulsions form when the organic solvent has a low "work of adhesion" value whereas 1-undecanol which has a high "work of adhesion" does not form a Pickering emulsion. The Pickering emulsion is deformed when it is warmed above the VPTT of PNIPAM. The emulsion collapses at 40°C, and a stable emulsion is regenerated by agitation at 25°C [21].

PNIPAM-*co*-methacrylic acid (MAc) microgels, which are prepared under different pHs, are used as stimuli-responsive Pickering emulsion stabilizers [22]. The stability of the microgels depends on the pH during synthesis; the microgels with high charges appreciably stabilize the emulsion. PNIPAM microgel-based Pickering emulsion was utilized for the preparation of Janus microgels [23].

pH Responsiveness of Microhydrogels

Weak acid or base containing microgels are pH and ionic strength sensitive. They are prepared by combining a small amount of an ionizable component with a hydrophilic monomer, and if necessary, a crosslinker [24, 25]. For example, ethyl acrylate, MAc, and butanediol diacrylate are copolymerized in water to form microgels used to repair damaged load-bearing soft tissue [26]. When used for biomedical purposes, the sensitivity of the microgel to divalent ions, such as Ca^{2+} and Mg^{2+}, must be taken into account [27]. Addition of Ca^{2+} causes significant decreases in the critical coagulation concentration (CCC), the degree of swelling and the electrophoretic mobility due to the ionic crosslinking of neighboring COO^- groups by the Ca^{2+}. However, the extent of ionic crosslinking is limited because the covalent crosslinks suppress the large-scale conformational rearrangement of polymer chains and decrease the chances for ionic crosslinking. Thus, the change in properties of a microgel caused by Ca^{2+} is controlled by the degree of covalent crosslinking.

Tertiary amine-carrying pH responsive microgels are prepared by copolymerizing diethylamino- or diisopropylaminoethyl methacrylate (DEAEMA and DPAEMA, respectively) with poly(propyleneglycol) diacrylate in the presence of macromonomer stabilizer. The transition between the swollen and shrunken states of the particle occur in the arpKs of DEAEMA and DPAEMA [28].

Responsiveness of Microhydrogels to Other Stimuli

Other stimuli-sensitive microgels include UV-, light-, and biomolecule-sensitive microgels. Photosenstive microhydrogels are created by the insertion of azobenzene as a pendant group to the hydrophilic polymer chain or in the main chain.

Multistimuli-Sensitive Microhydrogels

In addition to NIPAM homopolymeric microgel, copolymerization of NIPAM with carboxylic acid-containing monomers, such as AAc, MAc, and allylacetic acid [29], or amine-containing monomers, such as vinyl pyridine [30], form multistimuli-sensitive microgels that are temperature, pH, and ionic strength-sensitive. The incorporation of NIPAM and AAc to copolymerize with acrylamido-2-deoxyglucose (AADG) at different ratios of AADG to AAc forms temperature, pH, and ionic strength-sensitive microgels with different VPTTs and greater biocompatibility [29].

PMAc-poly(2-dimethylamino)ethyl methacrylate (DMAEMA) microgels, prepared by inverse microemulsion polymerization and stabilized with grafted poly(ethylene glycol), show not only pH responsiveness but also temperature responsiveness due to the LCST of PDMAEMA [31]. Generally, only small amounts of comonomers are added relative to the amount of NIPAM. Simple copolymerization using larger amounts of comonomer causes shifts in the VPTT as well as broadening or loss of transition. Microgels, with two components in the block structure, form core-shell microgels under more suitable conditions [32]. An alternative method to maintain the individual stimuli-sensitivity of each component is to make a division between different stimuli-sensitive components. Multistimuli-sensitive microgels made of microgel-polyelectrolyte complexes that are composed of poly(NIPAM-*co*-MAc) and poly(diallyldimethyl ammonium chloride) are stable irrespective of the complex composition [33]. The size, zeta-potential and pH and temperature-sensitivity of the microgel-polyelectrolyte complexes are influenced by the adsorbed polyelectrolytes.

