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Preparation and characterization of a novel pH-sensitive chitosan-*g*-poly (acrylic acid)/attapulgite/sodium alginate composite hydrogel bead for controlled release of diclofenac sodium

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ABSTRACT

A series of pH-sensitive composite hydrogel beads composed of chitosan-*g*-poly (acrylic acid)/attapulgite/sodium alginate (CTS-*g*-PAA/APT/SA) was prepared as drug delivery matrices crosslinked by Ca^{2+} owing to the ionic gelation of SA. The structure and surface morphology of the composite hydrogel beads were characterized by FTIR and SEM, respectively. pH-sensitivity of these composite hydrogels beads and the release behaviors of drug from them were investigated. The results showed that the composite hydrogel beads had good pH-sensitivity. The cumulative release ratios of diclofenac sodium (DS) from the composite hydrogel beads were 3.76% in pH 2.1 solution and 100% in pH 6.8 solutions within 24 h, respectively. However, the cumulative release ratio of DS in pH 7.4 solution reached 100% within 2 h. The DS cumulative release ratio reduced with increasing APT content from 0 to 50 wt%. The drug release was swelling-controlled at pH 6.8.

1. Introduction

Drug delivery systems are required for the drugs with a narrow therapeutic range of blood concentration or eliminate rapidly or maintaining the concentration below levels where potential harmful side effects become prevalent. Drug delivery systems have the advantage of increasing the residence time of a drug within a patient, reducing dosing frequency and toxic effects, improving patient compliance and consequently efficacy with most dosage requirements. The ideal delivery carriers will ensure that the drug is released at the right site, in the right dose and for the required time. Furthermore, they will also be biocompatible or biodegradable. Now, the drug delivery vehicle is transformed into non-toxic natural or synthetical polymers that are eliminated harmlessly from the body (Aguzzi, Cerezo, Viseras, & Caramella, 2007; Haznedar & Dortunc, 2004; Uhrich, Cannizzaro, Langer, & Shakesheff, 1999).

Chitosan (CTS), obtained by deacetylation of natural chitin, is one of the frequently used materials for the preparation of drug delivery systems because of its cationic nature and suitable sustained drug release properties, non-toxicity, good biocompatibility, biodegradability and bioadhesiveness (Sashiwa & Aiba, 2004). Recently, CTS based hydrogels sensitive to changes of external conditions such as pH (Krishna Rao, Naidu, Subha, Sairam, & Aminabhavi, 2006), temperature (Alvarez-Lorenzo et al., 2005), and electric currents (Liu, Liu, Chen, & Liu, 2007) are receiving increasing attention as drug delivery carriers. CTS based sensitive hydrogels are often fabricated by combination with other sensitive polymers such as poly (acrylic acid) (PAA) (Shim & Nho, 2003; Yang et al., 2005), poly (*N*-isopropylacrylamide) (Cai, Zhang, Sun, He, & Zhu, 2005; Guo & Gao, 2007), *N*,*N*′-dimethylacrylamide (Ramesh Babu, Hosamani, & Aminabhavi, 2008). These hydrogels not only have porous interpenetrated network structure but also have biocompatibility and biodegradable (Peniche, Fernández, Gallardo, López-Bravo, & Román, 2003). In these hydrogels, the drug is dispersed randomly within the polymer matrix and released as a consequence of erosion of the carriers. However, these materials have the disadvantage of burst release of drugs through breakdown of the matrices due to their poor mechanical properties and higher swelling ratio.

Polymer/clay composite hydrogels draw much attention for the drug delivery system because the introduced clay can improve physicochemical properties (such as mechanical properties, thermal stability and bactericidal activity) of the polymeric materials and also provide a slower and more continuous release of the drug in comparison with pure polymers (Xiang, Peng, & Chen, 2006). For example, Zheng, Li, Zhang, and Wang (2007) synthesized nanocomposite hydrogel with high thermal stability by grafting acrylic acid onto the vermiculite. Liu et al. (2007) reported the preparation of CTS/clay nano-composite hydrogel with excellent anti-fatigue property, and continuous and steady release for vitamin B_{12} by

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introducing the negatively charged delaminated montmorillonite. Depan's group (2009) obtained CTS-*g*-lactic acid/sodium montmorillonite nanohybrids with improved mechanical modulus, strength and the drug ibuprofen release rate. CTS/organic rectorite nano-composite films have also been successfully prepared and their properties such as mechanical property, anti-ultraviolet capacity and bactericidal activity were enhanced by introducing organic rectorite according to Wang, Du, Luo, Lin, and Kennedy (2007).

