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Hydroxypropylated starches of varying amylose contents as sustained release matrices in tablets

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ABSTRACT

Waxy corn, Hylon VII, and common corn starches were hydroxypropylated to low and high levels, and their sustained release properties and matrix characteristics were studied. Hydroxypropylation had a stronger impact on Hylon VII and common corn starch matrices than on waxy corn ones, suggesting that the behavior of starch tablet was dominated by its amylose content. The introduction of hydroxypropyl groups increased the water holding capacity of all starches and resulted in more fluid-like and softer matrices with increased chain mobility for amylose-containing starches. There was a decrease in the tablet porosity and in the storage modulus of swollen tablets of Hylon VII and common corn starches after hydroxypropylation. Microscopic analyses revealed smoother and less porous tablet structure upon hydroxypropylation of all starches. Hydroxypropylation improved the sustained release ability of amylose-containing starch matrices, and conferred additional resistance to the hydrolytic action of pancreatin under simulated gastrointestinal conditions. However, hydroxypropylation had a detrimental impact on drug release from waxy corn starch matrices.

1. Introduction

Starch as an ingredient has been extensively used in the food industry, mainly as a thickening and gelling agent. Its role in the pharmaceutical industry has expanded from a simple filler or binder (Roper, 1996) to a more functional ingredient in the formulation of capsules (Vilivalam et al., 2000), coatings (Milojevic et al., 1996), subcutaneous implants (Désévaux et al., 2002), and tablets. In tablets, starch has been mainly studied as a sustained release agent in matrix systems (Mulhbacher et al., 2001; Nabais et al., 2007).

Upon gelatinization, native starch shows poor shear and thermal resistance and high tendency of retrogradation. Modification via chemical, physical and/or enzymatic means is a common way to improve starch functionality, tailoring its physicochemical properties to desired applications. Hydroxypropylation is a type of chemical modification commonly used to improve starch clarity and cold-storage stability in the food industry because the presence of hydroxypropyl groups increases water holding and reduces reassociation of starch chains, thus facilitating the creation of a more stable gel (Pal et al., 2002).

Modified starches have been studied as functional ingredients in sustained release applications because of their improved functionality over their native counterparts (Herman and Remon, 1989; Te Wierik et al., 1997; Le Bail et al., 1999; Chebli et al., 2001; Mulhbacher et al., 2001; Yoon et al., 2007). Among them, cross-linked high amylose corn starch is the most extensively studied one (Mateescu et al., 1995). The sustained release properties of cross-linked and substituted high amylose corn starch matrices and their swelling behavior in media with various pH and ionic strengths have been reported by Mulhbacher et al. (2001, 2004). The matrix characteristics of cross-linked high amylose starches have been studied by Dumoulin et al. (1998) and Le Bail et al. (1999).

The potential of starch as a sustained release agent is attributed to its gel-forming ability, biodegradability, and biocompatibility (Zhang et al., 2005). The molecular structure of the gel layer and the mechanical and physicochemical characteristics of the matrix such as gel strength and porosity dictate to a great extent the sustained release properties of the matrix. Rheological analyses can provide insights into the molecular structure of gels and pastes, thus helping establish the relationship between matrix structure and drug release properties (Martinez et al., 2007; Alvarez-Manceñido et al., 2008; Onofre et al., submitted for publication). The porosity of a matrix may explain how drug is allowed to pass through the matrix to the surrounding medium (Collins et al., 2007). Image analysis such as scanning electron microscopy (SEM), and nuclear magnetic resonance imaging have been used to evaluate surface and morphological aspects of delivery systems such as tablets or particles, and to analyze how the gel layer is formed in tablets (Vlachou et al., 2004; Thérien-Aubin et al., 2008). Therefore, a thor-

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ough understanding of these characteristics will help elucidate the mechanisms involved in drug release from the system.

In this study, corn starches with varying amylose contents were hydroxypropylated and their sustained release ability in water and simulated gastrointestinal conditions in the presence of pancreatin was evaluated. The matrices were also characterized for their water holding capacity, porosity, rheological properties, and morphology, to be correlated with their sustained release properties.

