An Oral Colon-Targeting Controlled Release System Based on Resistant Starch Acetate: Synthetization, Characterization, and Preparation of Film-Coating Pellets

Huayin Pu,[†] Ling Chen,[†] Xiaoxi Li,*,[†] Fengwei Xie,[‡] Long Yu,[†] and Lin Li[†]

[†]Ministry of Education Engineering Research Center of Starch & Protein Processing, College of Light Industry and Food Sciences, South China University of Technology, Guangzhou 510640, China

[‡]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane, Qld 4072, Australia

ABSTRACT: An oral colon-targeting controlled release system based on resistant starch acetate (RSA) as a film-coating material was developed. The RSA was successfully synthesized, and its digestion resistibility could be improved by increasing the degree of substitution (DS), which was favorable for the colon-targeting purpose. As a delivery carrier material, the characteristics of RSA were investigated by polarized light microscopy, FTIR spectroscopy, and X-ray diffraction. The results revealed a decrease of the crystallinity of RSA and a change of its crystalline structure from B + V hybrid type to V type. To evaluate the colon-targeting release performance, the RSA film-coated pellets loaded with different bioactive components were prepared by extrusion—spheronization and then by fluid bed coating. The effects of the DS, plasticizer content, and coating thickness of the RSA film and those of the content and molecular weight of the loaded bioactive component on the colon-targeting release performance of the resulting delivery system were investigated. By adjusting the DS, the coating thickness, and the plasticizer content of the RSA film, either the pellets loaded with a small molecular bioactive component such as 5-aminosalicylic acid or those with a macromolecular bioactive peptide or protein such as bovine serum albumin, hepatocyte growth-promoting factor, or insulin showed a desirable colon-targeting release performance. The release percentage was less than 12% in simulated upper gastrointestinal tract and went up to 70% over a period of 40 h in simulated colonic fluid. This suggests that the delivery system based on RSA film has an excellent colon-targeting release performance and the universality for a wide range of bioactive components.

KEYWORDS: Colon-targeting, resistant starch acetate, bioactive component, film-coated pellets, in vitro release

■ INTRODUCTION

There have been an increasing number of reports detailing the bioactivity of the compounds isolated from various food sources, which show significant health benefits when consumed at appropriate concentrations. However, many bioactive compounds exhibit poor solubility, as well as being sensitive to the environment of the upper gastrointestinal tract (GIT) and subject to attack by acids or enzymes, resulting in low bioavailability.[1,2] To overcome these problems, delivery systems,[3−5] especially colon-targeting delivery systems, are attracting interest.[6−8]

The colon provides a site where poorly absorbable molecules could have improved bioavailability. There exist less digestive enzymes than in other gastrointestinal regions. Additionally, there are longer retention times and lower fluid volumes in the colon, where the absorption of poorly absorable components is enhanced and the high dilution effect is avoided. As a result, a reliable colon-targeting delivery could be an important starting position for some bioactive components and have a potential for the delivery of protein and peptide bioactive components.[9,10]

There are mainly two methods to achieve controlled release in the pharmaceutical sciences. In one method, the bioactive component is embedded in a polymeric matrix,[11,12] and the other method involves coating the bioactive component with a polymeric film.[13−15] Regarding the latter method, the dosage forms can be pellet, capsule, tablet, etc. Being a multiparticulate solid dosage form, pellets can offer several advantages:[16] Physiological advantages such as reduced gastric irritation effect, longer

gastrointestinal transit times, and minimized gastric emptying effects are attributed to the even distribution of pellets in the GIT, while technological advantages such as good sphericity, smooth surface properties, narrow size distribution, and low friability ensure the bioactive component content uniformity and the successful coating with minimized risk of dose "dumping".[17] Additionally, coating the pellets with a polymeric film benefits the sustainable release and the delivery of bioactive components to the specific absorption site in the GIT.[18]

In a controlled release system, the release property for a food bioactive component depends on the carrier materials. Most research has been focused on polysaccharides such as pectin,[19−21] guar gum,[22,23] insulin,[24,25] and chitosan.[26,27] The ideal polymers used for this purpose need to be poorly permeable for the bioactive component in the upper GIT but become quite permeable as soon as the colon is reached.[28] As a biopolymer from renewable resources, starch provides many advantages such as nontoxicity, biocompatibility, biodegradability, wide availability, and low cost. Nevertheless, native starch is traditionally considered to be unsuitable in some controlled release systems due to the fast release as results of its hydrophilic nature, substantial swelling, and rapid enzymatic degradation in biological systems.[29,30] Starch

derivatives, however, are much more resistant to enzymatic lysis than native starch.[31,32] Recently, studies have shown that starch derivatives such as cross-linked starch, starch-2-hydroxyethyl-methacrylate (HEMA) copolymer, starch-methacrylic acid (MAAc) copolymer hydrogel, and starch-ethylene vinyl alcohol (EVA) copolymer can be used as carrier materials for the antiphlogistic and peptide delivery systems.[33−36]