A novel chitosan-*g*-poly (acrylic acid)/attapulgite (CTS-*g*-PAA/APT) composite hydrogel with different APT content was synthesized through graft-copolymerization among CTS, APT and acrylic acid (AA) by our group (Zhang, Wang, & Wang, 2007), and has already been used in wastewater treatment as a superadsorbent. In order to extend the application fields of this composite hydrogel, in this work, the composite hydrogel beads composed of CTS-*g*-PAA/APT and sodium alginates (SA) were prepared as drug delivery carriers. pH-sensitivity of the composite hydrogel beads were discussed. Moreover, the controlled drug delivery behaviors of CTS-*g*-PAA/APT/SA hydrogel beads were investigated by using diclofenac sodium (DS) as the model drug. The main aim of this work is to decrease the swelling ratio of CTS-*g*-PAA hydrogel, reduce the burst effect, prolong the release time of the drug and sequentially improve the drug efficacy by introducing APT and SA.

2. Experimental

2.1. Materials

AA (distilled under reduced pressure before use), ammonium persulfate (analytical grade, recrystallized from distilled water before use) and *N*,*N*′-methylenebisacrylamide (analytical grade) were purchased from by Shanghai Reagent Corp. (Shanghai, China). CTS (degree of deacetylation is 0.85, average molecular weight is 90×10^4) was supplied by Zhejiang Yuhuan Ocean Biology Co. (Zhejiang, China). APT (supplied by Linze Colloidal Co., Gansu, China) was milled through a 320-mesh screen and treated with 37% hydrochloric acid for 72 h, followed by washing with distilled water until pH 6 was achieved, and then dried at 105 °C for 8 h before use. SA was purchased from Shanghai Chemical Co. Ltd (China). DS was purchased from Jiuzhou pharmaceutical factory (He'nan, China). All the other reagents used were analytical grade and all solutions were prepared with distilled water.

2.2. Preparation of CTS-g-PAA/APT composite hydrogels

CTS-*g*-PAA/APT composite hydrogels were prepared according to our previous reports (Zhang et al., 2007). CTS (0.5 g) was dissolved in 30 mL acetic acid solution (1%) in a 250 mL four-neck flask, equipped with a mechanical stirrer, a reflux condenser, a funnel and a nitrogen line. After being purged with nitrogen for 30 min to remove the oxygen dissolved from the system, the solution was heated to 60 °C, and then 0.10 g APS was introduced to initiate CTS to generate radicals. Ten minutes later, the mixed solution of 3.55 g AA, 0.15 g of MBA and a predetermined amount APT were added. The water bath was kept at 60 °C for 3 h. The resulting granular product was transferred into sodium hydroxide aqueous solution (1 M) to be neutralized to pH 7, and then dehydrated with ethanol. After wiping off excessive dewatering agents on the surface using filter paper, the samples were spread on a dish to dry overnight at room temperature. The products were milled through an 80 mesh screen. The preparation procedure of CTS-*g*-PAA was similar to that of CTS-*g*-PAA/APT except for the addition of APT.

2.3. Preparation of CTS-g-PAA/APT/SA composite hydrogel beads

A series of CTS-*g*-PAA/APT/SA composite hydrogel beads with different APT content were prepared according to the following procedure. A predetermined amount of DS (0.25 g) was dissolved in 50 mL distilled water in a 250 mL flask using a mechanical stirrer (200 rpm for 30 min), and then 0.50 g of CTS-*g*-PAA/APT microparticles was charged into the flask. The mixture was stirred for 2 h to facilitate the penetration of DS molecules into CTS-*g*-PAA/APT hydrogel. Subsequently, the appropriate amount of SA was added into the above mixture and was further stirred at 1000 rpm for 4 h to ensure homogeneity of the mixture. The mixture was dropped into a gently stirred calcium chloride solution through a 0.45 mm syringe needle at a dropping rate of 1.50 mL min^{-1}. CTS-*g*-PAA/APT/SA composite hydrogel beads were formed instantaneously and were allowed to crosslink with Ca^{2+} in solution for 2 h. The obtained hydrogel beads were rinsed with distilled water for three times to remove unreacted calcium chloride on surface and subsequently dried at 80 °C in an oven.

2.4. pH-sensitivity

Composite hydrogel beads (0.25 g) was immersed in 250 mL buffer solution with various pH values at room temperature for 12 h to reach swelling equilibrium. Swollen samples were then separated from unabsorbed water by filtering through a 100-mesh screen under gravity for 30 min without blotting the samples. Swelling ratio (SR) in buffer solution was calculated according to the following equation:

$$\mathrm{SR} = \frac{W_2 - W_1}{W_1} \quad (1)$$

where W_2 and W_1 represent the weights of the swollen and dry samples, respectively. The buffer solutions with various pH values were made by combining NaH_2PO_4, Na_2HPO_4, NaCl and NaOH solution properly. Ionic strengths of all the buffer solutions were adjusted to 0.2 M with NaCl solution. The pH values were determined with a pH meter (DELTA-320).

