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# Synthesis of Thermo-Sensitive Polyelectrolyte Complex Nanoparticles from CS-*g*-PNIPAM and SA-*g*-PNIPAM for Controlled Drug Release

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**Abstract:** In this paper, thermo-sensitive polyelectrolyte complex nanoparticles assembled from chitosan-*graft*-poly(*N*-isopropylacrylamide) (CS-*g*-PNIPAM) and sodium alginate-*graft*-poly(*N*-isopropylacrylamide) (SA-*g*-PNIPAM) were prepared for entrapment and release of 5-fluorouracil (5-FU). The morphology and size of the nanoparticles were observed by transmission electron microscopy (TEM) and dynamic light scattering (DLS). The polyelectrolyte complex nanoparticles showed a narrow size distribution. The hydrogen bonding interactions between nanoparticles and 5-FU, which was determined by fourier-transformed infrared spectroscopy (FTIR), increased drug loading. Glutaraldehyde, as a cross-linking agent, reinforced the nanoparticle structure and decreased the burst drug release. When changing temperature, pH, or ionic strength, a sustained and controlled drug release was observed. The novel complex nanoparticles with environmentally sensitive properties are expected to be useful in the field of intelligent drug delivery system.

*Keywords*: controlled release, 5-fluorouracil, nanoparticles, polyelectrolyte, thermo-sensitivity.

## Introduction

Polyelectrolyte complex (PEC) nanoparticles formed from two oppositely charged polyelectrolytes in aqueous solution have attracted much increasing research attentions for their potential applications in carriers for drug delivery, cell and enzymes immobilization, and protein separation, *etc*.[1-3] The combination of two different copolymers to form PEC nanoparticles provides a wide range of opportunities to design new materials with more functions. The stability of PEC nanoparticles are greatly based on the unique physicochemical properties of oppositely charged polyions as well as the temperature, pH and ionic strength of the medium, which endows the fabrication of environmental sensitive vehicles.[4,5] The environmentally sensitive drug carriers can effectively deliver the drug to a target site and thus increase the therapeutic benefit, while minimizing side effect. They also help to increase the stability of drug and possess useful controlled release properties.

Many different polyelectrolytes in nature (*e.g.* chitosan, sodium alginate, carboxymethyl cellulose, pectin and xanthan) have been used to form polyelectrolyte complexes.[6-9] Chitosan (CS) is a basic polysaccharide derived from chitin in nature. It contains a large number of hydroxyl and amino groups. The primary amine groups render special properties that make CS very useful in pharmaceutical applications. CS can interact electrostatically with anionic groups of other polyions, such as sodium alginate (SA), to form polyelectrolyte complexes through electrostatic interactions between $NH_3^+$ and $COO^-$. Such polyelectrolyte complexes can be used as drug carrier, controlling the release rate and enhancing the pH responsiveness. Li *et al.* reported PEC nanoparticles from carboxymethyl cellulose (CMC) with thermo-sensitive chitosan graft copolymers for microcapsules.[10] The release rate of drugs from nanoparticles was able to be controlled by the pH and temperature. Yan *et al*. studied the PEC nanoparticles containing dermatan sulfate (DS) formed from CS and SA for tissue regeneration.[11] These results provide a new method for sustained release of DS through PEC in tissue engineering.

Environmentally sensitive PEC nanoparticles have special advantage in drug delivery and tumor targeting.[12-15] Poly(*N*-isopropylacrylamide) (PNIPAM) is known as one of environmentally sensitive polymers to exhibit a reversible phase transition in aqueous solution around 32 °C.[16] This transition temperature is called the lower critical solution temperature (LCST). When the temperature is lower than LCST, PNIPAM is soluble in aqueous solution because the hydrogen bonding between polymer and water is dominant. Above the LCST, the hydrogen bonding between polymer and water becomes weaker and hydrophobic interaction is promoted, which gives rise to a sharp phase transition with a suddenly shrinking process. In light of the existence of $-NH_2$ or -COOH groups in natural polyelectrolyte polymers, such as CS, CMC and SA, they are often used as pH-sensitive polymers.[17,18] The combination of stimuli-responsive polymers with biocom-

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patible polymers to fabricate sensitive PEC nanoparticles develops an evolving approach for drug delivery and tumor targeting.

In this study, thermo-sensitive PEC nanoparticles for drug carriers were designed by self-assembly of chitosan-*graft*-poly(*N*-isopropylacrylamide) (CS-*g*-PNIPAM) and sodium alginate-*graft*-poly(*N*-isopropylacrylamide) (SA-*g*-PNIPAM) in aqueous solution. The structure and particle size of nanoparticles were observed by FTIR, TEM and DLS. Glutaraldehyde (GA) as a crosslinker was used to reinforce the nanoparticles structure. 5-Fluorouracil (5-FU), a pyrimidine antimetabolic acidic drug, has a broad spectrum of activity against solid tumors in clinic, but it also seriously hurts the healthy cells while it kills the tumor cells.[19] To improve its bioavailability and therapeutic index, reduce side effects, control release rate, the polyelectrolyte complex nanoparticle is served as the drug delivery.[20,21] The release performance of 5-FU from PEC nanoparticles was studied by changing environmental conditions, such as temperature, pH, ionic strength and the dosage of GA.