Resistant starch (RS) obtained through appropriate physical or chemical modification can withstand the environmental changes in the upper GIT and can be rapidly degraded by the enzymes produced by the colonic microbiota. As a result, RS can be used as a carrier material to achieve colon targeting. Starch acetate (SA) is a chemically modified starch with diverse applications such as water-soluble thickener in foods, coatings, plasma expanders, and adhesives, and the properties of SA depend on the overall degree of substitution (DS).[37,38] In our previous study, SA with high DS was successfully synthesized, which shows high digestion resistibility.[39] Therefore, SA can be used as a potential colon-targeting delivery carrier material for biomacromolecules.[7,39] However, it is still unclear whether the new delivery carrier based on SA is able to appropriately control the release kinetics of the coated pellets. The purpose of this study was to evaluate the ability of resistant starch acetate (RSA) as a film-coating material to construct the colon-targeting delivery system. The relationships between the DS and the properties (digestion resistibility and crystalline structure) of RSA based on high-amylose corn starch were determined. Four kinds of bioactive components with wide ranges of molecular weights and solubility were chosen as model bioactive components. The effects of the factors such as the coating thickness and the plasticizer content of the RSA film on bioactive component release performance of the resulting pellets in simulated GIT were evaluated. On the basis of the optimization of the pellet preparation and film-coating parameters, the construction of an oral colon-targeting film-coated pellet delivery system was achieved, which is important to preserve and deliver the bioactive food components and to broaden the applications of starch biopolymer.

■ MATERIALS AND METHODS

Materials. High-amylose corn starch (Penford, Australia) was chosen as a raw material due to its excellent film-forming property. Acetic anhydride was obtained from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China).

Microcrystalline cellulose was obtained from Anhui Shanhe Medicinal Accessary Material Co., Ltd. (Huainan, China). 5-Aminosalicylic acid (5-ASA) was supplied by Yuancheng Technology Development Co., Ltd. (Wuhan, China). Bovine serum albumin (BSA) was obtained from Boao Biotechnology Co., Ltd. (Shanghai, China). Hepatocyte growth-promoting factor (HGF) was purchased from Kaitai Biotechnology Co., Ltd. (Guangzhou, China). Insulin was purchased from Newprobe Bioscience & Technology Co., Ltd. (Beijing, China). Pancreatin was purchased from Sigma Chemical Co. (St. Louis, MO). Triacetin was purchased from Beilian Chemical Co. (Tianjin, China). All of these chemicals were of pharmaceutical grade and used as received.

Methods. *Synthetization of SA.* A 40% (w/v) high-amylose corn starch slurry was placed in a reactor equipped with magnetic stirrer at 80 °C. After the pH was adjusted to 8.0 with 3% NaOH solution, acetic anhydride (different content for obtaining the products with different DS) was added, and a constant pH was maintained by NaOH solution. After 2 h, the mixture was neutralized by 0.5 M hydrochloric acid. The mixture was filtered and washed with excess distilled water until acetate ion was not detected by the titration methods.[38] The solid was dried at

45 °C in vacuum oven and then sieved. Regarding the acetylation of starch, the DS (the average number of substituted hydroxyl group per anhydroglucose unit of SA) was determined by the published titration method.[38]

Digestion Resistibility of SA. The RS content was determined by using method 991.43, total dietary fiber (TDF), of the Association of Official Analytical Chemists (AOAC).[40]

Characterization of SA. The FTIR analysis was measured using a Tensor 37 spectrometer (Bruker, Germany) equipped with a deuterated triglycine sulfate (DTGS) detector. The KBr pellet method was used for the sampling of native starch and SA. The spectra, acquired at a resolution of 4 cm^{-1} in the range of 400−4000 cm^{-1}, were the averages of 64 scans and were recorded against an empty cell as the background. The spectra were baseline corrected, atmospheric compensated, and normalized by Min/Max method. For the 800−1200 cm^{-1} region, the deconvolution was conducted using Voigt type equations for all detected peaks. The intensities of the bands at about 1047, 1022, and 980 cm^{-1} were analyzed as a function of DS. Polarized light microscopy was performed using an Axioskop 40 A Pol polarized light microscope (Zeiss, Germany). X-ray diffraction analysis was performed with a Xpert PRO diffractometer (Panlytical, Netherlands). The samples were scanned using Cu Kα radiation with a wavelength of 0.1542 nm as X-ray source. The operation settings for the diffractometer was 40 mA and 40 kV. Data were collected at 2θ (θ being the angle of diffraction) of 4.00−40.00 using sequential scanning with a step width of 0.033° and scanning speed of 10°/min.

