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Synthesis, pH Sensitivity, and Drug-Release Behavior of Acrylic Acid and Polyhedral Oligomeric Silsesquioxane Copolymer

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ABSTRACT: pH-Sensitive organic–inorganic copolymers of hydrogels were developed as drug delivery systems (DDS) to improve the swelling behavior of polyacrylic acid (PAA). They were represented through FTIR, TGA and XRD characterization which revealed that the functional groups of methacryl-phenyl polyhedral oligomeric silsesquioxane (POSS) were successfully added to the acrylic acid (AA) molecular chains through radical solution polymerization. The DSC test results indicate that the addition of POSS could improve the thermal properties of the copolymers. The swelling properties at the pH range of 1.25–8.01 exhibited the pH sensitivity of POSS/AA copolymers (POSS-*co*-AA) and the lower swelling ratio in acidic conditions indicated that the DDS had low amount of release in SGF; this phenomenon suggested that the copolymer was available as DDS of theophylline. And it was proved by drug release curve and scanning electron microscopy. Since the addition of POSS reduced the release rate of theophylline and prolonged the release time of the drug, the concentration range of theophylline could remain low for an extended duration. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 129: 3162–3169, 2013

KEYWORDS: drug delivery systems; copolymers; swelling

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INTRODUCTION

Theophylline is methylated xanthine class of drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease and asthma. It has an extremely limited therapeutic range of 5–15 μg/mL. When the serum concentrations of theophylline exceed 15–20 μg/mL, it will produce a poisonous side effect.[1,2] Hence, a drug release system is needed to match the physiological needs of a patient at the proper time and/or site. Thus, great interest exists in developing controlled delivery systems.[3] However, further evaluation of side effects, more convenient methods of administration, and an improvement in patient compliance are still required.[4,5]

Hydrogels, which can transfer their volume in response to environmental stimuli, such as pH,[6,7] ionic strength,[8] temperature,[9] electric field,[10] or any combination thereof,[3] have been of interest to biomaterial scientists for several years because of their hydrophilic character and potential for biocompatibility.[11–21] This sensitivity to environmental stimuli has made hydrogels effective drug delivery device systems[22–26] through their modulation of the immune response, extension of the circulation time, and maintenance of the bioavailability of the therapeutic drugs.[27–29] These polymers are attractive because of their predictable drug release kinetics in responding to specific physiological conditions.[30–33] Among these sensitive hydrogels, pH-sensitive polymers are particularly attractive for targeted drug delivery applications because of the various pH values of different tissues within the body.

Typical synthetic pH-sensitive hydrogels, such as poly(methyl methacrylate)[34] and polyacrylic acid (PAA),[35] including chitosan,[36] have been used as pH-sensitive DDS. Among these pH-sensitive hydrogels, acrylic polymers with carboxylic acid groups can form hydrogen bonds, a glycoprotein secreted locally that coats the mucosal surface,[37] which can prolong the release time of a drug in a particular part of the body. In addition, poly(acrylic acid) has exhibited high *in vivo* tolerance in rats after subcutaneous implantation for up to 24 days.[38]

POSS with a molecule dimension of 1–3 nm have attracted a great deal of attention recently in bio materials area due to their potential as candidate materials for bridging the gap between organic polymers and inorganic ceramics.[39–42] So in this study, a new kind of organic–inorganic hydrogels was synthesized called POSS-*co*-AA by free radical solution polymerization. And we used theophylline as model drug. As the main absorption site of theophylline is in the gastricus and intestine, it has

Table I. Preparation of Hydrogels, Feed Composition, and Sample Designation

Sample code	POSS (wt %)	POSS (mol % × 10^{-3})	MBA (mol %)	AIBN (mol %)
POSS0	0	0	2	0.13
POSS2	2	1.33	2	0.13
POSS4	4	2.66	2	0.13
POSS6	6	3.99	2	0.13
POSS8	8	5.32	2	0.13
POSS10	10	6.65	2	0.13
POSS12	12	7.98	2	0.13

irritation to gastric mucosa.[43–45] So the drug release behavior of theophylline was studied in the simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Beyond that, the effect of pH sensitivity and drug release after the addition of POSS was also discussed.

EXPERIMENTAL

Materials

The AA was obtained from Tianjin Chemical, and POSS was obtained from Hybrid Plastics (Mississippi, USA). Azodiisobutyronitrile (AIBN) and *N,N′*-Methylenebisacrylamide (MBA) were purchased from Beijing Chemical (Beijing, China). *N,N*-dimethyl formamide (DMF) and tetrahydrofuran (THF) were purchased from Tianjin Tiantai Fine Chemical (Tianjing, China). Theophylline was purchased from Shanghai Baoman Biotechnology (Shanghai, China). All reagents were used as received.