## Experimental

**Materials.** Chitosan (CS) with a degree of deacetylation of 0.90 and a viscosity-average molecular weight of $10\times10^4$ g/mol was purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Sodium alginate (SA) was obtained from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). *N*-Isopropylacrylamide (NIPAM) was provided by Acros Organics. Cerium ammonium nitrate (CAN), potassium persulfate (KPS), sodium sulphite (SDS), glutaraldehyde (GA) and other reagents were all analytical grade and used as received. Distilled water was used for the preparation of all solutions in this study.

**Preparation and Characterization of Graft Copolymers.** CS-*g*-PNIPAM was synthesized by employing free radical polymerization using CAN as initiator. Briefly, a given amount of CS and NIPAM was first dissolved in 5% acetic acid aqueous solution. The solution was purged with nitrogen and heated to 40 ºC. Then CAN (0.1 g) was dissolved in 5 mL water and preheated to 40 ºC before poured into the solution. Polymerization was performed for 6 h after purging with nitrogen. The product copolymer was purified by reprecipitation into excess acetone three times and then extracted in methanol for 48 h and dried in vacuum at 30 ºC. The grafting ratio (GR) of copolymers was 46.2% calculated by the gravimetric analysis as reported in our previous work.[10]

SA-*g*-PNIPAM was synthesized by employing free radical polymerization using KPS and SDS as initiator. Briefly, a given amount of SA and PNIPAM was first dissolved in water. The solution was purged with nitrogen and heated to 30 ºC. Then 0.1 g KPS and 0.04 g SDS were dissolved in 8 mL water and preheated to 30 ºC before poured into the above solution. After 24 h of reaction, a solution containing SA-*g*-PNIPAM copolymers was obtained. To remove the homopolymer of PNIPAM, the copolymer solution was immersed into large amounts of acetone and then extracted in acetone for 48 h and dried in vacuum at room temperature. The GR of SA-*g*-PNIPAM was 35.2%.

**Preparation of PEC nanoparticles.** A given amount of CS-*g*-PNIPAM and SA-*g*-PNIPAM were dissolved separately in distilled water to form solutions with the same concentration. The PEC nanoparticles were prepared by mixing a given amount of solutions of CS-*g*-PNIPAM and SA-*g*-PNIPAM at pH 6.0 with stirring for 24 h. The polymer solution with a given pH values was adjusted by different buffer solutions.

A given amount of GA (2, 3, 4 mg) was added into the PEC nanoparticles solution to obtain crosslinked nanoparticles (marked as PEC-GA1, PEC-GA2 and PEC-GA3). By a dialysis against PBS to remove excess GA using a dialysis membrane bag (MWCO 3.5 kDa), core-crosslinked PEC nanoparticles were obtained after a further incubation at 25 ºC over 24 h.

**Preparation of 5-FU-Loaded Nanoparticles.** The drug-loaded nanoparticles were prepared by using 5-FU as a model drug in the same method as previous procedure by mixing a given amount of solutions of CS-*g*-PNIPAM/5-FU and SA-*g*-PNIPAM. After incubation in a 25 ºC water bath for 48 h, the solution was then dialyzed against distilled water using a dialysis membrane bag (MWCO 3.5 kDa) for 4h to remove the non-encapsulated drug. The concentration of 5-FU in dialysis fluid was analyzed by UV absorbance at a specific wavelength of 266 nm, using UV-vis spectrophotometer. The drug-loading content (DLC%) and entrapment efficiency (EE%) of nanoparticles was calculated according to formulas (1) and (2).

$$\%\mathrm{DLC} = (m_0 - cV)/(m + m_0 - cV) \times 100 \quad (1)$$

$$\%\mathrm{EE} = (m_0 - cV)/(m_0) \times 100 \quad (2)$$

Where $m_0$ is the weight of drug dosage; $m$ is the weight of polymer nanocarriers; $c$ is the concentration of 5-FU in dialysis fluid; $V$ is the volume of dialysate solution.

**Drug Release from PEC Nanoparticles.** The 5-FU-loaded nanoparticles solution was placed in a dialysis membrane bag. The dialysis membrane bag was then immersed in 50 mL phosphate buffer solution. All systems were kept at designed temperature and pH. After a predetermined period, 5 mL of the phosphate buffer solution was drawn out form the system for analysis and then 5 mL fresh buffer solution was added into the release system. The release amount of 5-FU was determined by a UV analysis with a standard calibration curve between the UV absorbance and 5-FU concentration. The 5-FU release was calculated according to formula (3). In order to apply the rigorous statistical analyses, three determinations were made in each case and an average value of three determinations was taken as the drug release (%) of the nanoparticles.

$$\%\ (\text{5-FU release}) = (50C_n + 5.0\Sigma C_{n-1})/(m_0 - cV) \times 100 \quad (3)$$

Where $C_n$ and $C_{n-1}$ are the concentration of 5-FU in buffer solution at $n$ and $n$-1 times, respectively; $n$ is the time of drawing out the buffer solution ($n$>0); other symbols are as the same as above mentioned.

