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Amide pectin: A carrier material for colon-targeted controlled drug release

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ABSTRACT: In order to deliver bioactive components to the colon, an oral colon-targeted bioadhesive microparticle delivery system based on pectin was developed. Unmodified pectin exhibited a poor hydrophobicity and weak tablet-crushing strength. Pectin was modified by an amide reaction, which results in a dramatic decrease in water solubility and viscosity, as well as favorable controlled release properties. Amide pectin (AP) were characterized by Fourier transform infrared spectroscopy (FTIR), Nuclear magnetic resonance (^{1}H-NMR), and Differential scanning calorimetry (DSC). Results of FTIR and ^{1}H-NMR revealed that amide groups were introduced into the pectin molecules; DSC analysis exhibited that the thermal stability of pectin was decreased. An *in vitro* release assay demonstrated that matrix tablets prepared by AP could deliver bioactive components to the colon when the pectin content and hydrophobicity were properly controlled. The relationship between the structure and *in vitro* release properties of amide pectin suggests that an optimal tablet structure and composition can be responsible for a suitable BSA release rate. The optimal tablets making conditions were using methylcellulose (MC) as tablet adhesive, amidation reaction time of 60 min, drug loading of 0.008 g and tableting pressure of 8 kg/mm. The results indicated that matrix tablets made by AP exhibited good colon-targeted drug release. © 2016 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2016**, *133*, 43697.

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INTRODUCTION

For better treatment of colonic diseases, colon-specific drug delivery systems have obtained significant attention from the researchers.[1,2] To deliver drug to the colon, the drug needs to be prevented from absorption at the upper gastrointestinal tract (GIT) and then be abruptly or slowly released into the proximal colon. The colon offers an environment of weak acidity, a relatively long transit time and a low proteolytic enzyme activity, which make the proximal colon an appealing site for drug absorption. Various forms of drug carriers have been utilized for effective colon-specific drug delivery. There are single-unit systems, including capsules, pellets, beads, microspheres, micro- and nanoparticles, and multiple-unit systems, including matrix tablets. The matrix tablets were proved to be better than single-unit systems due to their great stability and excellent drug release effect.

Due to their renewability, biocompatibility, biodegradability, and nontoxic nature, a variety of natural polysaccharides have been investigated to prepare carrier materials for colon-specific drug delivery, such as pectin,[3,4] chitosan,[5,6] konjac gum,[7] alginate,[8,9] starch,[10] and so on. Pectin is one of the most promising ones. Because, comparing with the above ingredients, pectin has good biocompatibility and biodegradability. In addition, its unique structure makes it easy to be modified, and its water solubility and swelling can be greatly reduced after proper chemical modification, so it can resist to digestion of enzymes in the stomach and the intestine, before reaching the colon, and then it is degraded by colon microflora for absorption and utilization.

Pectin is extensively used in various fields. In the pharmaceutical field, it can be applied to control local bleeding and to reduce blood cholesterol levels[11] as well as in the preparation of wound-care products, which have bactericidal and wound-healing effects.[12,13] In the food industry, it has been extensively used as a thickener, jellifying agent, texturizer, and emulsifier[14,15] as well as in the preparation of edible films intended for active food packaging.[16] Pectin has also been considered for tissue engineering, especially in hard tissue reparation.[17]

Pectin is promising for carrier materials intended to deliver drug to the colon. It can be modified slightly to make sure that

it remains as macromolecular aggregates in the upper portion of GIT, but it can be degraded later by colonic enzymes.[18,19] Moreover, pectin-muco-adhesiveness has some excellent properties, such as ease of dissolution in basic environments and resistance to degradation by proteases and amylases of the GIT, which provide advantages for the drug delivery. In addition, it can form gels in acidic environment allowing various drug delivery formulations (microspheres, beads, pellets, and microparticles) into completely different environments such as nasal, vaginal, ocular, gastric and, large intestine especially, colon.[20,21] However, pectin has not fulfilled its potential for drug delivery systems due to variability on its formulation, which depends on its source and processing that affect to its stability over time and behavior in a hydrated media. In order to improve its properties, such as chemical stability and drug release property, polymerizing pectin polymer with other substance, such as ethyl cellulose,[22] hydroxypropyl methyl cellulose,[23] gelatin,[24] corn protein,[25,26] whey protein,[27] chitosan,[28] or binding with a divalent or trivalent cation to improve the performance of pectin, have been adopted. These researches proved that preparing pectin polymer with other substance or binding with a divalent or trivalent cation can improve performance of pectin, after those modifications, the water solubility of these pectin polymer was decreased and the ability of antidigest the upper gastrointestinal tract was improved, which endue pectin a good colon targeting ability, but the drug release is not absolutely, so we should find more effective methods to further improve the chemical stability and release properties of pectin.