Preparation of Bioactive Component Pellet Cores. Pellet cores (270−550 μm in diameter) containing different bioactive components were obtained via extrusion-spheronization. 5-ASA, BSA, HGF, and insulin were chosen as model bioactive components. The bioactive component powder and the accessories (microcrystalline cellulose and starch in the ratio of 3:1) were blended in a high speed mixer and then added with purified water until a homogeneous mass was obtained. The wetted mixture was processed through a single-screw cylindrical extruder at rotation speed of 30 rpm and then spheronized at 800 rpm for 10 min (Mini-250, Xinyite Co., Ltd., Shenzhen, China). Afterward, the wet pellet cores were dried in the spheronizer by hot air at 40 °C for 30 min.

Film Coating of Pellets. The SA was dissolved in acetone, followed by the addition of triacetin as plasticizer. The solution was stirred for 6 h prior to coating. The pellet cores were coated by a bottom-spray method in a fluidized bed coater (Mini-XYT, Xinyite Co., Ltd., Shenzhen, China) until a proper film-coating thickness was achieved. The film-coating thickness was determined by the dry weight gain (%, w/w) of the pellets. The parameters for film-coating process were as followed: inlet temperature, 40 ± 1 °C; product temperature, 35 ± 1 °C; spray rate, 0.7−0.8 mL/min; atomization pressure, 1.0 MPa; and nozzle diameter, 1.2 mm. The coated pellets were further fluidized for 10 min.

In Vitro Release Tests. The release of each bioactive component from the RSA film-coated pellets was carried out using a dissolution rate test apparatus (RCZ-8B, Tianda Tianfa Co., Ltd., Tianjing, China) (100 rpm, 37 °C) according to the USP23 dissolution method. On the basis of the gastrointestinal transit time of food in human boday, the coated pellets were incubated in simulated gastric fluid (SGF) for the first 2 h, then in simulated intestinal fluid (SIF) for another 6 h, and afterward in simulated colonic fluid (SCF) for additional 40 h, in sequence, all at 37 °C.[39] The SGF, with pH of 1.2, consisted of NaCl (0.2 g), 37% HCl (7 mL), and pesin (3.2 g); the SIF, with pH of 6.8, consisted of KH_2PO_4 (6.8 g), 0.2 M NaOH (190 mL), and pancreatin (10.0 g); the SCF, with pH of 7.0, consisted of 0.1 M phosphate-buffered saline (PBS) without rat cecal contents. Five milliliter samples were taken at appropriate time intervals and analyzed for 5-ASA content using UV spectrophotometer (Unico, UV-3802, Shanghai, China) and for BSA, HGF, and insulin contents using high-performance liquid

Table 1. Experimental Conditions for Preparation of RSA with Different DS

starch (g)	acetate anhydride (mL)	DS
15	15	1.31
10	15	1.41
15	20	1.68
15	30	1.94
15	45	2.42
15	60	2.93
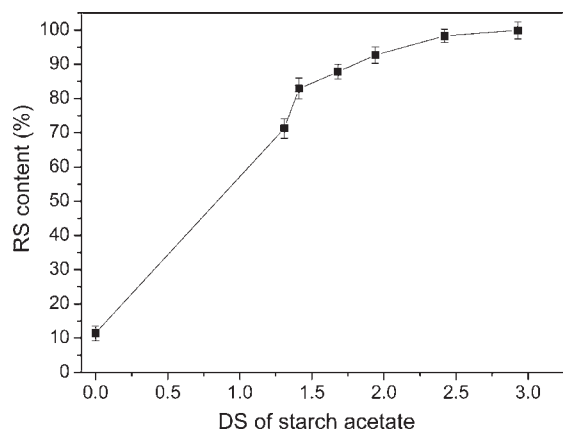
**Figure 1.** Effect of DS of SA on the RS content.

chromatography (HPLC, Waters 1515, Milford, MA). The surface morphology of the RSA film-coated pellets after each stage was investigated by scanning electron microscopy (SEM, LEO 1530VP, Oberkochen, Germany).

■ RESULTS AND DISCUSSION

Starch Esterification and Digestion Resistibility of SA. The experimental conditions of acetylation are given in Table 1. It can be seen that high-amylose corn SA was prepared by acetyl esterification with a DS from 1.31 to 2.93.