2. Materials and methods

2.1. Materials

Waxy corn (AMIOCA, ~100% amylopectin) and 70% high amylose corn (Hylon VII, ~70% amylose) starches were provided by National Starch and Chemical Company (Bridgewater, NJ), and common corn starch (C*Gel 03420, ~27% amylose) was obtained from Cargill, Inc. (Hammond, IN). Propranolol hydrochloride was purchased from TCI America (Portland, OR), magnesium stearate was from Riedel-de Haën (Seelze, Germany). Propylene oxide, and sodium sulfate and sodium phosphate tribasic (dodecahydrate) were from EMD Chemicals Inc. (Gibbstown, NJ). Pancreatin with activity of 8× USP specifications (EC 232-468-9) was obtained from Sigma–Aldrich (St. Louis, MO). All other chemicals were of ACS grade.

2.2. Hydroxypropylation (HP) of starches

Starches were hydroxypropylated according to the procedure of Wang and Wang (2000) with slight modification. In a 1-L reaction vessel, 320 g of starch was slowly added to 800 mL of deionized (DI) water containing 48 g of Na_2SO_4 (15%, w/w starch dry basis, db) with pH previously adjusted to 11.5 using 1 M NaOH. The pH was corrected to 11.5 after starch addition, and 10 or 20% propylene oxide (w/w starch db) was added to prepare low or high level of HP, respectively. The vessel was sealed, and the slurry was stirred at room temperature for 1 h before the temperature was raised to 45 °C in a water bath. The reaction was allowed to proceed at 45 °C for 18 h with constant stirring. After the reaction was completed, an aliquot (100 mL) of the slurry was mixed with 50 mL of 20% NaOH, stirred for 2 min to ensure complete starch gelatinization, and then neutralized to pH ~6 with 6 M and 1 M HCl. The gelatinized starch was precipitated with 100 mL acetone, then washed 5× with 1 vol. 50% ethanol solution. The final wash was done with pure acetone, and the starch was dried in an oven at 40 °C for 48 h before being ground using a Cyclone Sample Mill (UDY Corporation, Fort Collins, CO), and passed through a 75-μm sieve. A control from each starch was prepared in the same manner as just described, except without HP.

2.3. Determination of the degree of substitution (DS)

The hydroxypropyl content of starches was determined using the spectrophotometric method of Johnson (1969), and expressed as DS (Wurzburg, 1986):

$$\mathrm{DS} = \frac{162 \times (\%\mathrm{HP}/58)}{100 - [(57/58) \times \%\mathrm{HP}]}$$

2.4. Water holding capacity

Forty milligrams of starch was added to a pre-weighed 2-mL micro-centrifuge tube containing 1.5 mL of deionized water. The tube was placed in a heat block at 37.5 °C for 1 h, followed by immediately cooling in an ice bath. The tube was then centrifuged at 12,000 × g for 10 min using a micro-centrifuge (Eppendorf Centrifuge 5415D, Germany). The excess water was removed, and the tube containing the remaining gel was weighed. The water holding capacity was calculated as:

$$\text{water holding capacity (g/g)} = \frac{\text{gel weight (g)}}{\text{dry starch weight (g)}}$$

At least three measurements were done for each starch.

2.5. Preparation of tablets

Propranolol hydrochloride (30% loading, w/w of tablet) and starch were mixed in a mini-manual mixer (Inversina, Bioengineering AG, Wald, Switzerland) for 10 min. Magnesium stearate (1%, w/w of tablet) was then added and the mixture was mixed for an additional min. Tablets were prepared by compressing 500 mg of the mixture at 2.0 MT with a 13-mm die using a hydraulic press (Carver, Wabash, IN).

2.6. Drug release in water

Drug release in water was determined using an Apparatus II (USP, 2003) dissolution equipment (Varian Inc., Cary, NC) with a paddle rotation speed of 50 rpm. Tablets were placed in 900 mL of DI water at 37.5 °C for 24 h, and samples of the medium were taken without replacement. Drug released was measured using a spectrophotometer (Beckman Coulter, Fullerton, CA) at 290 nm. All experiments were performed in triplicate.

