



# Novel NaCS-CS-PPS microcapsules as a potential enzyme-triggered release carrier for highly-loading 5-ASA

Qing-Xi Wu, Shan-Jing Yao\*

*Key Laboratory of Biomass Chemical Engineering of Ministry of Education, Department of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310027, China*



## ARTICLE INFO

### Article history:

Received 28 November 2012

Received in revised form 13 March 2013

Accepted 15 March 2013

Available online xxx

### Keywords:

Microcapsules loaded drug

Enzyme-triggered release carrier

Sodium cellulose sulfate

Chitosan

5-Aminosalicylic acid

## ABSTRACT

In order to develop novel spherical micro-drug-carriers, an orifice-polymerization method was used to prepare spherical microcapsules which were composed of chemically crosslinked chitosan (CS) with sodium cellulose sulfate (NaCS) and sodium polyphosphate (PPS). 5-Aminosalicylic acid (5-ASA) was chosen as a model drug. The microcapsules prepared had an average diameter of 1.90 mm with loading efficiency of 60.77% and encapsulation efficiency of 90.03%. SEM results showed that the microcapsules had a double-walled capsule structure with an outer wall thickness of approximately 4.40 μm and inner wall (shell) thickness of approximately 187.14 μm. SEM transection images of the microcapsules showed that 5-ASA entrapped in the microcapsule was in a crystal form. The results of *in vitro* swelling/erosion and release analysis showed that the drug was preferentially and completely released in simulated colonic fluid (SCF, pH 6.4) under the mechanism of Anomalous transport. All these results indicate that the microcapsules could be a good candidate as an enzyme-triggered controlled release drug carrier.

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## 1. Introduction

Inflammatory bowel disease (IBD), usually referred to as Crohn's disease, and ulcerative colitis are chronic and immunologically mediated disorders. 5-Aminosalicylic acid (5-ASA) as an anti-inflammatory drug has been extensively used for the treatment of IBD [1]. It is effective for the treatment of mild inflammation and can also be used as a long-term maintenance therapy [2]. However, as an amphoteric small molecule with pH-dependent aqueous solubility, it can easily permeate into the upper gastrointestinal tract and the amount of drug reaching to the colon is fairly low. Therefore, a colon-specific drug delivery system which can release 5-ASA to the site of action (small bowel and/or colon) but with less side-effect to the gastrointestinal tract would be desirable [3].

In recent years, many oral colon-specific drug delivery systems (OCDDS) [4] have been designed to deliver 5-ASA to colon, such as prodrugs [5], pH-dependent OCDDS [6], time- and pH-dependent OCDDS [7], enzyme-triggered OCDDS [8], pressure-dependent OCDDS [9] and biological-adhesion OCDDS [10]. Enzyme-triggered OCDDS prepared with biodegradable polysaccharides, such as chitosan (CS), seem to be a more effective and site specific system for colonic drug delivery [11].

Chitosan (CS) is a polycationic polymer which is derived from naturally occurring chitin by alkaline deacetylation. It is non-toxic, biocompatible, mucoadhesive, biodegradable [12,13] and can be digested by the colonic bacteria [14]. Moreover, chitosan (CS) has the ability to conjugate with lots of anionic substrates *via* its  $-\text{NH}_3^+$  groups. All these properties make chitosan (CS) a good candidate for the preparation of colon-specific drug delivery systems. However, chitosan (CS) can be easily dissolved in acidic solutions. Therefore, drug delivery systems based on chitosan (CS) are difficult to pass through the stomach and small intestine without the dissolution of chitosan (CS). Hence, this material needs to be modified *via* chemical or physical methods. For instance, C. Mura et al. introduced the succinic group onto the N-terminals of the glucosamine units of chitosan to form N-succinyl-chitosan which was used for the development of 5-aminosalicylic acid loaded N-succinyl-chitosan microparticles or matrices for colon specific delivery [15,16]. Chitosan (CS) has also been developed to form mucoadhesive particulate drug delivery systems [17]. Moreover, it has been cross-linked with alginate or xanthan gum to form a polyelectrolyte complex (PEC), which has been used to develop a new multiparticulate system with microspheres/microparticles/chitosomes for colonic drug delivery [18–20].

Sodium cellulose sulfate (NaCS) as a novel cellulose derivative is a polyanionic polymer which is derived from cellulose sulfating processes [21–23]. It has favorable biological properties as a drug carrier material, such as hydrosolubility, nontoxicity,

\* Corresponding author. Tel.: +86 571 87951982; fax: +86 571 87951982.

E-mail address: [yaosj@zju.edu.cn](mailto:yaosj@zju.edu.cn) (S.-J. Yao).

biodegradability and good film-forming ability. More importantly, it is biocompatible [24–27]. NaCS can be used to form a polyelectrolyte complex (PEC) with chitosan (CS), which is insoluble in acidic conditions and can be biodegraded by enzymes that are originated from the colon microflora in the *in vitro* biodegradation tests [28,29].