Effect of DS of SA on the RS Content. The effects of DS on the RS content were examined, and the results are illustrated in Figure 1. As can be seen, the RS content increased with the increase of DS. The RS content exceeded 90% when the DS was higher than 1.9, and the maximal RS content reached almost 100% when the DS was 2.93. This result demonstrates that the digestion resistibility of starch could be improved by esterification and controlled by the DS value. It is expected that greater stereohindrance of acetyl groups could result from the introduction of more acetyl groups. Thus, the shielding of binding sites for starch and enzyme molecules greatly improved the digestion resistibility of starch.[41,42]

Characterization of Resistant SA. *Alteration of Molecular Chain Structure.* FTIR spectra were used to characterize the molecular chain structure of SA. Spectra of native starch and modified starches with different DS are shown in Figure 2. As compared with native starch, FTIR spectra of acetylated starches showed new absorption bands at 1748−1750, 1378, and 1238 cm^{-1}, which could be assigned to carbonyl group (C═O), CH$_3$ flexural vibration, and C−O−C stretch vibration, respectively.[39,43] With increasing DS, the intensities of three
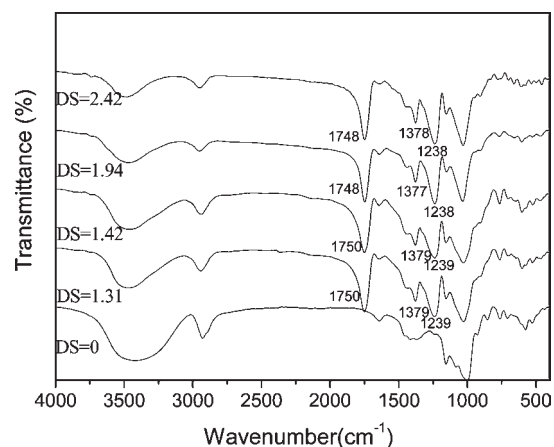
Figure 2. FTIR spectra of RSA with different DS.

peaks were gradually strengthened, which was clear evidence of the incorporation of acetyl groups onto starch molecular chains. On the other hand, as the DS increased, the intensity of absorption band at about 3400 cm^{-1} was gradually decreased, and the relative intensity of absorption band at 2952 cm^{-1} based on the intensity at 3400 cm^{-1} were gradually strengthened, indicating the introduction of CH$_3$ groups onto the starch molecular chains.

Alteration of Crystalline Stucture. The granular shapes and birefringence crosses of native starch and modified starches under polarized light microscope are shown in Figure 3. Birefringence crosses were distinct on almost all of the native starch granules, suggesting that the crystalline structures were intact. However, most of these crosses disappeared after esterification (DS = 1.42). When the DS increased to 1.94 or even 2.42, no crosses can be observed. These results demonstrate that the original crystal structures were destroyed by the esterification process.

X-ray diffraction measurements were performed to further investigate the changes of the crystalline structures of starch, and the results are presented in Figure 4. Native starch displayed both a B type pattern with peaks at 5.6 and 17.2° (2θ) and a V type pattern with a peak at 19.8° (2θ), suggesting a B and V type hybrid polymorph. After esterification with DS of 1.41, the B type peaks at 15.0, 17.2, and 23.1° disappeared, but the V type peak at 19.0−19.7° remained. In addition, a new V type peak at 6.0−7.5°[44] was generated, and its peak intensity was gradually strengthened with increasing DS. It was thus concluded that esterification caused the change of crystalline structures from B + V hybrid type to V type. On the other hand, the peaks for native starch disappeared and merged into a single, broad, rounded peak for modified starches, indicating the reduction of the original crystallinity.