Preparation of POSS-*co*-AA Hydrogels

The polymerization of the POSS-*co*-AA hydrogels was performed in THF/DMF-blended solutions to form a homogeneous mixture. MBA as cross-linking agent was then dissolved in the monomer solutions, the molar ratio of MBA to the monomer was 1 : 50. The molar ratio of the initiator (AIBN) to the monomer was 1 : 750. The specific sample designation and composition of the various hydrogels used in this study are shown in Table I. Then the reaction mixture was allowed to react at 60°C under nitrogen atmosphere for 4 h until the gel was completed, whereas the polymerization reaction of AA was retarded in the air atmosphere. The resulting POSS-*co*-AA hydrogels were repeatedly soaked in THF and distilled water to remove the residual monomer and unreacted initiator. After purification, the hydrogels were dried *in vacuo* at 50°C until their weight remained unchanged. The preparation of the copolymer and its structure is shown in Figure 1.

Characterization

Fourier transform infrared spectroscopy (FTIR) spectra were recorded on a Nexus 670 FTIR spectrometer (USA, Thermo Electron Company) using KBr pellets. X-ray diffraction (XRD) was performed on a D/Max 2500 PC X-ray diffractometer (Japan, Rigaku) at 5° to 40°. Thermal gravimetric analysis (TGA) measurement was performed using a Phyris 1 TGA apparatus (USA, Perkin Elmer) under a flowing air atmosphere at a scan rate of 20°C/min from 50°C to 800°C. The determination of glass transition temperature (T_g) was carried out using DSC (Q100 V9. 6 Build 290, America), all samples (about 5 mg) were scanned at a heat rate of 10°C/min under nitrogen flow of 200 mL/min. The glass transition temperature was taken from the midpoint of the capacity change.

To observe the morphology of hydrogels, the samples were first swelling equilibrated in SGF (buffer solutions of pH = 1.2) and SIF (buffer solutions of pH = 7.4) at room temperature[46] and then freeze-dried for at least 3 days until all the solvents were sublimed. The morphology of the freeze-dried hydrogel was studied using a SEM (XL30 ESEM FEG, FEI COMPANY). Before observation, the samples were fixed on a cuprum mount and sprinkled with gold palladium.

To determine the pH-dependent swelling properties of the hydrogels, the xerogels were immersed in buffer solutions with

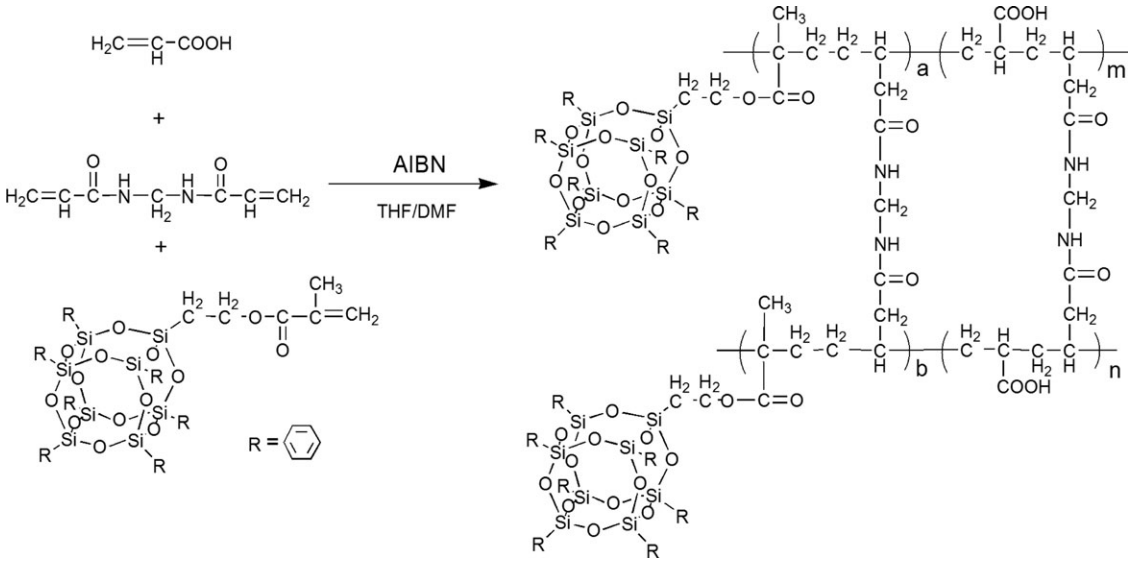

Figure 1. Preparation of POSS-*co*-AA copolymers.