In this study, AP was prepared and characterized by FTIR, ^{1}HNMR, and DSC. It was expected that amide pectin would reduce the hydration of the matrix tablets and play a role in network stabilization through hydrophobic interactions. The AP was then used to prepare matrix tablets, which were evaluated for their water solubility and viscosity. BSA is used because of its stability, its lack of effect in many biochemical reactions, and its low cost, since large quantities of it can be readily purified from bovine blood, a byproduct of the cattle industry and tablet dissolution was also analyzed to determine the potential of this material for the design of colonic drug delivery systems.

EXPERIMENTAL

Materials

Pectinex® UltraSP-L (pectinase/pectinolytic enzyme from *Aspergillus aculeatus*, Activity > 9500 PG mL^{-1}) was obtained from Novozymes (Denmark). High ester pectin was purchased from QuZhou pectin Co., Ltd. (China). Bovine serum albumin (BSA) was bought from Sinopharm Chemical Reagent Co., Ltd. ethylcellulose (EC, M70), methylcellulose (MC, M20), polyvinylpyrrolidone (PVP, K-30), and sodium carboxy methylcellulose (CMC, 300 ~ 800 mPa·S) were provided by Guang Yao Experimental Equipment Co., Ltd (Nanning, China). All reagents were analytical grade.

Preparation of Amide Pectin

Preparation. The AP was prepared according to the method described earlier.[29] AP was prepared with 2 mol/L ammonia solution in a heterogeneous system in isopropyl alcohol (Figure 1). 15 g of pectin were dispersed in 200 mL of isopropyl alcohol contain ammonia under the stirring at 25 °C. The addition of

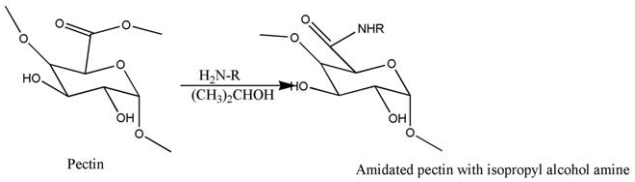

Figure 1. Reaction mechanism of amidation of pectin with isopropanolamine.

1 mol/L of HCl provided the required acidic environment, and the sample was freezed at −18 °C for 24 h. After thawing at room temperature, pectin was basified with 250 mL of deionized water for 1 h to fully swell. This solution was stirred at room temperature, sampling every 20 min for 4 times. The products were filtered and thoroughly washed 5 times with isopropyl alcohol. The precipitate was collected and washed with an excess of isopropyl alcohol for three times to eliminate unreacted chemicals. Finally, the products were dried at 50 °C for 24 h to obtain AP powders.

Solubility and Viscosity Assay. 0.5 g AP sample was dispersed with anhydrous ethanol in a 100 mL centrifugal tube. After adding 50 mL of artificial simulated gastric juice, the centrifugal tube was placed in a Shaker at 37 °C for 2 h and centrifuged at 4000 rpm for 15 min. The supernatant was kept for viscosity measurement. The residue was dried at 60 °C for 24 h and weighed. The solubility and viscosity of artificial simulated small intestinal and colonic fluid were carried by the same method, being sampled at 4 h and 12 h, respectively.

Solubility SM is calculated as:

$$\mathrm{SM}(\%) = \frac{W + W_1 - W_3}{W} \times 100 \quad (1)$$

W is the mass of the test sample; W_1 is the mass of the centrifuge tube; W_3 is the mass of wet base precipitation and centrifugation tube after drying.

Structural Analysis

FTIR Characterization. This operation procedures were carried out as previously described with slight modification.[23] FTIR spectra was recorded by a Spectrum One spectrophotometer (Nexus 470 FTIR, USA) equipped with a universal attenuated total reflectance device for tablet analysis in the spectral region (4000–650 cm^{-1}) with 64 scans recorded at a 4 cm^{-1} resolution. Samples were prepared in KBr discs (1 mg sample in 100 mg KBr) with hydrostatic pressure at the force of 5 cm^{-2}. Experiments were duplicated to check the reproducibility.

DSC Analysis. Preparation and operation procedures were carried out as previously described[30,31] with slight modification. DSC curves of pectin amidated for 0 min, 20 min, and 60 min were registered in a TA Instruments DSC200PC (NETZSCH, Germany) at a heating rate of 10 K/min between 20 and 350 °C, under nitrogen gas (50 mL/min). Experiments were performed by a sealed aluminum pans with a central pin-hole in the lid containing about 1 mg of the sample. A sealed aluminum pan with a central pin-hole in the lid was used as a reference.