Preparation of Inorganic Nanoparticles/Polymer Composite Microgel

Inorganic nanoparticles have several interesting functions. For example, Au and Ag exhibit surface plasmon resonance that emit specific colors depending on the particle size, refractive index of the medium, and inter particle interactions. Magnetic nanoparticles made from iron oxide are used as MRI contrast enhancer and hyperthermia materials and titanium nanoparticles have photocatalytic properties. These versatile inorganic nanoparticles present novel functions when they are incorporated with polymeric particles. Several inorganic/polymer composite microgels have been prepared that have unique features [34–36].

Preparation of Inorganic Microgel Composites

The preparation methods for inorganic microgel composites are categorized into six patterns; these patterns are illustrated in Fig. 2 except for methods 2 and 4. The steps are as follows:

1. Particles formed by polymerization in the presence of inorganic nanoparticles
2. Simultaneous reactions of particle-forming polymerization with inorganic nanoparticle precursors

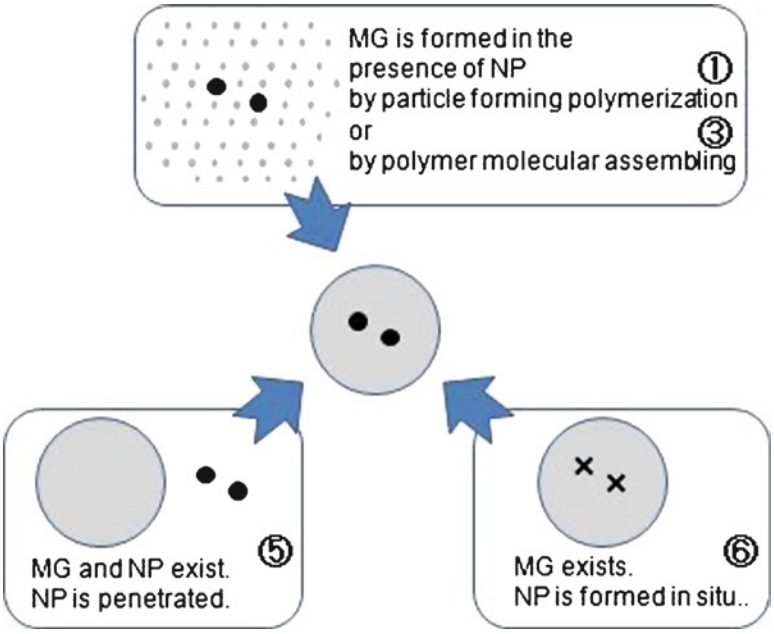


Fig. 2. Synthesis routes for nanoparticle (NP) containing composite microgel (MG).

3. Polymer molecular assembly involving inorganic nanoparticle as composites
4. Polymer molecule assembly involving inorganic nanoparticle precursors followed by in situ formation of nanoparticles
5. Introduction of inorganic nanoparticles onto/into polymeric microgels
6. Introduction of precursor of inorganic nanoparticles into polymeric microgel followed by in situ formation of inorganic nanoparticles

In method 1, an inverse mini-emulsion polymerization of a hydrophilic monomer in which inorganic nanoparticles are stably dispersed is used. The second method is not very practical because it is too difficult to carry two reactions at a comparable rate. Method 3 involves the formation of magnetite/CMC composite microgels; an affinity of magnetite for the COOH and OH groups causes the composite formation. A modified method of 3 entails successive deposition of polymer molecules onto magnetite particles. Negatively charged PNIPAM and positively charged PNIPAM are alternatively deposited layer-by-layer to prevent the deposited polymers from detaching from the magnetic particles [37].