The IR spectrum can be utilized to analyze the changes of crystallinity. For the 800−1300 cm^{-1} region, the FTIR spectra of modified starches were deconvoluted. Voigt type equation was used to calculate the areas of all detected peaks (i.e., the peaks at 980, 1022, and 1047 cm^{-1}) for SA with different DS. On the basis of the previous research, the IR absorbance band at 1047 cm^{-1} is sensitive to the original crystalline structure, the band at 1022 cm^{-1} is characteristic of amorphous structure, and the band at 1047 cm^{-1} reflects the new crystalline structure.[45,46] Hence, the peak area ratios of 980/1022, 980/1047, (980 + 1047)/1022, and 980/(1022 + 1047) cm^{-1} can be used to
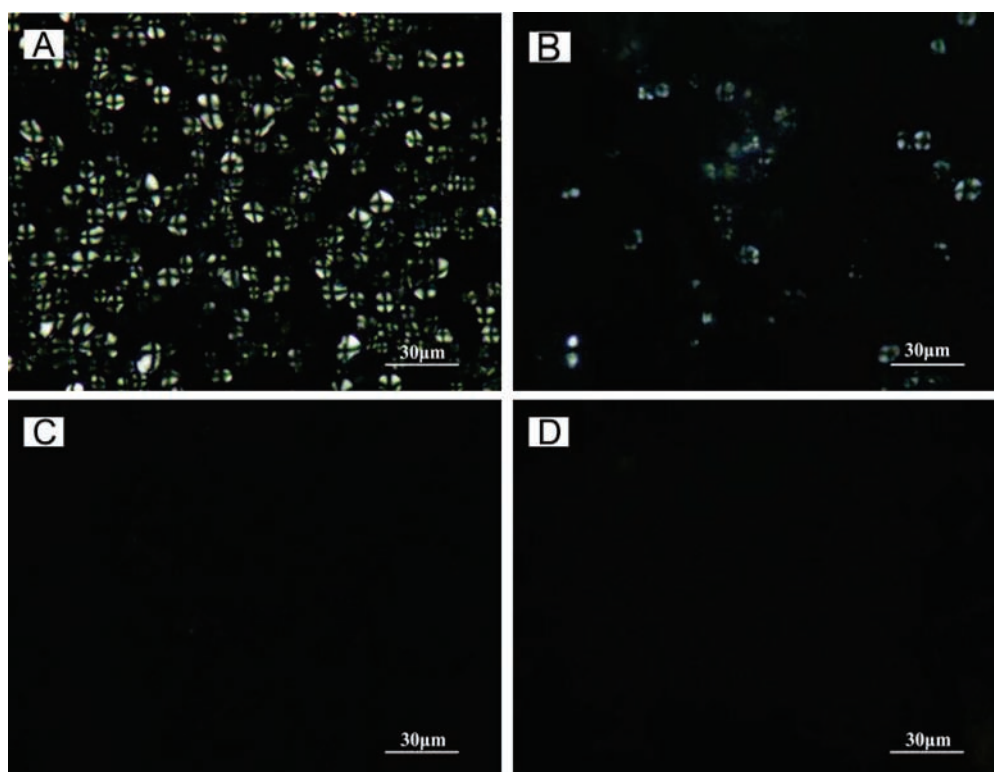
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Figure 3. Polarized light microscopic images (500×) of high-amylose corn starch (A) and RSA with DS of 1.42 (B), 1.94 (C), and 2.42 (D), respectively.
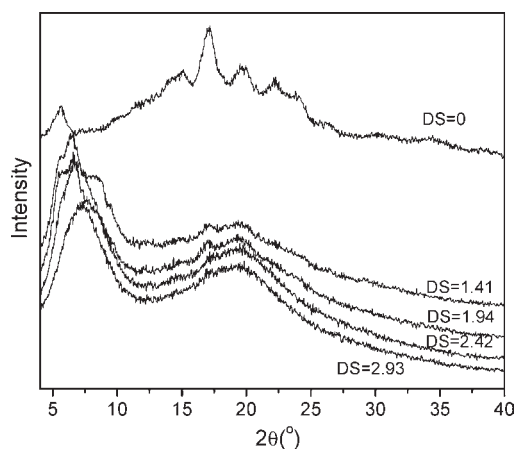

Figure 4. X-ray diffraction pattern of native starch and RSA with different DS.

Table 2. Crystallinity of RSA with Different DS

	relative ratio			
DS of SA	980/1022	980/1047	(980 + 1047)/ 1022	980/ (1022 + 1047)
0	0.935	1.635	4.086	1.284
1.31	0.605	0.933	1.991	0.754
1.42	0.517	0.818	1.928	0.711
1.94	0.464	0.776	1.019	0.272
2.42	0.471	0.752	0.941	0.260

reflect the content ratio of B type crystalline structure to amorphous structure, that of B type crystalline structure to V type crystalline structure, that of total crystalline structure to amorphous structure, and that of B type crystal structure to both V type crystalline structure and amorphous structure, respectively, as shown in Table 2. It can be seen that with the increase of DS, the peak area ratios of 980/1022, 980/1047, (980 + 1047)/ 1022, and 980/(1022 + 1047) cm^{-1} gradually decreased, indicating the decrease of B type crystalline structure content and the increase of V type crystalline structure content. Additionally, the content ratio of total crystalline structure to amorphous structure was decreased with the increase of the DS. Such

results were in good agreement with those from polarized light microscopy and XRD analysis.

The part of results revealed that esterification caused not only the changes of chain structure but also those of crystalline structures of starch. Swelling, gelatinization, and retrogradation in the esterification process broke the hydrogen bonds and caused such changes as the disintegration of double helix and the stretching of molecular chains. In aqueous media, the number of hydroxyl groups was greatly reduced due to the introduction of acetyl groups. New structures hampered intermolecular and intramolecular hydrogen bonds and led to the formations of only single helical structure in the reaggregation process for starch molecules. All in all, esterification resulted in the changes of crystalline structures: the decrease of the degree of crystallinity and the transformation of crystalline structures from B + V hybrid type to V type.

