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REVIEW ARTICLE

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New approaches to stimuli-responsive polymeric micelles and hollow spheres

Abstract This article briefly describes some new approaches to stimuli-sensitive polymeric micelles and hollow spheres, which were developed in the authors' laboratory in recent years. (1) Self-assembly of component polymers to non-covalently connected micelles (NCCM) driven by specific interactions. For example, in water, PCL and PAA formed core-shell nanospheres due to interpolymer hydrogen bonding. After crosslinking the PAA shell and removing the PCL core, "nanocages" made of PAA network were obtained. This hollow structure shows perfect reversible size-pH dependence. (2) Simultaneous in-situ polymerization of monomers and self-assembly of the polymers. In this approach, PNIPAM network was formed by radical polymerization covering PCL particles. Hollow spheres of PNIPAM network were then obtained by biodegradation of the PCL core. Both the core-shell spheres and hollow spheres show reversible size dependence on temperature change because of the phase transition of PNIPAM around 32°C. (3) Complexation-induced micellization and transition between the micelles and hollow spheres. Graft copolymers of hydroxylethyl cellulose (HEC) and PAA were prepared by free radical polymerization. The copolymers showed pH dependent micellization, i.e., micelles formed when pH of the graft copolymer solution decreased to around 3. The micellar structure could be locked by crosslinking the PAA grafts. The resultant cross-linked micelles undergo pH-dependent transition between the micelles and hollow spheres, which accompanies a remarkable particle size change. Both the micellization and the structure transition were found to be reversible and associated with H-bonding complexation between the main chain and grafts.

Keywords micelle, hollow sphere, hydrogen bonding, self-assembly, stimuli-sensitivity

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In recent years, efforts in our group have been made to develop new routes for polymer micellization. Based on our long-term research on interpolymer complexation [1], we succeeded in developing a series of routes for macromolecular assembly [2]. Differing from the traditional self-assembly of block copolymers in selective solvents, we obtained a series of new type polymeric micelles via macromolecular assembly driven by interpolymer hydrogen bonding complexation, in which homopolymer, random copolymer, graft copolymer and oligomer were used as building blocks. As the new micelles have no covalent bond connecting the core and shell, they are called non-covalently connected micelles (NCCM). The procedure is also called "block-copolymer-free" route for polymer micellization. In this paper, we briefly summarize a part of this work with emphasis on the new routes to stimuli-sensitive NCCMs and hollow spheres, and the structure and properties of the obtained assemblies.

Polymeric nanospheres or micelles (polymeric nanospheres, for simplification) with stable core-shell structures and hollow spheres with inner cavity structures in nano or sub-micro scales have many applications in biomedicine, micro-reactors, environmental protection and others. For example, they can be used as restricted reaction containers, carriers for drug delivery and bio-macromolecules such as catalysts and enzymes [3–5]. Therefore, polymeric nanospheres and hollow spheres and particularly the "intelligent" ones attract a lot of interest. The structure and properties of the "intelligent" or "stimuli-responsive" polymeric assemblies can change reversibly with environment stimuli, thus it may make loading and releasing of drugs controllable. In most cases, the stimuli response of polymeric nanospheres and hollow spheres comes from the related characteristics of

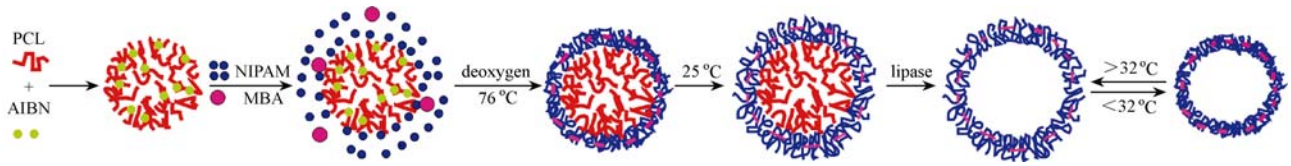

Fig. 1 Schematic illustration of the preparation route to thermo-sensitive core-shell nanospheres and hollow spheres

the component polymers [6–11]. In some cases, two polymers without stimuli-responsive characteristics can also form "intelligent" polymeric assembly due to their specific interactions [12, 13]. In this paper, the characteristics of polymeric nanospheres and hollow spheres responding to three environment stimuli, i.e., temperature, medium pH and ions, are chiefly discussed.