2.7. Drug release in a simulated gastrointestinal (GI) environment

Drug release in a simulated GI environment was performed using the same dissolution parameters as described in Section 2.6. The initial medium was 0.1 M HCl (pH ~1), and the pH of the medium was raised to 6.8 after 2 h, and to 7.4 after 4 h of dissolution using appropriate amounts of sodium phosphate tribasic (dodecahydrate). Pancreatin (450 mg) was added after pH adjustment to 6.8 at 2 h of dissolution, to achieve a final α-amylase activity of 100,000 IU/L medium. Aliquot samples were taken without medium replacement, and drug released was measured using a spectrophotometer at 290 nm. All experiments were done in triplicate.

2.8. Rheological properties

The tablet was placed on a microscope cover glass in a 5-cm diameter plastic petri dish, and 5 mL of DI water previously heated to 37 °C was added. The petri dish was then placed in a 37 °C water bath for 15 min to allow for water penetration into the matrix. Afterwards, the tablet was retrieved by removing the cover glass from the medium, and a sequence of frequency sweep test followed by creep test was performed. Six replicates were done for each starch prepared.

2.8.1. Frequency sweep test

The swollen tablet on the cover glass was placed on the bottom plate of an AR 2000 rheometer (TA Instruments, New Castle, DE) maintained at 25 °C, and a 40-mm sandblasted parallel plate was lowered to a gap of ~4 mm. After 30 s of equilibration, a frequency sweep of 100–1 Hz was initiated with a strain of 0.2%. Storage modulus (G'), loss modulus (G''), and complex viscosity ($|\eta^*|$) were measured as a function of frequency.

2.8.2. Creep test

Immediately following the frequency sweep test, a creep test was performed using the same tablet. A stress of 1.2 Pa was applied

Table 1
Degree of substitution and water holding capacity of hydroxypropylated starches and their controls.

Starch type	Level of substitution	Degree of substitution (DS)	Water holding capacity[a]
Waxy corn	Control[b]	–	21.38 ± 0.48 B
	Low	0.07	∞[c]
	High	0.19	∞
Hylon VII	Control	–	5.79 ± 0.04 E
	Low	0.07	10.43 ± 0.14 F
	High	0.20	∞
Common corn	Control	–	18.52 ± 0.47 C
	Low	0.08	16.92 ± 0.11 D
	High	0.20	23.01 ± 0.73 A

[a] Mean ± standard error of at least three observations. Means with different letters are significantly different ($P < 0.05$).
[b] Gelatinized but not hydroxypropylated.
[c] Water holding capacity too excessive to be quantified.

to the tablet for 3 min, and the compliance $J(t)$ was measured. Then, the stress was removed, and the recovery was measured for 3 min. The recoverable compliance (difference between maximum and final compliance) and the ratio of recoverable compliance/maximum compliance were calculated from the data obtained.

2.9. Porosity

Tablet porosity was measured using an AccuPyc 1330 Pycnometer (Micromeritics Instrument Corporation, Norcross, GA) by the Helium displacement procedure. The percent porosity was calculated by the difference between the bulk volume calculated from the dimensions of each tablet and the skeleton volume provided by the instrument. Five measurements were done for each sample.

$$\text{porosity}\,(\%) = \frac{\text{bulk volume}\,(\text{cm}^3) - \text{skeleton volume}\,(\text{cm}^3)}{\text{bulk volume}\,(\text{cm}^3)} \times 100$$

2.10. Morphology of swollen tablets

Tablets of control and highly hydroxypropylated starches were swollen in 900 mL of DI water at 37.5 °C for 4 h in the dissolution apparatus with a paddle rotation speed of 50 rpm. The tablets were then carefully removed from the vessel with a spatula, immediately frozen in a blast freezer (Model air-o-chill, Electrolux, Fort Lauderdale, FL), and freeze-dried using a Freezone 6 freeze-dryer (Labconco, Kansas City, MO). The tablets were fractured using a blade, placed on a carbon tab attached to a stub, coated with gold–palladium, and observed using an environmental scanning electron microscope (XL30, FEI Corporation, Eindhoven, The Netherlands) at an accelerating voltage of 5.00 kV. The cross-section and surface of the freeze-dried tablets were observed.