2.5. Determination of encapsulation efficiency and drug loading

Composite hydrogel beads (0.10 g) was immersed in 10 mL of the phosphate buffer solution (pH 6.8) in a 50 mL beaker for completely swelling. The swollen beads were crushed in an agate mortar with a pestle and transferred into a conical flask, and then about 20 mL of the fresh phosphate buffer solution was added to the conical flask and the homogeneous mixture was sonicated for 20 min. The DS solution was separated from the mixture after being centrifuged for 20 min at 5000 rpm. The amount of DS was determined using UV spectrophotometer (SPECORD 200, ANALYTIK JENA AG). The drug loading (%) and encapsulation efficiency (%) were calculated using the following equations, respectively:

$$\text{Drug loading } (\%) = \frac{\text{Weight of drug in hydrogel beads}}{\text{Weight of hydrogel beads}} \times 100 \quad (2)$$

$$\text{Encapsulation efficiency } (\%) = \frac{\text{Weight of drug in hydrogel beads}}{\text{Theoretical drug loading}} \times 100 \quad (3)$$

2.6. In vitro drug release

In vitro release experiments were carried out using an intelligent dissolution apparatus (ZRS-8G) by immersing 0.50 g of the dried DS-loaded composite hydrogel beads in 500 mL dissolution medium (Chinese Codex (II), 2005). The dissolution media of various pHs (2.1, 6.8 and 7.4) were prepared by combining HCl, KH_2PO_4 and NaOH solution properly according to the Chinese Pharmaco-

poeia 2005. The mixture was stirred at 50 rpm and kept at 37 ± 1 °C. At predetermined time intervals, 5 mL of the solution was taken and 5 mL of the fresh buffer solution was added to maintain a constant volume. The obtained 5 mL of the solution was filtrated through a membrane with a pore diameter of 0.45 μm. Filtrate (3 mL) was diluted to 25 mL with the fresh buffer solution. The concentration of DS was determined by a UV spectrophotometer at 280 nm, and then the cumulative percentage of DS released was calculated. The dissolution results were the average of three determinations.

2.7. Characterization

FTIR spectra of the hydrogel beads were taken as KBr pellets using a Thermo Nicolet NEXUS TM spectrophotometer. Micrographs of the hydrogel beads were taken using SEM (JSM-5600LV, JEOL, Ltd.). Before SEM observation, all samples were fixed on aluminum stubs and coated with gold.

3. Results and discussion

3.1. FTIR spectra analysis

FTIR spectra of DS, CTS-*g*-PAA/APT, DS-loaded CTS-*g*-PAA/APT, CTS-*g*-PAA/APT/SA and DS-loaded CTS-*g*-PAA/APT/SA composite hydrogel beads are shown in Fig. 1. The characteristic absorption bands of DS can be seen clearly in the spectra of DS-loaded CTS-*g*-PAA/APT (Fig. 1(c)) and DS-loaded CTS-*g*-PAA/APT/SA (Fig. 1(e)), indicating the successful entrapment of DS into CTS-*g*-PAA/APT network and CTS-*g*-PAA/APT/SA network, respectively. It can also be seen from Fig. 1(b), the characteristic peaks are observed at 1716, 1643, 1564, 1453 and 1037 cm^{-1}, which are ascribed to –COOH, amide I, amide II, $–COO^-$ and Si–OH of CTS-*g*-PAA/APT, respectively. However, the absorption band of –COOH (1716 cm^{-1}) disappears after crosslinked by Ca^{2+} and intensity of the absorption band of $–COO^-$ (1429 cm^{-1}) is enhanced as shown in Fig. 1(d). It is known that the contact between alginate and Ca^{2+} in solution immediately induces ionic crosslinking of alginate, and then forms hydrogel beads (González-Rodrıguez, Holgado, Sánchez-Lafuente, Rabasco, & Fini, 2002). The collapse of CTS-*g*-PAA/APT composite hydrogel was observed upon addition of a calcium chloride solution. The characteristic absorption bands of CTS-*g*-PAA/APT and SA can be observed in the spectrum of CTS-*g*-PAA/APT/SA which implies that the network structure has been formed. The information obtained from Fig. 1 indicates that $–COO^-$ and –COOH groups of CTS-*g*-PAA/APT micro-particles and SA are crosslinked by Ca^{2+} and CTS-*g*-PAA/APT micro-particles are closely attached to SA polymer chains through Ca^{2+}. The entrapment of DS by CTS-*g*-PAA/APT micro-particles and the attachment of the drug-loaded micro-particles to SA polymer chains during the sol–gel transition of SA under the existence of Ca^{2+} may have great influence on its structure, morphology, swelling behaviors and drug release behaviors.