**Characterizations.** The FTIR spectra of the polymers were carried out using KBr tablets at room temperature, recorded with FTIR spectrometer (MAGNA550, Nicolet, USA) and scanned from 4000 to 500 $cm^{-1}$. The turbidity of polymer solutions was monitored at 500 nm at given temperatures using a UV-Vis spectrophotometer (UV-2550, Shimadzu, Japan). The morphology of nanoparticles was analyzed by TEM (JEM-1230, JEOL, Japan). For TEM measurements, a drop of particle solution was placed on a copper grid and dried at room temperature after removing excess solution with filter paper. The size of nanoparticles was measured by DLS using a BI-200SM laser light-scattering goniometer (Brookhaven) at 632 nm. All samples with a certain concentration were first prepared by filtering with 0.45 μ Millipore filter and then characterized.

## Results and Discussion

**FTIR Analysis.** FTIR measurement was used to identify the chemical structure of the synthesized polymers as shown in Figure 1. Compared with the spectrum of CS, the shifting peak of CS-*g*-PNIPAM from 3420 to 3430 $cm^{-1}$ due to -OH stretching vibration indicated the participation of hydroxyl groups in chemical reaction. The broad peak at 1650 $cm^{-1}$ is the characteristic stretching of PNIPAM (amide I band, C=O stretching vibration mode conjugated with -NH groups on PNIPAM chains). The appearance of new peak at 1540 and 1380 $cm^{-1}$ is the -NH bending for secondary amides and isopropyl groups bending vibrations of PNIPAM.[22,23] Compared with the spectrum of SA, the broad peak at 1640 and 1550 $cm^{-1}$ is the characteristic stretching of PNIPAM. The appearance of new peak at 1388 and 1368 $cm^{-1}$ is due to dimethyl symmetric deformation vibration, and the new peak at 1114 $cm^{-1}$ is the contribution of isopropyl group's vibration. This indicates that the grafting reaction took place.

In comparison with the spectrum of separate CS-*g*-PNIPAM and SA-*g*-PNIPAM, the spectrum of PEC showed significant changes. The enhancement of spectral intensity at 2923 and 2854 $cm^{-1}$ may be assigned to the symmetrical and asymmetrical stretching of C-H. Meanwhile, the peak at 1460 $cm^{-1}$ can be observed due to the stretching vibration of $COO^-$ groups from SA, while the peak at 1633 $cm^{-1}$ is attributed to $NH_3^+$ from CS.[10] These results reveal that electrostatic interaction presents between the anionic $COO^-$ and cationic $NH_3^+$.

**Turbidimetric Analysis of PEC Nanoparticles.** Adding SA-*g*-PNIPAM into CS-*g*-PNIPAM solution gave rise to the formation of electrostatic interactions between cationic CS chains and anionic SA chains, which resulted in the formation of PEC nanoparticles with hydrophilic PNIPAM chains as the shell. The schematic representation of the formation of PEC nanoparticles was shown in Figure 2.

The formation of PEC nanoparticles was studied as a function of turbidimetric behavior. Upon mixing the solutions of positively charged SA-*g*-PNIPAM and negatively charged CS-*g*-PNIPAM, the solutions turned gradually turbid and the transmittance decreased, indicating that the polyelectrolyte complexes formed as expected due to the electrostatic interactions. Figure 3 shows the transmittance of the mixture solutions of PEC micelles. The minimum transmittance was observed when the weight ratio of CS-*g*-PNIPAM to SA-*g*-PNIPAM is 3:7. This value is corresponding to the charge neutralization state of the mixtures. In the following discussion, we used this ratio as the research sample for other characterizations. The change in transmittance of PEC-GA solutions was similar to that of PEC solutions. The transmittance of PEC-GA is slightly higher than that of PEC at the same composition which may be attributed to the denser structure and smaller