2.11. Statistical analyses

All statistical analyses were performed using JMP 8.0 software (SAS, 2008). Means comparison was done using the Tukey–Kramer HSD test, and non-linear analysis of drug release over time was used to calculate the diffusional exponent n that evidenced drug release mechanism. The level of significance α was set at 0.05.

3. Results and discussion

3.1. Substitution efficiency and water holding capacity

The DS and water holding capacity of the hydroxypropylated starches and their controls are listed in Table 1. Similar DS were observed for low and for high levels of hydroxypropylation (HP) for different starches, indicating that the reaction efficiency was not affected by the amylose/amylopectin ratio. Although Shi and BeMiller (2000) reported that amylose was preferentially hydroxypropylated over amylopectin, especially at higher DS levels, for common corn starch, an increase in HP probably progressively opened up starch structure and exposed amylopectin, leading to a more homogeneous reaction.

The water holding capacity of all starches significantly increased with increasing HP. The water holding capacity of hydroxypropylated waxy corn and highly hydroxypropylated Hylon VII starches was too excessive to be quantified by the method employed because no clear phase separation was observed after centrifugation. The amylose/amylopectin ratio and the differences in distribution of hydroxypropyl groups between amylose and amylopectin among these substituted starches likely contributed to their different water holding capacities.

3.2. Drug release in water

Fig. 1 displays the drug release profiles of hydroxypropylated starches and their controls in water. HP increased propranolol release from waxy corn matrices, especially after 4 h of dissolution, but there was no difference in drug release between the two levels of HP (Fig. 1a). The introduction of hydroxypropyl groups probably disturbed the molecular association of waxy corn starch chains, which led to matrices less capable of retaining the drug in their structures. Similar results were found when waxy corn starch was cross-linked to a high level at the granular state (Onofre et al., submitted for publication). In contrast, the release of propranolol from Hylon VII and common corn starch matrices was markedly improved with HP (Fig. 1b and c). The release rate from highly substituted Hylon VII matrices was significantly reduced, with 25% of drug released at 4 h, compared with 100% from the control. Furthermore, highly substituted Hylon VII matrices showed a steady release profile up to 8 h. Substituted common corn starch matrices also showed a steady drug release, with ~85 and 75% of drug released after 24 h for low and high levels of HP, respectively.

The results suggest that HP of amylose was the critical factor for better drug release because HP did not improve the sustained release properties of waxy corn starch matrix. The introduction of hydroxypropyl groups to amylose chains improved their water holding capacity, probably leading to the formation of a better matrix.

When the Power Law $M_t/M_\infty = k \times t^n$ (Peppas, 1985) was fit to the early stages of release ($M_t/M_\infty < 0.6$) from highly hydroxypropylated waxy corn, Hylon VII and common corn matrices, the exponent n were 0.80, 0.74, and 0.65, respectively. These values are characteristic of anomalous release from cylindrical slabs, as it is commonly found in gel-type matrices (Rahmouni et al., 2001).