^{1}H-NMR. High-resolution ^{1}H-NMR spectra were recorded on a Bruker AV-600 spectrometer (Switzerland). The samples were

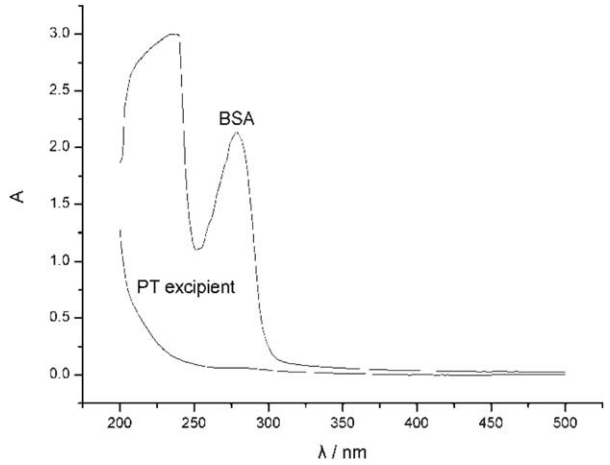

Figure 2. UV absorption spectrum of BSA and pectin excipient.

prepared as described by Heux *et al.*[32] Native or modified pectin was dissolved in deuterated water. These solutions were then frozen and thawed three times to exchange labile protons with deuterium, and their spectra were recorded three times at 330 K.[33]

Preparation of Matrix Tablets. Matrix tablets were prepared according to the method described by Weh with slight modification.[34] AP 0.0025 g, BSA 0.008 g, adhesives, calcium salt, and magnesium stearate were combined with a 2% hydroxypropyl methyl cellulose (HPMC) ethanol solution and sieved with sieve No. 40. The granules were dried 2 h in a conventional oven at 50 °C until a constant moisture content of the granules was achieved. The dried granules were passed through sieve No. 40. Talc and magnesium stearate (1 ∼ 2% of total mass) were added as a lubricant and glidant, and they were mixed with granules using a spatula before compression. Finally, granules were weighed and compressed using a manual single punch tablet machine. A pair of 6 mm stainless steel round flat punches with a break line were used. The granules were compressed with a pressure of 2500 psi.

Study on the Release of BSA from Matrix Tablets

Preparation of Artificial Simulated Digestive Fluid. Simulated gastric fluid: 9 mL of concentrated HCl was dissolved in 1000 mL of deionized water (sonicated for 1 h), and 0.1 M NaOH solution was added to adjust the pH value to 1. Simulated intestinal fluid: 13.6 g of potassium dihydrogen phosphate was dissolved in 1000 mL of deionized water (sonicated for 1 h), and 0.1 M NaOH solution was added to adjust the pH value to 6.8. Simulated colonic fluid: 6.8 g of potassium dihydrogen phosphate was dissolved in 1000 mL of deionized water (sonication 1 h), and 0.1 mol/L NaOH solution was added to adjust the pH value to 7.4.

Determination BSA Content

Ultraviolet Absorption Spectrum Scan. BSA, Skeleton material, and excipients were diluted with pH 7.4 of phosphate buffer and scanned using UV spectrophotometer at 200 ∼ 500 nm range.

Determination of in Vitro Release Rate of BSA. The in vitro release rate of BSA was determined using a method published in 2010 in the Chinese Pharmacopoeia of the People Republic of China. The different AP-matrix tablets were placed in 500 mL of artificial buffer solution and rotated at 100 rpm at 37.5 ± 0.5 °C for 10 h. Samples 5 mL were withdrawn from the dissolution apparatus hourly with sampling cannula with filter attachment. An equal amount of fresh medium of the same temperature was replaced in the apparatus. All samples were filtered through a 0.8 μm filter membrane before measurement of absorbance at 279 nm with a UV-visible spectrophotometer.

The cumulative percentage of release BSA for each time point was calculated as follows:

$$c(\%) = A_n + \frac{(A_{n-1} + \ldots\ldots + A_2 + A_1) \times V_1}{V_2}$$

Where A_n is the drug dissolution of all sampling time points, V_1 is the fixed sampling volume at each time point (mL), and V_2 is volume of the dissolution medium (mL).

Drug Release Kinetics. In order to determine the release mechanism and the order of drug release, the in vitro dissolution datas were fitted to mathematical models representing (1) zero order, (2) first order, (3) Higuchi's, (4) Ritger-Peppas, (5) corrosion, (6) diffusion relaxation, and (7) diffusion dissolution models.

