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Alkyl Pectin: Hydrophobic Matrices for Controlled Drug Release

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ABSTRACT: Alkyl pectin with various fatty acid (C_4–C_{16}) bromides increased its hydrophobic characteristic and made important changes in its structural features. Unmodified pectin exhibited a low degree of order (DO) and a weak tablet-crushing strength. Pectin alkylated with a short chain length (C_4) possessed similar properties but exhibited significant swelling. Alkylation with longer side chains (C_8–C_{16}) resulted in a higher DO and crushing strength but a lower swelling. The best mechanical characteristics and drug-release properties were found for octanoyl pectin (OP; degree of substitution = 7.06–15.41%) tablets with 20% bovine serum albumin as a tracer. The high stability of these monolithic tablets appeared to be due to hydrophobic interactions between side chains, as shown by a more organized structure. IR spectroscopy and differential scanning calorimetry analyses of OP were consistent with a hydrophobic self-assembling model. The drug dissolution kinetics showed longer release times for higher degrees of functionalization, that is, 35 h (for 10.88% substitution) and 80 h (for 15.41% substitution); this suggested OP excipients as interesting candidates for oral and subdermal pharmaceutical applications. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41302.

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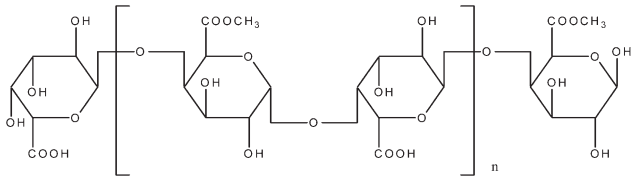
INTRODUCTION

Interest in polymeric matrices for pharmaceutical formulation continues to grow. Special attention is currently being given to pectin. Pectin carboxyl groups are reactive at higher pH values. They are a suitable site for chemical modifications and for enzyme immobilization.[1] Because pectin itself is nontoxic,[2] biodegradable,[3] and biocompatible,[4] several biological applications have been reported for pectin, including site-specific drug-delivery systems[5,6] and drug carriers.[7] Pectin has been modified by crosslinking (e.g., glutaraldehyde) to prepare polyion complex hydrogels.[8]

Pectin has been described as a drug carrier for colon-specific drug delivery.[9–11] Because pectin has good swelling behaviors, drugs with a high solubility display a premature release because of the expanded pore size of pectin formulations. To decrease their swelling abilities, pectin derivatives with hydrophobic residues were prepared. *N*-Octadecylpectinamide is an example with nonpolar side chains;[12] the hydrophobic relationship of such polymers depends on the degree of substitution (DS).[13] The chemical structure of pectin is as follows:



Colon targeted drug delivery has the potential to deliver bioactive agents for the treatment of a variety of colonic diseases and can be effectively treated by the local delivery of the drug to the large intestine. The targeting of drugs to the colon via the oral route can be achieved by different approaches, including different formulation systems,[14] for which the drug release is controlled by different pH conditions, transit time, and intestinal microbial flora.[15] The specific targeting of drugs to the colon is recognized to have several therapeutic advantages. The colon is an ideal site for both the systemic and local delivery of drugs.[16] To reach the colon and have the drug absorbed there, the dosage forms must be formulated with the obstacles of the gastrointestinal tract taken into account. Various strategies have been developed to achieve this goal, such as the use of specific

characteristics of the organ, for example, the pH,[17] microbial flora, enzymes, reducing medium, and transit time.[18] A number of serious diseases of the colon, for example, colorectal cancer, ulcerative colitis, and other inflammatory conditions, could be treated more effectively if drugs could be targeted to the colon.[19,20]