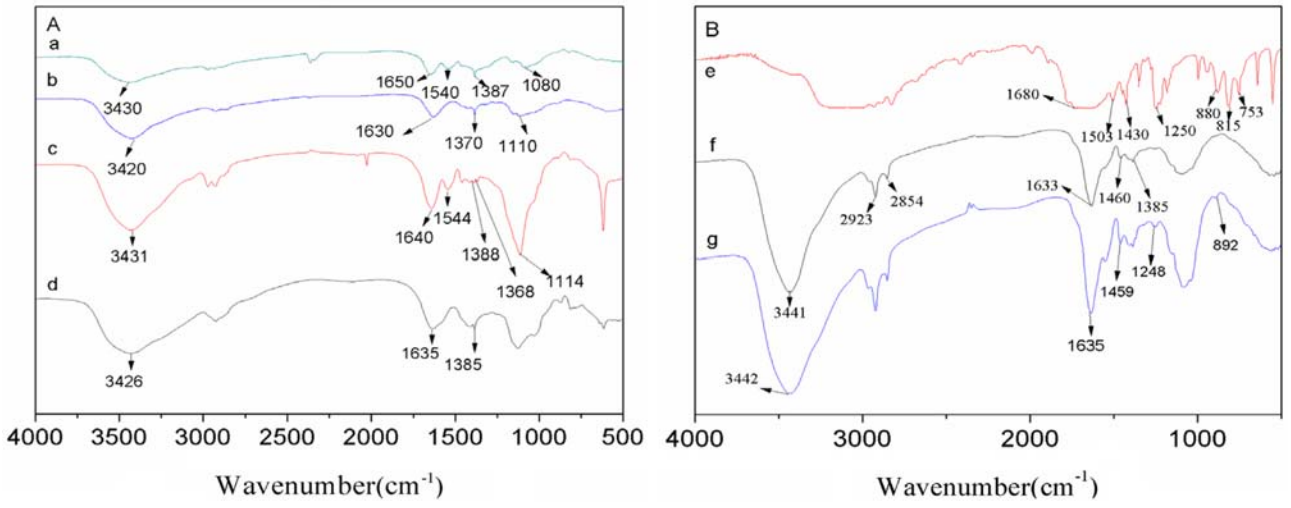


**Figure 1.** FTIR spectra of (a) CS-*g*-PNIPAM, (b) CS, (c) SA-*g*-PNIPAM, (d) SA, (e) 5-FU, (f) PEC, and (g) 5-FU-PEC.

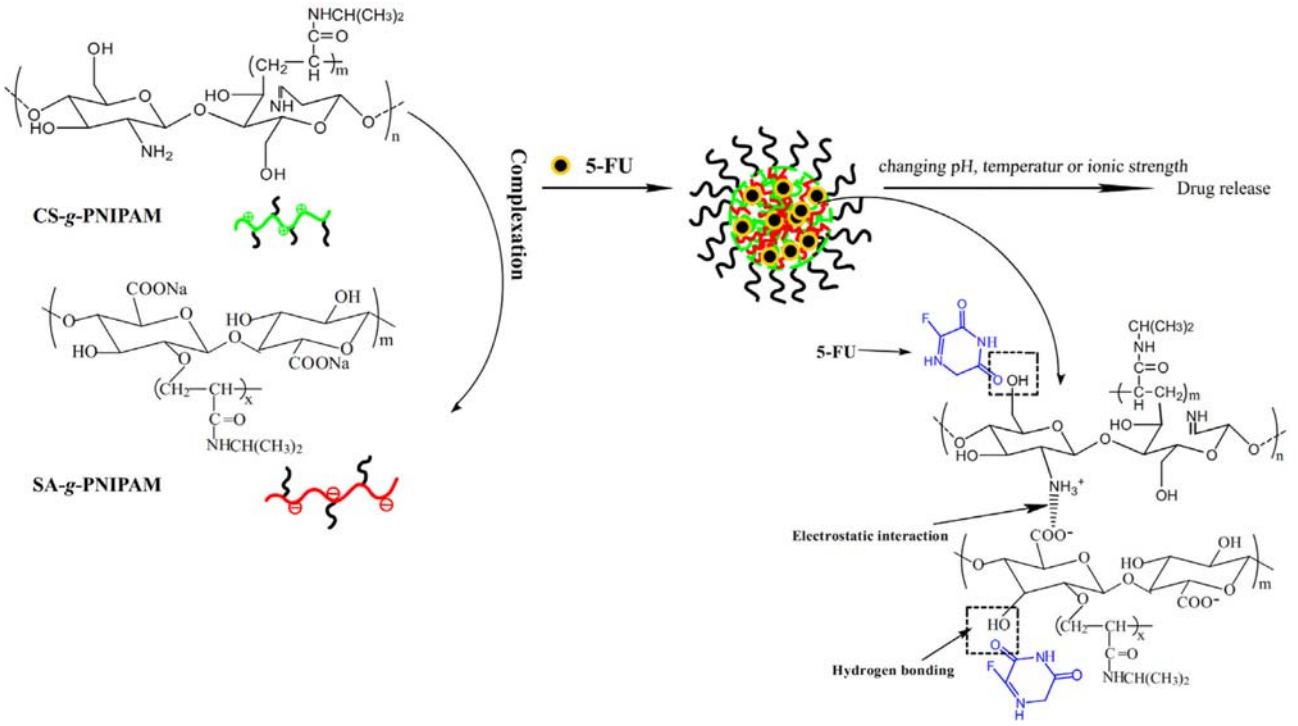


**Figure 2.** The schematic representation of the formation of PEC nanoparticles.

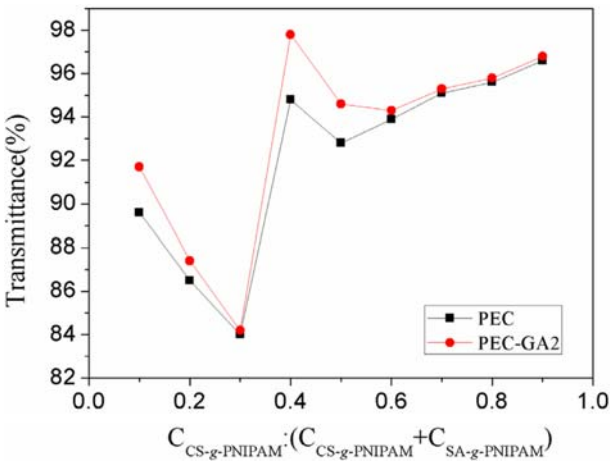


**Figure 3.** Transmittance of PEC and PEC-GA nanoparticles.

size of PEC-GA than that of PEC.

**Thermo-Sensitive Analysis.** Figure 4 shows the turbidity behavior of graft copolymers and PEC nanoparticles. The PNIPAM block is hydrophilic below the LCST; whereas, above the LCST, the stretched PNIPAM chains collapsed onto the nanoparticles. As expected, the transmission of CS-*g*-PNIPAM solutions decreased from 92.1% to 82.2% as the temperature is raised above the LCST at pH 6.0. The LCST of CS-*g*-PNIPAM solutions was about 31 ºC determined from the mid-point of the plots for transmittance changes, which was lower than that of pure PNIPAM homopolymer reported in literatures.[24] A similar result was reported by Chen and Cheng.[25] The transmission of SA-*g*-PNIPAM solutions decreased from 95.2 to 82.3% as the temperature was raised above the LCST at pH 6.0. The LCST of SA-*g*-PNIPAM solutions was about 34.7 ºC. The LCST value of PEC and PEC-GA was determined to be 34.3 and 34 ºC, which is higher than that