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Synthesis of Stimuli-responsive Nanoparticles by Solution Polymerization

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In this study, stimuli-responsive nanoparticles were prepared by solution polymerization. Two synthesis routes are proposed to synthesize the particles, the monomer route and the polymer/monomer route. For the monomer route, pH and thermal sensitive nanoparticles were synthesized from acrylic acid and N-isopropylacrylamide. For the polymer/monomer route, the pH sensitive nanoparticles were synthesized from chitosan and acrylic acid. The effect of reaction time, initiator concentration and agitation rate on the particle size and the size distribution were investigated. The stimuli-responsive nanoparticles could be directly blended with other polymers to prepare stimuli-responsive functional membranes.

Keywords: Nanoparticles, solution polymerization, pH-responsive, temperature sensitivity

1 Introduction

Stimuli-responsive ("intelligent") materials (SRMs) exhibit abrupt property changes in response to small changes in external stimuli such as temperature, pH, ionic and/or solvent composition of the media, concentration of specific chemical species, electric field, and photo-irradiation (1–5). Because of their intriguing properties, interest in the potential applications of SRMs in drug delivery (6–8), biotechnology (9–15), separation sciences (16–20), and chemosensing (21–23) is growing rapidly. The synthesis and application of nanoparticles, especially stimuli-responsive nanoparticles have attracted significant attention in recent years because of their potential use as building blocks for a variety of nanotechnology applications (24–26).

There are many techniques available for the preparation of nanoparticles. Self-assembly is a common method to prepare nanoparticles by non-covalent interactions, responsible for the formation of the self-assembled system which acts on a strictly local level. In other words, the nanostructure builds itself. Block copolymers (di- or tri-block copolymer) are mostly used to form the nanoparticles using self-assembly technique (27). In the copolymer, at least one sequence has stimuli-sensitivity for stimuli-responsive nanoparticles (28, 29). Layer-by-layer assembly is another technique to prepare stimuli-responsive nanoparticles (30). However, the organic synthesis processes of these methods were often complicated and at severe conditions. To synthesize these block copolymers, living polymerization was the most common method. Extremely high purity of the monomers, oxygen-free environment and some catalysts or chain transfer agents must be required in these methods. For the synthesis of nanoparticles, typically used techniques are waterborne heterogeneous systems such as emulsion, mini-emulsion, and suspension polymerization (31–33). By using these techniques, several kinds of temperature and/or pH-responsive nanoparticles (or hydrogels) were synthesized (34–36). However, the extra emulsifier or dispersing agent was needed, which made the system complex and restricted the choice of the solvent. Why not synthesize stimuli-responsive nanoparticles using homogeneous system such as solution polymerization? In fact, pH-sensitive hydrogel microspheres could be prepared by crosslinking copolymerization (37). By free radical copolymerization, monofunctional styrene (ST) and the bifunctional ethylene glycol dimethacrylate (EGDM) could form crosslinking nanoparticles in a homogeneous solution (24).

The nanoparticles synthesized by aqueous dispersion polymerization, were reported to be used as the functional additive for preparing the stimuli-responsive functional ultrafiltration membranes (38, 39). However, the nanoparticles should be purified by membrane dialysis and be dried before blending in the membranes. This problem might restrict the wide application of the method.