The utilization of enzymes produced by the bacteria residing exclusively in the colon is a means of obtaining site-specific delivery to this region.[21] Dosage forms have been prepared from or coated[22–24] with selected polysaccharides to achieve this aim. The polysaccharide pectin has been investigated extensively.[25] To overcome the problem of the dissolution of pectin in the upper gastrointestinal tract, relatively thick compression coats have been used,[26] or pectin has been combined with an insoluble polymer, such as ethyl cellulose, to produce a film coat.[27] The potential of pectin as a carrier for colonic drug delivery has been demonstrated previously.[28,29] The use of high-methoxy pectin or crosslinking[30] with calcium have been investigated as methods for reducing its inherent solubility. An alternative approach is the formation of an interpolymer complex with pectin in a similar manner to that investigated by Meshali and Gabr.[31]

In this study, pectins with various substituted alkyl groups were prepared and characterized by the methods of FTIR, ^{1}H NMR, and DSC. In this article, we describe alkyl pectin with alkyl bromide as a way to introduce hydrophobicity for use in a matrix for drug delivery. It was expected that such derivatization would reduce the hydration of the matrix and play a role in network stabilization through hydrophobic interactions. The pectin derivatives were examined by Fourier transform infrared (FTIR) spectroscopy, ^{1}H-NMR spectroscopy, differential scanning calorimetry (DS) analysis, and elemental analysis, and the data were compared to those of native pectin (NP).

EXPERIMENTAL

Materials

Pectin was purchased from Fuda Pectin Chemical Co. (China). Its degree of methylation was 70%, as determined by elemental analysis. 1-Bromoctane, 1-bromododecane, and 1-bromohexdecane were purchased from Aldrich Chemical Co., Inc. Bovine serum albumin (BSA; Shanghai Dongfeng Method Biological Technology Co., China.), hydroxypropyl methylcellulose, sodium carboxymethyl starch, and sodium starch glycolate were purchased from the National Medicine Group Chemical Reagent Co. (China). All commercially solvents and reagents were used without further purification. All other chemicals were analytical grade.

Preparation of Alkyl Pectin

Preparation. The *N*-alkylation of pectin was carried out with alkyl bromide in a heterogeneous system in isopropyl alcohol. An amount of 1 g of pectin was dispersed in 25 mL of isopropyl alcohol under stirring. The addition of 1 g of NaOH provided the required alkaline environment, and the sample was cooled at −18°C for 24 h. After thawing at room temperature, pectin was basified with 15 mL of deionized water to fully swell for 1.5 h; the swelling sample was placed into a 100-mL three-necked flask with 20 mL of isopropyl alcohol, and then, 0.2 g of tetrabutyl ammonium bromide (as a phase-transfer catalyst) was added to the solution described previously. This solution was stirred at room temperature for 0.5 h and heated to 80°C to react for 8 h. The products were precipitated with a 1:1 mixture of ethanol and ether, filtered, and thoroughly washed with hexane and acetone. The precipitate, collected by filtration, was washed with an excess of hexane and decanted. The washing was repeated three times to eliminate free reagents. Finally, the products were dried with pure acetone to obtain the corresponding derivative powders.

Solubility Assay. The pectin derivatives (10 mg) were weighed in a small beaker and wetted with a drop of ethanol. Then, 10-mL samples were added to various solutions. The mixtures were stirred on a magnetic stirrer for 1 h and filtered on paper filters. The filters with residual solids were dried and weighed for the estimation of the amounts of insoluble solids. The samples were defined as very soluble, partially soluble (with a markedly lower amount of solids), and insoluble (<5%).

Measurement of the DS of Alkyl Pectin

The DS of alkyl pectin was evaluated by elemental analysis (MOD 1106, Carlo Erba Corp.) analyses from the content of carbon. The carbon contents of the powdered samples of pectin and alkyl pectin were analyzed and recorded as C_p and $C_{A\text{-}p}$, respectively. The DS of alkyl pectin was evaluated by the following formula, and each sample was measured three times.

