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Investigation on properties of re-dispersible cationic hydrogel nanoparticles

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Abstract

P(DMAEMA-g-EG) cationic hydrogel nanoparticles (CHNPs) were prepared by distillation–dispersion copolymerization of poly(ethylene glycol) methyl ether methacrylate (MPEGMA) and *N,N*-dimethylaminoethyl methacrylate (DMAEMA) using acetonitrile (AN) as dispersion medium. The results of FTIR spectra indicate that the composition of P(DMAEMA-g-EG) CHNPs is consistent with the designed structure. The TEM image shows that P(DMAEMA-g-EG) CHNPs are of spherical morphology before and after swelling. The investigations on the properties of P(DMAEMA-g-EG) CHNPs indicate that P(DMAEMA-g-EG) CHNPs have pH-, ionic strength- and thermo-sensitive characters. This type of P(DMAEMA-g-EG) CHNP is very promising as environment-sensitive drug carriers.

Keywords: Cationic hydrogel; Nanoparticles; Environment-sensitive; Distillation–dispersion copolymerization

1. Introduction

Nanoparticles (NPs) have been studied extensively as particulate carriers for low molecular mass drugs, oligonucleotides and peptides [1–5]. NPs perform several advantages, such as controlling the release of drugs, improving the bioavailability of drugs with poor absorption characteristics, delivering vaccine antigens to the gut-associated lymphoid tissues, reducing the gastrointestinal (GI) mucosa irritation caused by drugs, and assuring the stability of drugs in the GI tract etc. However, some drawbacks limit NPs' application in biomedicine, such as relatively low drug loading capacity and complicated preparation procedure, which requires presence of drug in the reaction mixture and often causes the drug inactivation.

Environment-sensitive hydrogel nanoparticles (HNPs) are ideal carriers to overcome the above drawbacks of NPs mentioned above because HNPs can be synthesized without drug existence and load drug resulting in a gel collapse and then form nanoparticles [6–12]. HNPs are a new family of nanoscale materials on the basis of dispersed networks of three-dimensional crosslinked ionic and nonionic hydrophilic polymers, which are swollen, but not dissolved by water, soft and pliable. These properties make HNPs useful in biomedicine, especially in oral drug

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delivery of protein and peptide [13–17]. It is well known that the bioavailability of biomacromolecule is very low after oral administration because of their instability in GI tract and low permeability through intestinal mucosa. Environment-sensitive HNPs are promising for oral drug delivery of proteins and peptides. The thermo-sensitive nanoparticles of poly(ethylene glycol) and *N*-isopropyl acrylamide (PEG-PNIPAAm NPs) show a high loading efficiency of 65% for insulin and the loading capacity reaches to 2.1% (w insulin/w nanoparticles). These insulin-loaded PEG-PNIPAAm NPs can protect insulin from high temperature so that 80% of the insulin can still be detected after 8 h at 60 °C [18,19]. Poly(methacrylic acid-grafted-poly(ethylene glycol)) (P(MAA-g-EG)) HNPs, a kind of pH-sensitive anionic hydrogel, assume a hydrophobic structure with a low degree of swelling and permeability at low pH values, which protects the protein drugs from degradation as they travel through the stomach. P(MAA-g-EG) HNPs can increase their swelling and permeability capacity with Increasing pH in the intestine, which causes the drug release [20–22].

As effective non-viral gene delivery vehicles, the cationic hydrogel nanoparticles (CHNPs) become hot issue, such as poly(ethylene oxide) (PEO)/polyethyleneimine (PEI) (PEO-*cl*-PEI) CHNPs [8,23–26]. Interaction of anionic oligonucleotides with PEO-*cl*-PEI results in formation of nanocomposite materials. In the hydrophobic regions of the nanocomposite, hydrophilic PEO chains were conjugated, which increased the antisense activity of an oligonucleotide in a cell model. It is known that the homopolymer, poly(2-(*N*,*N*-dimethylamino)-ethyl methacrylate) (PDMAEMA), is both a pH-responsive cationic polyelectrolyte containing a tertiary amine group ($pK_a \sim 7.0$) [27–29] and a thermosensitive polymer with phase transition temperature [30–32]. PDMAEMA has been used in Polyelectrolyte complexes (PECs) as DNA binding agent for non-viral gene delivery systems [28,33]. Recently, the PDMAEMA CHNPs, showing thermo- and pH-dependent swelling, have been prepared by photocrosslinking reaction [34]. The PDMAEMA CHNPs may find applications in nanotechnology applications such as sensors, actuators, valves, and other devices working on the basis of the temperature and pH-responsiveness of PDMAEMA. However, flock coagulation can be seen from the SEM images because of the high concentrations of colloidal nanohydrogels at these places as well as surface tension effects caused by the drying process. Therefore, it is important to prepare re-dispersible PDMAEMA CHNPs for nanotechnology applications.