In this work, a polyelectrolyte complex (PEC) produced by NaCS, chitosan (CS), and sodium polyphosphate (PPS, a water soluble food additive that can crosslink with chitosan (CS) [30,31]) was introduced to the reaction system for improving the microcapsule's structure. An orifice-polymerization method was used to prepare NaCS-CS-PPS microcapsules loaded with 5-ASA. By evaluating the morphology of the microcapsules, the complex structure of NaCS-CS-PPS and *in vitro* drug release behaviors, a potential microcapsule system with enzyme-triggered and controllable release properties was developed.

## 2. Materials and methods

### 2.1. Materials

Chitosan (CS) with 85% deacetylation and  $M_w$  of 60.0 kDa was supplied by Jinan Haidebei Co., Ltd. (China). The viscosity of 1% (w/v) solution in acetic acid (1%, v/v) is 50 mPa s. NaCS with degree of substitution (DS) 0.57 was prepared via heterogeneous reaction as described previously [23]. Sodium polyphosphate (PPS) and glucanoglucanohydrolase were purchased from Sinopharm Chemical Reagent Co., Ltd. (China). 5-Aminosalicylic acid (5-ASA) was purchased from Sangon Biotech (Shanghai) Co., Ltd. (China). All other chemicals and reagents were of analytical grade and used without further purification.

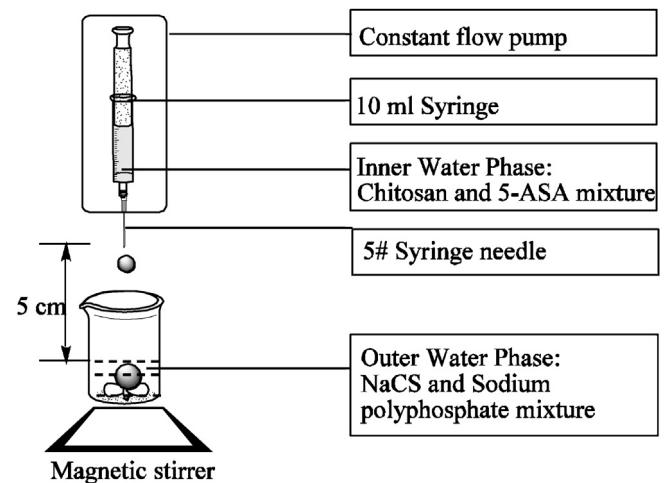
### 2.2. Microcapsules preparation

Chitosan solutions (4%, w/v) were first prepared with 1% (v/v) acetic acid/water solution. 5-ASA (2.0 g) was added in the chitosan solution (20 ml) and mixed with a High-Speed Dispersor (XHF-D, Scientz Co., Ningbo, China) (3000 rpm, 2 min, five times). The mixture was then adjusted to pH = 4.0 at room temperature and ultrasonicated for 5 min, which was later used as the inner water phase material. Meanwhile, 10 ml of 2% (w/v) aqueous NaCS and 10 ml of 1% (w/v) aqueous sodium polyphosphate solutions were mixed and stirred at 1000 rpm for 5 min. The mixture was adjusted to pH = 6.0 at room temperature and used as the outer water phase material. Subsequently, 2 ml of inner water phase was added into 20 ml of outer water phase drop by drop controlled with a constant flow pump (LSP01-1BH, Baoding Longer Precision Pump Co., Baoding, China, 650  $\mu$ l/min, as shown in Fig. 1) [32]. A mass ratio of 2.5:2.5 (CS:NaCS:PPS) was applied in the reaction system. The NaCS-CS-PPS microcapsules were separated from the outer water phase after 15 min of reaction under room temperature, rinsed three times with distilled water and freeze-dried (Freeze Drier, Thermo Modulyod-230, USA) for 2 h (as a batch).

### 2.3. Microcapsules characterization

#### 2.3.1. Size analysis

The size and size distribution of the freeze-dried NaCS-CS-PPS microcapsules was measured by an optical microscope (Eclipse E200, Nikon Co., Japan) and analyzed by the image analysis software Image-Pro Plus 5.0 (Media Cybernetics Inc., USA). Approximately 167 microcapsules (a batch) were studied. The size distribution was



**Fig. 1.** Experimental schematics of the NaCS-CS-PPS microcapsule preparation system with an orifice-polymerization method.

calculated by a coefficient of variation (CV) defined in Eqs. (1) and (2):

$$CV = \left( \sum_{i=1}^n \frac{(d_i - \bar{d}_n)^2}{n-1} \right)^{1/2} \frac{1}{\bar{d}_n} \times 100\% \quad (1)$$

$$\bar{d}_n = \frac{\sum_{i=1}^n d_i}{n} \quad (2)$$

where  $d_i$  is the diameter of the  $i$ th microcapsule,  $n$  is the total number of the microcapsules counted, and  $\bar{d}_n$  is the average diameter.

