Synthesis and pH-Induced Phase Transition Behavior of PAA/PVA Nanogels in Aqueous Media

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ABSTRACT: Polyacrylic acid (PAA) and polyvinyl alcohol (PVA) are well-known FDA-approved biocompatible polymers. A novel method for preparing PAA/PVA complex nanoneedles in PVA aqueous solution is presented in this article. The PAA/PVA complex nanogels are obtained via polymerization of acrylic acid monomer after PVA nanoparticles formed in water/acetone cosolvent. The results of TEM images showed that the PVA chains were aggregated to form gel particles with some erose nanoparticles. As AA monomers polymerized around PVA nanoparticles, PAA/PVA complex nanogels formed. The PAA/PVA nanogels had an average diameter of 300–100 nm with AA concentration of 0.5–2 g/100 mL. As acetone concentration varied, TEM images demonstrated that the morphologies of resulting nanogels are different. Without acetone in PVA aqueous solution, however, PAA/PVA complexes aggregated to form earthnut-like particles. These results show that the shape and size of PVA/PAA nanogels can be tailored as a template or core for the formation of PAA/PVA nanogels. These PAA/PVA nanogels exhibited pH-induced phase transition due to protonation of PAA chains. The novel PVA/PAA nanogels promise to be developed into pH-controlled drug delivery system. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 111: 358–362, 2009

Key words: nanogel; polyacrylic acid; polyvinyl alcohol; polymerization; aqueous solution

INTRODUCTION

Polyvinyl alcohol (PVA) and poly(acrylic acid) (PAA) are approved by FDA for use in several medical applications including transdermal patches, the preparation of jellies, and sustained release tablet formulations, and some PVA microspheres are also used for controlled release of oral drugs.[1,2] Also PAA, its nano- and microparticles are used for many drugs release controlling materials for the entrapment of hydrophilic drug candidates.[3] To improve the functionality, PVA is often combined with PAA,[4–6] for example, the pure PVA hydrogels are insensitive to pH changes and the addition of PAA results in pH sensitive gels.[7]

Nanogel particles, with diameters in the range of tens to hundreds of nanometers, have attracted significant interest.[6,8–10] Relative to bulk hydrogels, nanogels can show an unusually rapid response to microenvironmental stimuli such as temperature[11] and pH with their very small size. These polymeric nanoparticles have found important applications in numerous areas of controlled drug release, biotechnology, environmental control, as well as in optical applications.[11–14]

Many classes of nanogels have been synthesized via emulsion precipitation polymerization,[3] and hydrophilic nanogels, i.e., PAA nanogels had been synthesized by pulse radiolysis,[15] and polyacrylamide nanogels are usually synthesized via inverse microemulsion polymerization.[10] It is very difficult to completely remove organic solvent and surfactant from resulting nanogels; consequently, these nanoparticles are all not suitable for drug delivery systems.

Recently, nanoparticles formed by a reversible volume-phase transition (VPT) of thermoresponsive polymers[6,16] and by the assembly of amphiphilic block copolymers in aqueous solution have been researched as potential drug carriers.[14] The first method is because at elevated temperatures thermosensitive polymer chains can collapse to form stably dispersed nanospheres above the lower critical solution temperature (LCST) in aqueous media, with or without adding surfactant depending on the material, and the second is based on a self-emulsion process of these amphiphilic block copolymers to form micelle in aqueous media. The PAA nanogels are a kind of pH-responsive hydrogels and can be prepared by PAA or AA and thermoresponsive HPC because the PAA or AA can decrease the phase transition temperature of HPC.[6] However many different polymers are not thermoresponsive, and amphiphilic block copolymers are few, accordingly, a new method being created is necessary.