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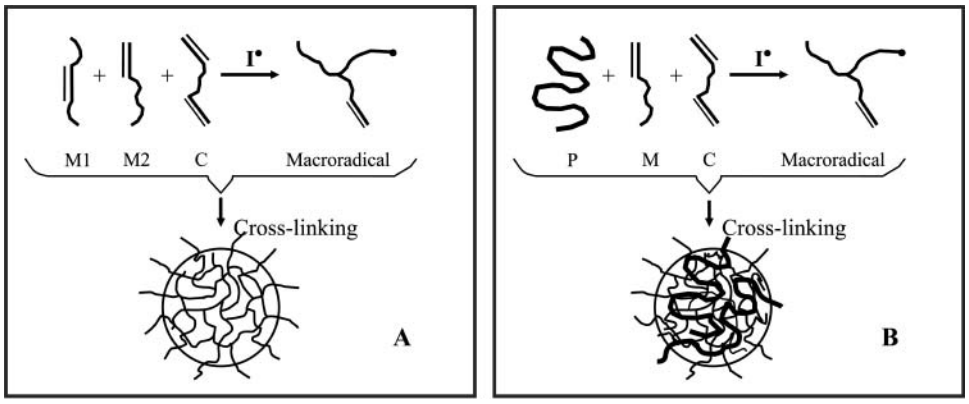

Fig. 1. Formation of crosslinking nanoparticles by solution polymerization. A: monomer route; B: polymer/monomer route; M1, M2 and M are monovinyl monomers; P is a linear polymer; C is the crosslinker; and I represents the initiator.

In this paper, we demonstrated that stimuli-responsive nanoparticles could be synthesized by solution polymerization. Solution polymerization, which was a simple and mature method to synthesize polymers, was much more convenient for industry production of nanoparticle than other pathways described above. The effect of reaction time, initiator concentration and agitation rate on the particle size and the size distribution were investigated. These stimuli-responsive nanoparticles could be directly blended with other polymer using the same solvent to prepare stimuli-responsive functional membranes. In this study, two synthesis routes are proposed to synthesize the particles, as shown in Figure 1.

2 Experimental

2.1 Materials

Chitosan powder, with a deacetylation degree of about 90% and viscosity below 100 cps, was purchased from Boao Biological Tech. Co., Ltd., Shanghai. Acrylic acid (AA, Kelong Chemical Reagent Inc, Chengdu, China) was pretreated by distillation.

N-Isopropylacrylamide (NIPAA, Kelong Chemical Reagent Inc, Chengdu, China) was purified by recrystallization from hexane and toluene. Azo-bis-isobutryonitrile (AIBN, Shisihewei Chemical Reagent Inc., Shanghai, China) was purified by recrystallization from ethanol. Ammonium persulfate (AP), N,N-methylenebisacrylamide (MB), and dimethyl sulfoxide (DMSO) were obtained from Kelong Chemical Reagent Inc, Chengdu, China, and were used as received.

2.2 Synthesis of Nanoparticles By Monomer Route

Stimuli-responsive nanoparticles by monomer route were synthesized by solution polymerization from AA and NIPAA with a molar ratio of 1:1. AA (M1), NIPAA (M2) and MB (C) were dissolved in H_2O or DMSO with a molar ratio of 1:1:0.01 at a total concentration of 2 mmol/g. The mixture was first heated to 65°C and purged with nitrogen for 0.5 h, then the AIBN dissolved in 5g DMSO or the AP dissolved in 5g H_2O was injected into the polymerization system. The reaction was carried out in an airtight equipment at 65°C for 3 h with agitation. The compositions of the nanoparticles are shown in Table 1.

2.3 Synthesis of Nanoparticles by Polymer/Monomer Route

Nanoparticles by polymer/monomer route were synthesized from chitosan and AA with a ratio of 1:5 (w/w) by solution polymerization. Chitosan (P), AA (M) and MB (C) were dissolved in water with a mass ratio of 1:5:0.01 at a total concentration of 6 wt%. The mixture was first heated to 65°C and purged with nitrogen for 0.5 h, and then the AP (the molar ratio of AA: AP was 500:1) dissolved in 5g H_2O was injected into the polymerization system. The reaction was carried out in an airtight equipment at 65°C for 4 h with constant stirring at 100 rpm.