pH values of 1.25, 2.62, 4.26, 5.21, 7.64, and 8.01 at 37°C. The xerogels were weighed and placed into 30 mL of buffer solution. At predetermined time intervals, the swollen hydrogels were removed, and excess water was blotted from the surface using filter paper. The weight of the wet hydrogels was repeatedly measured at all time points. The weight-swelling ratio (R_t) was calculated using the following equation:

$$R_t = (w_t - w_d)/w_d \quad (1)$$

where w_t and w_d are the sample weight at time t in the wet and dry states, respectively.

Before the investigation of drug release behavior, the standard calibration curve of the absorbance as a function of the theophylline concentration was studied at 272 nm on the T6 UV (China, puxitongyongyiqi company) spectrophotometer. The linear relationship of the standard calibration curve can be quantificationally described as the following equation:

$$A = 60.943c - 0.0166 \quad (2)$$

where c is the concentration (mg/mL) of the drug (theophylline), and A is the absorbance, the correlation coefficient (R^2) of 0.9971.

The drug release experiments were conducted at 37°C in SGF and SIF to investigate the effect of pH-sensitive property of the POSS-*co*-AA hydrogels in terms of theophylline release profiles. Theophylline release experiments were conducted by immersing the theophylline-loaded hydrogel samples in a glass bottle filled with 50 mL of SGF and SIF, as the pH range of succus gastricus is 0.9–1.5 and the pH range of succus entericus is 6.8–8.4, so in this article we chose pH 1.2 (HCl aqueous solutions) and pH 7.4 (buffer phosphate) for SGF and SIF. At a predetermined period of the *in vitro* release experiment, 2 mL aliquots of the buffer medium was removed from the glass tube, and the concentration of the theophylline was measured using a UV spectrophotometer at 272 nm. Then, 2 mL fresh buffer solution was again added to the glass tube to maintain the same total solution volume. All release studies were conducted in duplicate

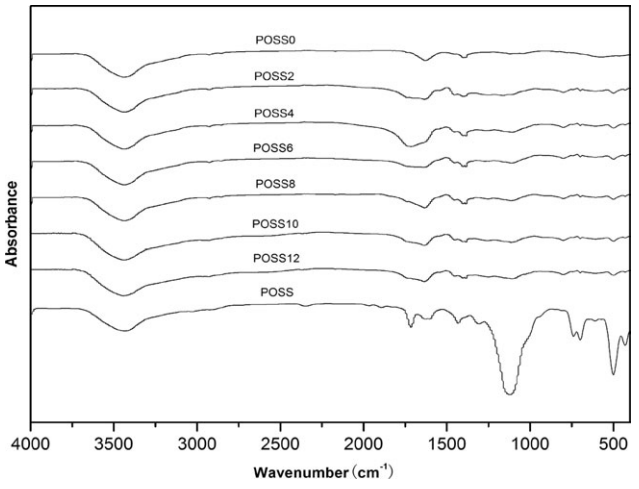

Figure 2. FTIR spectra of POSS and POSS-*co*-AA copolymers.

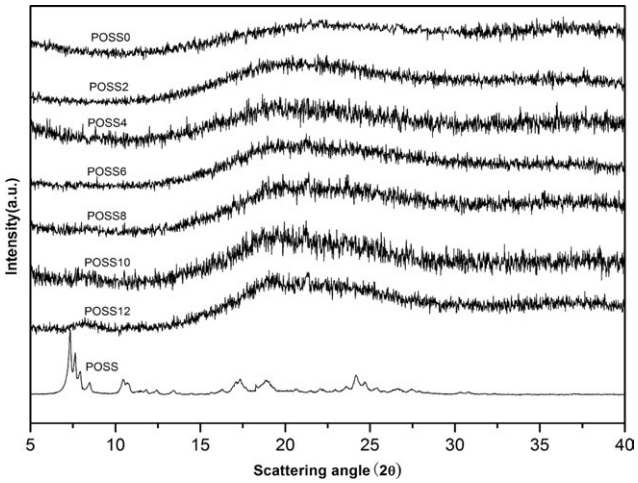

Figure 3. XRD patterns for POSS and POSS-*co*-AA copolymers.

and we took the average values as the final results. The results were presented in terms of cumulative release concentration as a function of time:

$$\text{Cumulative release}(\%) = (M_t/M_\infty) \quad (3)$$

where M_t is the amount of theophylline released from the hydrogels at time t and M_∞ is the estimated amount of theophylline loaded in the hydrogels and was calculated from the weight difference of the initial theophylline solution concentration (before loading) and the remaining theophylline solution concentration after loading.