In this article, the PVA is an initial core of PAA nanogels, and the core was formed in an aqueous

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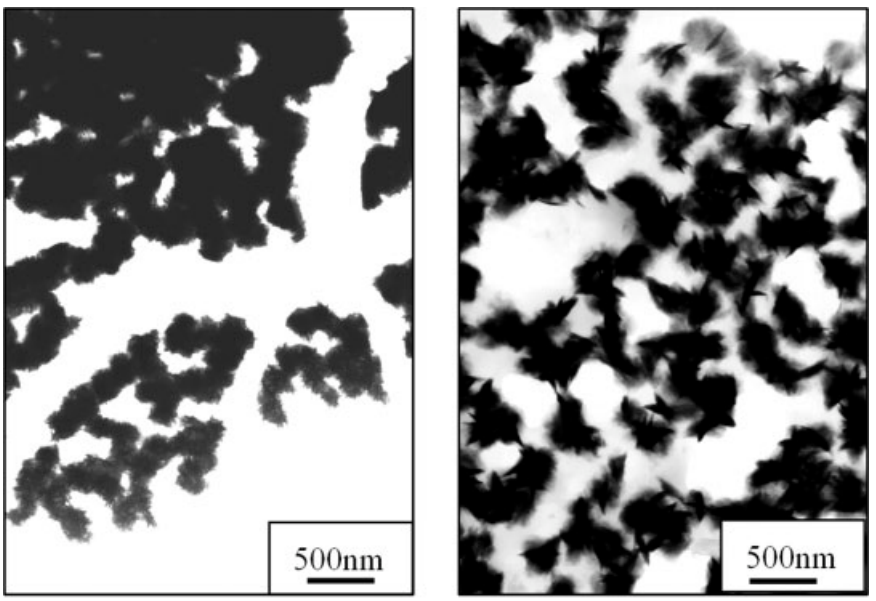

Figure 1 TEM micrographs of aggregate and dispersed state of PVA (1 g/100 mL) in different solvents: (a) water; (b) acetone/water (15/85, v/v).

acetone solution. An innovative synthesis method was used to synthesize PAA/PVA nanogels directly in an aqueous system and also the pH-sensitivity of the hybrid nanogels was researched.

EXPERIMENTS

Materials

Acrylic acid (AA, purified by rectify, purchased from Acros); PVA (polymerization degree is 1750 ± 50, purchased from Acros); *N*,*N*′-methylene-bisacrylamide (Bis) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) were all purchased from Tokyo Chemical Industry; ammonium peroxydisulfate (APS) was used without further purification.

Synthesis of PVA/PAA nanogels

PVA (1 g) was dissolved in 85 mL water at 85°C. After the PVA water solution was cooled to room temperature, 15 mL acetone was added dropwise to the vigorously stirring PVA water solution for 15 min to form about 1% (W/V) PVA solution. Then the solution was placed at 5°C for 24 h and it became weak blue, which indicated that the long chains of PVA shrank to nanoparticles. Then different amount of AA was added to the solution. The solution was purged by N_2 for 30 min, and the 4.0 mmol Bis, 0.4 mmol APS, and 0.67 mmol TEMED were added into the solution to carry out polymerization for 15 h at 30°C.

Characterization techniques

Transmission electron micrographs of the colloidal nanogel particles were taken using an H-800 electron microscope (Hitachi, Tokyo, Japan). The TEM sample was prepared by placing a dilute drop of aqueous particles onto the copper grids and allowing it to dry.

The pH of solutions was adjusted with very small amounts of 0.1*M* hydrochloric acid and sodium hydroxide and determined using a digital pH meter (pHS-4CT, Shanghai Dazhong Analytical Instrument).

RESULTS AND DISCUSSION

PVA is a hydrophilic macromolecule and readily dissolves in water, so that the dynamic behavior of PVA polymer chains is highly sensitive to the solvent quality in a dilute solution.[17] Figure 1 shows that the PVA polymer chains form aggregate about 150 nm in diameter and over 5 μm in length, like a caddice or rope, in 1 wt % PVA aqueous solution. PVA aggregates may be attributed to strong hydrogen bonding of PVA interchains. As acetone (15%, v/v) was added into PVA aqueous solution, PVA chains collapse to form physically crosslinked nanogels ranged from 200 to 500 nm. These erose particulates seemed to be some fragments divided form the PVA "caddice." These results indicates that the PVA configuration in water solution had gotten some changes from its initial coil or aggregate caddice like to unattached particulates with acetone addition and

TABLE I
Calculation of Flory Interaction Parameter (χ_1)

Volume fraction of acetone (ϕ_b)	0	7	12	15	22
δ_1	23.2	22.28	21.62	21.22	20.3
χ_1	0.276	0.506	0.714	0.858	1.237

The volume fraction of the mixed solvent in PVA solutions $\phi_1 \approx 1$, $T = 298.2$ K.

the PVA nanoparticulate or microparticulate could be formed in a mixed solvent of water and acetone.