2.4 Scanning Electron Microscope of the Nanoparticles

For the SEM observation, the nanoparticles in solvent were diluted by double distilled water in a volume ratio

Table 1. The compositions of the nanoparticles

Nanoparticle No.	*Initiator*	*Initiator concentration (μmol/g)*	*Agitation rate (rpm)*	*Solvent*
P-1-1-d	AIBN	1	100	DMSO
P-2-1-d	AIBN	2	100	DMSO
P-2-1-w	AP	2	100	Water
P-2-2-d	AIBN	2	200	DMSO
P-4-1-d	AIBN	4	100	DMSO

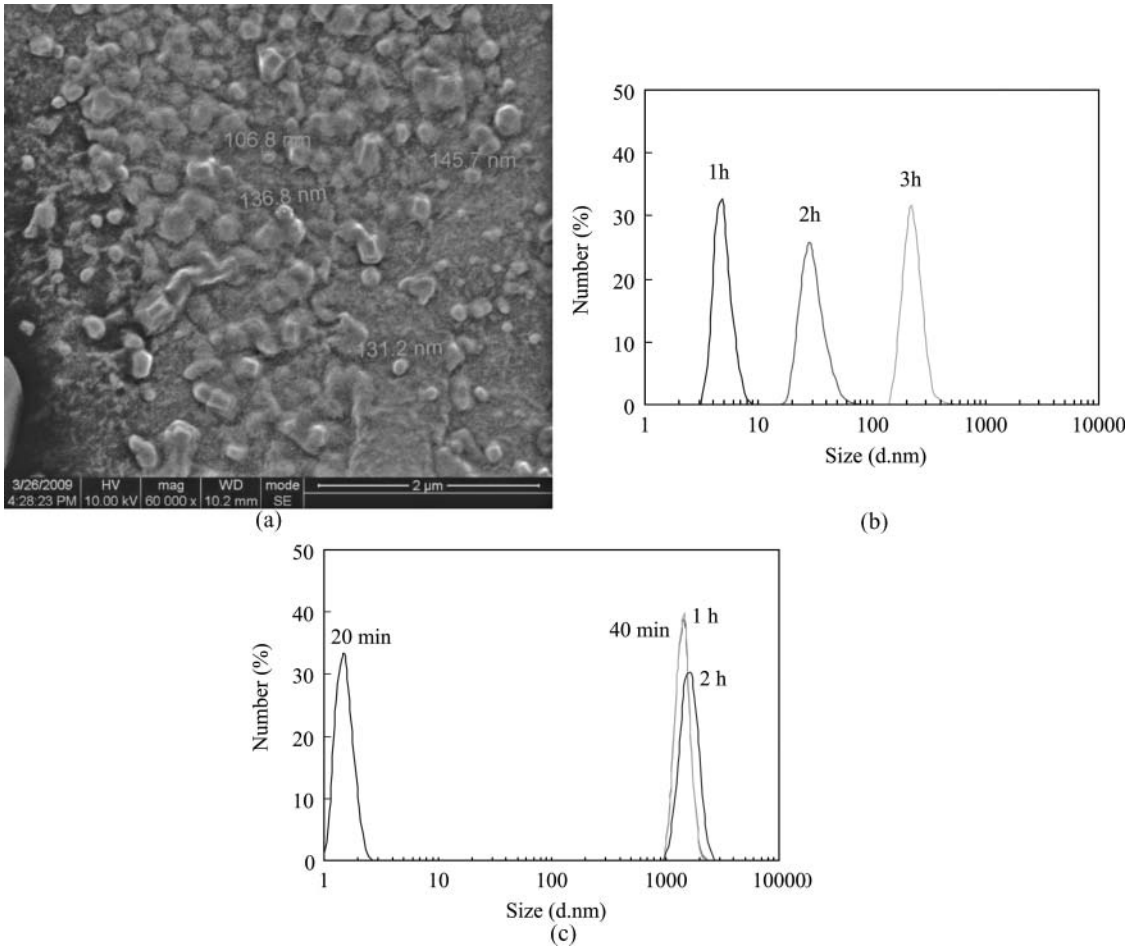

Fig. 2. Typical particle SEM picture and the particle sizes. (a) Typical particle SEM picture with the reaction time of 3 h using DMSO as the solvent; particle size and size distribution with different reaction times (b) in DMSO and (c) in water.

of 1:4, and then freeze-dried at their non-ionic form. After attaching to the sample supports and coated with a gold layer, a scanning electron microscope (JSM-5900LV, JEOL, Japan) was used for the morphology observation of the nanoparticles.