In Vitro Release Tests. *Effect of DS of SA on Colon-Targeting Release Performance.* The release behaviors of 5-ASA pellets coated by different DS of RSA films in simulated human GIT are
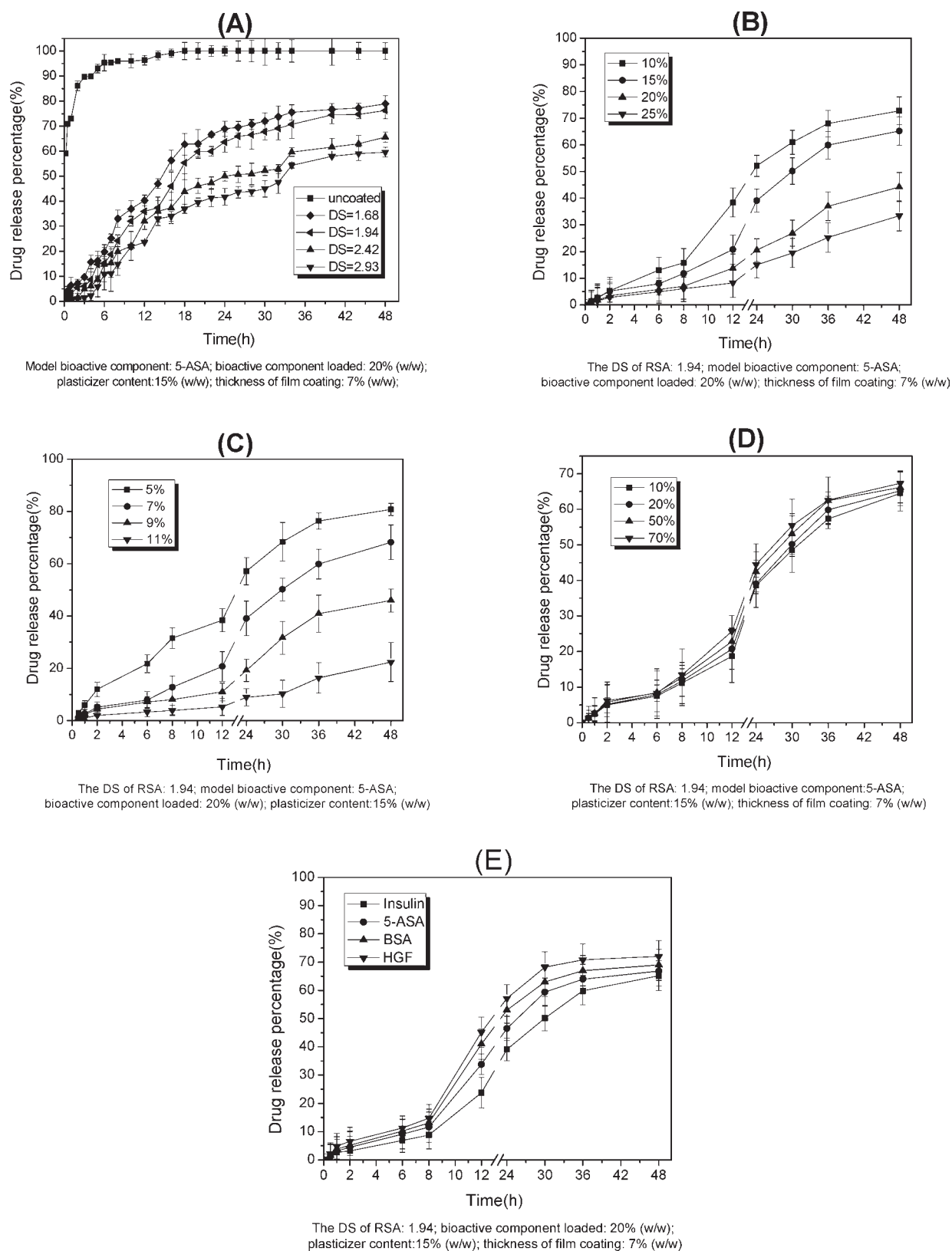
Figure 5. Effects of DS (A), plasticizer content (B), thickness (C) of RSA coating film, and the effects of bioactive component load (D) and type (E) on the colon target and release properties.

shown in Figure 5A. As seen in the figure, uncoated pellets showed a rapid release. The release rate was up to 44.4% for