$$\frac{M_t}{M_\infty} = kt \quad (1)$$

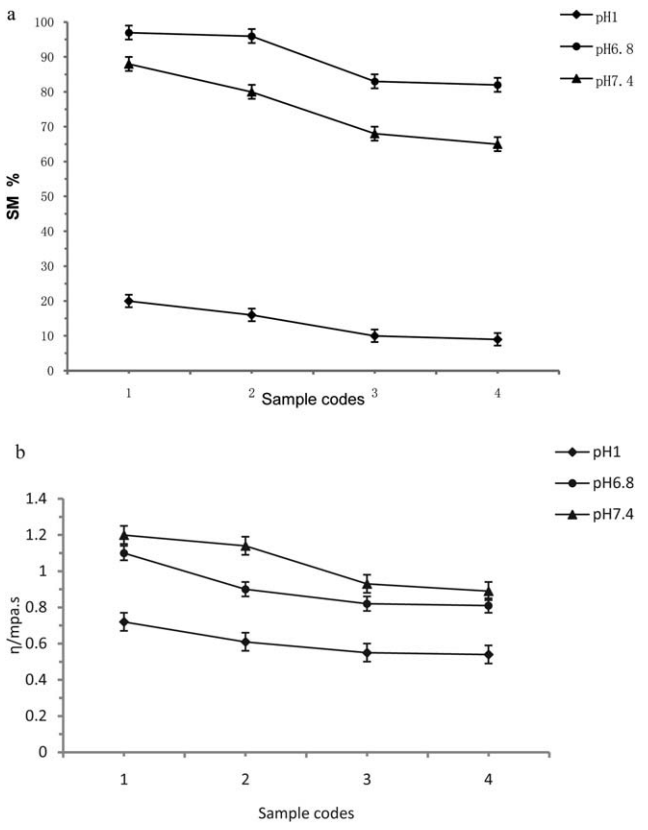

Figure 3. Solubility ratio and viscosity of amidated pectins in different pH values (Pectin amidated for 20 min, 40 min, 60 min, and 80 min are the samples of 1, 2, 3, 4, respectively).

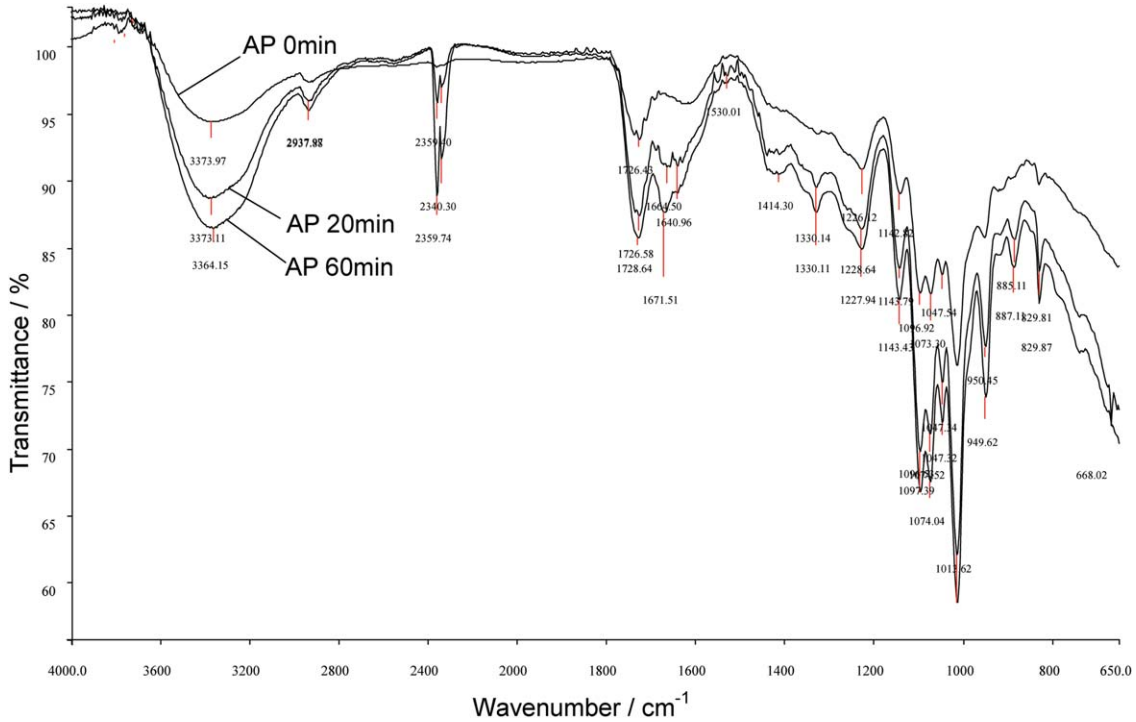

Figure 4. FT-IR spectrum of amidated pectins. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$$\frac{M_t}{M_\infty} = 1 - e^{-kt} \quad (2)$$

$$\frac{M_t}{M_\infty} = kt^{\frac{1}{2}} \quad (3)$$

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

$$\frac{M_t}{M_\infty} = k_1 + k_2 t^2 + k_3 t^3 \quad (5)$$

$$\frac{M_t}{M_\infty} = k_1 t^{\frac{1}{2}} + k_2 t^3 \quad (6)$$

$$\frac{M_t}{M_\infty} = k_1 t_2^{T\prime} + k_2, t + k_3, t^{2\prime} + k_4 t^3 \quad (7)$$

M_t/M_∞ is the cumulative drug release at time t, k_1, k_2, k_3, and k_4 are constants that differ depending on the prescription, drug, and release conditions. In the Ritger-Peppas model, n is the characteristic parameter of the release mechanism. Drug release from the matrix tablets obeys Fickian diffusion when the matrix tablet has a cylindrical shape and $n < 0.45$. In the range $0.45 < n < 0.89$, the drug release occurs through a mixed mechanism, which includes the dual mechanisms of drug diffusion and matrix dissolution. At $n > 0.89$, drug releases occurs through bulk erosion mechanisms.