RESULTS AND DISCUSSION

Characteristics of P(AA-*co*-POSS) Hydrogels

The attachment of the PAA chain from the functional groups of POSS was confirmed using FTIR analysis. Figure 2 shows the infrared spectra of the pure POSS and POSS-*co*-AA. The FTIR spectrum of the purified POSS-*co*-AA shows that the characteristic stretching vibration at 1700 cm^{-1} ($\nu_{C=O}$) corresponds to the carbonyl group of PAA, along with a broad peak at around 1107 cm^{-1}($\nu_{Si-O-Si}$) attributable to the POSS moiety. In addition, the peaks at 800 and 500 cm^{-1} are attached to the aromatic hydrogen, indicating that POSS is present in the PAA matrix. In addition, a broad shoulder band in the 3100–3600 cm^{-1} (ν_{OH}) region is attributed to the presence of hydroxyethyl groups and PAA chains containing OH moieties and to traces of water in the KBr pellet used for the analysis, which cannot be fully removed.

Figure 3 displays the wide-angle XRD (WAXD) patterns for the pure POSS and POSS-*co*-AA. The diffractogram of the pure POSS shows very intense characteristic POSS crystalline peaks at 7.33°, 7.65°, 17.26°, 18.84°, and 24.17°, indicating that POSS is highly crystalline. For the pure PAA, the XRD pattern usually shows broad peaks from 10.66° to 28.85°, a characteristic amorphous structure. In addition to the amorphous broad peaks, a small diffraction peak centered at $2\theta = 7.68°$ is observed for the 12% POSS-*co*-AA copolymers, which corresponds to the primary diffraction peak of neat POSS, along with a broad

amorphous diffraction peak centered at $2\theta = 20.84°$, which is close to the amorphous peak centered at $2\theta = 21.55°$ of the neat PAA. Such a diffraction peak results from the small aggregation of POSS blocks in the polymer matrix. By contrast, these intense reflections could not be observed in the other POSS-*co*-AA copolymers with low POSS content, indicating that POSS was dispersed in the PAA chains without aggregation when its mass content is less than 12 wt %.

The defunctionalization of an organic group can be realized by thermal decomposition. In the present study, TGA is used to determine the relative amount of copolymers of POSS-*co*-AA. Figure 4 shows the TGA traces of POSS and POSS-*co*-AA under air, wherein all TGA curves of POSS-*co*-AA display similar degradation profiles, implying a similar mechanism. In addition, the incorporation of POSS into hydrogels results in a retarded mass loss rate and an enhanced char yield. This effect is increasingly pronounced with the increase in the concentration of covalently bound POSS in the copolymer systems, indicating that the addition of POSS improves the thermal properties of the copolymer and the interaction between molecules. These results are in good agreement with the reaction conditions and our assumption.

It has been reported that the addition of POSS could improve the T_g.[47] Figure 5 shows the DSC of POSS-*co*-AA and indicate the T_g of the copolymers. As can be seen from the figure, the addition of POSS could improve the glass transition temperature (T_g) and related report about the T_g transformation has been reported. The T_g of pure PAA hydrogels is 145.7°C, the T_g is increased with the increasing content of POSS, when the content of POSS is 12 wt %, the T_g is 167.1°C. This phenomenon is attributed to the fact that the addition of POSS limits the movement of the molecular chain segment.

Swelling Kinetics

Dynamic swelling studies are conducted to investigate the swelling behavior of POSS-*co*-AA hydrogels prepared with different mass ratios under different pH conditions. Figure 6 shows the swelling behavior of the composites, and each datum point refers to the average value between three independent runs. For the same substance, the swelling ratio increases as the pH is

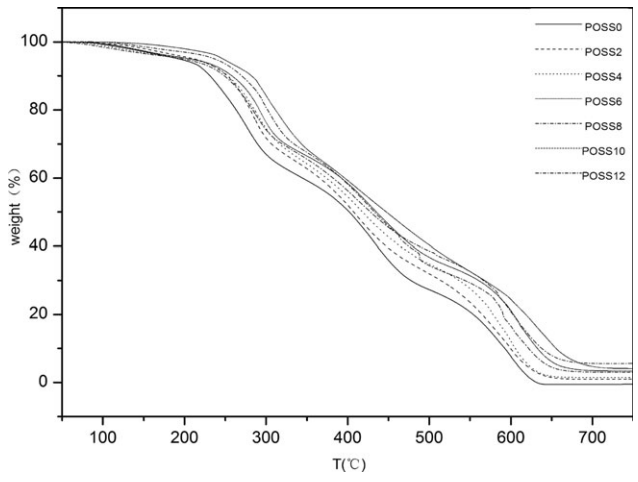

Figure 4. TGA of POSS and POSS-*co*-AA copolymers.