2.5 The Particle Size and Size Distribution of the Nanoparticles

The nanoparticles in solvent were diluted by double distilled water at various temperatures or by buffer solutions at different pH values with a volume ratio of 1:4. The particle size and the size distribution of the nanoparticles were measured by a Nano-zatasizer (Zetasizer Nano ZS model number: ZEN3600, Malvern Instruments, UK).

3 Results and Discussion

3.1 Characterization of the Monomer-route Nanoparticles

Typical stimuli-responsive nanoparticles were synthesized by free radical copolymerization of acrylic acid (AA, M1), *N*−isopropylacrylamide (NIPAA, M2) monomers, and cross-linker N,N′-methylene-bis(acrylamide) (MB, C) in a homogeneous solution. DMSO and H_2O were chosen as two kinds of solvent. DMSO is a good solvent for polyethersulfone and polysulfone which are the common materials for preparing ultrafiltration membranes. The particle size and the size distribution were analyzed. Figure 2 represents the SEM micrographs and the size distribution of the particles (P-2-1-d and P-2-1-w) with different reaction times. For SEM observation, the nanoparticles were freeze-dried. In this process, the shape of the nanoparticles would alter due to the contraction, therefore, the nanoparticles are not standard spheres. The molecular weight of the polymers prepared by solution polymerization distributes broadly, and the size distribution reflects the molecular weight to some degree as shown in Figure 2b.

Hydrodynamic diameters of the particles isolated at 60, 120, and 180 min reaction time were measured. At 60 min reaction time, the hydrodynamic diameter of the nanoparticles synthesized in DMSO solvent is in a range of 2–9 nm; at 120 min, it ranges from 17 to 80 nm; and at 180 min, it ranges from 105 nm to 500 nm, and the

size distribution is broad (Fig. 2b). The results indicated that the size of the particles increased and the distribution curves shift toward the large particle size region with reaction time. At longer reaction time and higher monomer concentration, some macroparticles radicals formed in the solution. These results are in agreement with that of the ST/EGDM particles (24), except that a longer reaction time is needed to obtain the particles due to the third monomer, which may affect the copolymerization.

The average hydrodynamic diameter of the nanoparticles synthesized in water is shown in Figure 2c. Similar results are observed, the size of the nanoparticles increases and the distribution curves shift toward the large particle size region with a shorter reaction time than that in DMSO solvent. The sizes of the nanoparticles synthesized in DMSO or in water are different because of the different reactive activities in these two systems. The size synthesized in water was larger than that in DMSO.

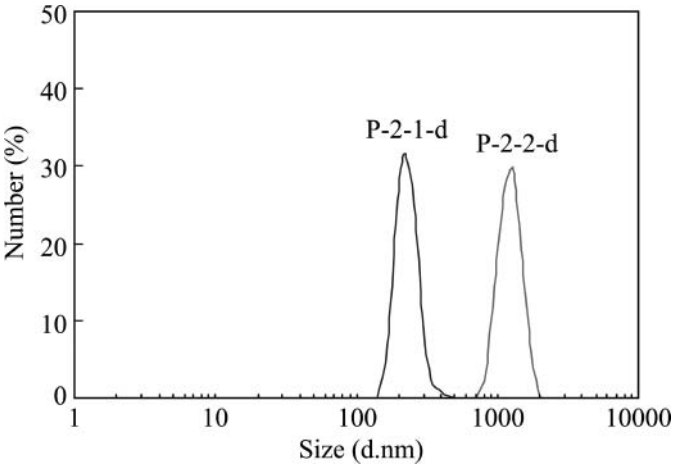

Fig. 4. Particle sizes and the size distributions at two different agitation rates.