$$\mathrm{DS}(\%) = \frac{C_{A-p} - C_p}{C_p} \times 100\%$$

Structural Analysis

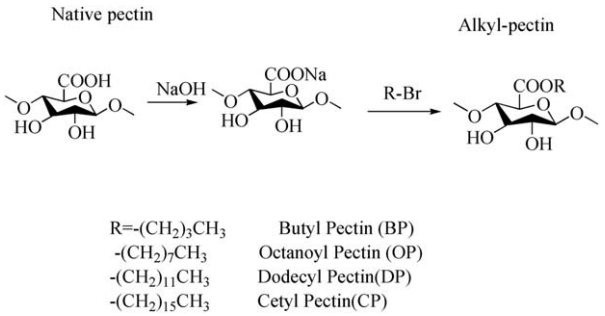
FTIR Analysis. FTIR spectra were recorded with a Spectrum One spectrophotometer (Nicolet 200SXV FTIR, PerkinElmer) equipped with a universal attenuated total reflectance device for tablet analysis in the spectral region (4500–500 cm^{-1}) with 64 scans recorded at a 4 cm^{-1} resolution.

DSC Analysis. The thermal properties were measured by DSC analysis with a DSC 823 instrument (Mettler-Toledo, Columbus, OH) with a quench-cooling accessory. Aliquots of approximately 10 mg of the samples previously conditioned (at 23°C and 50% relative humidity for 2 weeks) were placed in hermetically sealed aluminum pans to prevent moisture loss during analyses and were then heated at 10°C/min from 5 to 110°C in an inert environment (100 mL of N_2/min). The first scan was immediately followed by quick cooling to 5°C at a rate of 40°C/min with liquid nitrogen, and the second scan was then run.

^{1}H-NMR. High-resolution ^{1}H-NMR spectra were recorded on a Varian Unity INOVA-400 spectrometer. The samples were 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 at 330 K.

Preparation of Prescription

BSA powder (0.2 g) was weighed by an 80-mesh sieve into a flask and stirred evenly with octyl pectin (3.0 g), soluble starch (3.6 g), and sodium carboxymethyl starch (0.5 g). Hydroxypropyl methylcellulose was dissolved in ethyl alcohol (2% w/v).



Scheme 1. Pectin derivatization with alkyl bromides.

The solution was gradually added to the flask under stirring, and the moist materials were prepared by an 18-mesh sieve and were dried in the oven for 40 min at 60°C. The dry granules were passed through an 18-mesh to sieve whole to add 4% (ca. 0.292 g) of thoroughly mixed talcum powder (with a 5.5-mm shallow concave punch-molded piece) to create BSA release tablets, with each tablet containing 10.0 mg of BSA 10.0. Octanoyl pectin (OP) tablets with different DS were prepared with the same method described previously.

Dissolution Tests *In Vitro*

BSA tablets (10.0 mg, 11 mm in diameter, and 3.0 mm in thickness) of the native or alkyl pectin were obtained by the direct compression of powders. The kinetics of drug release were recorded with a dissolution tester (RCZ-1 A) coupled with an UV Hewlett-Packard spectrophotometer for the detection of BSA (279 nm) and were presented with the diffusion equation[33] as the ratio of the amount of drug released at time t to the total amount of drug released from the tablet.

RESULTS AND DISCUSSION

Characteristics of Alkyl Pectin in Powder and Tablet Forms

Two main aspects were examined in this study: the effect of the alkyl pectin length (Scheme 1) and the DS on the structure and behavior of pectin.

FTIR Analysis

After alkylation, the vibrational band corresponding to the primary carboxyl groups at 1600 cm^{-1} disappeared (Figure 1),

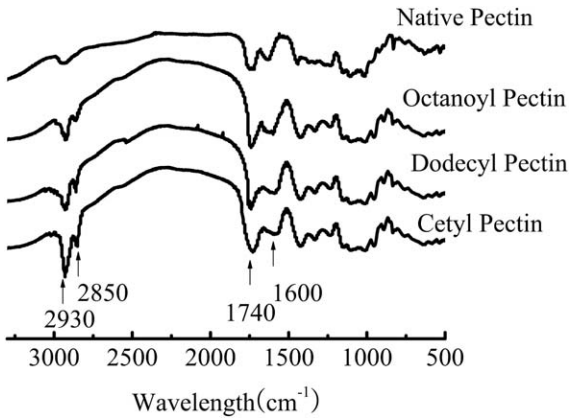


Figure 1. FTIR spectra (D_2O) of unmodified and acylated pectins with different acyl lengths (DS = 10–20%).