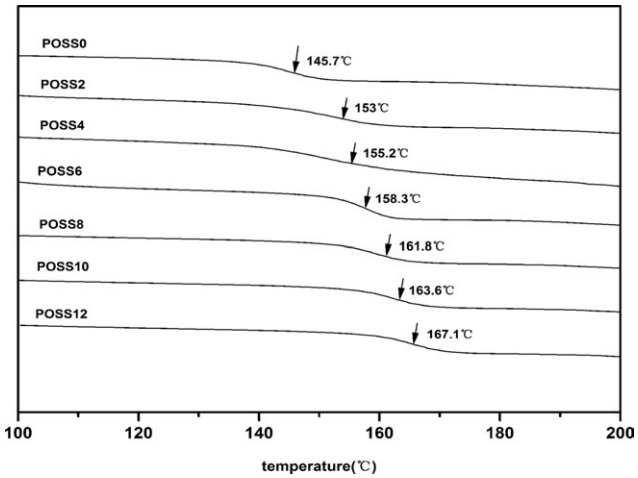

Figure 5. DSC of POSS-*co*-AA copolymers.

increased because of the ionization of —COOH with the comparison among the six figures under different pH. As the pH is increased, the ionization of —COOH is increased because of the higher concentration of H^+, thus leading to an increase in the $—COO^-$ concentration. So in acidic conditions, the swelling ratio of the hydrogels is relatively low. Whereas in alkalescent environment, the intermolecular repulsive interaction of $—COO^-$ between molecular chains leads to the increase of spaces between molecular chains, favoring the penetration of water into the hydrogels.

It shows that the swelling ratio is decreased with the addition of POSS comparing swelling curves with different proportion content of POSS. And the decrease is obvious when the mass percentage content of POSS exceeds 4 wt % under acid conditions. These phenomena could be attributed to the addition of POSS limiting the movement of the molecular chains; this has negative effects on the penetration of water molecules into the polymers. Thus, we could adjust the swelling behavior of PAA hydrogels in buffer solutions by the addition of a certain amount of POSS. These properties indicate that the copolymer is available as DDS for theophylline.

To study the water transport mechanism from P(AA-*co*-POSS) hydrogels with different POSS contents, Fick's equation is applied to fit the experimental data, the equation is shown as following:[48]

$$F = w_t/w_e = kt^n \quad (4)$$

where w_e is the amount of the absorbed water after the hydrogels achieve swelling equilibrium, k is a constant incorporating characteristic of the polymer network system, and n is the diffusion exponent. The exponents n and k are values determined from the slope and intercept of the plots of $\ln(w_t/w_e)$ versus $\ln t$ for the hydrogels at different POSS contents. Table II shows the value of n under different pH. It is demonstrated that the value of n is from 0.7 to 0.5, this indicates that the swelling transport mechanism is the non-Fickian type diffusion, and the swelling process is controlled by water diffusion and relaxation of polymer chains.[48] It is clear from the analysis that with the increasing content of POSS, the exponent n decreases. However,