3.2 Effect of the Initiator Concentration on the Synthesis of Monomer-route Nanoparticles

The effect of the initiator concentrations ranged from 1 to 4 μmol/g (P-1-1-d, P-1-2-d, P-1-4-d) was investigated, and the results are shown in Figure 3. With the increase of the AIBN concentrations, the particle size decreased. The particle sizes ranged from about 6.5 to 12.5 nm, 105 to 500 nm, and 700 to 1100 nm for the AIBN concentrations of 4 μmol/g, 2 μmol/g, and 1 μmol/g, respectively. It is well known that the molecular weight of a polymer would increase with the decrease of the initiator concentration for free-radical polymerization. Preparing the particles is similar to the preparation of linear polymers, the particle size increased with decreasing the initiator concentration. Furthermore, it can also be observed from Figure 3 that the distribution of the particle dimension became broad when initiator concentration increased. With the increase of initiator concentration, more active sites were formed at the beginning of the polymerization, and more primary particles were formed. Thus, the contacting probability of primary particles in the uniform solution increased, the distribution of the particle size became broad as the particles grew.

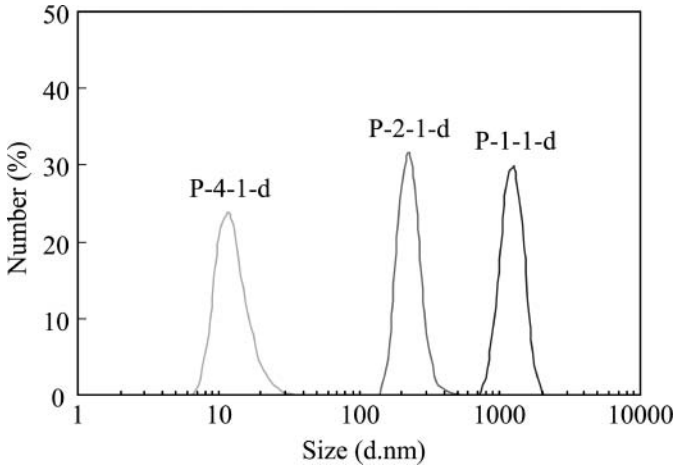

Fig. 3. Particle size and the size distribution with different initiator concentrations.

3.3 Effect of the Agitation Rate on the Synthesis of Monomer-route Nanoparticles

The agitation rate in the polymerization reaction affected the size and distribution of the nanoparticles. Figure 4 shows the sizes and the size distributions of the nanoparticles (P-2-1-d and P-2-2-d) prepared at two different agitation rates. At the agitation rate of 200 rpm, the average hydrodynamic diameter of the gels was about 1200 nm; while that was about 220 nm at 100 rpm. The higher agitation rate, the larger gels were obtained.

It is known that with the increase of the agitation speed, the particle size decreased in emulsion polymerization (40), this was opposite to our result; however, a similar result had been reported in a previous study (37, 41). In fact, the effects of agitation rate on the properties of nanoparticles have not been clarified by far, although many mechanisms for the nanoparticles formation have been postulated. Nevertheless, because the initiator, AIBN, was applied in the polymerizations, which dominantly partitioned in the continuous phase, the capture of entities generated in the continuous phase into growing particles played an important role in the formation of the particles (37). Thus, with the increase of the agitation rate, the capture of the monomer into the growing particles increased, and the contacting probability of small particles to form large particles in the uniform solution increased. Furthermore, with the increase of the agitation rate to 300 rpm, a large number of individual macroradicals starts to grow in the solution.