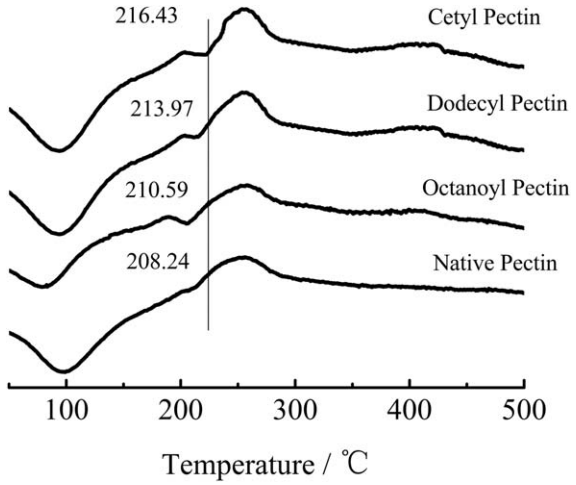


Figure 2. DSC of unmodified and acylated pectins with different acyl lengths (DS = 10–20%).

whereas prominent bands at 1740 cm^{-1} were observed. The absorption peaks at 2850–2930 cm^{-1} were ascribed to —CH_2; their intensity was proportional to the alkyl chain length. These results clearly confirm that the pectin was substituted.

Thermal Properties

The thermal properties were measured by DSC. The glass-transition temperature of pectin was gradually altered with increasing alkyl pectin length (Figure 2). DSC of pectin showed peaks of moderately low intensity, which were broader than those of dodecyl pectin (DP) and cetyl pectin (CP). In the case of OP (short chain), the glass temperature showed only a diffuse peak (at 210.59°C), which was higher than that of pectin. With longer alkyl chains lengths (C_8–C_{16}), the glass temperature peaks became higher; moreover, the peak areas became broader. These major changes suggested a more stable organization than for other forms of pectin. Furthermore, it seemed that these hydrophobic interactions could enhance the stability and participate in a self-assembled network organization.

^{1}H-NMR

The ^{1}H-NMR spectra of NP and octyl pectin with 10.88 and 15.41% DSs, respectively, are presented in Figure 3. For NP, the peaks at 4.8–4.9 ppm were ascribed to the H-1 protons of galacturonic acid (GalpA), and those at 4.0–4.1 ppm were ascribed to the H-2 proton of the GalpA residues.[34] The H-3 and H-4 protons were found around 3.7 and 3.6 ppm, respectively. The peaks at 4.5–4.6 ppm were assigned to the H-5 protons of the GalpA residues. New peaks at 0.99, 1.46, and 1.7 ppm were ascribed respectively to the —CH_3, —CH_2—, and —(COO)CH_2 of the octyl residue and appeared with intensities that varied directly with the degree of octylation.

Drug-Release Kinetics from the Alkyl Pectin Matrix

The release kinetics of BSA from the tablets obtained from pectin derivatives with different lengths of alkyl chains are presented in Figure 4. The release kinetics were followed in 1:1 phosphate buffer (50 m*M*, pH 7.8) at 37.5 ± 0.5°C, a pressure of 8 kg/mm^2, and 100 rpm with a dissolution device. The NP tablets rapidly disintegrated ($t_{90\%} \approx 1$ h, where $t_{90\%}$ is time for