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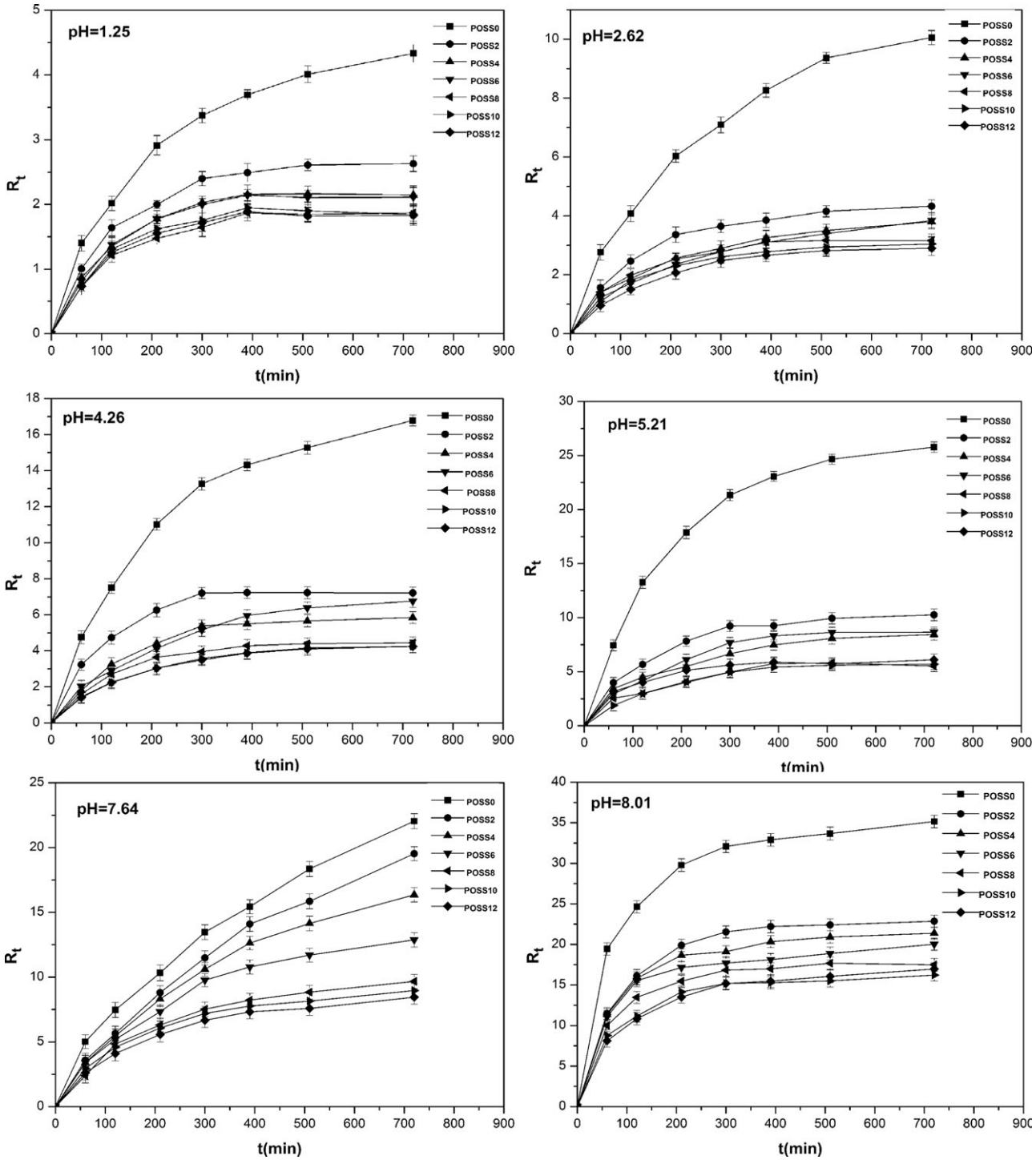

Figure 6. Swelling ratios as a function of time in different pH buffer solutions of POSS-*co*-AA copolymers (ionic strength $I = 0.3$, 37°C).

the value of n increases with the increasing pH of the buffer solutions. This was attributed to the addition of POSS that limits the diffusion of water in the copolymers, which has been shown in the above explanation.

In Vitro Theophylline Release in SGF and SIF

Figure 7 shows the cumulative drug release from the polymer network in SGF and SIF at 37°C. The drug release rate is obviously faster in SIF than in SGF. Besides, all POSS-*co*-AA hydrogels exhibited a slower release rate than PAA hydrogels. However, all hydrogels show an initial burst release of theophylline within the first 3 h in SGF. During this burst release in SGF, the cumulative theophylline release was 42% for POSS0, 37% for POSS2, 33% for POSS4, 31% for POSS6, 28% for POSS8, 26% for POSS10, and 22% for POSS12. Beyond the burst period, the release rate slowed down. In SIF, theophylline is released from

Table II. The Kinetic Parameters at Different pH for POSS-co-AA Copolymers

	pH = 1.25		pH = 2.62		pH = 4.26		pH = 5.21		pH = 7.64		pH = 8.01	
Sample Code	*n*	R^2	*n*	R^2	*n*	R^2	*n*	R^2	*n*	R^2	*n*	R^2
POSS0	0.534	0.992	0.592	0.997	0.606	0.991	0.606	0.976	0.686	0.998	0.654	0.946
POSS2	0.513	0.969	0.560	0.962	0.575	0.972	0.580	0.979	0.673	0.999	0.634	0.963
POSS4	0.512	0.979	0.543	0.996	0.561	0.965	0.574	0.995	0.665	1.000	0.606	0.983
POSS6	0.509	0.962	0.537	0.998	0.553	0.998	0.563	0.994	0.632	0.997	0.583	0.984
POSS8	0.507	0.965	0.525	0.992	0.540	0.957	0.551	0.968	0.607	0.957	0.583	0.960
POSS10	0.507	0.939	0.522	0.964	0.533	0.990	0.532	0.994	0.555	0.989	0.536	0.928
POSS12	0.506	0.953	0.521	0.990	0.523	0.988	0.541	0.988	0.523	0.993	0.536	0.979