#### 2.3.2. Surface and interior morphology of microcapsules

The morphology of dried NaCS-CS-PPS microcapsules and drug (5-ASA) was observed by a scanning electron microscope (SIRION-100, Philips, Netherlands). The dried microcapsules and pure 5-ASA samples were sputter-coated with gold before observation (E-1045 Ion sputter, Hitachi, Japan). The freeze-dried samples were cut with a blade in order to investigate the inner structure of the NaCS-CS-PPS microcapsules.

#### 2.3.3. X-ray diffraction analysis

X-ray diffraction analysis was conducted with Cu-K $\alpha$  radiation (voltage: 40 kV, current 40 mA, X' pert PRO, PANalytical, Holland) to investigate the structure of 5-ASA entrapped in the microcapsule. The samples were ground into powder before the measurement and XRD patterns were recorded from 5° to 80° with a scanning speed of 2°/min.

#### 2.3.4. Drug loading efficiency and encapsulation efficiency

The concentration of 5-ASA in the NaCS-CS-PPS microcapsule was determined with a UV spectrometer (Ultrspec 3320 pro, GE Healthcare, USA). A standard curve was acquired with pure 5-ASA aqueous solution under 298 nm. 10 mg of NaCS-CS-PPS microcapsules were ground sufficiently with 1 ml of distilled water, and diluted with distilled water to 250 ml. Subsequently, the diluted solution was ultrasonicated for 5 min and filtered with 0.45  $\mu$ m hydrophilic membranes. The filtrate was analyzed at 298 nm and the results were converted to 5-ASA concentration following the regression equation. The drug loading efficiency (LE%) and encapsulation efficiency (EE%) were obtained with the following equations:

$$LE\% = \frac{M_a}{M_q} \times 100\% \quad (3)$$

$$\text{EE\%} = \frac{M_a}{M_t} \times 100\% \quad (4)$$

where  $M_a$  is the measured value of 5-ASA loaded in the NaCS-CS-PPS microcapsules,  $M_t$  is the theoretical amount of 5-ASA loaded in the microcapsules, and  $M_q$  is the total mass of the microcapsules. Each measurement was performed in triplicate.

### 2.3.5. Swelling and erosion properties of microcapsules

The swelling and erosion properties of the NaCS-CS-PPS microcapsules were characterized in simulated colonic fluid (SCF, pH 6.4) and phosphate buffer (PBS, pH 6.4). SCF (pH 6.4) was prepared with 1200 U/l glucanoglucanohydrolase and phosphate buffer (PBS, pH 6.4). 10 mg of NaCS-CS-PPS microcapsules were incubated in SCF (pH 6.4) (20 ml) and PBS (pH 6.4) (20 ml), respectively, and then the solutions were maintained at  $37 \pm 0.5^\circ\text{C}$ , 100 rpm up to 12 h. The microcapsules were removed from the medium at predetermined time points. Meanwhile, 1 ml medium was sampled and replaced by an equal volume of fresh medium. For the swelling study, filter papers were used to absorb excessive water on the surface of the microcapsules which were then weighed when their weight reached to a constant. These microcapsules were then put back into the previous solutions. Moreover, for the erosion study, the samples obtained from different time points were freeze-dried for 2 h and weighed immediately, while control experiments were continued without other treatments. The swelling ratio (SR%) and erosion ratio (ER%) were calculated using the following equations:

$$\text{SR\%} = \frac{W_{\text{wt}} - W_0}{W_0} \times 100\% \quad (5)$$

$$\text{ER\%} = \frac{W_0 - W_{\text{dt}}}{W_0} \times 100\% \quad (6)$$

where  $W_0$  is the initial dry weight of the microcapsules,  $W_{\text{wt}}$  is the wet weight of the microcapsules at a certain time and  $W_{\text{dt}}$  is the dry weight of the microcapsules. All measurements were repeated for three times.

### 2.3.6. In vitro drug release

In vitro drug release studies of the NaCS-CS-PPS microcapsules were performed in different simulated solutions. 10 mg of NaCS-CS-PPS microcapsules were immersed in SCF (pH 6.4) (20 ml) and PBS (pH 6.4) (20 ml) at  $37 \pm 0.5^\circ\text{C}$ , 100 rpm up to 12 h, respectively. At predetermined time points, 1 ml medium was sampled and replaced with an equal volume of fresh medium.