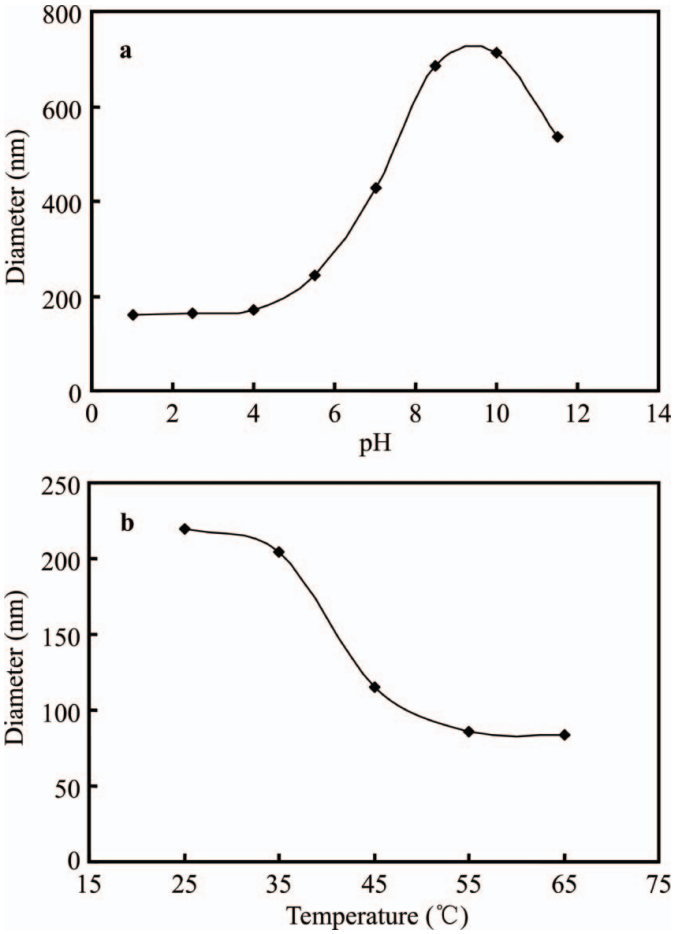

Fig. 5. Particle sizes and the size distributions with different (a) pH values and (b) temperatures.

3.4 pH and Temperature Sensitivity of the Monomer-route Nanoparticles

The pH sensitivity and thermal sensitivity of the prepared nanoparticles (P-2-1-d) were investigated.

The diameter of the particles exhibited chemical valve behavior at pH between 4 and 9, and hardly changed at the pH value lower than 4, shown in Figure 5a, at 25°C. The particle diameter increased from 159 nm at pH 1.0 to 712 nm at pH 10.0, up to a 3.5-fold augment in diameter. The chain configuration of weak polyacid is a function of pKa of the polymer. The pKa of PAA in solution is about 6–7 dependent upon the measurement method (42, 43). At pH lower than 4, there were at least 90% of all the carboxyl groups in their unionized state. The PAA section of the particles coiled down resulting in volume shrinkage. At pH higher than 9, about 90% of the carboxyl groups dissociated and extended resulting in volume expansion. When the pH value was larger than 10.0, the particle diameter did not increase, but decreased. This is accompanied by the particle swelling, with the decrease in the volume charge density of the ionic groups. The mobility of gels surrounded by a polyelectrolyte layer is an increasing function of the volume charge density of the ionic groups (44). This effect, combined with the appreciable ionic strength due to the added base, appears to overwhelm the expected total increase in net charge (45).

It is well-known that PNIPAA hydrogels have LCST (46, 47). At the temperatures below the LCST, hydrogen bonds between water molecules and hydrophilic groups give the hydrogels good solubility. When the external temperature increased to the LCST, the hydrogen bonds are overwhelmed by the hydrophobic interactions among the hydrophobic group, causing a phase separation and shrinkage of the gel matrix (48–50). Similar to the PNIPAA hydrogels, the prepared P(NIPAA-co-AA) nanoparticles became swollen at temperatures below the LCST, but underwent a de-swelling process when the external temperature increased (51).We chose temperatures between 25°C and 65°C to test the thermo-sensitivity of the nanoparticles; data are shown in Figure 5b. In double-distilled water, the particle diameter decreased from 220 nm at 25°C to 84 nm at 65°C, about 1.6-fold reduction in the diameter.