the hydrogels with definite velocity for long time. Besides, the time of drug release is lengthened with the increased content of POSS and the drug release rate in SIF is decreased at a certain rate with increasing POSS content. This occurrence is understandable because the accession of POSS limits the motion of the molecular chains, as demonstrated in Figure 7. The addition of POSS also prolongs the release time of theophylline.

The phenomena shown above make the application of this copolymer as drug release system of theophylline possible. The obvious decrease in drug release rate in the SGF could lower the stimulation of gastric mucosa by theophylline and control the release rate and concentration of the drug at a certain range in SIF through the addition of a small amount of POSS. That is to say, we could realize the release of theophylline at the appointed site due to the pH sensitivity of the hydrogels and control the release amount of theophylline by the addition of POSS. Beyond that, the addition of POSS could lower the irritative effect on gastric mucosa. This confirms the aforementioned assumption given in the beginning of this article.

Morphology of Swelling Hydrogels

To evaluate the effect of the addition of POSS on the morphology of the swelling hydrogels, SEM of POSS0 and POSS8 under swollen conditions in SGF and SIF are shown in Figure 8. The swollen hydrogels were freeze-dried before SEM morphological investigation. Although this treatment may generate structural artifacts in the specimens, the dramatic differences in morphology observed between the hydrogels are presumably intrinsic in nature because of the addition of POSS. The most distinctive feature in Figure 8 is that the aperture of the polymer network is obviously bigger in SIF than in SGF. Moreover, the aperture of the hydrogels decreased rapidly with the addition of POSS, which means that the addition of POSS reduces the swelling properties of hydrogels, consequently reducing the swelling aperture. These results are in accordance with what is shown in swelling kinetics and drug release systems.

CONCLUSIONS

The pH-sensitive hydrogels of POSS-*co*-AA copolymers were prepared through radical solution polymerization. FTIR, XRD,

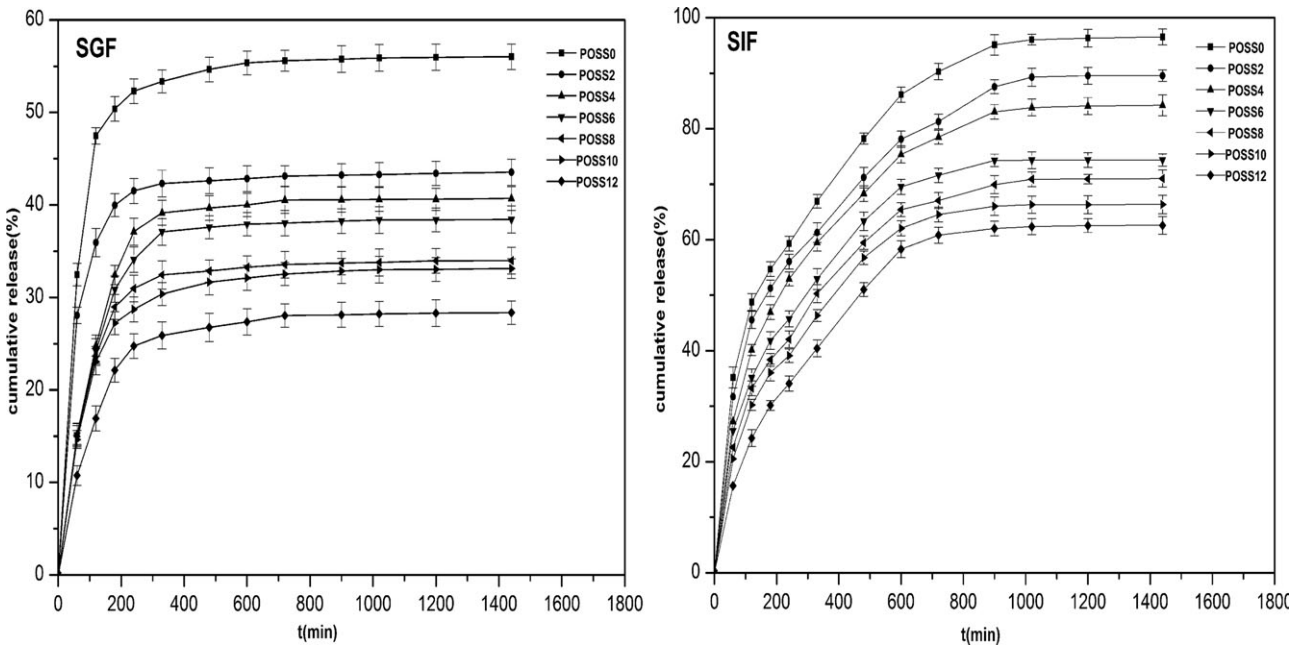

Figure 7. Theophylline release profile of POSS-*co*-AA copolymers in SGF and SIF at 37°C.