1 Thermo-sensitive polymeric nanospheres and hollow spheres

It is well known that Poly(*N*-isopropylacrylamide)(PNIPAM) has a low critical solution temperature (LCST), so it is dissolved in water at low temperatures while it aggregates and precipitates at high temperatures. Therefore, PNIPAM and its copolymers [8, 9, 14–16] are widely used as the basic materials for constructing thermo-sensitive polymeric nanospheres and hollow spheres. Recently, we developed a new convenient approach to prepare thermo-sensitive polymeric nanospheres and hollow spheres at a high concentration by a combination of self-assembly and in-situ free radical polymerization [17]. The principle of the method is illustrated in Fig. 1.

A suitable amount of initiator azodiisobutyronitrile(AIBN) and poly(ε-caprolactone) (PCL) were first dissolved in *N*,*N*-dimethylformamide(DMF), then the solution was added dropwise into water, causing PCL macromolecules to assemble into surfactant-free nanoparticles containing most of hydrophobic AIBN molecules. Then, water-soluble monomer NIPAM and crosslinker methylene bisacrylamide (MBA) were added to the PCL particle dispersion, followed by increasing the temperature to 76°C to initiate the polymerization. As the preliminary free radicals produced mainly existed in the PCL nanoparticles, and the monomer and crosslinker in water, the polymerization mainly took place on the periphery of the PCL nanoparticles. Since the reaction temperature of 76°C was much higher than the LCST of PNIPAM (about 32°C), once the crosslinked PNIPAM chains formed, they would collapse and enwrap the surface of PCL nanoparticles. The first PNIPAM layer formed would further trap the monomer and crosslinker from the water phase so that the polymerization continued and hence the shell grew. Finally, polymeric nanospheres with a PCL core and a crosslinked PNIPAM shell formed. The hydrodynamic diameter of the nanospheres depended on the reaction parameters such as the initial concentration of PCL, the ratio of monomer to PCL, the amount of crosslinker and etc., and could be adjusted over a range of 150–400 nm.

We further obtained hollow spheres (also called nanocage) made of crosslinked PNIPAM by PCL core degradation of the nanospheres with enzyme. The obtained polymeric nanospheres and hollow spheres exhibit excellent thermo-sensitivity. A typical result is given in Fig. 2. The size of polymeric nanospheres shrinks substantially with increasing temperature and the corresponding hollow spheres show an even larger shrinkage. More importantly, the thermo-sensitivity of the hollow spheres is completely reversible.

It is clear that the principle of this new approach is different from the methods reported in the literature for preparing thermo-sensitive polymeric nanospheres and hollow

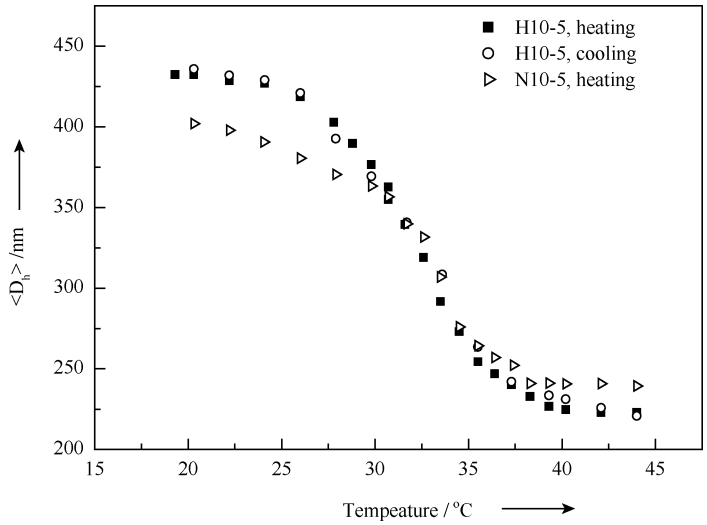

Fig. 2 Average hydrodynamic diameters of the core-shell nanospheres N10-5 and hollow spheres H10-5 as a function of temperature

spheres, such as emulsion polymerization, dispersion polymerization, template polymerization, graft polymerization and Layer-by-Layer (LBL) [8, 9, 12–16]. Further studies on the generality of the new route are being undertaken using different core polymers and monomers or co-monomers.