Many methods have been investigated for the preparation of HNPs, such as emulsion polymerization [8,35], radiation polymerization [36–38], dispersion polymerization [15,39], and self-assembly method [11,40,41]. Recently, a novel polymerization technology to prepare polymeric particles, distillation–precipitation polymerization, has been developed by Huang [42–46]. The polymeric particles are formed simultaneously through a precipitation polymerization manner during the distillation of acetonitrile off the reaction system without any stabilizers and agitation. In this paper, P(DMAEMA-g-EG) CHNPs with nanoscale size were prepared by distillation–dispersion polymerization, a modified distillation–precipitation polymerisation method. The environment-sensitive characters of P(DMAEMA-g-EG) CHNPs, including pH-, ionic strength- and thermo-sensitivity, were mainly investigated.

2. Materials and methods

2.1. Materials

Poly(ethylene glycol) methyl ether methacrylate (MPEGMA, $M_n = 2080$ Da) was obtained from Sigma Chemical Co. *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA) and tetra(ethylene glycol) diacrylate (TEGDA) were purchased from Aldrich Chemical Co. 2,2′-Azobisisobutyronitrile (AIBN) and acetonitrile were purchased from Tianjin Chemical Reagent Factory (China). All reagents were the analytical grade.

2.2. Synthesis of P(DMAEMA-g-EG) CHNPs

P(DMAEMA-g-EG) CHNPs were prepared by distillation–dispersion polymerization. DMAEMA was used as monomer and MPEGMA was used as macromonomer, i.e. reactive stabilizer. The monomers were mixed in a certain mass ratio of DMAEMA/MPEGMA and the concentration of total monomers in acetonitrile varied from 10 mg/ml to 100 mg/ml. TEGDA, the crosslinker, was dissolved in the monomer mixture in amount of 2 mol% of DMAEMA. Nitrogen was bubbled through the mixture for 20 min to remove the dissolved oxygen. When the reaction system was heated from ambient temperature to boiling state, AIBN, the initiator, was added into the reaction system in amount of

2.9 mol% of DMAEMA and then the solvent began to be distilled. The initially homogeneous reaction mixtures became milky white after boiling for about 15 min. Water was dropped into the reaction system when two thirds of acetonitrile was distilled and the reaction was ended after complete distillation of acetonitrile. The resulting dispersion was centrifuged by a centrifuger (LD5-2A, Beijing, China) at 5000 rpm for 15 min and the large gel aggregates (about 5% volume fraction) were removed. In order to eliminate any unreacted monomer, oligomer and non-crosslinked polymer chains, the dispersion was dialyzed opposite to water for approximately 3 days by using a dialysis membrane (12 KDa molecular weight cut-off) by changing water daily. The obtained dispersion could be used directly or frozen and lyophilized into freeze-dried powder of P(DMAEMA-g-EG) CHNPs, which can easily redisperse into water and form nanoparticle dispersion. The yield of P(DMAEMA-g-EG) CHNPs was 70–90%. P(DMAEMA-g-EG) CHNPs prepared in this paper were listed in Table 1.

2.3. Characterization of P(DMAEMA-g-EG) CHNPs

Fourier transform infrared (FTIR) spectroscopy (FT3000, Bio-Rad, Hercules, CA) was used to confirm the composition of P(DMAEMA-g-EG) CHNPs at a resolution of 2 cm^{-1} at room temperature. Polymer samples were pressed into KBr pellets (1:100 copolymer/KBr ratio) and analyzed with IR data manager software.