The results indicated that these nanoparticles have both pH and temperature sensitivities, and the results are comparable with the stimuli-responsive nanoparticles prepared by other polymerization methods (27–33).

In our preliminary experiments, the PAA nanoparticles synthesized in the DMSO solvent with a relatively large diameter were blended with polyethersulfone solution (using DMSO as the solvent) directly to prepare membrane using a phase separation technique. The composite membranes showed evident pH and temperature sensitivity. The flux at acid condition was about 2.6 times larger than that at basic conditions.

3.5 Characterization of the Polymer/monomer-route Nanoparticles

Nanoparticles by the polymer/monomer route were also synthesized from chitosan and AA, and the samples were analyzed. Figure 6 represents the particle sizes and the

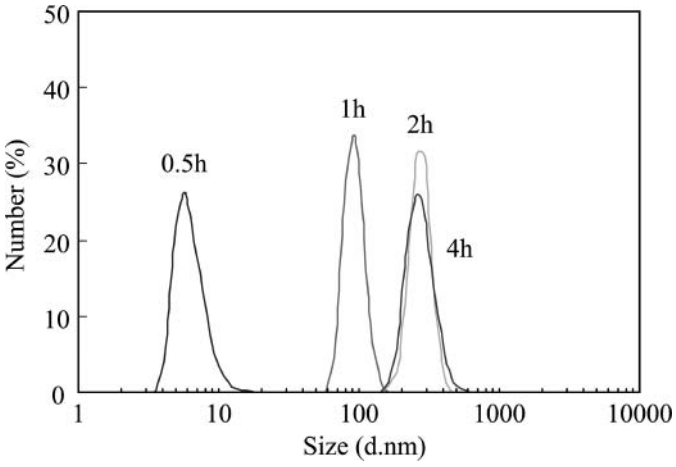

Fig. 6. Particle size distribution with different reaction times.

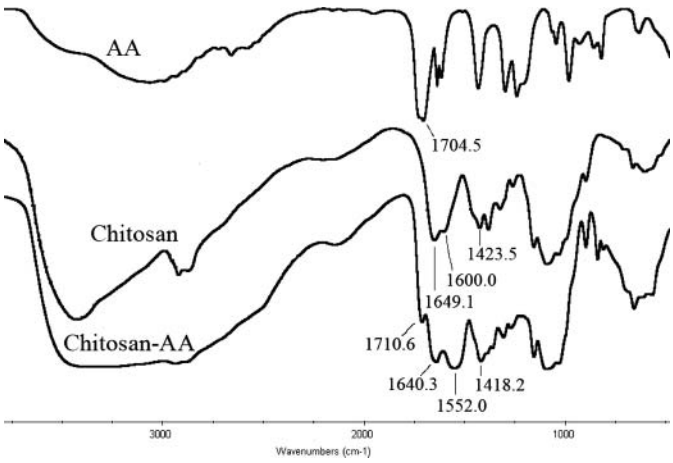

Fig. 7. FT-IR spectra of AA, chitosan and chitosan-PAA particles.

size distributions of the particles with different reaction times.

The hydrodynamic diameters of the particles isolated at 30, 60, 120, and 240 min reaction time were measured. At 30 min reaction time, the hydrodynamic diameter of the nanoparticles is in a range of 3–15 nm; at 60 min it ranges from 65 to 140 nm; at 120 min it ranges from 160 to 460 nm; and at 240 min it ranges from 160 to 600 nm. The results show that the size of the particles increases and the distribution curves shift toward the large particle size region with reaction time. The average hydrodynamic diameter of the particles at 240 min is nearly the same as that at 120 min, but the size distribution at 240 min is slightly broader than that at 120 min. The result is in agreement with the linear polymers by solution polymerization, the molecular weight distribution increased with time.