of CS-*g*-PNIPAM and similar to that of SA-*g*-PNIPAM. The hydrophilic carboxyl group influenced the changes in the hydrophilic/hydrophobic nature of PEC due to the ionized carboxyl groups sufficiently soluble to counteract the aggregation of the hydrophobic temperature-sensitive units. Thus, the incorporation of more hydrophilic groups results in the shifts of LCST to high temperature.

**Particle Size and Morphology Analysis.** Table I shows the hydrodynamic diameter distributions of PEC and PEC-GA nanoparticles measured by DLS. It was seen that the apparent hydrodynamic diameter $D_h$ of PEC was large and broader than that of PEC-GA. The average diameter of PEC was 178.5 nm whereas the average diameter of PEC-GA decreased from 152.6 to 132.3 nm with the increase of GA amount.

Figure 5 shows the TEM images of PEC and drug-loaded PEC nanoparticles. It was clearly that the dried nanoparticles were observed as a regular spherical structure with good dispersity. The shape of drug loaded nanoparticles was similar to that of non-drug loaded nanoparticles, but only the particle size was slightly large. The size of nanoparticles from TEM was in a range of 50~80 nm, which was smaller than that of observed by DLS. This is because the nanoparticles are swollen in water, while TEM observation shows the diameters of the dried nanoparticles.