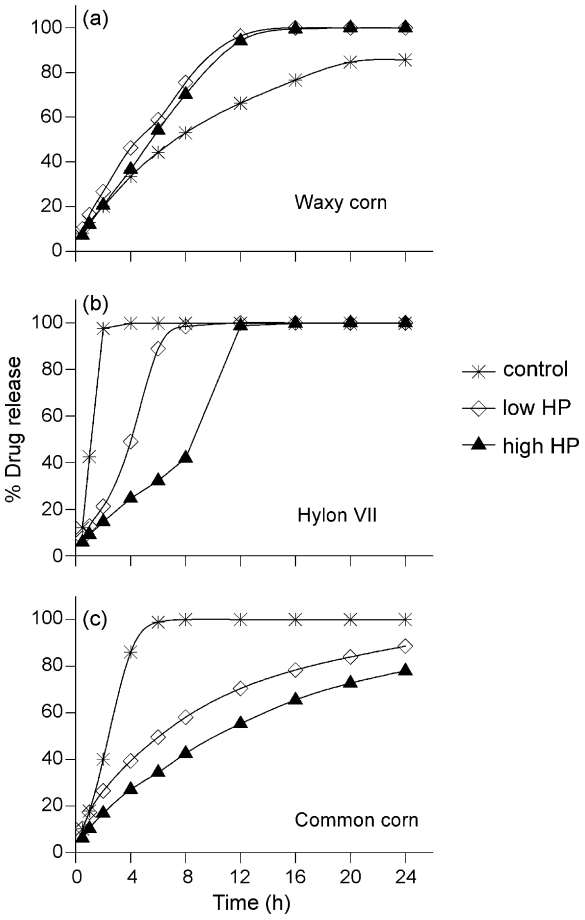

Fig. 1. (a–c) Propranolol release in water from hydroxypropylated starch matrices and their controls. Control: gelatinized only; HP: hydroxypropylation.

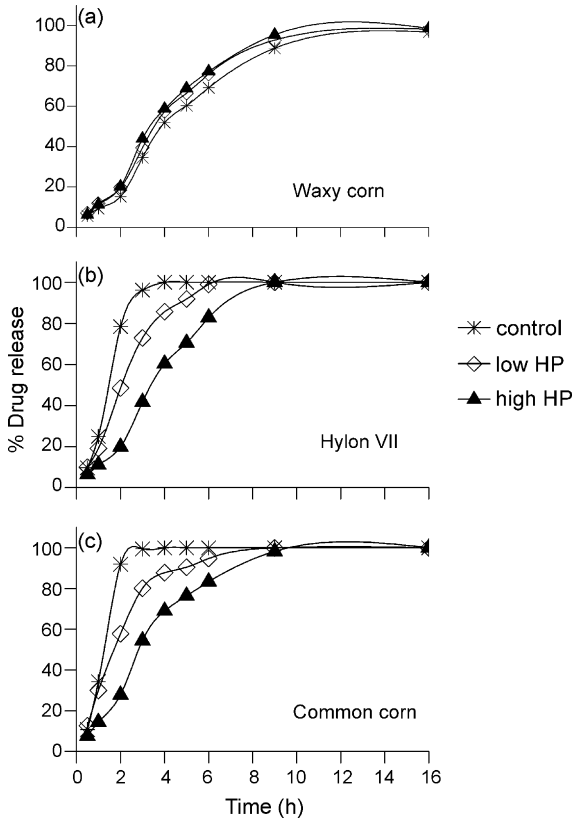

Fig. 2. (a–c) Propranolol release in simulated GI conditions in the presence of pancreatin from hydroxypropylated starch matrices and their controls. Control: gelatinized only; HP: hydroxypropylation.

3.3. Drug release in simulated GI environment

In this study, pancreatin was used to simulate human gastrointestinal enzymes, and it readily digests amylose and more slowly amylopectin. All matrices were susceptible to hydrolysis by α-amylase in pancreatin, and showed more rapid drug release than in the absence of α-amylase (Fig. 2). There was no difference in drug release from hydroxypropylated waxy corn matrices and their control (Fig. 2a), whereas hydroxypropylated Hylon VII and common corn starch matrices showed slower drug release than their controls (Fig. 2b and c). HP likely conferred protection to starches against α-amylase hydrolysis because the presence of hydroxyl groups, particularly on C-2 of the glucose unit, causes steric hindrance to the binding of α-amylase to starch molecules (Hoover and Zhou, 2003; Chung et al., 2008). In addition, HP led to the formation of better gel matrices, particularly for amylose-containing starches, which might delay the diffusion of enzyme into the tablet (Rahmouni et al., 2001). The time to release 80% of propranolol from waxy corn and highly hydroxypropylated Hylon VII and common corn starch matrices (~6 h) was comparable to that reported by Rahmouni et al. (2001, 2003) for the release of sodium diclofenac from Contramid® in the presence of α-amylase.