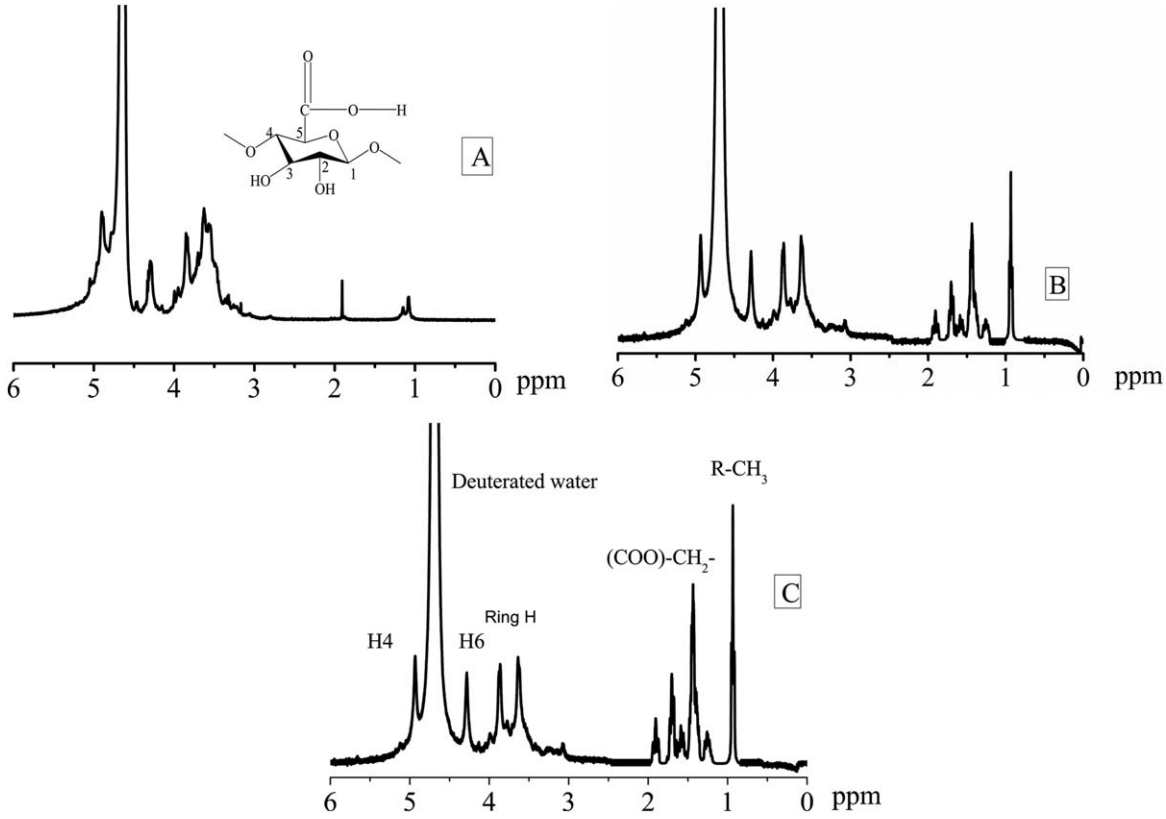


Figure 3. ^{1}H-NMR spectra of (A) NP and (B,C) octyl pectin with degrees of acylation of 10.88 and 15.41%, respectively.

the drug release of 90%), whereas those based on alkylated pectins remained intact in the aqueous medium (with no erosion or sticking observed). The butyl pectin (BP)-based tablets showed short release times ($t_{90\%} \approx 3$ h). A moderately long release (10 h) was observed for OP, and longer releases (15 and 20 h) were observed for DP and CP, respectively. This was attributed to a hydrophobic barrier limiting the access of water and dissolution of the drug. OP maintained better mechanical properties and preservation of the tablet shape during the release than BP. According to Peppas and coworkers,[35,36] there are three primary mechanisms by which the release of active agents can be controlled: erosion, diffusion, and swelling followed by diffusion. Erosion may take place via the hydration and hydrolysis of the bulk, with the polymer being slowly degraded starting at the periphery of the tablet. Diffusion can occur as the unhydrated polymer gradually swells when it is in contact with body fluids. The delivery mechanisms for OP, DP and CP appeared totally different. In the case of the OP-based tablet (gel), the release mechanism may be controlled by swelling followed by diffusion, whereas for DP and CP (less swelling or no swelling), it may be based on diffusion alone.