The concentrations of 5-ASA were determined with a UV spectrometer (Ultrospec 3320 pro, GE Healthcare, USA). A standard curve was acquired with 5-ASA/PBS (pH 6.4) solutions under 329.5 nm. The samples were filtered with 0.45  $\mu\text{m}$  hydrophilic membranes and analyzed under the same condition and the results were converted to 5-ASA concentration following the regression equation. The drug release percentage was calculated using the following equation:

$$\text{DR\%} = \frac{R_t}{L_0} \times 100\% \quad (7)$$

where  $L_0$  and  $R_t$  represent the initial amount of drug loaded at time  $t=0$  and the cumulative amount of drug released at time  $t$ . Each measurement was performed in triplicate. In order to describe the drug release mechanism, the mean drug release profiles (cumulative drug release up to 60%, in SCF pH 6.4) were fitted with two mathematical models:

Ritger-Peppas model:

$$\frac{M_t}{M_\infty} = kt^n \quad (8)$$

First-order model:

$$\frac{M_t}{M_\infty} = 1 - e^{-kt} \quad (9)$$

where  $M_t$  and  $M_\infty$  are the amount of drug released at time  $t$  and infinite, respectively;  $k$  is a constant incorporating structural and geometric characteristics of the device, and  $n$  is the release exponent, indicative of the mechanism of drug release.

The microcapsule samples were freeze-dried (Freeze Drier, Thermo Modulyod-230) for 2 h and then analyzed with a scanning electron microscope (SIRION-100, Philips, Netherlands). The drug release mechanism of the microcapsules was described according to the fine structural changes.

## 3. Results and discussion

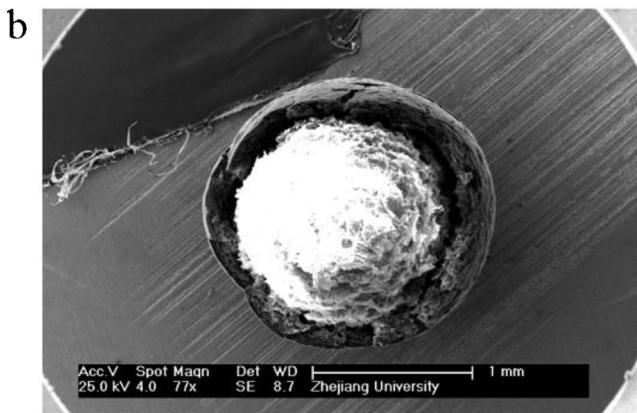
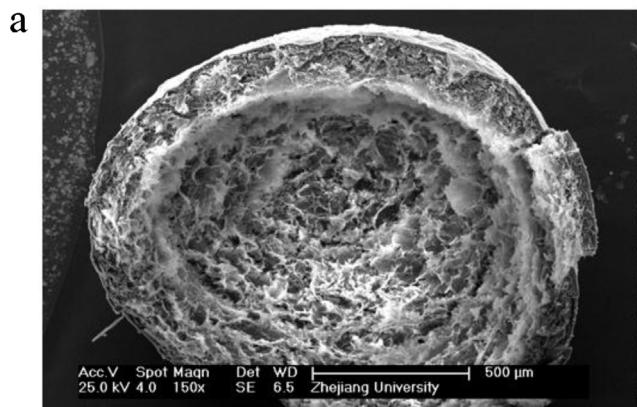
### 3.1. Preparation and morphology characteristics

Chitosan (CS) microcapsules designed for colonic delivery are usually prepared through extrusion-spheronization method and then coated to prevent the release of drug in acidic media [33]. Such preparation processes are complicated and may cause damage to the drug during the coating-preheating procedure. In this work, a simple preparation process is used based on the principle of forming a polyelectrolyte complex (PEC) via ionization reaction [34]. Here NaCS is used as a polyanion with  $-\text{SO}_3^-$  groups while chitosan (CS) is a polycation with  $-\text{NH}_3^+$  groups. Meanwhile, the sodium polyphosphate (PPS) can penetrate through the polyelectrolyte complex (PEC) into the chitosan (CS)-core, and then consolidate/crosslink with chitosan. Thus the NaCS-CS-PPS microcapsules with the structure of a double-walled capsule can be produced.