Drug release from waxy corn matrices in the presence of α-amylase did not markedly differ from that in water (Fig. 1), indicating that the branched structure in amylopectin retarded α-amylase hydrolysis. It is to be noted, however, that the drug release profile from Hylon VII matrices was comparable to that of common corn starch ones for the same level of HP in the presence of α-amylase, although common corn starch matrices showed much slower release than Hylon VII ones in the absence of α-amylase (Fig. 1). The smaller shift on drug release profile of Hylon VII matrices in the presence of amylase implies the occurrence of re-associated amylose that was resistant to α-amylase degradation. The re-associated amylose was not prevalent in common corn starch probably because of its much lower amylose content.

In the presence of α-amylase, highly hydroxypropylated Hylon VII and common corn starch matrices showed hydrolysis patterns similar to those of waxy corn ones, suggesting that the drug release rate from starch matrices was affected not only by starch composition but also by other matrix characteristics such as gel formation and matrix cohesiveness upon swelling.

When the Power Law model was fit to the drug release data in GI environment from highly hydroxypropylated waxy corn matrices, the exponent n was 1.38. For highly hydroxypropylated Hylon VII and common corn matrices, the exponent n was 1.32 and 1.29, respectively. This increase indicated a change in mechanism of drug release from an anomalous pattern to a Super Case II transport in all starch matrices after HP. The erosion of matrices as a consequence of hydrolysis by α-amylase became more dominant than diffusion of drug through the swollen matrix under the simulated GI conditions. An increase in n value of starch matrices as a result of enzymatic hydrolysis was also reported by Rahmouni et al. (2001).

3.4. Rheological properties

3.4.1. Frequency sweep test

The G' and G'' moduli were the highest for Hylon VII matrices, followed by common corn and waxy corn ones, respectively, indicating that amylose-containing corn starch gels are more rigid than waxy corn ones (Fig. 3). These results are in agreement with Luyten et al. (1992), who reported that the extent of amylose gel network

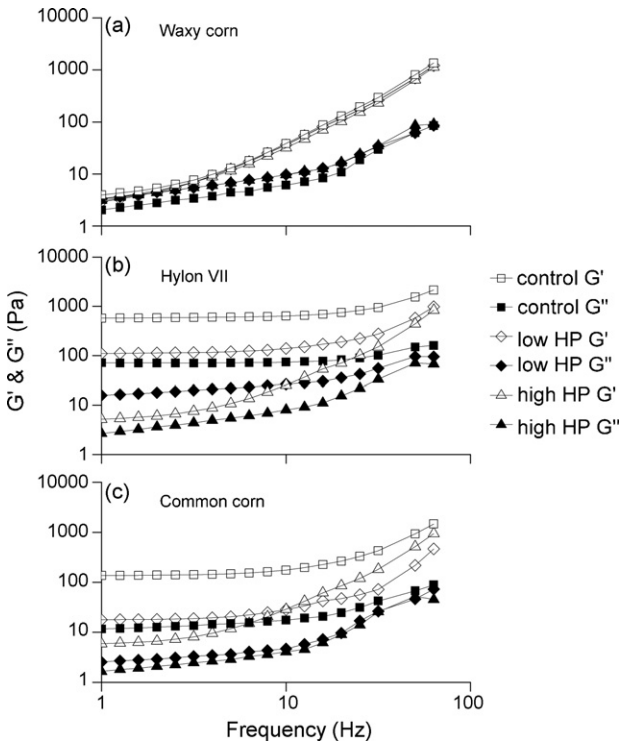

Fig. 3. (a–c) G' and G'' values of hydroxypropylated starch matrices and their controls from frequency sweep test. Control: gelatinized only; HP: hydroxypropylation.

was one of the main factors that contributed to gel characteristics such as strength in starch gels.

HP only slightly changed G' and G'' of waxy corn starch matrices (Fig. 3a), but significantly decreased both moduli of Hylon VII and common corn ones (Fig. 3b and c). The results support the drug release observations that HP had a greater impact on the properties of amylose-containing starches. The reduction in both moduli indicates the formation of a less rigid structure after HP.