The fourth method is not as common. It uses ferric and ferrous ions instead of magnetic nanoparticles. The ions have an affinity for –COOH and –OH groups of CMC. Therefore, combinations of ferric and ferrous ions and CMC form composite microgels by the conversion of ferric and ferrous ions to magnetite nanoparticles in the CMC matrix. In method 5, the network structure of the microgels allows inorganic nanoparticles to penetrate into the microgels that have an affinity with inorganic nanoparticles. The electro-attractive interaction is very strong between the inorganic nanoparticles, and the microgels enable composite microgel formation. Method 6 is the most promising in which the location of the inorganic nanoparticles inside of the microgel can be controlled.

Precipitation polymerization of NIPAM with a small amount of glycidyl methacrylate (GMA) forms PNIPAM microgels with the GMA evenly distributed. The GMA glycidyl groups react with the alkyl diamine to form ammonium sites in the microgel; when $AuCl_4^-$ is added to the dispersion, it is electrostatically attracted to the amino groups in the core of the microgel. After reaching equilibrium, the Au ions are reduced with $NaBH_4$ in situ to Au, to provide microgels that contain evenly distributed Au^0 nanoparticles [38–40].

Polymer Composite Microgel Functions

Noble Metal Nanoparticles/PNIPAM Composite Microgel

The Au^0 nanoparticles, prepared above, can be grown by successive reduction of additional Au and Ag ions in the microgel. The size of the metal nanoparticles/PNIPAM composite microgel significantly affects the VPTT of PNIPAM. A change in the Au nanoparticles distribution in the microgel occurs that changes the spectrum of the surface plasmon resonance and consequently, and the color emitted [41]. To expand the application of Au^0 nanoparticle-containing PNIPAM microgel, more sophisticated microgels with layered structures were prepared [42]. Another efficient method to entrap Au nanoparticles in PNIPAM microgel involves a two-step protocol. In the first step, Au nanoparticles are coated with cetyltrimethyl ammonium bromide (CTAB) and a thin polystyrene shell; in the second step, the coated Au nanoparticles are emulsion polymerized. The resulting Au nanoparticle core/PNIPAM shell microgels exhibit changes in UV-visible light in response to the VPTT of PNIPAM with changes in temperature [26]. Thermosensitive PNIPAM hairy nanoparaticles that have temperature-responsive catalytic activity can also be made [43].

Metal Oxide Nanoparticles/Thermosensitive Polymer Composite Microgels

Magnetite Nanoparticles/PNIPAM Composite Microgels

Composite microgels, composed of magnetic nanoparticles and PNIPAM, are used for heat-triggered release of drugs. The heat generated by the magnetic nanoparticles is transferred to thermosensitive matrix which leads to the collapse of the gels when the temperature of matrix exceeds the VPTT. The morphology ranges from a magnetic island/PNIPAM to a magnetic core/PNIPAM shell [44]. Control of location and the amount of magnetic nanoparticles in the thermosensitive microgel are very important [45]. A series of microgels composed of

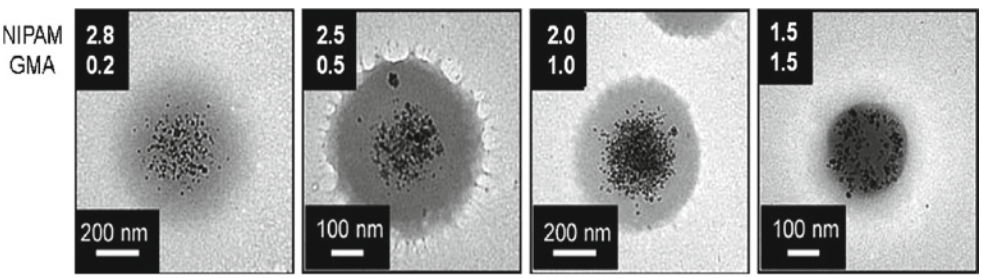


Fig. 3. Magnetite nanoparticles in poly(NIPAM-*co*-glycidyl methacrylate) microgel.