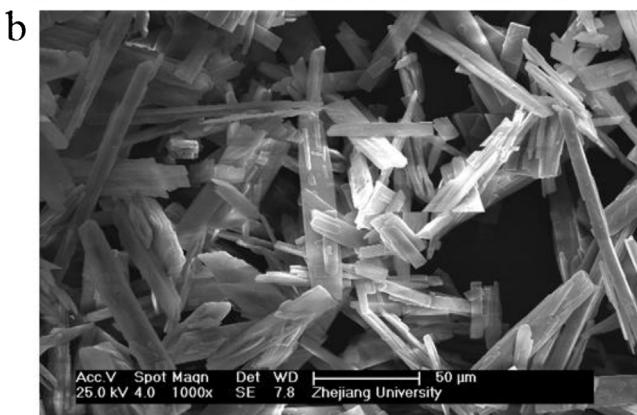
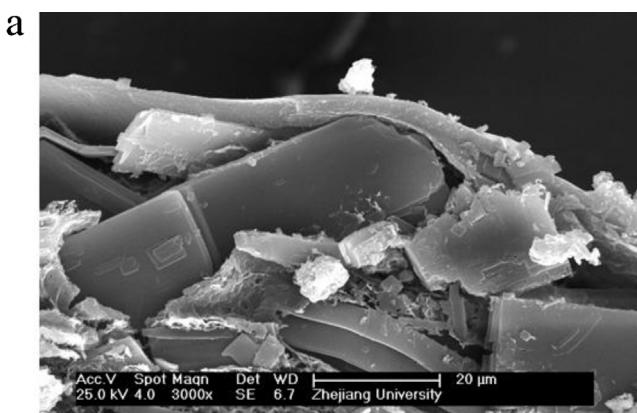
The average diameter of NaCS-CS-PPS microcapsules was 1.90 mm, and the CV value was 4.74%. The morphology of microcapsules is shown in Figs. 2 and 3. The NaCS-CS-PPS microcapsules were spherical in shape and had smooth surface but rough inner structure (Fig. 2). The transversal SEM image shows that the NaCS-CS-PPS microcapsules had a typical structure of double-walled capsules (Fig. 2), in which a coated membrane layer (outer wall) was observed at the outermost of the inner wall (shell) (Fig. 3a). This imaging result confirms the double-walled capsule structure of NaCS-CS-PPS microcapsules, and similar results were reported by Liu et al. [31]. The thickness of the inner wall (shell) was approximately 187.14  $\mu\text{m}$  (Fig. 2a) and the thickness of the outer coated membrane layer (outer wall) was approximately 4.40  $\mu\text{m}$  (Fig. 3a). The transversal SEM image (Fig. 3a) also clearly shows that 5-ASA was embedded in the double-walled capsule structure in a crystal form, which was consistent with the crystal structure of pure 5-ASA (Fig. 3b). This result indicates that 5-ASA loaded in the NaCS-CS-PPS microcapsules was in its crystal form. Therefore, small molecule drugs with similar crystal structure may be encapsulated in the double-walled capsule structure.

### 3.2. X-ray analysis of the loaded-drug in microcapsules

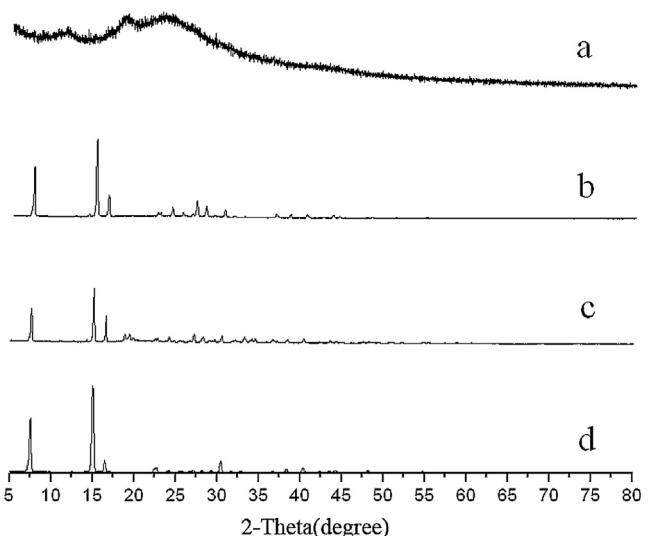
Fig. 4a shows the XRD pattern of microcapsules without drug. The results show that the signal intensity was not distinctive which is because these signals were formed by the polyelectrolyte complex (PEC) that existed mainly in amorphous form. Fig. 4b–d clearly shows that there were two major peaks at  $7.5^\circ$  and  $15^\circ$  from pure 5-ASA, which was similar with that of the loaded microcapsules and the physical mixture. These results confirm that 5-ASA loaded in the NaCS-CS-PPS microcapsules was presented in crystal form. The difference of intensity between pure 5-ASA and the drug-loaded microcapsules was probably due to the interference of the polyelectrolyte complex (PEC). Similarly, due to the effect of the



**Fig. 2.** SEM images of (a) transection image of the double-wall and (b) transection image of the double-walled capsule.



**Fig. 3.** SEM images of (a) transection image of the outer coated membrane layer (outer wall) and (b) pure 5-ASA.



**Fig. 4.** XRD patterns of (a) blank microcapsules (b) drug-loaded microcapsules, (c) physical mixture and (d) pure 5-ASA.

non-uniformity of the physical mixing and other ingredients, the intensity of the physical mixture was not the same as the pure 5-ASA but similar to that of the loaded microcapsules. Similar results were reported by Mura et al. [15].