For Hylon VII and common corn controls, the difference between their respective G' and G'' moduli was of a decade of magnitude, but the difference was significantly reduced with HP, and the viscous modulus (G'') became more dominant. Furthermore, the frequency dependence of both moduli also increased with increasing HP. Thus, amylose-containing gel matrices transitioned from a more "true gel" behavior to a more "viscous fluid" one (Clark and Ross-Murphy, 1987; Almdal et al., 1993). In fact, highly hydroxypropylated amylose-containing matrices showed profiles and moduli magnitudes similar to those of waxy corn ones, suggesting that they behaved similarly. This transition to a "viscous fluid" behavior of amylose-containing matrices may be a critical step for the development of a satisfactory sustained release starch matrix.

The Power Law proposed by Ramkumar and Bhattacharya (1996) can be used to describe gel properties, and can be expressed as:

$$G' = A\omega^B$$

where G' is the storage modulus, A is a constant, ω is the angular frequency, and B is the slope of a log–log plot of G' vs ω. B represents gel characteristics such as strength, and can be used to differentiate types of gel (Hsu et al., 2000; Yoneya et al., 2003). Values of $B = 0$ represent a covalent gel, whereas values of $B > 0$ represent a physical gel. The B values for Hylon VII matrices were 0.2286, 0.5415, and 1.2862 for the control, low level, and high level of HP, respectively. For common corn starch matrices, the B values were 0.4658, 0.7943,

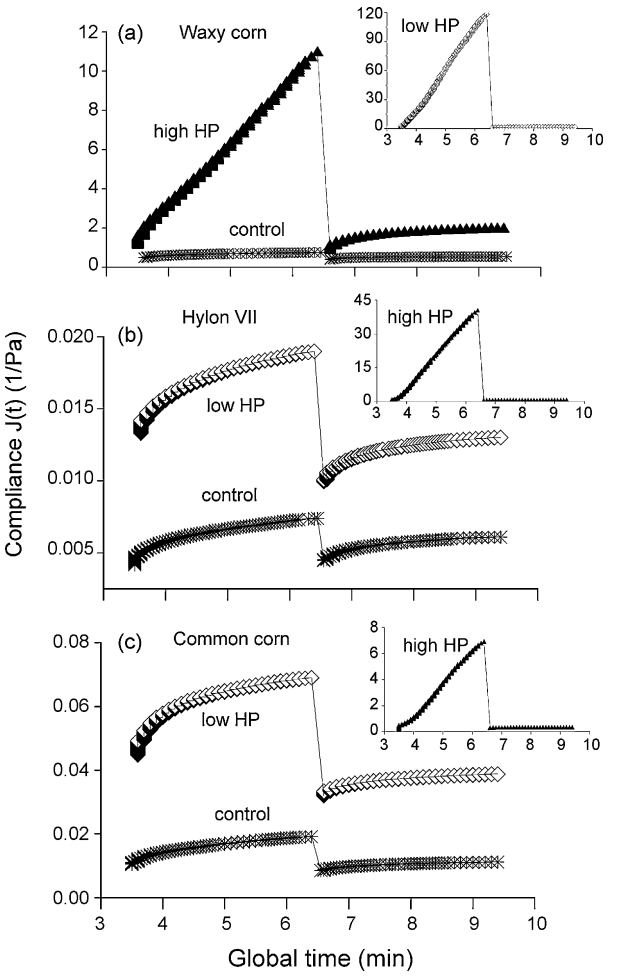

Fig. 4. (a–c) Creep and recovery profiles of hydroxypropylated starch matrices and their controls. Control: gelatinized only; HP: hydroxypropylation.

and 1.3101 for the control, low level, and high level of HP, respectively. There was a steady increase in B values with HP for both Hylon VII and common corn matrices, indicating a progressively more pronounced physical interaction among chains, characteristic of weaker systems. When amylose-containing starch matrices were hydroxypropylated, the transient physical entanglements of the chains became more dominant in the matrix structure. Jeong and Panitch (2009) reported that gels with more physical than covalent entanglements showed higher frequency dependence and a more pronounced increase in G′ with increasing frequency, which was attributed to the high reversibility, movement, and association/dissociation from polymer interactions. For waxy corn starch matrices, the B values were 1.4318, 1.5254, and 1.4919 for the control, low level, and high level of HP, respectively, evidencing that they were physical gels and not strongly affected by HP.