3.2. Morphological analysis

Micrographs of CTS-*g*-PAA/SA and CTS-*g*-PAA/APT/SA composite hydrogel beads were observed and are shown in Fig. 2. It can be seen from Fig. 2(a) that most of DS-loaded CTS-*g*-PAA/APT/SA composite hydrogel were spherical in shape with a smooth surface and the sizes are around 4–5 mm. After dried in an oven, the beads had a rough and lacunaris surface with large wrinkles as shown in Fig. 2(b). In addition, CTS-*g*-PAA/SA shows a very tight surface (Fig. 2(c)); whereas a loose surface is observed for CTS-*g*-PAA/APT/SA composite hydrogel beads (Fig. 2(d)). This surface morphology changing by introducing APT may influence swelling ability of corresponding composite hydrogel beads, and then may has some influences on the release of DS from the composite hydrogel beads.

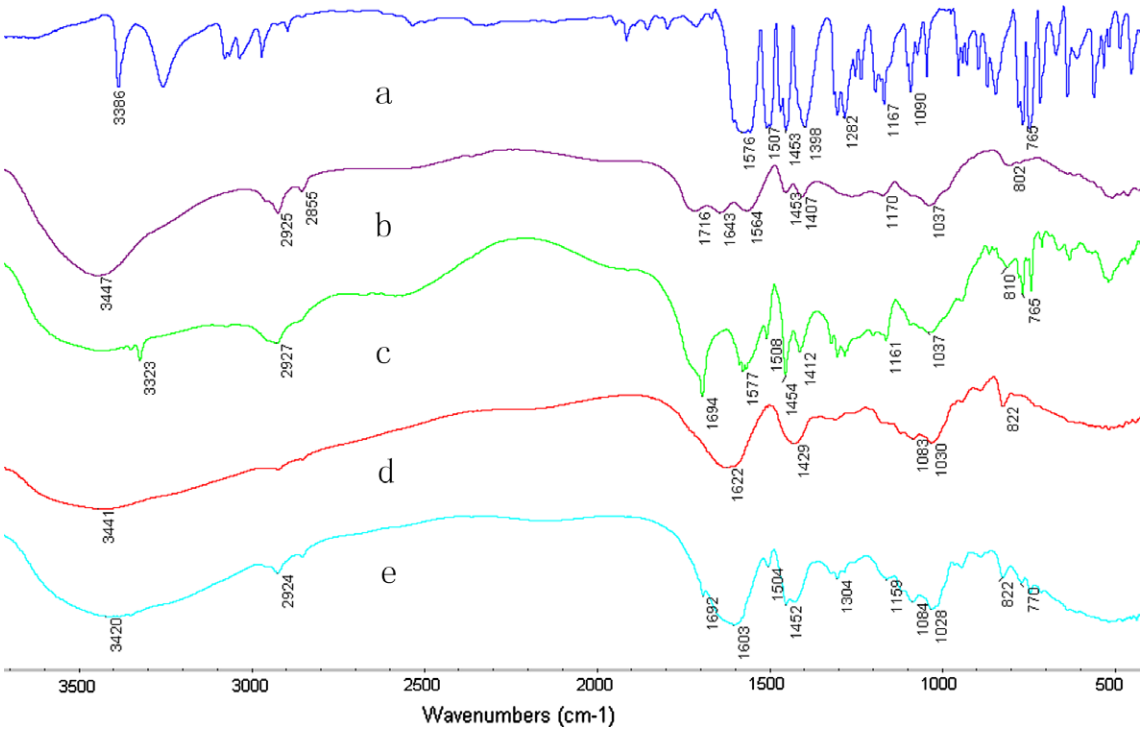

Fig. 1. FTIR spectra of (a) DS, (b) CTS-*g*-PAA/APT (10 wt% APT), (c) DS-loaded CTS-*g*-PAA/APT (10 wt% APT), (d) CTS-*g*-PAA/APT/SA (10 wt% APT) and (e) DS-loaded CTS-*g*-PAA/APT/SA (10 wt% APT). Weight ratio of CTS-*g*-PAA/APT to SA is 1:6; $CaCl_2$ concentration is 3% (w/v).