2 pH-sensitive polymeric nanospheres and hollow spheres

There are many reports on pH-sensitive polymeric nanospheres and hollow spheres in the literatures [6,7,18–26]. Wooley et al. [6, 18] reported a sophisticated procedure containing successive steps: micellization of a block copolymer in the selective solvent forming a degradable core and cross-linkable shell, crosslinking the shell and chemical degradation of the core. Thus, for example, pH-sensitive hollow spheres (or nanocages) of crosslinked poly(acrylic acid) (PAA) were obtained thereby. However, in this method one first has to prepare block copolymers having a degradable block and a crosslinkable block. This is usually difficult and only limited monomer species can be used. In our "block-copolymer-free" routes, one can prepare nanospheres and hollow spheres from common homopolymer pairs or homopolymer-copolymer pairs. Here, three routes for preparing pH-sensitive polymeric nanospheres and hollow spheres are discussed.

Route one is illustrated in Fig. 3 [27]. Add PCL/DMF solution dropwise into a PAA aqueous solution, PCL chains aggregate and the soluble PAA chains assemble around the surface of the PCL nanoparticles driven by hydrogen bonding interactions, which makes the nanoparticles stable and prevents further macroscopic precipitation. As a result, NCCMs with PCL core and PAA shell form. Then, crosslink the PAA shell with diamine to obtain pH-sensitive polymeric nanospheres with a fixed structure. Finally, remove the PCL core via enzyme degradation or DMF dissolution leading to pH-sensitive PAA hollow nanospheres.

The obtained PAA hollow nanospheres have excellent pH-sensitivity (Fig. 4). The pH and hydrodynamic diameter of the starting solution are 5.8 and 150 nm, respectively. When pH of the solution rises from 5.8 to 8.0, the diameter of PAA hollow spheres increases drastically and their volume increases about 75 times, while pH decreases from 5.8 to 4.6, there is a substantial decrease in the sphere size. The results of size change of PAA hollow spheres in a whole pH cycle indicate that, at the same pH value, in the acidic medium, the sizes in the second half cycle are always bigger than those in the first half cycle, while it is the opposite in the basic medium. This is due to the fact that ionic strength in the second half cycle (circles) is much higher than that in the first half cycle (squares). After the influence of the salt is