15 min, and the complete release was reached within 2 h, suggesting the inability of colon targeting. In contrast, coating
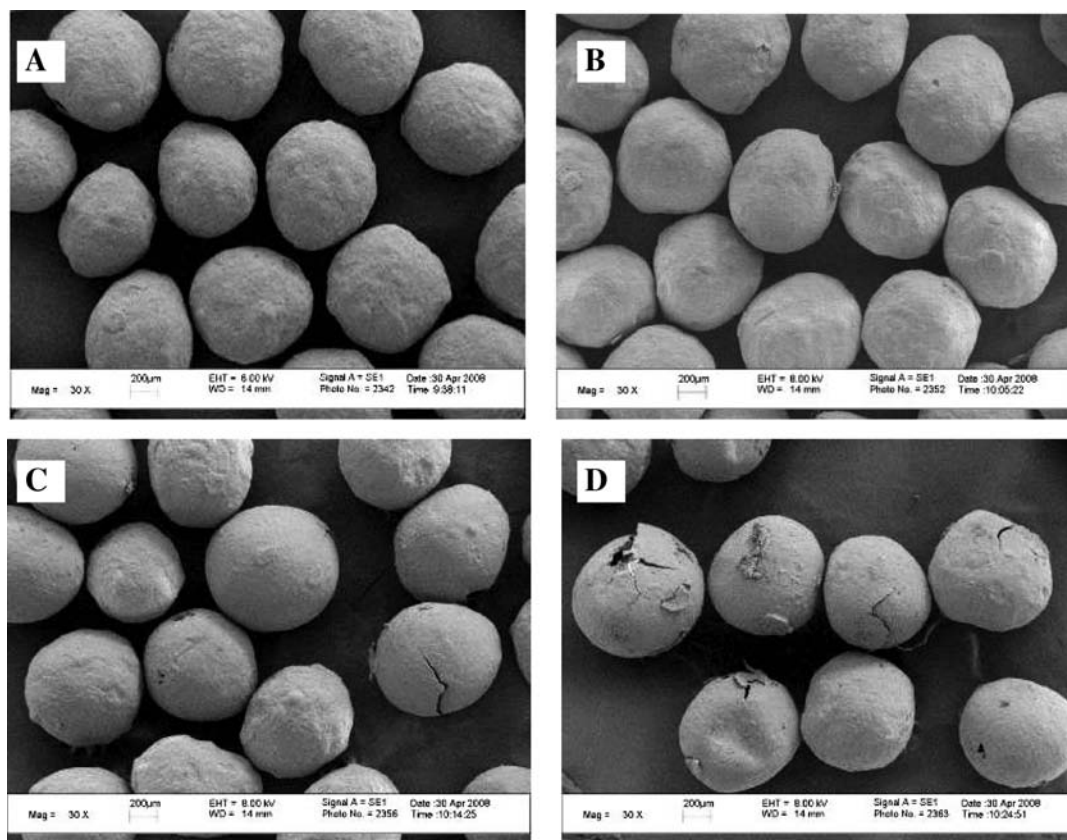
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Figure 6. Surface morphologies of RSA film-coated BSA pellets after incubation for 2 (A), 8 (B), 12 (C), and 48 h (D) (magnification, 30×).

with RSA film could significantly reduce the release rate. The DS of RSA had a great impact on the colon targeting and release performance of the film-coated pellets for 5-ASA. With the increase of DS, the introduced acetyl groups could afford a larger stereospecific blockade effect, which offered a greater ability to defend the attack by the acids and enzymes in SGF and SIF. Time-dependent model was used in this study to simulate the release in the colon environment. However, microflora-activated release should also be considered in the colon environment in human body. As a result, the release rate in the colon should be higher than that shown in Figure 5A. On the basis of all of these considerations, a desirable colon-targeting release performance could be obtained by choosing the RSA with DS between 1.94 and 2.42 as the film-coating material.

Effect of Plasticizer Content on Colon-Targeting Release Performance. It is impossible to prepare the coating film only from RSA, which can cause early release or burst (crack and fracture) as a result of the poor mechanical property. However, film quality can be improved by adding a suitable plasticizer. Therefore, the in vitro release of 5-ASA from the RSA film-coated pellets containing different content (10−25%, w/w) of plasticizer (triacetin) were evaluated, and the results are shown in Figure 5B. The coating thickness was fixed at 7% (w/w). It can be seen that the release rate of 5-ASA from the pellets in SGF and SIF decreased with the increase of triacetin content. When the content of triacetin was more than 15%, the release percentage from the pellets was less than 10% for the first 8 h in the upper GIT, indicating that the RSA film-coated pellets could target the bioactive components to the colon. However, for a higher content (25%) of triacetin in the RSA film, the release percentage

decreased, indicating that the compacted RSA film had poor permeability for 5-ASA in the colon. Therefore, a triacetin content of 15% should be suitable for preparing a RSA film-coated pellet delivery system with good colon-targeting and release performance.