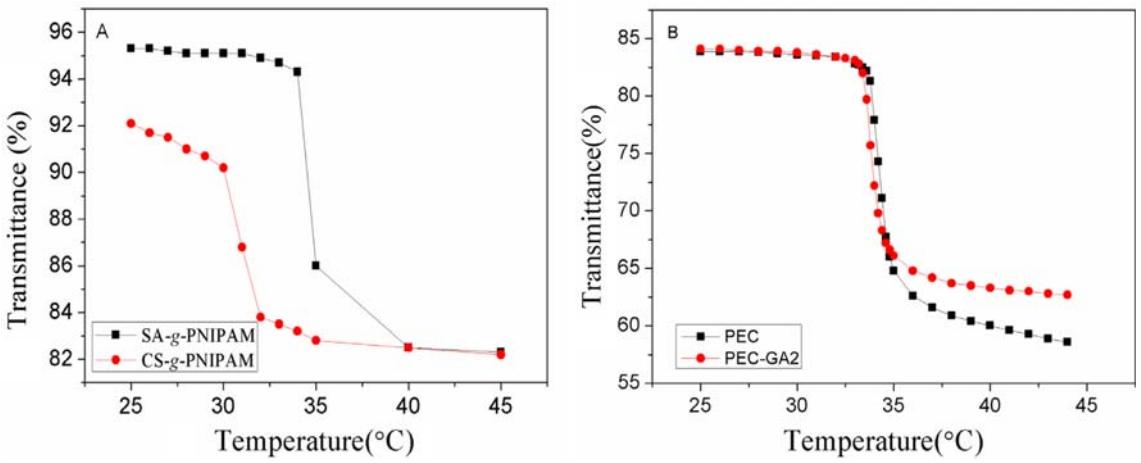


**Figure 4.** Temperature dependence of light transmittance for synthesized materials.

**Table I. Size and Polydispersity (PDI) of PEC and PEC-GA Nanoparticles**

| Samples | $\overline{D}_h$ (nm) | PDI |
|---|---|---|
| PEC | 178.5 | 0.21 |
| PEC-GA1 | 152.6 | 0.18 |
| PEC-GA2 | 138.5 | 0.20 |
| PEC-GA3 | 132.3 | 0.21 |

**Table II. Drug-Loading Content (DLC%) and Entrapment Efficiency (EE%) of PEC Nanoparticles**

| $m_0/m$ [a] | DLC% | EE% |
|---|---|---|
| 0.1 | 4.44±0.33 | 46.51±2.25 |
| 0.2 | 6.94±0.52 | 37.43±1.42 |
| 0.4 | 8.43±0.94 | 22.78±4.74 |
| 0.6 | 12.13±0.42 | 23.18±2.31 |
| 0.7 | 14.92±0.58 | 25.27±2.29 |
| 0.8 | 16.81±0.34 | 25.27±0.94 |
| 1.0 | 17.54±1.24 | 21.56±2.65 |

[a] $m_0$ is the weight of drug dosage; $m$ is the weight of polymer nanocarriers.

**Entrapment of 5-FU in PEC Nanoparticles.** In this study, 5-FU was selected as a model drug to determine the influence of PEC nanoparticles on the encapsulating and releasing behavior. 5-FU containing negative O, N, F atoms could form hydrogen bondings with PEC nanoparticles due to the amount of amino and hydroxyl groups of CS and SA. The interactions between 5-FU and PEC were investigated by FTIR. From Figure 1(e), the characteristic absorption bands of 5-FU are 1680 $cm^{-1}$ (C=O stretching vibration mode conjugated with C=C), 1430 and 880 $cm^{-1}$ (the -CH bending vibrations for -CF=CH-), 815 and 753 $cm^{-1}$ (the -CH deformation vibrations for -CF=CH-), 1250 $cm^{-1}$ (C-N stretching vibration). In comparison with PEC, the peak of PEC-5-FU (Figure 1(g)) at 3442 $cm^{-1}$ becomes slight stronger and narrower which confirms the hydrogen bonding interactions between PEC and 5-FU.[26]

Table II shows the variation of the drug-loading content and entrapment efficiency of PEC nanoparticles with the feed drug dosage. It was seen that DLC increased from 4.44±0.33% to