The size and distribution of P(DMAEMA-g-EG) CHNPs were determined by BI-90Plus laser particle size analyzer (LPSA, Brookhaven Instruments, USA). In all cases, λ of measurement was 678 nm, the angle of measurement was 90° and the temperature of measurement was 25 °C.

The transmission electron microscopy (TEM) specimens for P(DMAEMA-g-EG) CHNPs were observed under a JEM-100CX II instrument. The samples were prepared by adding a drop of P(DMAEMA-g-EG) CHNPs dispersion on the Formvar-coated copper TEM grid, and then dyed by phosphatotungstic acid.

2.4. Swelling behaviors of P(DMAEMA-g-EG) CHNPs

The equilibrium swelling was performed to characterize the pH-responsive behavior of P(DMAEMA-g-EG) CHNPs. To determine the equilibrium swelling behavior, 100 mg freeze-dried P(DMAEMA-g-EG) CHNPs was dispersed in 10 ml buffer solution at pH values of 4.00–8.00 and ionic strength of 0.4. The pH values of solutions were determined by a pH meter ((PHS-3C, Shanghai LeiCi Technology Co, China) and size of P(DMAEMA-g-EG) CHNPs was measured by laser particle size analyzer before and after swelling. The swelling degree was defined as the volume ratio of P(DMAEMA-g-EG) CHNPs after and before swelling.

In order to investigate the thermo-sensitivity of P(DMAEMA-g-EG) CHNPs, the transmittances of P(DMAEMA-g-EG) CHNPs dispersion were measured at 800 nm by WFZ-26A UV–visible spectrophotometer (Tianjin Science Instrument Plant, China) with temperature control equipment.

3. Results and discussions

3.1. Composition and morphology of P(DMAEMA-g-EG) CHNPs

The FTIR spectra of P(DMAEMA-g-EG) CHNPs are illustrated in Fig. 1. As shown in Fig. 1C, the spectra of P(DMAEMA-g-EG) CHNPs

Table 1
P(DMAEMA-g-EG) CHNPs prepared in this paper

P(DMAEMA-g-EG) CHNPs[a]	DMAEMA/MPEGMA (wt)	Crosslinker dosage (mol%)	Diameter (nm)[b]	Yield (%)
CHNPs-1	10/1	2	350	85
CHNPs-2	2/1	2	290	87
CHNPs-3	1/1	2	250	90
CHNPs-5	2/1	0.5	300	45
CHNPs-6	2/1	3.5	310	75

[a] The monomer concentration was 14 mg/ml and initiator dosage was 2.9 mol% of DMAEMA. The reaction was carried out at boiling state without agitation.

[b] The size of P(DMAEMA-g-EG) CHNPs was detected by Laser particle size analyzer.

present the characteristic peaks of DMAEMA and MPEGMA. The peak at 2891 cm^{-1} corresponds to the methyl and methylene vibrations. The peak at 1104 cm^{-1} features the asymmetric vibrations of C–O–C. Meanwhile, the peaks at 1732 cm^{-1} and 1150 cm^{-1} are respectively the characteristic peaks of C=O and C–O of ester group. Comparing to curve A and B (presenting MPEGMA and DMAEMA, respectively), the disappearance of the peak at 1633 cm^{-1} assigned to C=C in curve C suggests that the copolymerization of DMAEMA and MPEGMA took place. The curve D is the spectrum of P(DMAEMA-g-EG) CHNPs·HCl. The multipeaks at 2250–3000 cm^{-1} further prove the existence of amino group in P(DMAEMA-g-EG) CHNPs, which indicates that the composition of copolymers is consistent with that of the designed polymer.

Fig. 2 shows TEM micrograph and particle size distribution of P(DMAEMA-g-EG) CHNPs. TEM micrograph (Fig. 2A) proves that the spherical P(DMAEMA-g-EG) CHNPs are formed during the distillation–dispersion polymerization and the average size of P(DMAEMA-g-EG) CHNPs is approximately 200 nm. The results of LPSA (Fig. 2B) show that P(DMAEMA-g-EG) CHNPs possess a bimodal size distribution at about 450 nm and 70 nm, respectively. The mean particle size is 290 nm and the polydispersity index is 0.296. Compared to the results of LPSA, the size of P(DMAEMA-g-EG) CHNPs measured by TEM is smaller because the specimens of P(DMAEMA-g-EG) CHNPs for TEM are at dry state but P(DMAEMA-g-EG) CHNPs in the specimens for LPSA were more or less swelled.