RESULTS AND DISCUSSION

Ultraviolet Absorption Spectrum Scan

BSA had maximum absorption peak at 279 nm (Figure 2), but the skeleton material and excipients had almost no absorption at this wavelength range, namely, the skeleton materials and excipients had no interference for the maximum absorption wavelength of BSA at 279 nm, so the content of BSA in dissolution medium can be measured at a wavelength of 279 nm to examine the release degrees of matrix tablets.

Solubility and Viscosity Analysis. The results of solubility and viscosity were described in Figure 3.

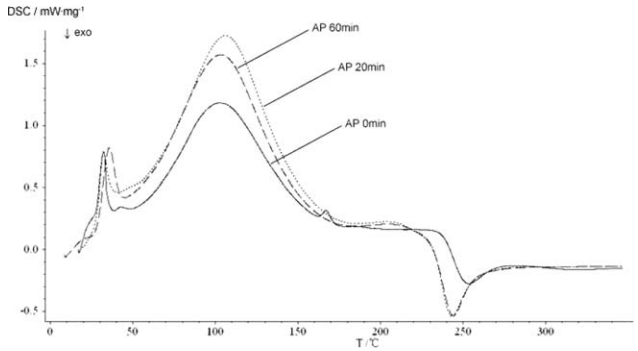

Figure 5. DSC curves of amide pectin (0 ~ 350 °C).

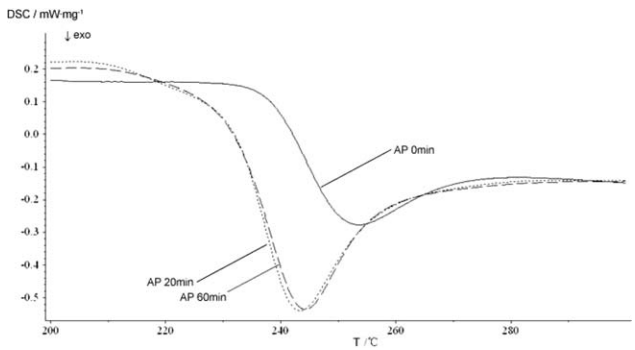

Figure 6. DSC curves of amide pectin (200 ~ 300 °C).

Table I. Parameters of Thermal Analysis of Amidated Pectin

Sample	Ton DSC (°C)	Tp DSC (°C)	Toff DSC (°C)	E_{max} (mW·mg−1)
AP 0 min	237.8	253.7	269.6	−0.2779
AP 20 min	232.2	243.3	256.8	−0.5407
AP 60 min	232.7	243.9	255.1	−0.5803

Pectin amidated for 20 min, 40 min, 60 min, and 80 min are the samples of 1, 2, 3, 4, respectively. Both solubility and viscosity were decreased with the increase of amination time in different pH buffer solutions. From Figure 3(a), it can be seen that pectin solubility was largest in pH 6.8 buffer solution. This may be that free carboxylic acids transform into the salt in the pH 6.8 buffer solution, so the AP particles can be stretched sufficiently to increase the solubility. In Figure 3(b), pectin viscosity was increased with the increase of the value of pH, which concluded that AP had a larger viscosity in alkaline condition.

FTIR Analysis. The infrared spectra of pectin amidated for 0 min, 20 min, and 60 min are presented in Figure 4.

The FTIR spectrum of pectin indicated a broad band at 3370 cm^{-1}, which is related to OH groups[35] (Figure 4), and bands at 1227 cm^{-1} is due to C—O groups.[36] AP is the product of the partial methyl ester converted to primary amide, so it had the infrared absorption peaks of the primary amide groups.

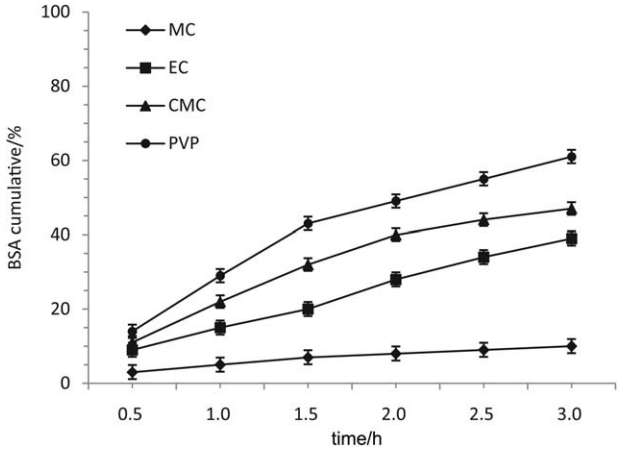

Figure 8. Effect of various adhesive on the release of AP-based matrix tablets in SGF.