### 3.3. Drug loading efficiency and encapsulation efficiency

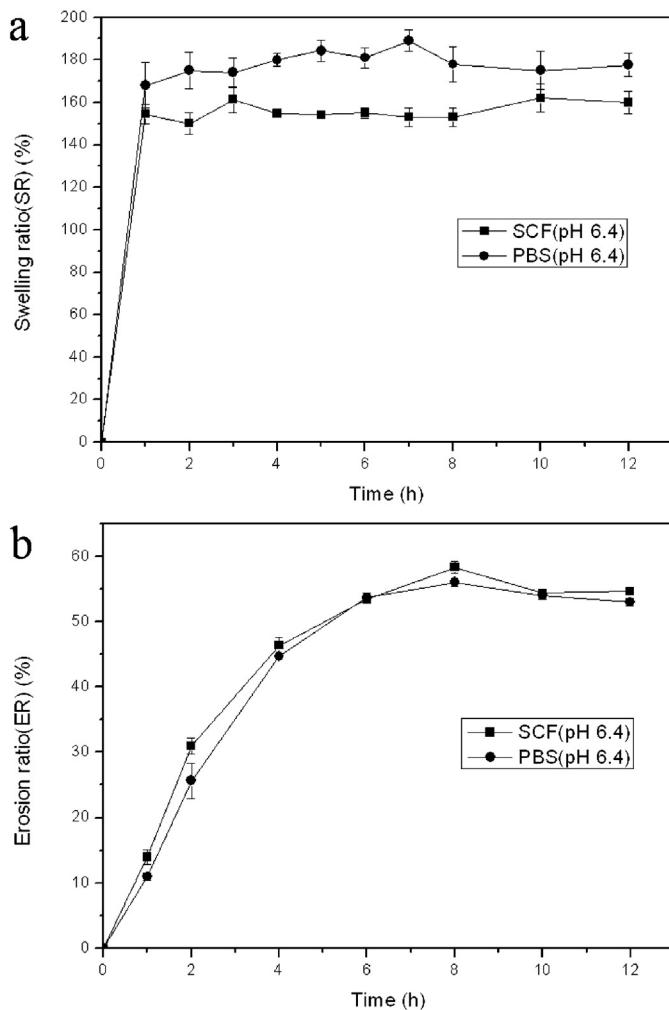
The drug loading efficiency (LE%) represents the percentage of drug embedded within the crosslinked double-walled capsule structure. The drug loading efficiency (LE%) directly decides the dosage administration in clinical. The encapsulation efficiency (EE%) represents the percentage of drug actually loaded in the NaCS-CS-PPS microcapsules, which decides the quality and feasibility of the preparation technology.

Since 5-ASA is an amphoteric small molecule, it could easily permeate into the outer water phase. According to the  $pK_a$  values of the carboxyl (2.30) and amino groups (5.69), the solubility of 5-ASA increases at pH < 2 and pH > 5.5 while reduces between pH 2 and pH 5.5 [35]. Therefore the pH values of the inner water phase and the outer water phase were set as 4.0 and 6.0, respectively. 5-ASA might entrapped in the NaCS-CS-PPS microcapsule in crystal form which may reduce the drug dissolved into the outer water phase. Moreover, chitosan (CS) has a  $pK_a$  value of about 6.2–7.0 [36]. It will be protonated at low pH during gel formation in an aqueous solution (pH 4.0, pH 6.0), which provides more  $-NH_3^+$  groups to form the polyelectrolyte complex (PEC) with NaCS and sodium polyphosphate (PPS). Both processes would be helpful to improve the LE% and EE%.

The regression equation of 5-ASA concentration in the aqueous solution was calculated as:

$$y = 20.506x \quad (R^2 = 0.9989, n = 7) \quad (10)$$

where  $y$  is the absorbance,  $x$  is the concentration of 5-ASA. The concentrations of 5-ASA in NaCS-CS-PPS microcapsules can be measured and the LE% and EE% of drug in NaCS-CS-PPS microcapsules can be calculated by Eqs. (3) and (4), which are  $LE\% = 60.77\%$  and  $EE\% = 90.03\%$ . These values are higher than similar soluble drug encapsulation systems reported, which had the maximal drug loading and encapsulation efficiency of 50.0% and 17.9%, respectively [37].



**Fig. 5.** In vitro studies of (a) swelling ratios and (b) erosion ratios in SCF (pH 6.4) and PBS (pH 6.4). Error bars represent the standard deviation,  $n=3$ .