Collapse of PVA chains in acetone/water cosolvent are due to the solubility of PVA chains in the cosolvent. Although acetone and water is miscible, the cosolvent becomes poor solvent for PVA chains, leading to aggregated globules. Because the δ_a of water is 23.2 and the δ_b of acetone is 10, according to the χ_1 $(\delta_1 - \delta_2)^2$ ϕ_1/RT, $\delta_1 = \phi_a\delta_a + \phi_b\delta_b$ and $\delta_2 = 25.8$. As the volume ratio of water to acetone is 85/15, there are $\delta_1 = 21.22$, $\phi_1 \approx 1$, and $\chi_1 \approx 0.846$. Therefore, this mixed solvent is a poor solvent ($0.8 < \chi_1 < 1.3$) that make the polymer chains collapse and the intramolecular aggregation. As for the nanoneedle state of PVA aggragates, one possible explanation is that the heterogeneous aggregation of PVA chains and pending chains aggregates.

Extensive research have showed that Flory-Huggins theory prediction is reasonable, the polymer chains should exhibit unperturbed coils in θ solvent (Huggins constant, $\chi_1 = 0.52$).[18] In fact, water is quite close to a θ-solvent ($\chi_1 = 0.53$; the second virial coefficient $A_2 = 1.8 \times 10^{-4}$ mL mol/g^2) for PVA at 30°C, and the phase separation of PVA aqueous appears with changing the polymer–solvent interactions. Although water and acetone are cosoluble with each other, acetone as a suitable poor solvent was added into water to make the PVA chain from a unperturbed coils to an aggregated globe according to the $\chi_1 = (\delta_1 - \delta_2)^2\phi_1/RT$, and the values of the solubility parameter of water $\delta_a = 23.2$ $(J/cm^3)^{1/2}$ acetone $\delta_b = 10$ $(J/cm^3)^{1/2}$, PVA $\delta_2 = 25.8$ $(J/cm^3)^{1/2}$, and the mixture solvents $\delta_1 = \phi_a\delta_a + \phi_b\delta_b$. From these relationships, calculated values of Flory interaction parameter (χ_1) of PVA and the mixed solvents of acetone and water are given in Table I. In a poor solvent ($0.8 < \chi_1 < 1.3$), the polymer chains collapse and the intramolecular aggregation occurs easily.

Based on the calculated values of χ_1 in Table I, the water can be thought as a good solvent, the 7% (v/v) acetone solution is close to a θ-solvent and the 12% (v/v) acetone solution is a no good solvent, and the 15 and 22% (v/v) acetone solution belong to poor solvent. As a result, the PVA chains could get some changes from its initial coil to aggregation and to gelation in the range of 0–22% (v/v) acetone. The driving force aggregating the PVA is attributed to the hydrogen bonding and hydrophobic interaction between the macromolecule and acetone, because H-bonding between the "C═O" group of acetone and the "O─H" group of PVA is more stable than that between the "O─H" groups of water and PVA, the hydrophobic interaction of the PVA chains increase with the increase in the volume of acetone.

Figure 2 shows TEM images of the PAA/PVA particles obtained by polymerization with different AA concentration in the 1 g/100 mL PVA acetone water solution: (a) 0.5, (b) 1, and (c) 2 g/100 mL. In Figure 2(a), all particles polymerized from the