Characteristic peak of amide are stretching vibration peak of N—H (ν_{NH} 3540 ~ 3125 cm^{-1}), Stretching vibration peak of C=O ($\nu_{C=O}$ 1690 ~ 1620 cm^{-1}), and the bending vibration peak of N—H (δ_{NH}). The amide V N—H peak and the strong broad peak of O—H bond had the same frequency (Figure 4), so the peak at 3373 cm^{-1} was increased significantly. νC=O peak of amide at 1660 cm^{-1} is different from the stretching vibration absorption peak of pectin. Amide peak (νCN + δNH) focused on νCN vibration, and this peak of primary amides appear in 1430 ~ 1400 cm^{-1}. AP also had this weak peak at

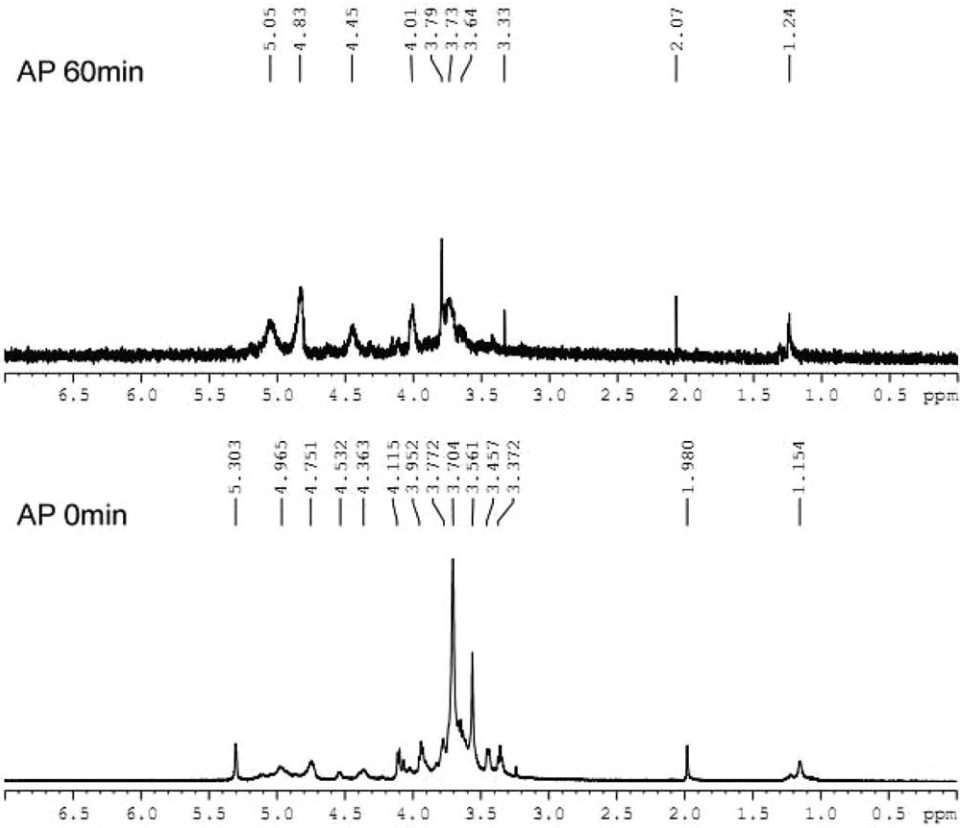

Figure 7. ^{1}HNMR spectrum of amidated pectin.

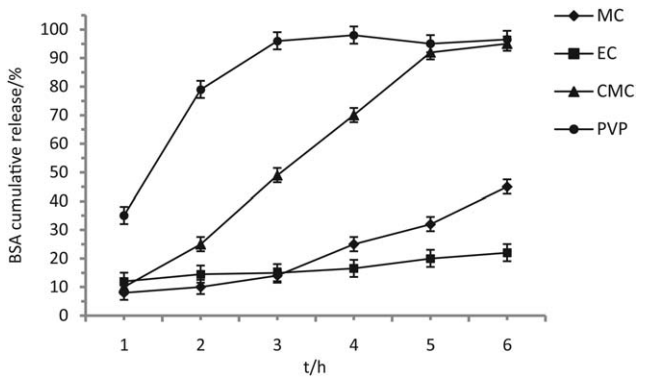

Figure 9. Effect of various adhesive on the release of AP-based matrix tablets in SIF.

1434.79 cm^{-1} and 1414.30 cm^{-1}, so it can be explained the amide group were planted into pectin molecules.

Thermal Properties. DSC curves for pectin amidated for 0 min, 20 min, and 60 min are presented in Figures 5 and 6.

We can see from Figure 5, the peak area of AP was larger than that of the original pectin. As shown in Figure 6, the T_{on}, T_p, and T_{off} temperature of AP were decreased with the increase of degree of amination. Both temperature and reaction enthalpy of AP were higher than that of original pectin, and AP was more sensitive to thermal degradation. Its specific thermodynamic parameters are shown in Table I. This is because the functional groups of the —$CONH_2$ have active hydrogen easier to form intermolecular and intramolecular hydrogen bonds, which changed the physical state and functional properties of pectin molecules.

^{1}H-NMR. The ^{1}H-NMR spectra for pectin amidated for 0 min and 60 min are presented in Figure 7.

Comparison of the two figures concluded that hydrogen of pectin had chemical shift to downfield. Moreover, a significant nitrogen methyl protons vibration peak was present at 3 ∼ 4 ppm. This may be that some methoxy of pectin molecules were partially methylated, so we can conclude that the we prepared AP successful.