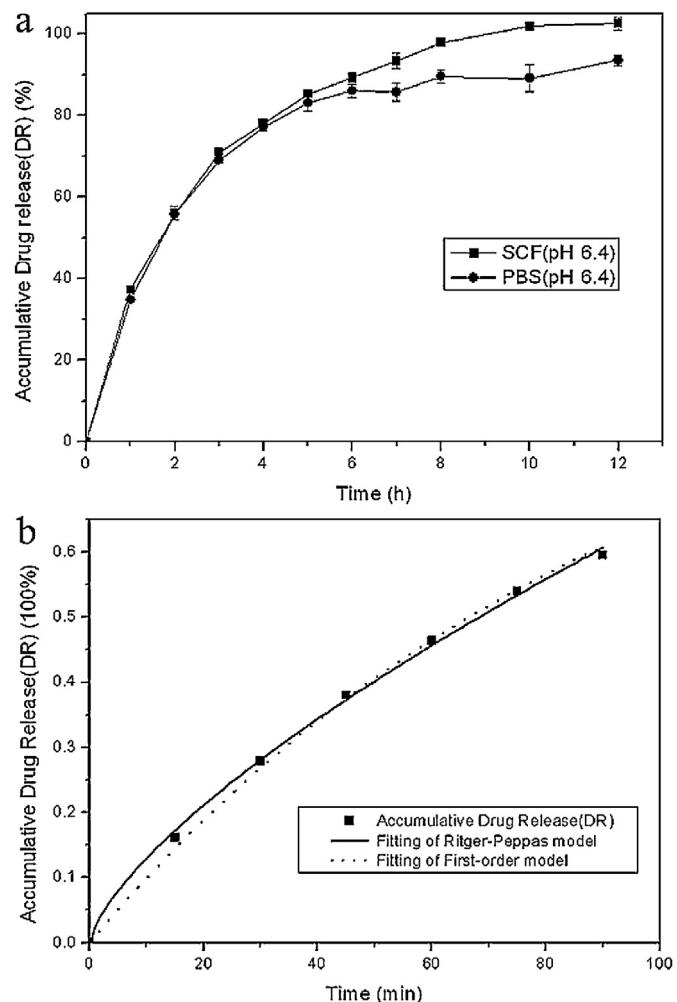
#### 3.4. Swelling ratio and erosion ratio of microcapsules

The swelling ratio (SR%) and erosion ratio (ER%) of NaCS-CS-PPS microcapsules were calculated according to Eqs. (5) and (6) and the results were compared between studies in SCF (pH 6.4) and PBS (pH 6.4). Fig. 5a shows that the swelling ratio was lower in SCF (pH 6.4) than that in PBS (pH 6.4) from 1 h to 12 h. It is probably due to the degradation of the NaCS/chitosan (CS) complex under glucanoglucanohydrolase in SCF (pH 6.4). With the degradation of the polyelectrolyte complex (PEC), the structure became less entangled which reduced the water holding capacity. Therefore, the swelling ratio was lower than that in PBS (pH 6.4) without enzymatic degradation. Fig. 5b shows that the erosion ratio was slightly higher in SCF (pH 6.4) than that in PBS (pH 6.4). It verifies that the decrease of the swelling ratio was partially because of the increase of the erosion ratio in SCF (pH 6.4) with enzymatic degradation.

#### 3.5. Drug release behaviors of microcapsules

The amount of 5-ASA released from the NaCS-CS-PPS microcapsules was determined with or without glucanoglucanohydrolase (SCF, pH 6.4 or PBS, pH 6.4). The regression equation of standard curve of 5-ASA in PBS (pH 6.4) solution is:

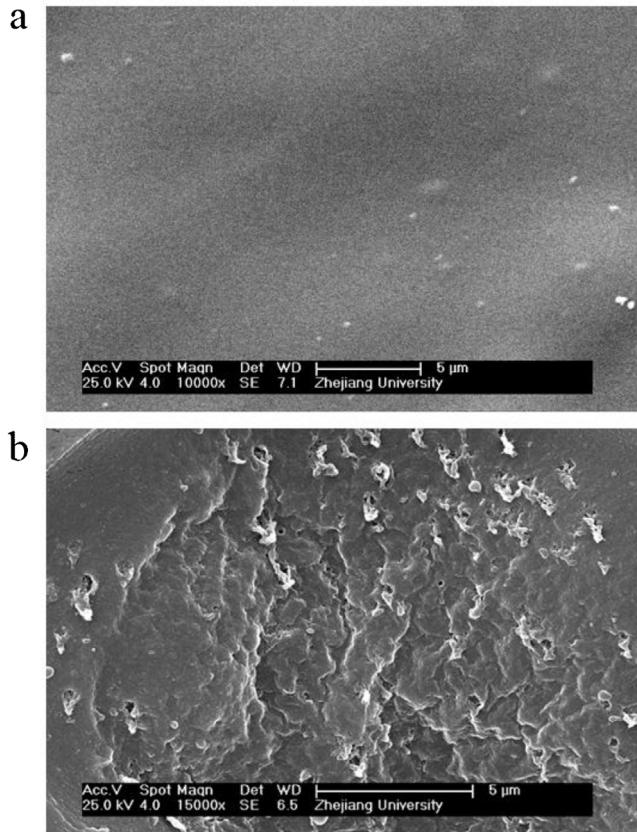
$$y = 18.265x (R^2 = 0.9996, n = 7) \quad (11)$$



**Fig. 6.** (a) In vitro release studies in SCF (pH 6.4) and PBS (pH 6.4). Error bars represent the standard deviation,  $n=3$ ; and (b) nonlinear curve fitting of accumulative drug release in SCF (pH 6.4).

where  $y$  is the absorbance,  $x$  is the concentration of 5-ASA. Fig. 6a shows that the percentage of drug release was slightly higher in SCF (pH 6.4) than that in PBS (pH 6.4). This is probably due to the enzymatic degradation of SCF (pH 6.4).