To investigate the complex formation of AA and chitosan, FT-IR studies were conducted. Figure 7 shows the FT-IR spectra of AA, chitosan and chitosan-PAA nanoparticles. For Chitosan-PAA nanoparticles, the intensities of amide band I at 1649.1 cm^{-1} and amide band II at 1600.0 cm^{-1}, which can be observed clearly in pure chitosan, decreased dramatically, and two new absorption bands at 1710.6 and 1640.3 cm^{-1}, which can be assigned to the absorption peaks of the carboxyl groups of PAA (the absorption peak of carboxyl groups in pure AA appears at 1704.5 cm^{-1}), and the NH^{3+} absorption of CS, respectively, are observed. The broad peaks which appeared at 2200 cm^{-1} also confirmed the presence of NH^{3+} in the chitosan-PAA nanoparticles. Furthermore, the absorption peaks at 1552.0 and 1418.2 cm^{-1} could be assigned to the asymmetric and symmetric stretching vibrations of COO^- anion groups. These results indicate that the carboxylic groups of PAA are dissociated into COO^- groups, which interact with the protonated amino groups of chitosan through electrostatic interaction to form the polyelectrolyte complex during the polymerization procedure (52).

3.6 Functional Filtration Membrane Blended with the Particles

The stimuli-responsive particles could be used to prepare the stimuli-responsive filtration membranes by blending with other polymers (38, 39). However, the nanoparticles synthesized by the reported aqueous dispersion polymerization should be purified by membrane dialysis and dried before blending in the membranes.

By the solution polymerization method, we could synthesize the particles in the same solvent as the polymers (which were used to prepare membranes) were dissolved in. Then, the particles in the solvent could be directly blended with the polymer solution (the same solvent) to prepare stimuli-responsive functional membranes. In fact, in one of our studies, we had synthesized PAA particles in DMAC (DMAC was also a good solvent for polyethersulfone) by the monomer route as described above, and then the PAA particle solution was blended with a PES/DMAC solution. By using a phase inversion method, pH-responsive membranes were prepared successfully (41), and in another study, the PES-PVP particles were synthesized by the polymer/monomer route in DMAC using the same method as described in section 2.3. The PES-PVP particle solution was also blended with a PES/DMAC solution directly to prepare the PES-PVP functional membranes (data not published till now).

4 Conclusions

The goal of this study is to develop a solution polymerization method for the preparation of stimuli-responsive nanoparticles. Two synthesis routes, the monomer route and polymer/monomer route, are proposed to synthesize the particles. For the monomer route, different functional monomers could be used to synthesize nanoparticles with different functions. Many kinds of functional acrylic monomers could be used in this system. For the polymer/monomer route, many functional linear polymers could be used, the monomers polymerized, crosslinked and wrapped onto the linear polymer to form semi-IPN nanoparticles. When the particles were used to prepare functional membranes, the polymer/monomer route was good. Using the same polymer as used to prepare the membranes, the nanoparticles would be barely eluted from the blended membranes. We have successfully accomplished by synthesizing PAA-NIPAA nanoparticles by monomer route, and chitosan-PAA nanoparticles by polymer/monomer route. The size of the particles can be controlled by the initiator concentration and agitation rate in the polymerization process. With the increase of the initiator concentration, the size of the particles decreased; and with the increase of the agitation rate, the size of the particles increased. The pH and temperature sensitivity of the PAA-NIPAA nanoparticles is evident, and it can be comparable with the stimuli-responsive nanoparticles by other

polymerization methods. The particles could be directly blended with other polymers using the same solvent to prepare ultra filtration membranes with stimuli-responsivity.

Acknowledgements

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