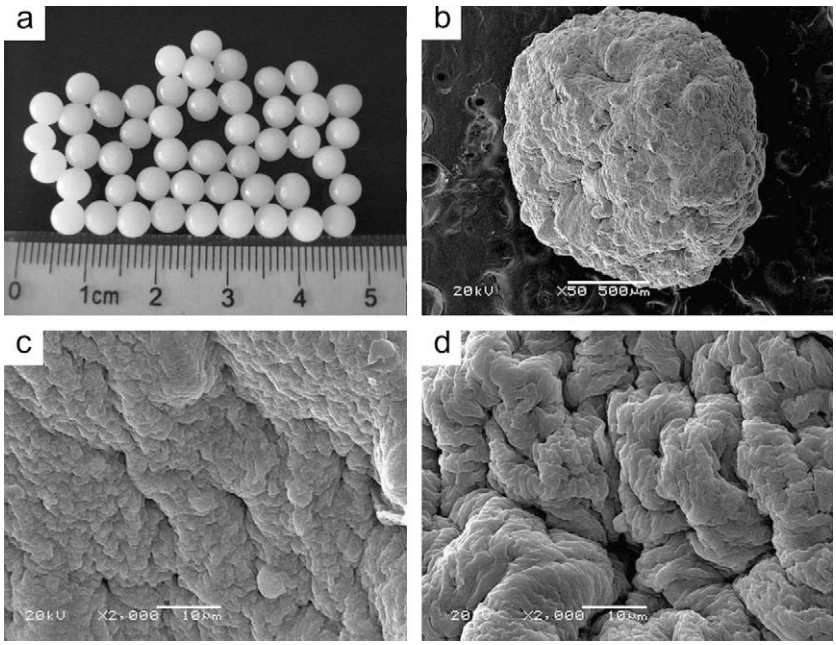

Fig. 2. Digital photo of (a) CTS-*g*-PAA/APT/SA composite hydrogel beads after preparation. SEM images of (b) CTS-*g*-PAA/APT/SA composite hydrogel bead in a dry state (×50), (c) CTS-*g*-PAA/SA composite hydrogel bead (×2000) and (d) CTS-*g*-PAA/APT/SA composite hydrogel bead (×2000). APT content is 10 wt%. Weight ratio of CTS-*g*-PAA/APT to SA is 1:6. $CaCl_2$ concentration is 3% (w/v).

3.3. Drug encapsulation efficiency of the composite hydrogel beads

During the determination of the drug encapsulation efficiency and drug loading, it was found that the drug loading of the composite hydrogel beads increased rapidly with the increase of loading time from 0 to 90 min and more than 80% of the equilibrium loading capacity for DS occurred within 60 min. After 90 min, the loading capacity became constant and the amount of drug loaded reached equilibrium. Therefore, 120 min was selected as the loading time for the loading of DS onto the composite hydrogel beads in this study. The encapsulation efficiency and the drug loading of the composite hydrogel beads with different APT content were shown in Fig. 3. As can be seen, the amount of drug loaded in the composite hydrogel beads decrease with increasing the content of APT. The decrease tendency may be attributed to the following facts. APT could react with AA and acts as crosslinking points in the network, which caused the increase of the crosslinking density of hydrogel bead with the increase of APT content. The greater the crosslinking density, the worse the elasticity of the polymer chains (Zhang et al., 2007), which could restrict the penetration of DS into CTS-*g*-PAA/APT composite hydrogel, and then leads to the decrease of the encapsulation efficiency and the loading amount for DS. Additionally, the excess APT acts as filler and prevents DS entering the polymeric network with further increasing APT content to 30 wt%, which is also responsible for the decrease of encapsulation efficiency and drug loading.

3.4. pH-sensitivity of the hydrogel beads

Fig. 4 shows variation of the swelling ratio for CTS-*g*-PAA/APT/SA composite hydrogel beads with pH of external buffer solution. As can be seen, the swelling ratio of the hydrogel beads is very

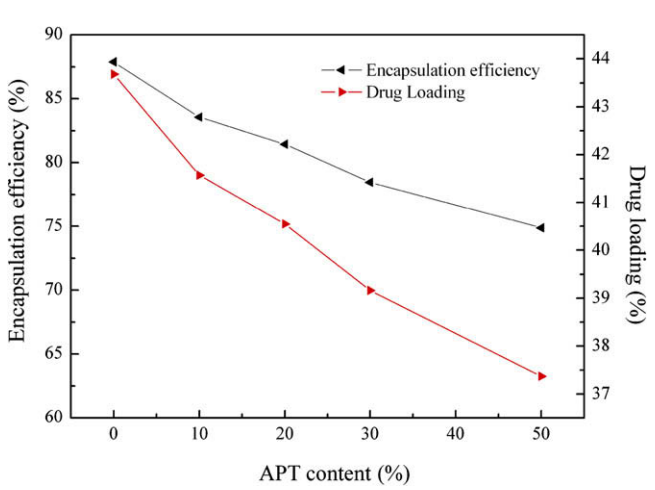

Fig. 3. Loading of DS into CTS-*g*-PAA/APT/SA composite hydrogel beads with different APT content (wt%). Weight ratio of CTS-*g*-PAA/APT to SA is 1:6. $CaCl_2$ concentration is 3% (w/v).