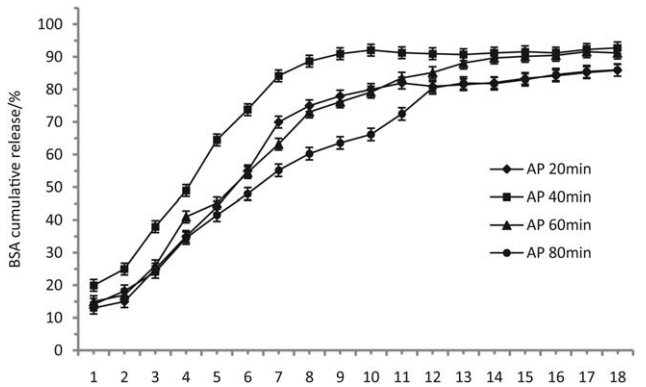

Figure 10. Effect of Amide reaction time on the release of AP-based matrix tablets.

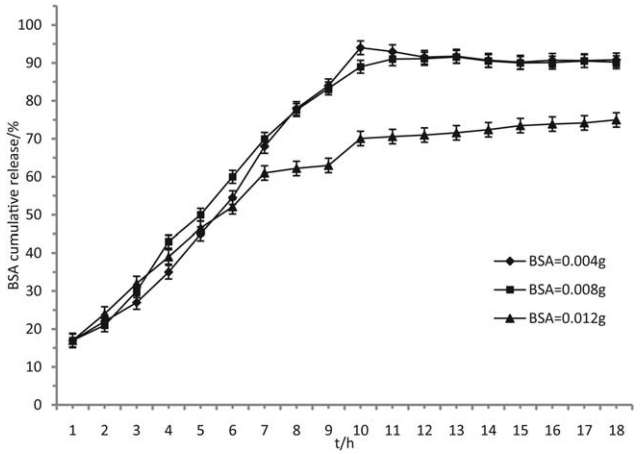

Figure 11. Effect of drug ratio on the release of AP-based matrix tablets.

Effect of Various Adhesives on the Release of AP-Based Matrix Tablets. BSA release from matrix tablets was less than that of the other 3 in artificial gastric juice when the adhesive was MC (Figure 8). It can be seen from Figure 9, the initial release of matrix tablets containing EC, MC and CMC were less PVP in the artificial intestinal fluid. After 6h, BSA release from matrix tablets containing EC was the least. From comprehensive comparison of the ability of controlled release of MC and EC in artificial gastric fluid and intestinal fluid, MC was better than EC, so using MC as adhesive of matrix tablets is suggested.

Effect of Amide Reaction Time on the Release of AP-Based Matrix Tablets. As shown from Figure 10, drug release time of AP 60 min was the longest. This may be that the AP amidated for 20 min and 40 min had a larger solubility [Figure 3(a)], resulting in the BSA early release. When AP amidated for 60 min, pectin solubility was decreased greatly, and adhesive was dissolved slowly, resulting in a long release time before a completely release of BSA. However, when the amide reaction time was too long (Ap 80 min), AP, adhesive and auxiliary were hardly dissolved, and the BSA was difficult to be released. Therefore, pectin amidated for 60 min may be the best sample for drug delivery.

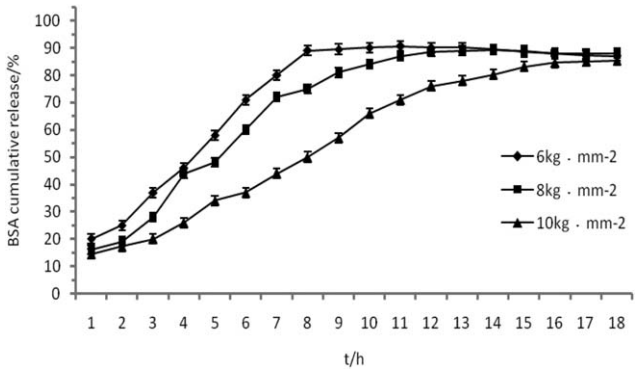

Figure 12. Effect of prepared pressure on the release of AP-based matrix tablets.

Table II. Correlation Coefficients of Drug Release Models from AP-Based Matrix Tablets

Sample	Zero-order	First-order	Higuchi	Ritger-Peppas	Corrode	Diffusion-relaxation	Diffusion-corrode
1	0.5597	0.9417	0.8787	0.8803	0.9831	0.8789	0.9886
2	0.3067	0.9604	0.8588	0.8652	0.9828	0.8795	0.9862
3	0.5530	0.5193	0.9080	0.9087	0.9905	0.9085	0.9911
4	0.5801	0.9734	0.9173	0.9186	0.9928	0.9173	0.9928
5	0.8384	0.9052	0.7941	0.8733	0.9686	0.8622	0.9793
6	−0.2122	0.9737	0.8280	0.9015	0.9725	0.9366	0.9849
7	0.06708	0.9357	0.8570	0.8882	0.9527	0.9071	0.9659

Effect of Drug Loading on the Release of AP-Based Matrix Tablets. From Figure 11, we can see that when the drug loading was 0.008 g, the BSA release rate was slightly slower than that of 0.004 g. When drug loading was 0.012 g, the drug was released in advance. This is because when drug loading was too larger, the drug density was larger in the same volume, and the matrix tablets could form more pores and dissolve more BSA, which accelerate drug release. However, when the drug loading was too small,the drug density was low, and thus water can enter the matrix tablets easily, which increases free diffusion of drug and also results in early drug release. Therefore, we concluded when the drug loading was 0.008 g, the matrix tablets may be able to ensure an endurable drug release time.