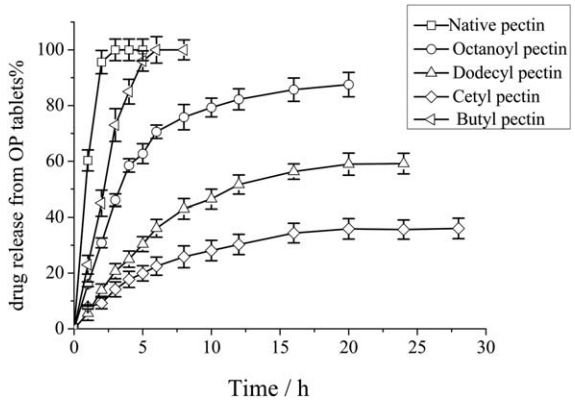


Figure 4. BSA release profiles as a function of the length of the alkyl pectin of functionalized pectin-based tablets (10.0 mg) containing 20% bovine serum albumin. The DSs of OP, DP, and CP were 15.41, 10.51, and 11.23%, respectively. The release kinetics were followed in a 1:1 phosphate buffer (50 m*M*, pH 7.8) at 37.5 ± 0.5°C, 8 kg/mm^2 (pressure), and 100 rpm with a dissolution device.

The cetyl derivative exhibited the best mechanical properties and release characteristics. However, the cumulative drug-release rate of CP was less than 40%; CP was not the best sample for future study. OP showed better mechanical properties and release characteristics than CP, so studies were continued with OP with different DSs to better evaluate its usefulness as a controlled release system. OP as a matrix for controlled drug release has good prospects.

DS

Table I shows the DS and solubility of alkyl pectin. The DSs of the alkyl groups were from 4.51 to 15.41% because of

Table I. DS and Solubility of Alkyl Pectin

Sample	Pectin/alkyl bromide (mol/mol)	DS (%)	Analysis conclusion: C (%)	Solubility	
				Water	0.05 mol/L NaOH
1	1:9 (C_4H_9Br)	12.58	31.685	Soluble	Soluble
2	1:2 ($C_8H_{17}Br$)	7.06	30.083	Soluble	Soluble
3	1:6 ($C_8H_{17}Br$)	10.88	31.157	Partially soluble	Soluble
4	1:9 ($C_8H_{17}Br$)	15.41	32.428	Insoluble	Swelling
5	1:9 ($C_{12}H_{25}Br$)	10.51	30.479	Insoluble	Swelling
6	1:9 ($C_{16}H_{33}Br$)	11.23	31.273	Insoluble	Swelling

NaOH concentration = 0.5%, time = 8 h, and temperature = 80°C.

differences in the amount and kinds of 1-bromoctane. The DSs of the alkyl groups decreased with increasing alkyl chain length and decreasing amount of 1-bromoctane. These results clearly demonstrate that the DSs of the products were strongly controlled by the activity of alkyl bromide.

Influence of the Dissolution Medium on the Drug-Release Behavior. The drug-release rate was 92.3% from OP tablets in a pH 7.8 buffer solution (simulated colon liquid, Figure 5). However, the drug-release rates were 21.5 and 2.82% in pH 6.86 (simulated small intestine liquid) and 1.0 (simulated gastric liquid) buffer solutions, respectively; this was attributed to the lack of pectin enzyme in the stomach and small intestine solutions. The drug of the OP tablets could be sent to the site-specific targets in the colon.

Influence of the Compressing Pressure on the Drug-Release Behavior

The diffusion of the drug was controlled by low water access. For tablets based on OP, the kinetics of drug release persisted for up to 25,15, and 8 h with compressing pressures of 10, 8, and 6 kg/mm^2, respectively (Figure 6). When the compression pressure was bigger, the drug release was lower.

Influence of the Rotational Speed on the Drug-Release Behavior

The rotational speed affected the drug release from the OP tablets obviously. The release percentages of the drug were found to be 97.5% at 150 rpm, 92.7% at 100 rpm, and 59.6% at 50 rpm (Figure 7). Considering the physiological conditions of the human body, a rotational speed of 100 rpm was selected for the best conditions.