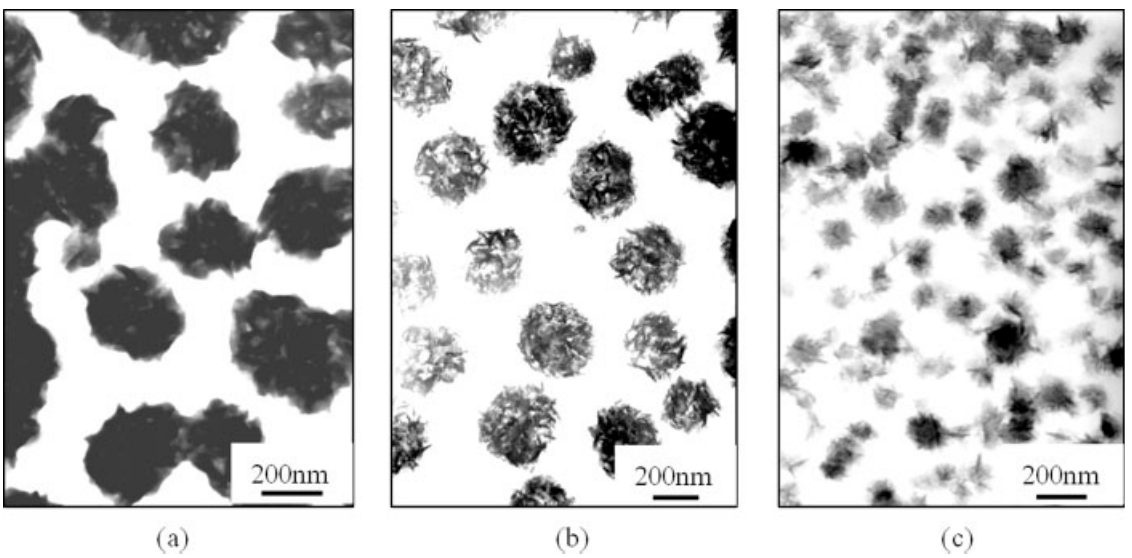

Figure 2 TEM picture of PAA/PVA nanogels with different AA concentration in acetone/water solution: (a) 0.5, (b) 1, and (c) 2 g/100 mL.

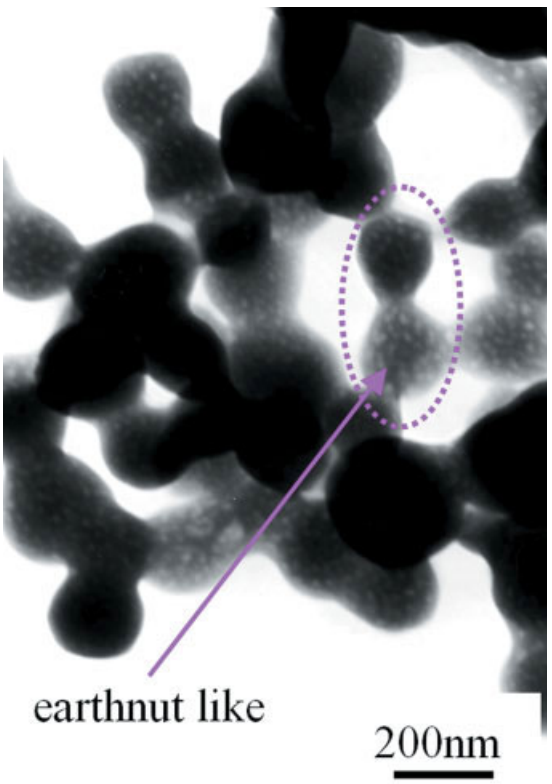

Figure 3 TEM picture of PAA/PVA nanogels from the solution of AA 20% (v/v) and water 80% (v/v). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

solution of 0.5 g/100 mL AA, an average diameter of ~ 300 nm, tend toward glomeration when compared with the reference of Figure 1(b), and they look like a packed dumpling ball with radish bars. The most interesting shapes were obtained using mixtures of 1 g/100 mL AA, these sphere-shaped particles with an average diameter of ~ 300 nm were constructed with a shell-like cactus or chestnut shell, as seen from Figure 2(b), the colloid were almost disappeared when compared with low concentrations of AA of 0–0.5 g/100 mL. The spheres look like empty capsules, and the capsules shell was composed of the assembled needles. This nanocapsule is different from the PAA click capsules synthesized through the silica particle template by Caruso and coworkers.[19] Figure 2(c) shows that high concentrations of AA of 2 g/100 mL resulted in nanogels with diameters of 80–150 nm. These results show that with an increasing concentration of acrylic acid, the resulting PAA/PVA particle sizes decreased.