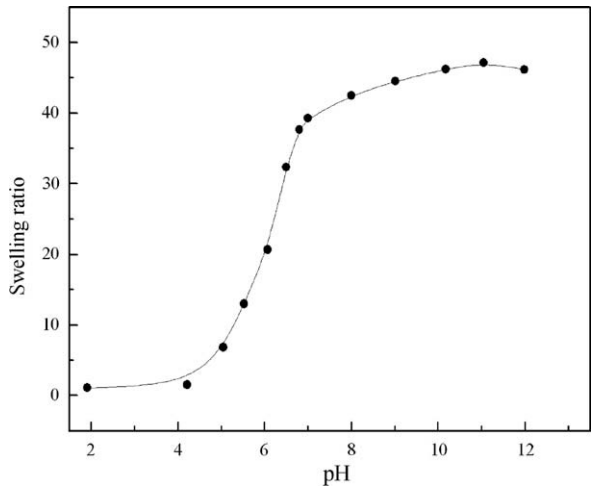

Fig. 4. Variation of swelling ratio for CTS-*g*-PAA/APT/SA composite hydrogel beads at different pH solution. APT content is 10 wt%. Weight ratio of CTS-*g*-PAA/APT to SA is 1:6. $CaCl_2$ concentration is 3% (w/v).

small when the pH is lower than 5.0. The swelling ratio increases sharply to 42.5 with increasing pH to 8.0, and then further increases slowly to 45.0 with further increasing pH to 12.0. These behaviors are interpreted as follows: $-COO^-$ groups can convert to –COOH groups, and the hydrogen bonding can be formed among –OH, –NHCO and –COOH groups of CTS-*g*-PAA/APT/SA in the acid solution, which is responsible for the small swelling ratio when pH < 5.0. As pH is increased to the basic regions, most of –COOH groups changes into $-COO^-$ groups and the hydrogen bonding among –COOH, –OH and –NHCO groups is dissociated, furthermore, the surface of APT is also negatively charged at above pH 5.5 (Chen, 1999). Thus, the electrostatic repulsion within the test hydrogel beads makes the hydrogel dramatically swell. Characteristic for the variation of swelling ratio with pH of external buffer solution indicates pH-responsive behavior of CTS-*g*-PAA/APT/SA composite hydrogel beads.

3.5. Drug release studies

3.5.1. Effect of pH on release of DS

pH is a key factor in the oral drug delivery which determines the release of drug in pH-sensitive hydrogels. It is known that pH is about 1.2–2.0 in stomach and is about 7.0 in small intestine, with the pH in the distal part as high as 8.0 (Shargel & Yu, 1999). The effect of pH on the release rate of DS from the composite hydrogel beads is shown in Fig. 5. As can be seen from Fig. 5, when pH of the medium is 2.1, the cumulative release ratio of DS from the test hydrogel beads is below 5% at the end of the experiment (24 h). At pH 6.8, the drug cumulative release ratio is 20% after 2 h, and 50% after 7 h, up to a maximum of 100% after 24 h, whereas almost all the loaded DS is released within 2 h in pH 7.4 medium. The variation of the release ratio of DS in these media of different pH is attributed to the following facts. This difference of their swelling behavior is responsible for the difference of the drug release ratio with changing pH of the medium. It is very difficult for the DS to migrate out of the composite hydrogel beads at pH 2.1 because of shrinkage of the composite hydrogel beads. However, the swelling of the composite hydrogel beads increases dramatically at pH 6.8 or 7.4. Consequently, there is enough space among the polymer chains of the composite hydrogel beads, which facilitates migration of DS out of the beads, and then the evident release of DS was observed. Similar phenomenon had also been observed by Shu, Zhu, and Song (2001). Moreover, compared to the release behavior in pH 6.8, the burst release of DS in pH 7.4 medium is because of higher concentration of phosphates besides the difference of swelling ratio. There are three anions ($H_2PO_4^-$, HPO_4^{2-}, and PO_4^{3-}) in pH 6.8 or 7.4 buffer solutions which are made by combining KH_2PO_4 and NaOH solutions properly. HPO_4^{2-} is the prevalent form when pH 6.8, while PO_4^{3-} is the prevalent form when pH 7.4. In pH 7.4 buffer solution, PO_4^{3-} reacts with Ca^{2+} to form a precipitation, namely $Ca_3(PO_4)_2$, which accelerates the hydrogel beads cracked and results in the very quick release of DS from the hydrogels. Therefore, the release of DS at pH 6.8 is slower than that at pH 7.4 under the same APT content. In additional, CTS-*g*-PAA/APT/SA composite hydrogel beads hardly crack after DS releasing for 24 h at pH 6.8, while the composite hydrogel beads rupture after releasing for 5 h at pH 7.4.