In order to understand the mechanism of drug release, the results were analyzed according to Ritger-Peppas and First-order models (Eqs. (8) and (9)). Ritger-Peppas model usually used to describe the Fickian and non-Fickian release behavior of swelling-controlled release systems, in which the diffusion exponent  $n$  is the important indicator of the mechanism of the drug transport through the carrier. According to Ritger-Peppas model, the criteria of release kinetics for spherical samples of swellable controlled release systems is  $n$  (release exponent value)=0.43,  $0.43 < n < 0.85$  and  $0.85$ , which indicates the release mechanism of Fickian diffusion, Anomalous (non-Fickian) transport and Case-II transport, respectively [38]. The results of nonlinear curve fitting with Ritger-Peppas model showed that the correlation coefficient value  $R^2$  was 0.9983 (Eq. (12) and Fig. 6b), which indicates that this model can be well applied for the system studied. The  $n$  value (0.702) was between 0.43 and 0.85, therefore, the drug release was under Anomalous (non-Fickian) transport, which could be regarded as the superposition of both Fickian diffusion (diffusion controlled drug release) and Case-II transport (swelling and erosion controlled drug release) [15,39].



**Fig. 7.** Morphology of the NaCS-CS-PPS microcapsule films in SCF (pH 6.4). (a) Initial state in the *in vitro* experiment at 0 h and (b) after 12 h in the *in vitro* experiment.

In the First-order model, the drug release from the carrier is assumed to decline exponentially and the rate of drug release is proportional to the residual drug. The results of nonlinear curve fitting with First-order model showed that the correlation coefficient value  $R^2$  was 0.9977 (Eq. (13) and Fig. 6b), which indicating that the drug release rate from the microcapsules declined exponentially [40]. Therefore, both of the two models could be used for estimation of the drug release.

Regression equation of Ritger-Peppas model:

$$\frac{M_t}{M_\infty} = 0.026t^{0.702} \quad (12)$$

Regression equation of First-order model:

$$\frac{M_t}{M_\infty} = 1 - e^{-0.01t} \quad (13)$$

In the experiment of *in vitro* drug release (SCF, pH 6.4), the microcapsule samples at 0 h and 12 h were thoroughly freeze-dried and observed with SEM to investigate the change of the microscopic structure of the microcapsule film. Fig. 7a shows the SEM micrograph of the NaCS-CS-PPS microcapsule film at 0 h. It can be seen that the microcapsule film had a relatively smooth morphology. Fig. 7b shows the SEM micrograph of the NaCS-CS-PPS microcapsule film which was taken out of the SCF (pH 6.4) at 12 h. The results show that the surfaces of the film became rough, and the umbos increased. Moreover, the pores can be clearly observed on the film after 12 h which was probably due to the enzymatic degradation. These results are similar to the NaCS-chitosan film degradation results reported by Wang et al. [28].

Therefore, since the polyelectrolyte complex (PEC) formed by NaCS and chitosan (CS) was a hydrophilic and swellable system, the drug release process was a combination of diffusion and

macromolecular relaxation processes, and followed by the solubilization/erosion procedures of the system [16]. These results indicate that NaCS-CS-PPS microcapsules had favorable properties of enzymatic degradation in SCF (pH 6.4) and can be used as a potential enzyme-triggered drug release carrier.

#### 4. Conclusions

With the polymerization and chemical crosslinking of NaCS, chitosan (CS) and sodium polyphosphate (PPS), novel NaCS-CS-PPS microcapsules were prepared with simple procedures and the results showed potential application of the system as enzyme-triggered drug release carriers. SEM studies showed that the microcapsules had a double-walled capsule structure and 5-ASA entrapped in the double-walled capsule was in a crystal form. Drug loading and encapsulation efficiency analysis showed the microcapsules had relatively high loading efficiency (60.77%) and encapsulation efficiency (90.03%). *In vitro* swelling, erosion and release studies showed that the system were able to control the drug release process and the drug was completely released in simulated colonic fluid (SCF, pH 6.4) under a mechanism of Anomalous (non-Fickian) transport. All these results indicate that the microcapsules could be a good candidate for enzyme-triggered, controllable drug release carrier. Moreover, the method could be used to encapsulate similar drugs.

#### Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 21036005), the Doctoral Programs Foundation of Ministry of Education of China (No. 20110101130007).

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