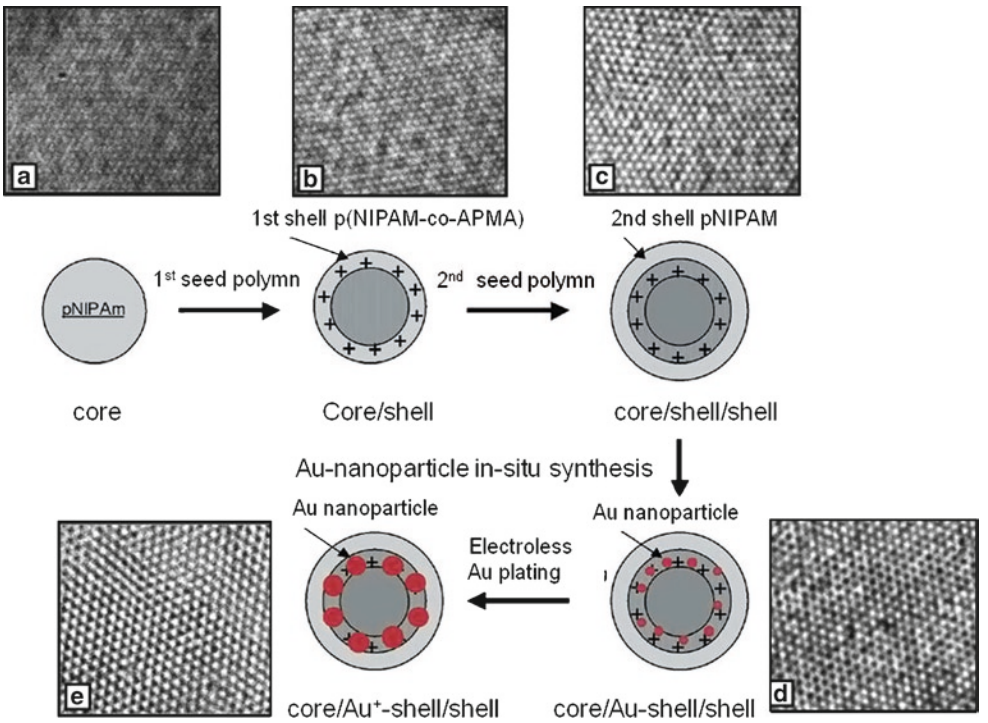


Fig. 4. Composite microgels with designed inner structures and their colloid crystal.

poly(NIPAM-*co*-GMA) with different monomer ratio are formed using radial gradient monomer compositions (Fig. 3). The core of microgel is rich in GMA and the shell is rich in NIPAM. This gradient is attributed to the difference in reactivity and solubility-in-water between GMA and NIPAM. The glycidyl groups of GMA react with 3-mercapto-1-propane sulfonic acid sodium salt (MPSA) and then ferrous ions (Fe_2^+) are added which are attracted to the negative sulfonic groups in the core of microgel. After reaching equilibrium, the ferrous ions are reduced to magnetite (Fe_3O_4) to form microgels containing magnetite nanoparticles in the core. As shown in Fig. 4, more magnetite nanoparticles are in the microgels that contained more GMA. However, if the amount of GMA in the core is too high, they pack so densely that the diffusion of ferrous ions in the gels is prevented limiting the magnetite nanoparticles content.

Zinc Oxide Nanoparticles/Thermosensitive Composite Microgels

A precursor of ZnO, $Zn(CH_3COO)_2\ 2H_2O$, was introduced into poly(VCL-*co*-acetoacetoxyethyl methacrylate (AEM)), a thermosensitive microgel, and then hydrolyzed in situ. The composite microgel formed retained thermosensitivity similar to that of P(VCL-*co*-AEM) even with ZnO nanoparticles as high as 16 wt%. A dispersion of these composite microgels cast on a glass substrate forms a transparent film that is used for UV-shielding. These composite microgels are also used in optoelectronic and photonic fields. As optoelectronic microdevices, UV-detectors, and photocatalysts [46].