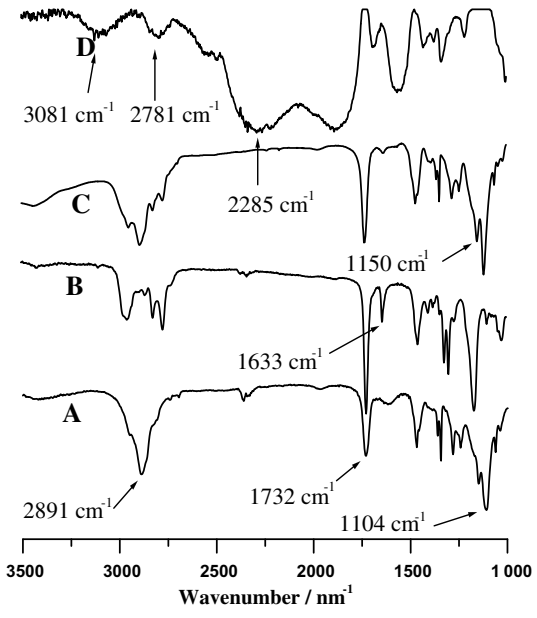

Fig. 1. FTIR spectra of MPEGMA (A), DMAEMA (B), CHNPs-2 (C) and P(DMAEMA-g-EG) CHNPs HCl (D). CHNPs-2 were synthesized with the DMAEMA/MPEGMA mass feed ratio of 2/1, monomer concentration of 14 mg/ml, crosslinker dosage of 2 mol% of DMAEMA, initiator dosage of 2.9 mol% of DMAEMA at boiling state without agitation.

3.2. Swelling behaviors of P(DMAEMA-g-EG) CHNPs

3.2.1. Swelling kinetics of P(DMAEMA-g-EG) CHNPs

P(DMAEMA-g-EG) CHNPs are one kind of cationic pH-sensitive hydrogel, where the tertiary amino pendent groups on PDMAEMA main chain can be protonated. In order to investigate the swelling kinetics of P(DMAEMA-g-EG) CHNPs, 100 mg freeze-dried P(DMAEMA-g-EG) CHNPs was dispersed in 10 ml buffer solution with pH value of 5 and ionic strength of 0.4 at 37 °C and the size of P(DMAEMA-g-EG) CHNPs was measured at an appropriate time interval. As shown in Fig. 3, P(DMAEMA-g-EG) CHNPs are swelled in buffer solution and their size is sharply increased. After swelling for 20 h, the P(DMAEMA-g-EG) CHNPs tend to the swelling equilibrium and their TEM image is shown in Fig. 4. This image confirms that the swelled CHNPs have a hollow morphology and discrete particles in aqueous media. This may be related to the preparation method of the sample of CHNPs for TEM.

3.2.2. pH-sensitive character of P(DMAEMA-g-EG) CHNPs

The pK_a of DMAEMA is approximately 7.0 [27,28]. When the environmental pH is lower than pK_a, $-N(CH_3)_2$ group assumes in a state of protonation and appears hydrophilic character. Whereas, when pH is greater than pK_a, $-N(CH_3)_2$ presents a hydrophobic character. As a result, the pH variation of environment can lead to the volume change of P(DMAEMA-g-EG) CHNPs. The pH sensitivity of P(DMAEMA-g-EG) CHNPs is shown in Fig. 5. It can be seen that the size of P(DMAEMA-g-EG) CHNPs increases sharply when pH value changes from 7 to 6. Apart from this pH range, the change of particle size is slight with pH variation.