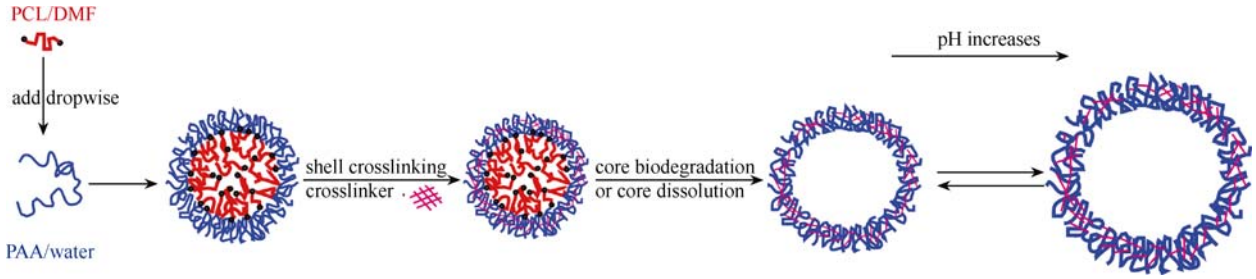

Fig. 3 Schematic illustration for preparing pH-responsive PAA hollow spheres

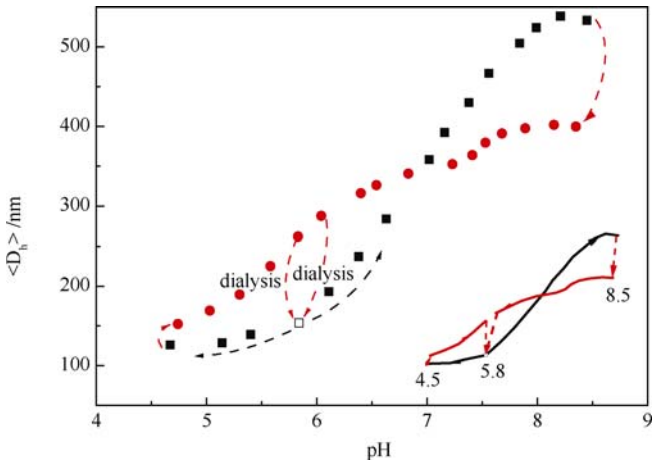

Fig. 4 $\langle D_h \rangle$ of PAA hollow spheres as a function of pH, squares and circles refer to the first half and second half circle, respectively. □ is the starting point

excluded by dialysing the solution at the end of the cycle against water, the size of hollow spheres returns to its starting value (150 nm), indicating that pH-response of PAA hollow spheres is completely reversible.

The second route was based on the self-assembly of random copolymer bearing short grafts and homopolymer in water [28]. We found that, when a PCL/DMF solution was added into an aqueous solution of MAF (a graft-like copolymer with a hydrophilic backbone and PCL short side chains obtained by copolymerization of methyl acrylic acid (MAA), methyl methylacrylate and PCL macro-monomer), PCL chains aggregate to form small particles. However, due to the structural similarity between the PCL side chains of MAF and PCL homopolymer, MAF gathered around and thus stabilized the PCL nanoparticles. Therefore, NCCMs with a PCL core and MAF shell form. The core and the shell of the micelles are connected due to the affinity between PCL homopolymer and PCL grafts of MAF. The micellar structure was then locked by crosslinking MAA units of the shell with diamine, followed by enzyme degradation of PCL core to obtain polymeric hollow spheres (Fig. 5). Since MAA is the main component of the shell, one can expect that the obtained polymeric nanospheres and hollow spheres exhibit pH-responsive behavior.

Furthermore, we also prepared pH-sensitive polymeric nanospheres and hollow spheres from a graft copolymer of hydroxylethyl cellulose (HEC) and PAA (HEC-g-PAA), and realized the reversible transition between polymeric nanospheres and hollow spheres, which is schematically illustrated in Fig. 6 [29]. When pH value is high, HEC backbones and PAA grafts both dissolve in water. As pH decreases (<3), carboxyls of PAA are protonated completely and thus form hydrogen bonding with ether oxygen of HEC to form insoluble complexes. Meanwhile, due to the low degree of grafting, parts of HEC chains remain soluble. Therefore, HEC-g-PAA can self-assemble into micelles with the interpolymer complex of HEC and PAA as the core, and free HEC as the shell. Then, the micellar structure was efficiently locked by crosslinking PAA with diamine. Thus, pH-sensitive polymeric nanospheres were obtained. After dialysing the acidic solution of the nanospheres against water to remove impurities and increasing pH, the carboxyl groups of PAA dissociate and lose the ability to complex with HEC. In this case, the nanosphere cores disintegrate and the crosslinked copolymers swell substantially, therefore, polymeric hollow spheres form. It means that we realized pH-dependent micellization and pH-dependent reversible transition between micelles and hollow spheres.

3 Ion-sensitive polymeric nanospheres and hollow spheres

Due to the shielding effect of ions on the charge, pH-sensitive polymers often exhibit ion-response behavior. Therefore, the corresponding polymeric nanospheres and hollow spheres are usually ion-responsive. The hollow spheres of crosslinked PAA and HEC-g-PAA we prepared both show a size-ionic strength (the concentration of NaCl) dependence [27, 29]. Besides, we found that the medium pH strongly affects the size-ionic strength dependence of the PAA hollow spheres. Specifically, as the salt concentration increases, the hydrodynamic diameter ($<D_h>$) of PAA hollow spheres increases in the acid medium but decreases in the basic medium. In the neutral medium, there is a little change in $<D_h>$ with the salt concentration (Fig. 7).