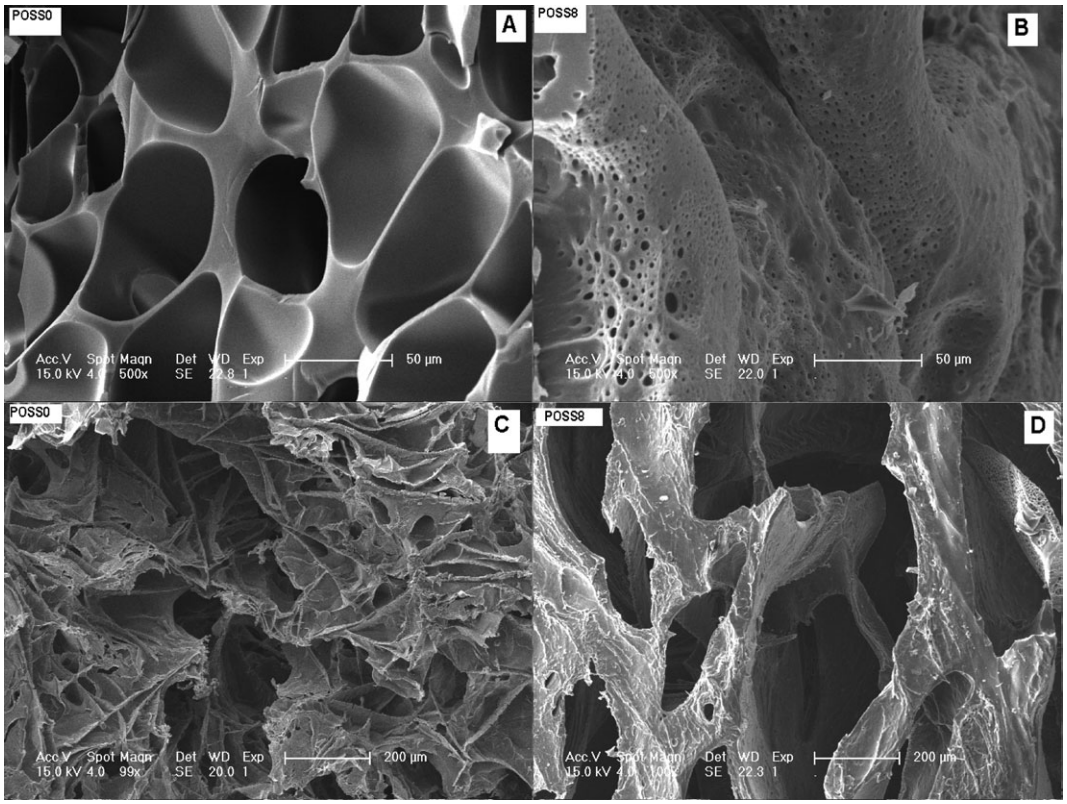

Figure 8. SEM micrographs of the swollen hydrogels of POSS-*co*-AA copolymers in SGF (A, B) and SIF (C, D).

and TGA demonstrated that POSS was successfully added to the polymer network to form a homogeneous copolymer. DSC results stated that the addition of POSS increase the T_g of the copolymers. The swelling kinetics showed that the swelling ratio increased with increasing pH, that is to say, the copolymer has good pH sensitivity. Beyond that, the employing of POSS decreased the swelling ratio of the copolymer whereas the pH sensitivity stay the same, these phenomena were described by Fick's law of diffusion. The drug release study demonstrated the given assumption that the addition of POSS improves the swelling performance of PAA hydrogels as DDS because the addition of POSS decreased the drug release rate and prolonged the drug release time in SIF. The low drug release of POSS-*co*-AA in SGF indicated that the addition of POSS could lower the irritative effect of theophylline on gastric mucosa. So this novel hydrogel existed significantly potential applications as DDS. The SEM results displaying the variation in the aperture also showed the morphological properties of the swelling hydrogels, and the results of morphology analysis are in accordance with the swelling kinetics and drug release test results.

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