Similar to poly(methacrylic acid-grafted-poly(ethylene glycol)) (P(MAA-g-EG) anionic hydrogel

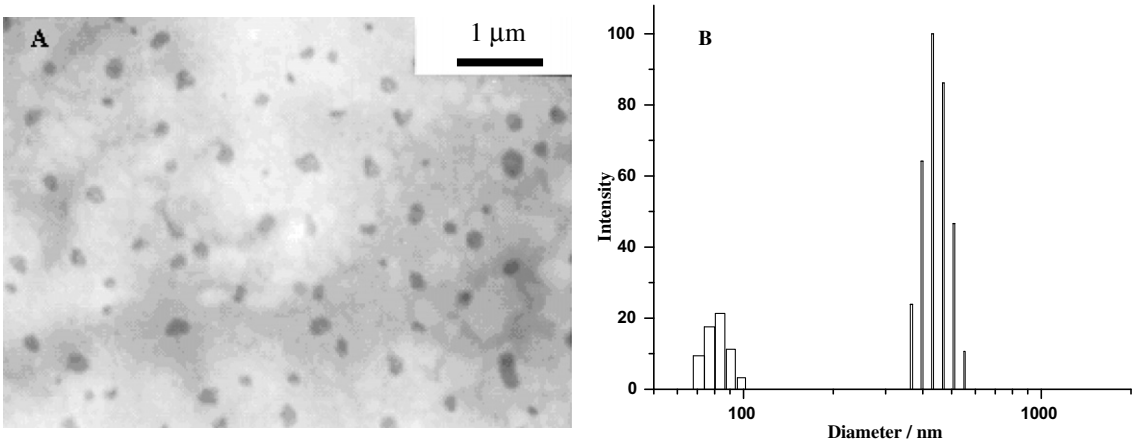

Fig. 2. TEM micrograph (A) and particle size distribution (B) of CHNPs-2. CHNPs-2 were synthesized with the DMAEMA/MPEGMA mass feed ratio of 2/1, monomer concentration of 14 mg/ml, crosslinker dosage of 2 mol% of DMAEMA, initiator dosage of 2.9 mol% of DMAEMA at boiling state without agitation. For TEM, after the freeze-dried CHNPs-2 were dispersed in diethyl ether, the specimens was prepared. For LPSA, the size of CHNPs-2 was detected as soon as the freeze-dried CHNPs were dispersed in the buffer solution with pH value of 5 and ionic strength of 0.4.

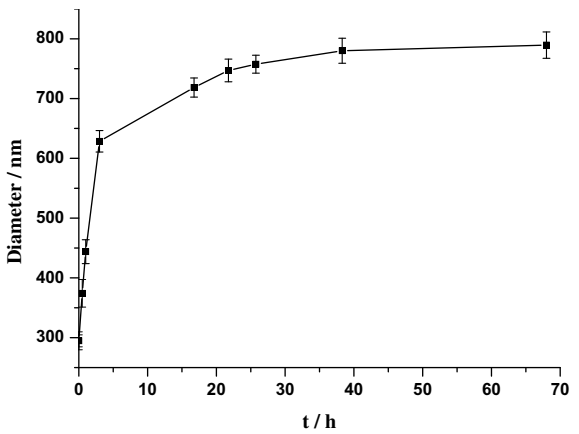

Fig. 3. Swelling kinetics curve of CHNPs-2. 100 mg freeze-dried CHNPs-2 was dispersed in 10 ml buffer solution with pH value of 5 and ionic strength of 0.4 at 30 °C and the size was measured by LPSA at certain time interval.

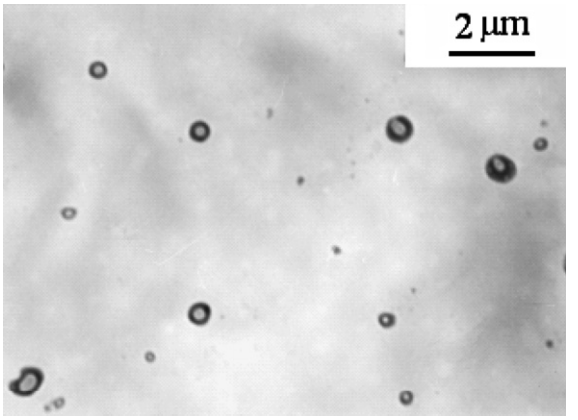

Fig. 4. TEM image of CHNPs-2. 100 mg freeze-dried CHNPs-2 was dispersed in 10 ml buffer solution with pH value of 5 and ionic strength of 0.4 at 30 °C, and then the specimens were prepared after swelling for 24 h.