3.5.2. Effect of APT content on release of DS

In vitro drug release was performed in simulated intestinal fluid at pH 6.8. Fig. 6 shows the time-dependent cumulative release of the drug from the hydrogel beads with different APT content in pH 6.8 buffer solution. As can be seen from Fig. 6, the DS cumulative release ratio from CTS-*g*-PAA/SA hydrogel beads is 86% after 5 h, and the release of DS is already complete after 7 h. However, after 10 wt% APT is added to CTS-*g*-PAA matrix, the DS release is complete within 12 h. Moreover, the release time of DS from CTS-*g*-PAA/APT/SA hydrogel beads prolongs with the increase of APT content. This may be attributed to the role of APT playing in CTS-*g*-PAA/APT/SA composite hydrogel beads. As has been reported by Sorby and Wang, APT could be used as vehicles for the slow-release of promazine and DS (Sorby, 1965; Sorby & Liu, 1966; Wang, Wang, & Wang, 2008). Thus, the DS adsorbed on APT need to migrate out of the composite hydrogel beads through a longer path, and then the improved release behavior was observed as shown in Fig. 6.

In order to prove the relation of the swelling ratio and the cumulative release ratio, the drug release mechanism of the test beads with various APT contents was discussed and the results are shown in Table 1. In many release experimental situations, including the case of drug release from hydrogel polymeric systems, the mechanism of drug diffusion deviates from the Fickian equation and follows a non-Fickian behavior. In these cases the diffusion exponent n is determined using the Power law (Ritger & Peppas, 1987a, 1987b):

$$M_t/M_\infty = kt^n \quad (4)$$

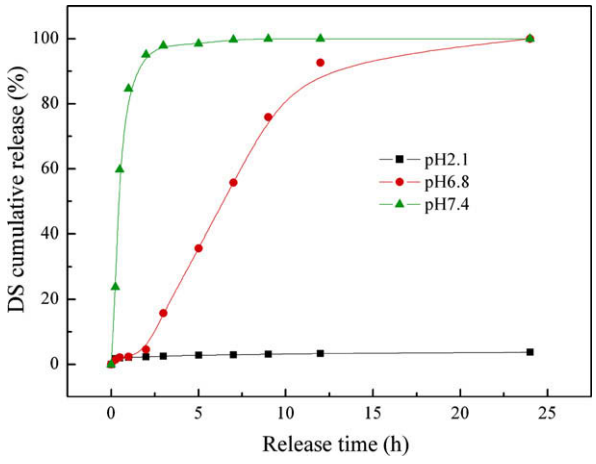

Fig. 5. The cumulative release curves of DS from CTS-*g*-PAA/APT/SA composite hydrogel beads at various pHs at 37 °C after 24 h. APT content is 10 wt%. Weight ratio of CTS-*g*-PAA/APT to SA is 1:6. $CaCl_2$ concentration is 3% (w/v).

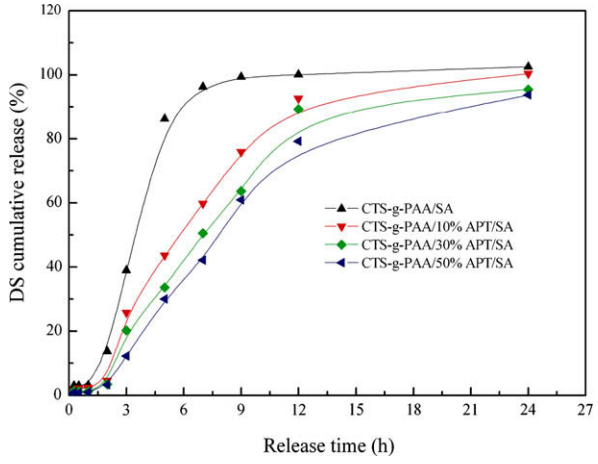

Fig. 6. *In vitro* cumulative release data of DS from CTS-*g*-PAA/APT/SA composite hydrogel beads with different APT content at 37 °C after 24 h. Weight ratio of CTS-*g*-PAA/APT to SA is 1:6. $CaCl_2$ concentration is 3% (w/v).

Table 1
Estimated parameters and drug release mechanism of DS-loaded CTS-*g*-PAA/APT/SA composite hydrogel beads at different APT content: Kinetic constants (k), diffusional exponents (n), correlation coefficient (r) and drug transport mechanism.