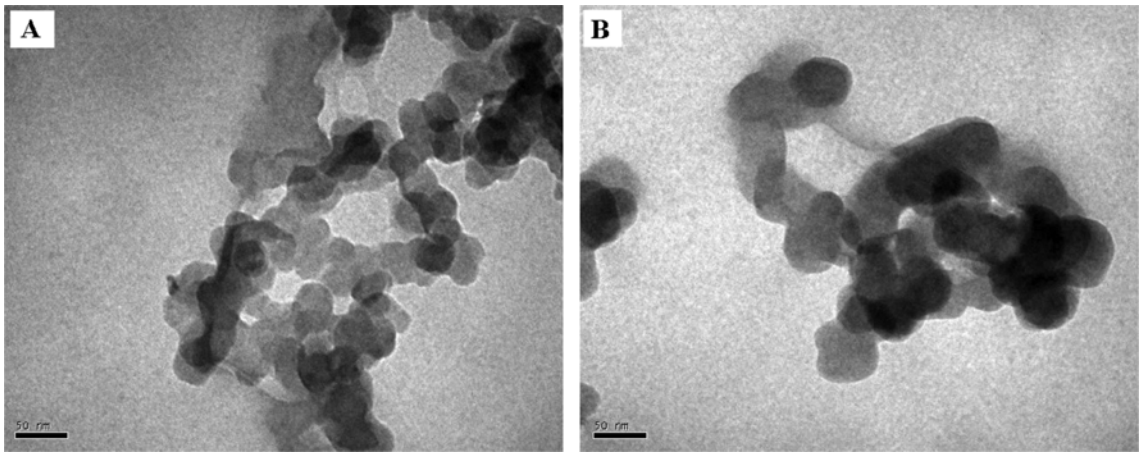


**Figure 5.** TEM images of (A) PEC and (B) 5-FU-PEC nanoparticles.

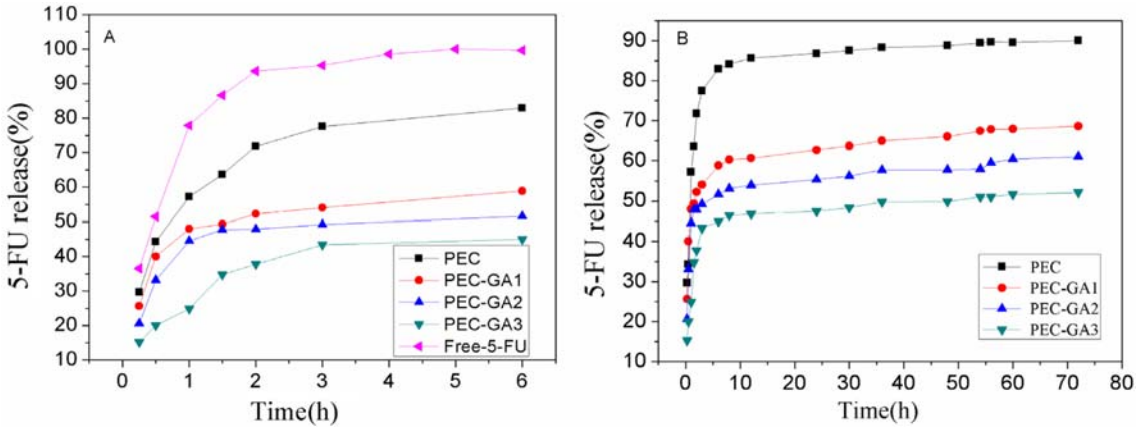


**Figure 6.** Release of 5-FU from PEC nanoparticles with different dosage of GA (A) during 6 h and (B) during 72 h ($T$=37 °C; pH=5.2; [$Na^+$]=0.5 M).

17.50±1.24% and EE decreased from 46.50±2.25% to 21.50±2.65% with the increase of feed drug. The decrease of EE may be attributed to the drug loading capacity of the nanoparticle. When the drug loading capacity achieved the maximum, the excessive 5-FU was almost dissolved in the solution or adsorbed on the surface of nanoparticles, which led to the increase of drug-loading content and the decrease of entrapment efficiency. In the following experiment, the feed ratio of the drug dosage at 60% was chosen for drug release.

**Effect of GA on 5-FU Release.** Figure 6(A) shows the sustained release of 5-FU from PEC nanoparticles with different dosage of crosslinker GA during 6 h. It was observed that the carrier materials had a remarkable effect on the drug release. Almost 100% of the free 5-FU was released during 4 h. However, the release rate of 5-FU from PEC and PEC-GA nanoparticles was dramatically decreased. The release rate of 5-FU from PEC nanoparticles was faster during the initial 2 h but slower at the later stage. The dramatically difference of concentration around nanoparticles accelerated the drug release at the earlier stage. In the meanwhile, the presence of unbound free 5-FU onto nanoparticles surface could spread into the medium, which also accelerated the release rate. At the later stage, the hydrogen bonding interaction between nanoparticles and 5-FU slowed down the release, which was in favor of prolonging drug release.

The sustained release of 5-FU from PEC nanoparticles during 72 h with different dosage of crosslinker was shown in Figure 6(B). Obviously, the chemical cross-linking using GA as a crosslinker resulted in the denser structure which caused a reduced drug release. Compared with PEC nanoparticles, the sustained release of 5-FU from PEC-GA decreased from 68% to 52% with the increasing of GA dosage from 2 mg, to 4 mg. Without crosslinker, part of polymer chains from CS or SA stretched in PEC nanoparticles, making the chains of PEC easy to move. With the adding of GA, the condensation reaction occurred between amine groups of stretched polymer chains and GA. The structure of PEC-GA nanoparticles became more and more denser. On the other hand, the quantity of GA affects the swelling of the nanoparticles and thus it influences the rate of drug release. This led to the 5-FU release decreased.

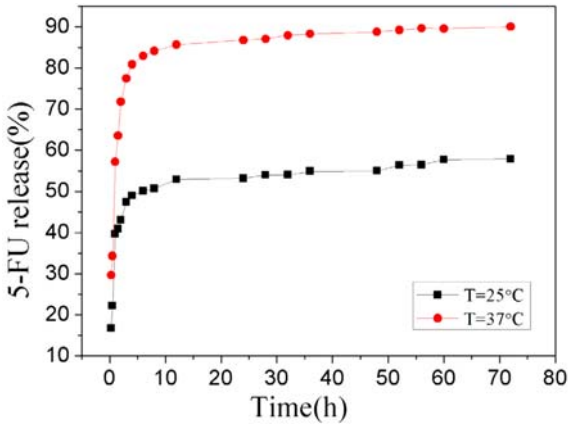


**Figure 7.** Release of 5-FU from PEC nanoparticles at different temperatures (pH=5.2; [$Na^+$]=0.5 M).

**Effect of Temperature on 5-FU Release.** The sustained release of 5-FU from PEC nanoparticles at different temperature during 72 h was shown in Figure 7. About 60% of the incorporated 5-FU was released from PEC at 25 °C; whereas, the release of 5-FU at 37 °C was increased to 90%. At low temperature, a certain amount of drugs still remained in nanoparticles may be due to the highly hydrated PNIPAM chains stabilizing the drugs loaded in nanoparticles. When the temperature was raised above the LCST, the release of 5-FU accelerated on account of temperature-induced structural changes of the nanoparticles. The PNIPAM chains became hydrophobic above the LCST leading to the second-aggregation of nanoparticles, which promoted the drug release. On the other hand, PEC nanoparticles would lose the hydrogen bonding interactions with 5-FU at high temperatures. Hence, the drug-carrier interactions would be less and car-