In conclusion, different from the macromolecular micellization reported in the literature, we developed a series of new routes to construct polymeric micelles and hollow spheres based on interpolymer-specific interactions, mainly, hydrogen bonding. Here, the building blocks we used are all common and cheap polymers and the conditions for assembly and preparation are simple and convenient. In addition,

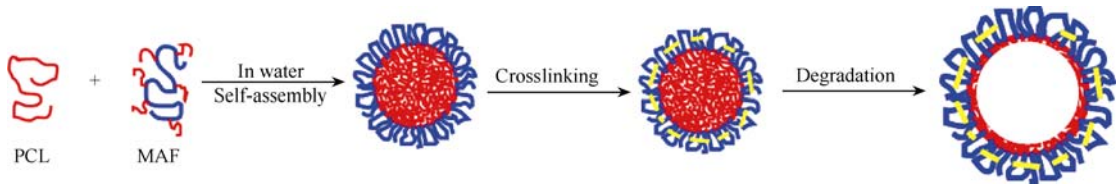

Fig. 5 A schematic illustration of the processes of self-assembly, crosslinking and degradation based on MAF copolymer

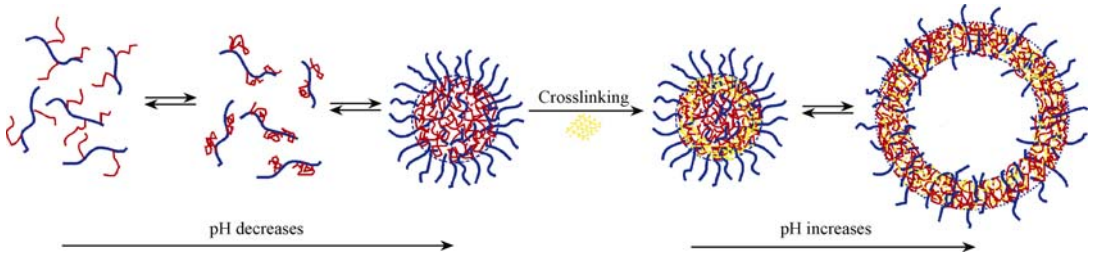

Fig. 6 Scheme of the pH-dependent micellization and transition of HEC-g-PAA from micelle to hollow sphere

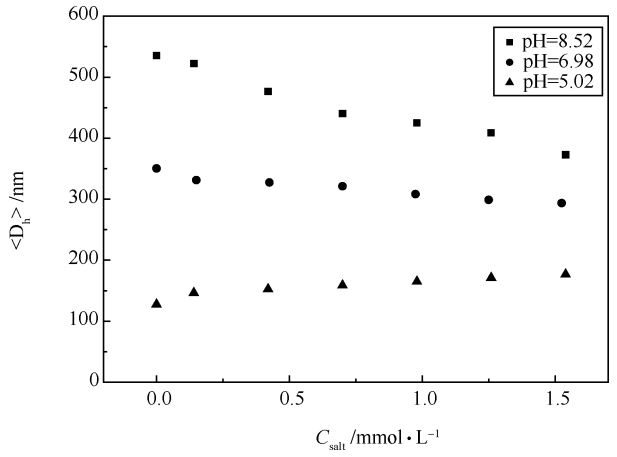

Fig. 7 Salt concentration dependence of $<D_h>$ of PAA hollow spheres at different pH

some methods can even be carried on at a high concentration of the polymers. Meanwhile, the obtained nanospheres and hollow spheres can be functionalized further. Further functionalization of the intelligent polymeric nanospheres and hollow spheres will benefit the improvement and extension of their applications in many fields, especially in biomedicine such as bio-separation, biomedicine tests and diagnosis, and so on.

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