Effect of Tableting Pressure on the Release of AP-Based Matrix Tablets. When the tableting pressure was 8 kg mm^{-2} and 10 kg mm^{-2}, the matrix tablets had a better controlled-release and sustained-release properties (Figure 12). When the compression pressure was too low, water are more easily penetrates into the framework of matrix tablets, which form more pores and accelerate the drug release, which resulting in the early release. When the compression pressure was too high, the hardness of matrix tablets were increased, so it is very hard for the water to enter the tablet matrix resulting in a very low drug release rate. Therefore, the best tableting pressure was 8 kg mm^{-2}.

Drug Release Kinetics. Dissolution dates for all formulations were fitted to mathematical models to study drug release kinetics and mechanisms. The mathematical models included a zero order model, first order model, Higuchi release model, Ritger-Peppas model, corrode model, diffusion-relaxation model, and diffusion-corrode model. Regression coefficients of the drug release kinetics for all formulations are summarized in Table II.[33]

Table III. Diffusion-Corrode Model Parameter of AP-Based Matrix Tablets

Sample	k_1	k_2	k_3	k_4
1	−15.48	23.49	−1.116	0.01682
2	−10.72	23.12	−1.337	0.02638
3	−4.773	16.16	−0.6882	0.007217
4	−0.9646	12.23	−0.4291	0.0008875
5	−18.46	14.77	−0.2228	−0.009010
6	18.14	8.224	−0.5236	0.006973
7	19.91	4.581	−0.06787	−0.008755

The linear correlation coefficient was highest for the diffusion dissolution model (Table II). Therefore, drug release behavior for formulations prepared with AP can be fitted to the diffusion dissolution model. The n values of the Ritger-Peppas empirical model were 0.5268, 0.4524, 0.5168, 0.5243, 0.7788, 0.3692, 0.4060. N values of samples 1–5 were between 0.89 and 0.45, which shows that matrix tablets prepared with AP. The drug release behavior in nonenzymatic release medium exhibited dual mechanisms of drug diffusion and matrix dissolution. The n values for samples 6 and 7 were less than 0.45. This may be due to the presence of pectinase in the release environment of these matrix tablets, which accelerated the dissolution of the matrix tablets and the release of the drug.

Experimental data and fitting parameters for the diffusion dissolution model for matrix tablets formulated with AP are shown in Table III, and the fitting diagram is shown in Figure 13.

CONCLUSIONS

Taking BSA as a drug model, matrix tablets were prepared with AP for colon-specific delivery. We evaluated their in vitro release properties. The results exhibited that the BSA sustained-release kept for 18 h in phosphate buffer solution at pH 7.4, whereas they hardly released at pH < 6.8. The cumulative release rate was above 90%. FTIR and ^{1}HNMR analyses demonstrated that amide group was introduced into the pectin molecules, resulting in lower solubility. DSC analysis showed that thermal stability of pectin was decreased with amidation; In vitro drug

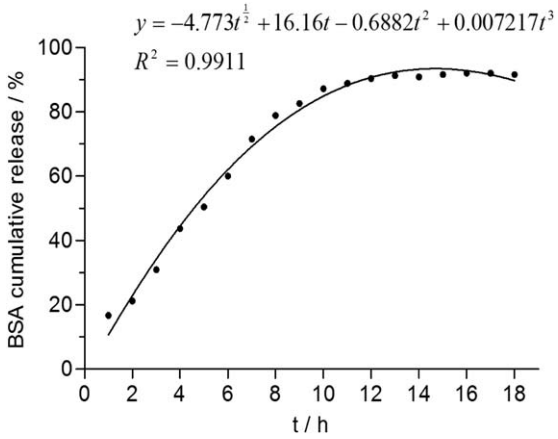

Figure 13. Diffusion-corrode model fit curve of AP-based matrix tablets.

release studies and drug release kinetics indicated that formulations prepared with AP exhibited sustained drug release in enzymatic medium. The optimal tablets making conditions were using methylcellulose (MC) as tablet adhesive, amidation reaction time of 60 min, drug loading of 0.008 g and tableting pressure of 8 kg/mm. The prepared AP matrix tablets demonstrated specific degradation by pectinase, effective colon-targeted drug delivery, and biological degradation. These results indicate that AP may be a promising technological strategy for the oral dosage forms intended for colon-specific drug delivery.

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