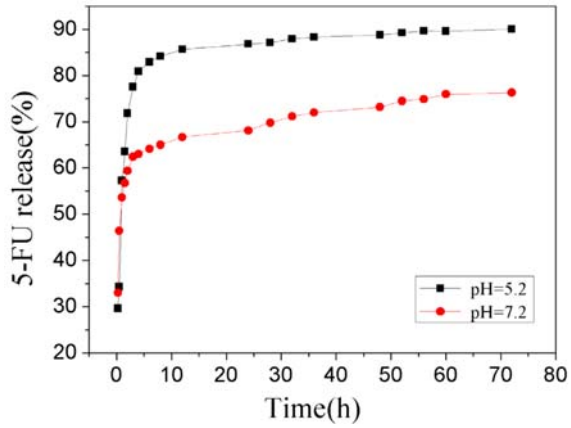


**Figure 8.** Release of 5-FU from PEC nanoparticles at different pH ($T$=37 °C; [$Na^+$]=0.5 M).

rier-carrier molecules interactions would be more higher.[22] On the contrary, below the LCST, hydrogen bonding was capable of holding drugs in nanoparticles.

**Effect of pH on 5-FU Release.** The sustained release of 5-FU from PEC nanoparticles at different pH was shown in Figure 8. The release of 5-FU from PEC nanoparticles increased from 76% to 90% with the decrease of pH from 7.2 to 5.2. The higher release of 5-FU in weak acid medium than in neutral medium was due to the broken of the static electricity balance between CS and SA. Because CS and SA are weak electrolyte, the pH has effect on the stability of polyelectrolyte complex nanoparticles. The same result was also discussed by Kennedy.[27]

**Effect of Ionic Strength on 5-FU Release.** The sustained release of 5-FU from PEC nanoparticles in different ionic strength buffer solutions during 72 h was shown in Figure 9. It was seen that sustained release of 5-FU was 67% in distilled water. When the ionic strength increased from 0.1 M to 0.5 M, the 5-FU release increased from 81% to 90%. This phenomenon was due to that the ionic strength affected the

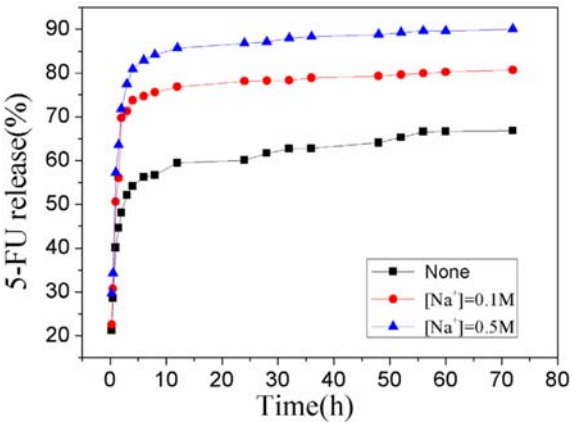


**Figure 9.** Release of 5-FU from PEC nanoparticles in different ionic strength solutions ($T$=37 °C; pH=5.2).

stability of polyelectrolyte nanoparticles. The electrostatic field in solutions made ions around the polyelectrolyte, enhancing the shielding effect between charged groups of polyelectrolyte segments. The increase of ion pairs formed between polyelectrolyte and the counter ion decreased the effective charge density of polyelectrolyte. As a result, the contraction of polyelectrolyte chains made polyelectrolyte complexes easy to disaggregate. Moreover, the osmotic pressure increased as the ionic strength increased, making the sustained release higher.

## Conclusions

In summary, thermo-sensitive polyelectrolyte complex nanoparticles formed from two oppositely charged graft copolymers CS-*g*-PNIPAM and SA-*g*-PNIPAM were prepared. The average diameter of nanoparticles with a narrow size distribution was about 130~180 nm. The hydrogen bonding interactions between nanoparticles and 5-FU improved the drug loading capacity. The release of 5-FU was controlled by external conditions. When increasing temperature and ionic strength or decreasing pH of the solutions, release of 5-FU from nanoparticles increased. The drug release was also affected by the amount of GA. Thus the novel polyelectrolyte complex nanoparticles with environmentally sensitive properties are expected to be utilized in the field of intelligent drug delivery system.

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