nanoparticles, the crosslinker dosage has a great effect on the swelling degree of P(DMAEMA-g-EG) CHNPs [47]. As shown in Table 2, when the crosslinker dosage is 2 mol% of DMAEMA, the equilibrium swelling degree of P(DMAEMA-g-EG) CHNPs reaches the maximum. When the crosslinker dosage is 0.5 mol%, the degree of crosslinking is very low, which makes the particles themselves loose. Therefore, the swelling degree of P(DMAEMA-g-EG) P(DMAEMA-g-EG) CHNPs is lower than that of particles prepared under the crosslinker dosage of 2 mol%. When the crosslinker dosage is 3.5 mol%, the greater crosslinker dosage elevates the degree of crosslinking of P(DMAEMA-g-EG) CHNPs, and leads to more compact network, which hinders the expansion of polymer chains and the swelling degree of P(DMAEMA-g-EG) CHNPs is low.

3.2.3. Ionic strength-sensitivity of P(DMAEMA-g-EG) CHNPs

100 mg freezed-dried P(DMAEMA-g-EG) CHNPs were dispersed in 10 ml buffer solution at pH 5 at 30 °C. The total ionic strength of the buffer solution was adjusted to a desired level with a calculated amount of NaCl or Na_2SO_4 in order to

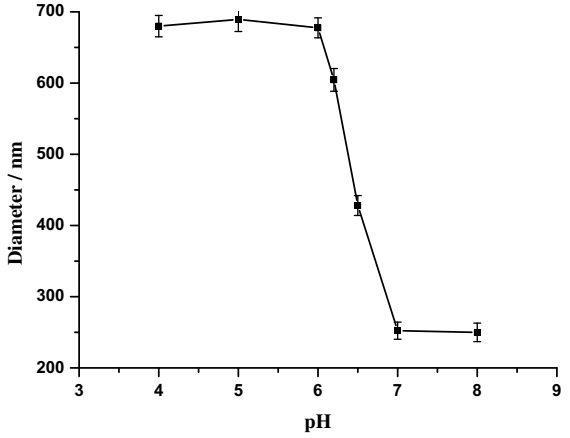

Fig. 5. Effect of pH value on swelling behavior of CHNPs-2. 100 mg freeze-dried CHNPs-2 was dispersed in 10 ml buffer solutions with ionic strength of 0.4 and then CHNPs-2 were swelled for 24 h at 30 °C. The size of CHNPs-2 was detected by LPSA.

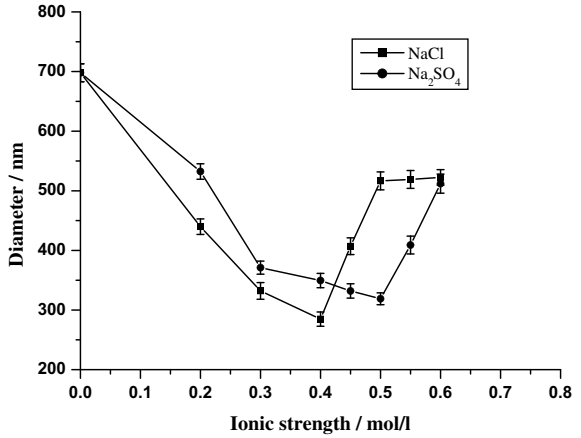

Fig. 6. Effect of ionic strength on swelling behavior of P(DMAEMA-g-EG) CHNPs-2. 100 mg freeze-dried CHNPs-2 was dispersed in 10 ml buffer solution with pH value of 5.

Table 2
Effects of crosslinker dosage on the swelling degree of P(DMAEMA-g-EG) CHNPs[a]

Crosslinker dosage (mol%)	Diameter before swelling (nm)	Diameter after swelling[b] (nm)	Swelling degree[c] (v/v)
0.5	237	524	10.81
2	252	689	20.43
3.5	185	306	4.5

[a] CHNPs were synthesized with the DMAEMA/PEG mass feed ratio of 2/1, monomer concentration of 14 mg/ml, initiator dosage of 2.9 mol% of DMAEMA at boiling state without agitation.