APT (wt%)	n	$k \times 102$	r^2	Drug release mechanism
0	1.52	3.47	0.9753	Swelling-controlled
10	1.59	2.53	0.9962	Swelling-controlled
20	1.78	1.46	0.9912	Swelling-controlled
50	2.06	1.03	0.9905	Swelling-controlled

Kinetic constants (k), diffusional exponents (n) and correlation coefficients (r^2) by linear regression of $\log(M_t/M_\infty)$ vs $\log t$; k is the constant related to the structural and geometric characteristic of the device; n is the diffusional exponents, indicative of the drug release mechanism.

where M_t/M_∞ is the fractional solute release, t is the release time, k is a constant incorporating structural and geometric characteristics of the device and n is the diffusion exponent characteristic of the release mechanism. For spheres, the values below 0.43 indicate that drug release from polymer was due to Fickian diffusion. The values of n between 0.43 and 0.85 are an indication of both diffusion controlled drug release and swelling-controlled drug release. The values above 0.85 indicate swelling-controlled drug release which relate to the polymer relaxation during hydrogel swelling (Dai, Li, Zhang, Wang, & Wei, 2008; Siepmann & Peppas, 2001). The changes of calculated values of n of the hydrogel beads with different APT content are shown in Table 1. It can be observed that the values of the diffusion exponent n are above 0.85 and increase with increasing APT content, which indicates that the drug release of the composite hydrogel beads is swelling-controlled. The result proves that the cumulative release ratio of DS from CTS-*g*-PAA/APT/SA composite hydrogel beads is relating to swelling ratio of the composite hydrogel beads.

3.6. Release of DS from the composite hydrogel beads

As have been observed above, the combination of CTS-*g*-PAA/APT and SA as well as the introduction of APT have great influences on the release of DS. The structure of CTS-*g*-PAA/APT/SA composite hydrogel beads and the role that APT plays in the composite hydrogel beads may be the main reasons for the observed results. The structure of CTS-*g*-PAA/APT/SA composite hydrogel bead is shown schematically in Fig. 7. As can be seen from the left graph, a large portion of DS were entrapped in CTS-*g*-PAA/APT micro-particles which were attached to the SA polymer chains by Ca^{2+} during the sol–gel transition of SA. The entrapment of DS into CTS-*g*-PAA/APT micro-particles is one of the main reasons for the improved release behaviors of DS from CTS-*g*-PAA/APT/SA composite hydrogel beads. The DS-loaded CTS-*g*-PAA/APT micro-particle is also a complicated system (right graph) which is a three-dimensional network composed of DS, CTS-*g*-PAA and APT micro-particles. As has been reported previously, APT could also be used as carriers for the slow-release of drugs including DS (Sorby, 1965; Sorby & Liu, 1966; Wang et al., 2008). Thus, a part of DS could also be adsorbed onto APT, which is also an important factor influencing the release of DS from the matrices. A portion of DS need to migrate from APT to CTS-*g*-PAA/APT network firstly, and then from CTS-*g*-PAA/APT network to CTS-*g*-PAA/APT/SA network which is followed by the migration of DS from CTS-*g*-PAA/APT/SA network to the buffer solution and is detected. There is a longer path for DS to migrate from CTS-*g*-PAA/APT/SA composite hydrogel beads to the buffer solution comparing with the traditional SA hydrogel beads and CTS-*g*-PAA/SA, and then the improved the release behavior of DS is observed by introducing APT and CTS-*g*-PAA.

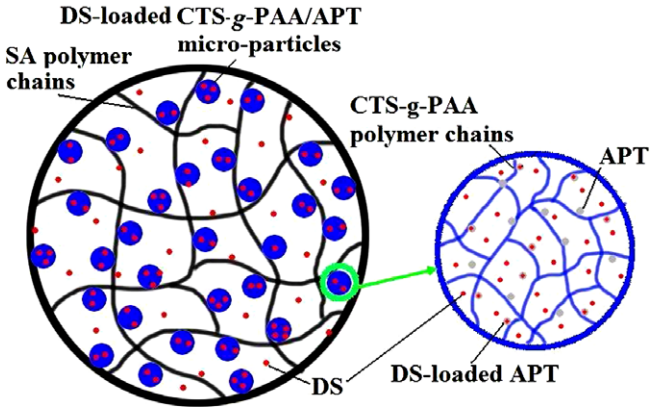

Fig. 7. Schematic structure of CTS-g-PAA/APT/SA composite hydrogel bead.

4. Conclusion

In this study, a novel pH-sensitive CTS-*g*-PAA/APT/SA composite hydrogel bead is successfully prepared. At pH 6.8, the drug cumulative release ratio of DS from the hydrogel beads is slower than that at pH 7.4, and decreased with the increase of APT content. At pH 6.8, the drug release mechanism of the hydrogel beads was swelling-controlled mode. The introduction of APT into CTS-*g*-PAA polymeric network and then dispersing CTS-*g*-PAA/APT composite hydrogel in the aqueous solution of SA by crosslinked with Ca^{2+} have formed a longer path for DS to migrate from the composite hydrogel bead into the media, and then its release time prolonged. These results showed that the introduction of clay in polymeric network may offer simple and unique approaches for the preparation of new controlled drug delivery systems.

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