As AA volume fraction is up to 20%, AA in 1 g PVA/100 mL water solution resulted in the formation of PAA/PVA complex gels after polymerization as the AA volume fraction in 20% without acetone, and these particulates are earthnut like and coherent, and their sizes have 100–200 nm diameters, as seen in Figure 3. Similarly, Mrkic and Saunders reported that hydrophobic monomers, *N*-methylpyrrole, had been polymerized to form PNIPAM-xPMPy complex particles with poly(*N*-isopropyl-acrylamide) microgel particles as a matrix in water,[20] because the poly(*N*-isopropyl-acrylamide) is a thermosensitive polymer which can collapse to form stably dispersed nanospheres above the LCST in aqueous media. PVA is not a thermoresponsive polymer and cannot aggregate to a spherical matrix for the polymerization of AA monomers in PVA water solution without acetone, so the nanoscale sphere of PAA/PVA complex is based on a cooperation of the PVA solution polarity and the hydrogen-bonding between AA and PVA.

Since PAA is a weak acid and is in the molecular state at pH < p*K*a (= 4.7), there is a strong hydrogen bonding between the —COOH group of the PAA and —OH group of the PVA. Figure 4 demonstrates that the transmittance of the nanogel dispersions increased with the increase of the pH value. It is found that the transmittances of PAA/PVA complex nanogels rise sharply at pH 6.5–7.0 for 2/1 (w/w) of PAA/PVA, pH 8–8.5 for 1/1 (w/w) of PAA/PVA, and pH 8.5–9 for 1/2 (w/w) of PAA/PVA. At low pH, there is a very strong hydrogen bonding between the polymer chains of PAA/PVA nanogels, thus leading to a lower transmittance in acetone aqueous solution. As pH increases, PAA becomes ionized, and the ionized PAA weakened the H-bonding between PAA and PVA and strengthened the water-solubility of PAA, so that the PAA/PVA particles swell and the nanogel dispersion becomes transparent.

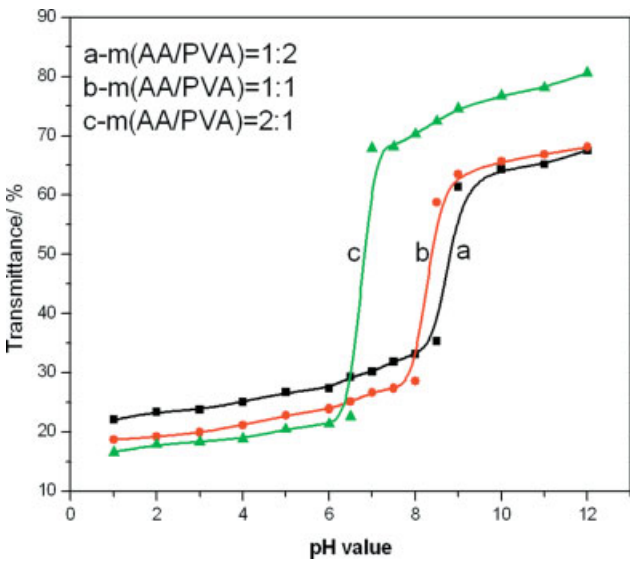

Figure 4 Effect of pH value on the transmittance of the nanogels. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

CONCLUSIONS

In the course of the formation of PVA nanogels, the size and shape of the nanogels depend strongly on the ratio of water/acetone. When the AA concentration increased, the resulting PAA/PVA nanogels indicate that their diameter decreased. In other words, PVA nanoparticles dispersed in water/acetone cosolvent can be used as a template or core for the surfactant-free preparation of PVA/PAA nanogels by polymerizing AA on PVA nanoparticles. Because of the compatibility of PVA and PAA as well as the "green" preparation progress, novel PVA/PAA nanogels can be developed for various nanoscale biomedical devices, such as drug delivery system and nanogel magnetic resonance image contrast agents.

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