Influence of the DS on the Drug-Release Behavior

The control of drug release was improved by the hydrophobic stabilization of the matrices and the DS. The diffusion of the drug was controlled by low water access. For tablets based on OP with a 10.88% DS [Figure 8(A)], the kinetics of drug release persisted up to 35 h, even with high drug loadings (40 and 60% of BSA). On the other hand, the kinetics of drug release by OP tablets with a 15.41% DS were dependent on the initial drug loading [Figure 8(B)]. For tablets with a 20% drug loading, the duration of release was up to 80 h. For higher drug loads, the duration of release decreased to 45 h for a 40% drug loading and 25 h for a 60% drug loading. The explanation of this phenomenon may reside with the drug solubility, particularly in the case of hydrophilic drugs that alter the hydrophilic or hydrophobic characteristics of the system. At a high drug

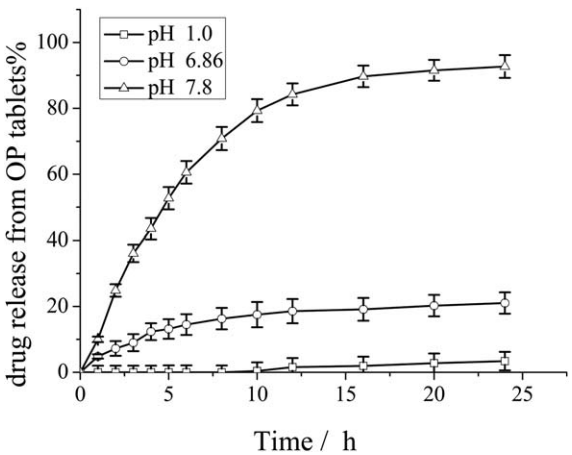


Figure 5. Release of OP tablets (10.0 mg) containing 20% bovine serum albumin with different pH values (1.0, 6.86, and 7.8) at 37.5 ± 0.5°C, 8 kg/mm (compression pressure), and 100 rpm.

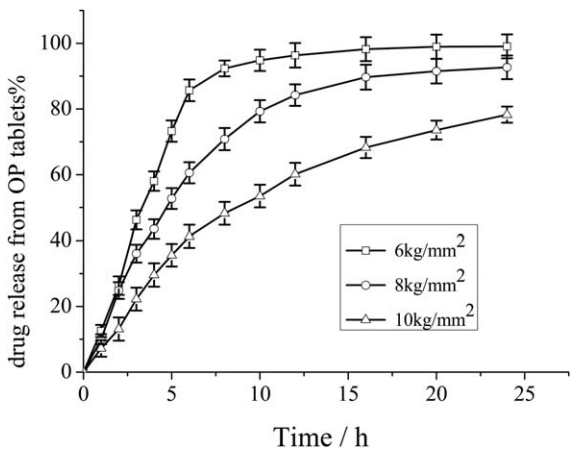


Figure 6. Release of OP tablets (10.0 mg) containing 20% bovine serum albumin in a 1:1 phosphate buffer (50 m*M*, pH 7.8) at 37.5 ± 0.5°C and 100 rpm.

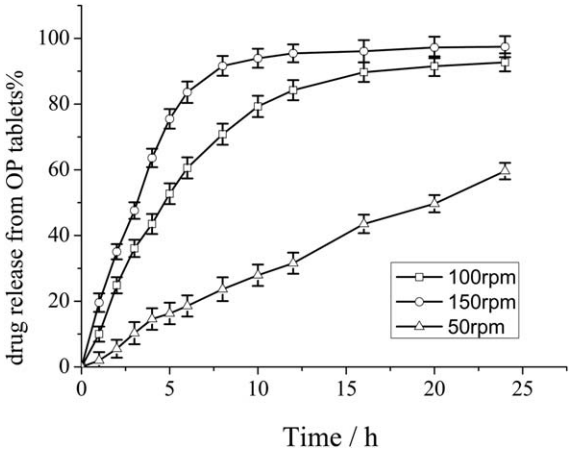


Figure 7. Release of OP tablets (10.0 mg) containing 20% bovine serum albumin in a 1:1 phosphate buffer (50 m*M*, pH 7.8) at 37.5 ± 0.5°C and 8 kg/mm^2.

loading (60%), there was an increase in hydration-creating pores, which favored drug diffusion. In this case, the release profile was very similar to OP with a 10.88% DS ($t_{90\%}$ = 25 h).