[b] 100 mg freeze-dried CHNPs was dispersed in 10 ml buffer solution with ionic strength of 0.4 and then CHNPs were swelled for 24 h at 30 °C.

[c] The swelling degree was defined as the volume ratio of CHNPs after and before swelling.

research the effect of ionic strength on the swelling behavior of P(DMAEMA-g-EG) CHNPs. As shown in Fig. 6, with increment of ionic strength, the size of P(DMAEMA-g-EG) CHNPs sharply decreases and then increases. The swelling behaviors of gels are mainly affected by the osmotic pressure with the network of P(DMAEMA-g-EG) CHNPs. When ionic strength is increased, the osmotic pressure with network of P(DMAEMA-g-EG) CHNPs is decreased. Therefore, the size of P(DMAEMA-g-EG) CHNPs sharply decreases. If the salt dosage is too great, the structure of water area around PEG chains is destroyed. Because the hydrogen bonds among PEG and water are destroyed, the solubility of PEG in water is decreased and the interactions among PEG chains are changed into attractive force. Therefore, the aggregation of nanoparticles makes the size of P(DMAEMA-g-EG) CHNPs increase and flock coagulation precipitate from the dispersion finally.

3.2.4. Thermo-sensitivity of P(DMAEMA-g-EG) CHNPs

The researches about the effects of temperature on the swelling behavior of P(DMAEMA-g-EG) CHNPs will help to confirm the swelling conditions of P(DMAEMA-g-EG) CHNPs and further choose the condition of loading or releasing drug. In this paper, effects of the environmental pH value and composition of P(DMAEMA-g-EG) CHNPs on the thermo-sensitivity are shown in Fig. 7.

It can be seen from Fig. 7 that P(DMAEMA-g-EG) CHNPs have obvious thermo-sensitivity under alkali conditions and but the transmittance of the P(DMAEMA-g-EG) CHNPs dispersion is not affected by temperature under acidic conditions. When the pH value is 3.29, the tertiary amino pendent groups are completely protonated and P(DMAEMA-g-EG) CHNPs can be completely swelled. Therefore, the transmittance of P(DMAEMA-g-EG) CHNPs dispersion is 100% at any temperature. When the pH value is 9.18, the tertiary amino pendent groups associate with water by the hydrogen bonds. However, when temperature is greater than the lower critical solution temperature (LCST), the hydrogen bonds are destroyed and the solubility of PDMAEMA moieties in water decreases, which

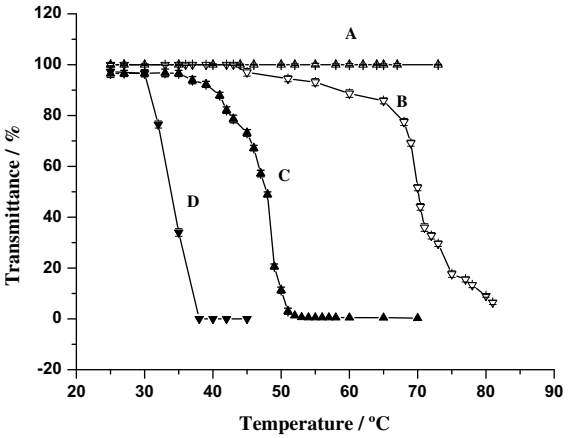

Fig. 7. Effects of temperature on transmittances of P(DMAEMA-g-EG) CHNPs aqueous dispersion. 100 mg freeze-dried P(DMAEMA-g-EG) CHNPs was dispersed in 10 ml buffer solution with ionic strength of 0.4 and then CHNPs were swelled for 24 h at 30 °C. The transmittance of P(DMAEMA-g-EG) CHNPs dispersion was measured at 800 nm by UV and all the measurements were carried out at a heating rate of 1 °C/min from 25 °C to 80 °C. A: the pH value of the P(DMAEMA-g-EG) CHNPs dispersion was 3.29 and P(DMAEMA-g-EG) CHNPs used in the experiment was CHNPs-1 or CHNPs-2; B: the pH value of the P(DMAEMA-g-EG) CHNPs-2 dispersion was 9.18; C: the pH value of the P(DMAEMA-g-EG) CHNPs-1 dispersion was 9.18; D: the pH value of the PDMAEMA homopolymer solution was 9.18.