Titania Nanoparticles/Thermosensitive Composite Microgels

The incorporation of titanium dioxide into poly(NIPAM-*co*-AAc) microgel was carried out by reacting ammonia with the AAc carboxyl groups in the copolymer microgel [47, 48]. The microgels are added into an ethanolic solution of poly(vinylpyrrolidone) and then titanium tetraisopropoxide is added under stirring for 24 hours. The composite microgels exhibit high catalytic activity in the decomposition reaction of methylene blue under UV irradiation at room temperature, but loose their catalytic activity at high temperatures. It seems that the titania is shielded in the shrunken, opaque PNIPAM matrix at temperatures above the VPTT.

Interpenetrating PNIPAM-PAAc microgels (average diameters at swollen and shrunken states: 750 and 350 nm, respectively), prepared by precipitation polymerization of NIPAM in the presence of PAAc, are used to absorb titania nanoparticles (71 nm). The absorption is carried out at pH 6, near the isoelectric point of titania (6.2). The titania/PNIPAM/PAAc composite microgels thus obtained contain 10–75 wt% titania. The composite microgels exhibit rapid sedimentation which is useful for gravity separation of composite microgels from dispersions after photocatalytic application of microgels, while the sedimentation behavior is temperature controlled [49].

Photoluminescent Nanocrystals/Thermosensitive Composite Microgels

Fluorescent thermosensitive composite microgels are prepared by covering PNIPAM microgels with CdTs nanocrystals [44]. The nanocrystals are covalently immobilized on the microgel surface to form composite microgels that respond to the changes of environmental conditions reversibly and reproducibly. The nanocrystal photoluminescence of microgel is quenched under the VPTT of PNIPAM and restored above the VPTT.

CdSe quantum dots, stabilized with trioctylphosphine oxide, can be incorporated into PNIPAM microgels via ligand exchange, and those stabilized with oleic acid are incorporated into microgels with pendant COOH groups. This method is also used to prepare thermosensitive microgels composed of poly(AEM-*co*-*N*-vinylcaprolactam) [50]. Photoluminescent nanocrystal/thermosensitive polymer composite microgels were prepared by incorporating PbS quantum dots in the interior of PNIPAM microgel [51]. The composite microgels exhibit room temperature quantum efficiency and strong luminescence.

Miscellaneous Nanoparticles/Thermosensitive Composite Microgels

Poly(3,4-ethylenedioxythiophene) (PEDOT) nanorods were incorporated into the shell of PVCL core/poly(AEM) shell microgels [52]. The responses of these composite microgels to environmental temperature and to the repulsion/attraction due to reversible oxidation/reduction by addition of acid and base are very interesting. PEDOT nanorods in microgel are oxidized when the pH is decreased and the Cl^- ions are transformed from the aqueous phase into microgels interior, causing the microgels to shrink. Reduction of the PEDOT causes a reversion; consequently, shrinking/swelling can be controlled reversibly by oxidation/reduction. Microgels, which contain rutherium complexes, catalyze the Belousov–Zhabotinsky self-oscillation reaction [53]. Clay can serve as a crosslinker in PNIPAM microgels; the amount of clay affects the size of microgels [37].

Assemblies and Colloid Crystals of Thermosensitive Microgels

PNIPAM-based microgels self-assemble to form colloid crystals. For example, a dispersion of layered PNIPAM composite microgels was condensed and then a heating–cooling cycle was applied to complete the crystallization [42]. PNIPAM colloid crystal was fixed by self-crosslinking using *N*-hydroxymethylacrylamide [54]. The thermosensitive properties of PNIPAM microgels embedded in the hydrogels remain unperturbed in the volume transition of microgels [55].

Summary

Stimuli-sensitive microgels, also called smart microgels, have significant potential as sensors, energy transferring devices, photonic devices, and bio-separators. Among the many stimuli-sensitive microgels available, PNIPAM microgels have been extensively studied and used for variety of bioapplications. The inorganic nanoparticles, included into PNIPAM microgels, and provide the potential for many new bioapplications without affecting the thermosensitive properties of PNIPAM.

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