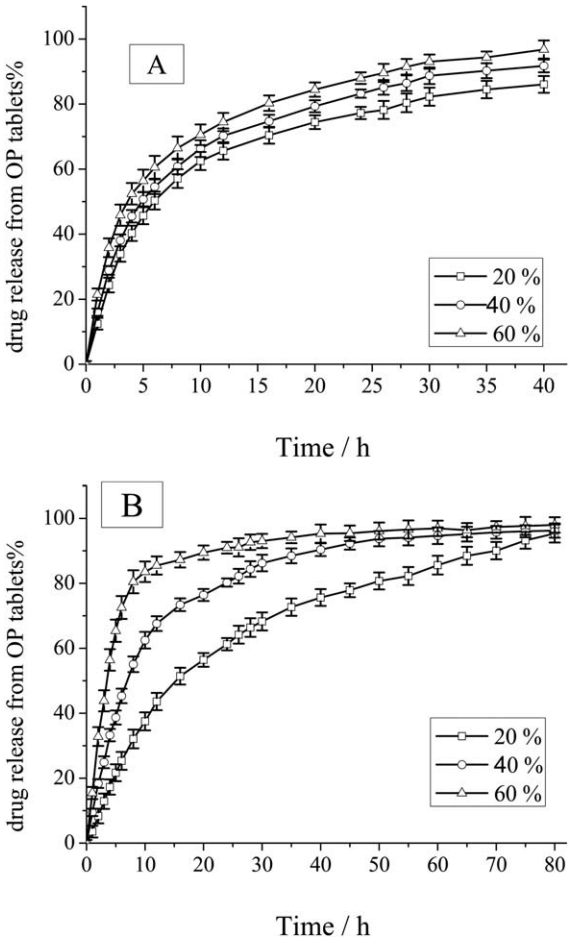


Figure 8. Release profiles of BSA from tablets (10.0 mg) based on OP with (A) 10.88 and (B) 15.41% DSs and containing 20, 40, and 60% drug in a 1:1 phosphate buffer (50 m*M*, pH 7.8) at 37.5 ± 0.5°C, 8 kg/mm^2, and 100 rpm.

Until now, no extensive study has been reported on the biocompatibility of OP. This compatibility, which is higher for longer alkyl side lengths, was explained by a higher susceptibility of longer chain alkyl pectins to enzymatic degradation by lysozymes. We also considered that the DS of alkyl pectin contributed to their biodegradability. Consequently, pectin, having a high degree of high octanoyl, seems of interest as an implant for the controlled release of bioactive compounds, such as antibiotics, steroids, peptide hormones, contraceptives, and so on that are useful for human and veterinarian therapy.

CONCLUSIONS

Taking BSA as a drug model, alkyl pectin tablets (as skeleton materials) were prepared for colon-specific delivery, and we evaluated their release properties *in vitro*. The results show that the BSA sustained-release tablets kept releasing for 20 h in phosphate buffer solution at pH 7.8, whereas they hardly released at all in environments at pH < 6.8. The cumulative release rate was above 90%. The different rotational speeds and compaction pressures caused significant differences in the release rates in the phosphate buffer solution at pH 7.8. The cumulative drug-release rate was significantly affected by both the alkyl chain length and the DS of alkylation because of the hydrophobic interactions that enhanced the stability of the substituted pectins. In particular, the OP tablets showed not only better mechanical properties but also better release characteristics than CP and were more suitable for controlled drug release. Therefore, alkyl pectins are of interest for use as excipients in controlled drug-delivery systems, and the tablets have good prospects for applications in drug-delivery systems as well.

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