makes the cores of P(DMAEMA-g-EG) CHNPs compact. Therefore, the transmittance of the P(DMAEMA-g-EG) CHNPs dispersion decreases sharply when temperature is greater than LCST.

As shown in Fig. 7, the composition of P(DMAEMA-g-EG) CHNPs exerts great influences on the thermo-sensitive character of P(DMAEMA-g-EG) CHNPs. For P(DMAEMA-g-EG) CHNPs-2 with PDMAEMA/MPEGMA of 2/1 (wt), two inflection points occur at 43 °C and 65 °C, respectively with increasing the temperature, which illustrates that two phases transitions occur during the calefactive process. When the temperature is higher than 43 °C, the hydrogen bonds among PDMAEMA moieties and water are destroyed and the transmittance of the P(DMAEMA-g-EG) CHNPs dispersion decreases. But due to the existence of PEG in P(DMAEMA-g-EG) CHNPs, the decreasing extent of the transmittance is only lower than 20%, which indicates that only the cores of P(DMAEMA-g-EG) CHNPs become compact while the P(DMAEMA-g-EG) CHNPs dispersion is stable all the same. However, when the temperature is greater than 65 °C, the hydrogen bonds among PEG moieties and water are destroyed and the solubility of PEG in water decreases. The shrinkage of PEG chains leads to the sharp decrease of the transmittance of P(DMAEMA-g-EG) CHNPs dispersion. For P(DMAEMA-g-EG) CHNPs-1, only one phase transition temperature occurs at 35 °C, and this phase transition temperature is lower than that of P(DMAEMA-g-EG) CHNPs-2. Due to the low content of PEG in P(DMAEMA-g-EG) CHNPs (less than 10%), the influence of PEG on the P(DMAEMA-g-EG) CHNPs dispersion is slight and even can be ignored. The phase separation is due to destruction of hydrogen bonds among PDMAEMA moieties with water. Therefore, with increasing the temperature, there is only one phase transition temperature and it closes to LCST of PDMAEMA homopolymer.

4. Conclusion

Stable and small-sized P(DMAEMA-g-EG) CHNPs with spherical morphology were prepared successfully by distillation–dispersion copolymerization of MPEGMA and DMAEMA. The obtained P(DMAEMA-g-EG) CHNPs possess the character of re-dispersing into the water after freeze-drying.

P(DMAEMA-g-EG) CHNPs have pH-, ionic strength- and thermo-sensitive characters. P(DMAEMA-g-EG) CHNPs perform pH-responsive swelling behavior, which is strongly influenced by the crosslinker dosage. With increasing ionic strength, the size of P(DMAEMA-g-EG) CHNPs sharply decreases due to the decrease of the osmotic pressure with the networks of P(DMAEMA-g-EG) CHNPs. However, when the ionic strength is too strong, the breakage of the hydrogen bonds among PEG with water makes P(DMAEMA-g-EG) CHNPs aggregate and the size of P(DMAEMA-g-EG) CHNPs increase. The pH value of P(DMAEMA-g-EG) CHNPs dispersion and composition of P(DMAEMA-g-EG) CHNPs can strongly affect the thermo-sensitivity of P(DMAEMA-g-EG) CHNPs. P(DMAEMA-g-EG) CHNPs have obvious thermo-sensitivity under alkali conditions but do not have the thermo-sensitivity under acidic conditions. With decreasing the content of PEG in P(DMAEMA-g-EG) CHNPs, the phase transition temperatures of P(DMAEMA-g-EG) CHNPs change from two into one. These environment-sensitive characters of P(DMAEMA-g-EG) CHNPs will endue this kind of P(DMAEMA-g-EG) CHNPs

great potential application in the environment-sensitive drug delivery systems.

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