Effect of Thickness of Coating Film on Colon-Targeting Release Performance. The thickness of the coating film can also play an important role in controlling the bioactive component release. Figure 5C shows the percentages of release from the pellets with film coating at different thicknesses (5−11%, w/w) when the plasticizer (triacetin) content was fixed at 15% (w/w). As expected, the release percentage decreased with increasing the film-coating thickness. When the thickness of film coating was 5% (w/w), the release percentage was up to 31.46% within 8 h, indicating that the film-coating thickness was too small to prevent the component from being released in SGF. In this case, a very fast release could be presented. However, when the film-coating thickness was too large, that is, 11% (w/w), the release percentage was only 3.89% in the initial 8 h. In this case, the colon-targeting ability was improved, but the release percentage was significantly reduced in SCF (only 22.4% at last). This is because the increase of film-coating thickness significantly increases the length of the diffusion pathway for the bioactive component. When the film-coating thickness was 7% (w/w), the release percentage was 12.8% in the initial 8 h and then was up to 68.2% in 48 h, suggesting that the pellets had good colon-targeting and release performance. In fact, different release kinetics could be obtained by varying the film-coating thickness. Considering the matching of colon-targeting and release performance, a film-coating thickness of 7% was selected for the following experiments.

Effect of Bioactive Component Load on Colon-Targeting Release Performance. The bioactive component load is another important aspect affecting the quality of a delivery system. In general, a higher bioactive component load is preferred. However, with the increase of bioactive component load, the release rate of pellets would be increased due to the greater concentration gradient between the pellet core and the simulated GIT fluid. It is shown in Figure 5D that although the release percentage was increased slightly with the increase of bioactive component load from 10 to 70%, the bioactive component load has little effect on the colon-targeting and release performance of RSA film-coated pellets. Therefore, these pellets can be reasonably loaded with a large content of bioactive component.

Effect of Molecular Weight and Solubility of Bioactive Component on Colon-Targeting Release Performance. For investigating the effect of bioactive component molecular weight on the colon-targeting and release performance of RSA film-coated pellets, 5-ASA, HGF, insulin, and BSA were chosen as model bioactive components. Their molecular masses are 153, 3000, 5800, and 68000 Da, respectively. HGF and BSA showed good water solubility, while 5-ASA and insulin are insoluble in water. Under the conditions of 15% (w/w) plasticizer content, 7% (w/w) film-coating thickness, and 70% bioactive component load, the release behaviors of RSA film-coated pellets in simulated GIT were determined and are shown in Figure 5E. It can be seen that the release rates of HGF and BSA pellets were higher than those of 5-ASA and insulin pellets in SCF. It was thus concluded that water-soluble bioactive component pellets displayed a faster release rate than water-insoluble bioactive component pellets. On the other hand, the release rate of HGF pellets was higher than that of BSA pellets. 5-ASA pellets also showed a faster release rate than insulin pellets in SCF. This can be explained by the slower diffusion of the bioactive component with higher molecular weight through the RSA film. Nevertheless, all of the pellets loaded with different bioactive components showed a good colon-targeting and release performance. The release percentage was less than 12% in SGF and SIF, while in 48 h the total release percentage was up to 70% in all simulated fluids.

Bioactive Component Release Mechanism of RSA Film-Coated Pellets. To evaluate the bioactive component release mechanism of the RSA film-coated pellets in simulated GIT, SEM was used to observe the coating film surface of the pellets after incubation in SGF, SIF, and SCF for selected periods, and the results are shown in Figure 6. It is revealed that the surface morphology of RSA film-coated BSA pellets could be affected by the incubation time. The RSA film had good ability to resist the degradation by acid and enzymes in simulated upper GIT (Figure 6B,C). With the increase of incubated time in SCF, holes and cracks emerged on the coating film, resulting in a controlled release of bioactive component in the colon (Figure 6D,E).

This part of results showed that the constructed RSA film-coated pellets were suitable to be used as a colon-targeting controlled release delivery system not only for small molecular bioactive components such as 5-ASA but also for peptide and protein macromolecular bioactive components such as BSA, HGF, and insulin.

In conclusion, the RSA showed high digestion resistibility, which can be controlled by the DS. It can be applied as a potential film-coating material for oral colon-targeting delivery system. Importantly, for the RSA film-coated pellets, a desired colon-targeting and release performance can easily be obtained by adjusting the film-coating thickness as well as the plasticizer content of the coated RSA film. Furthermore, the novel release system is suitable for loading a wide range of food bioactive components with different molecular weights and solubility.

■ AUTHOR INFORMATION

Corresponding Author
*Tel: +86 20 8711 3252. Fax: +86 20 8711 3252. E-mail: xxlee@scut.edu.cn.

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