3.4.2. Creep test

In general, HP markedly increased the compliance of starches from their controls. Furthermore, the compliance of hydroxypropylated matrices (particularly highly substituted ones) did not reach a plateau during the creep measurement time. This progressive and linear increase in creep compliance is a characteristic of a viscous liquid (Agoub and Morris, 2008). Waxy corn matrices hydroxypropylated at the low level had a 100-fold higher compliance than the highly substituted one (Fig. 4a), which however was not observed in amylose-containing matrices (Fig. 4b and c). In Hylon VII and common corn starch systems, highly substituted matrices

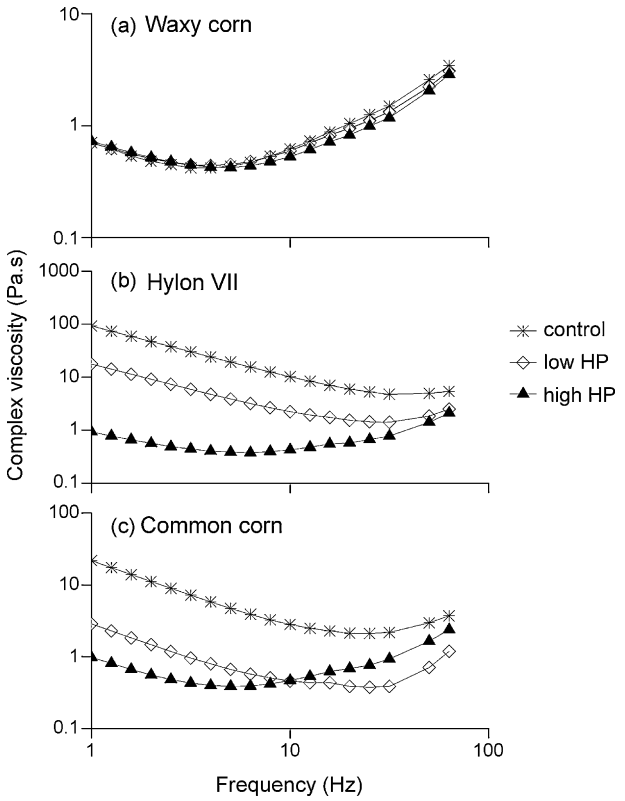

Fig. 5. (a–c) Complex viscosity values of hydroxypropylated starch matrices and their controls. Control: gelatinized only; HP: hydroxypropylation.

possessed the highest compliance, followed by the ones substituted at the low level and the controls, respectively. The highly substituted Hylon VII and common corn matrices had compliances 8000- and 350-fold higher than their respective controls (Fig. 4b and c). These marked increases in compliance and slope of the creep curves indicated that HP resulted in a much more fluid characteristic, regardless of starch type, agreeing with the dynamic test results. The presence of hydroxypropyl groups likely interfered with the association among chains, allowing more chain mobility and the formation of weaker systems. Wischmann et al. (2005) also reported a weakening of the gel structure with increasing phosphate level in genetically modified potato starch.

Fig. 5 displays the complex viscosity of hydroxypropylated starch matrices and their controls. Hylon VII matrices showed the highest viscosity, followed by common corn and waxy corn, respectively, agreeing with the creep test results. Amylose-containing matrices showed a stiffer structure of higher viscosity, whereas waxy corn ones showed a much more fluid structure of lower

Table 2
Recoverable compliance of hydroxypropylated starches and their controls.

Starch type	Level of substitution	Recoverable compliance (1/Pa)
Waxy corn	Control[a]	0.288
	Low	0.987
	High	0.822
Hylon VII	Control	0.176
	Low	0.316
	High	0.991
Common corn	Control	0.419
	Low	0.437
	High	0.957

[a] Gelatinized but not hydroxypropylated.

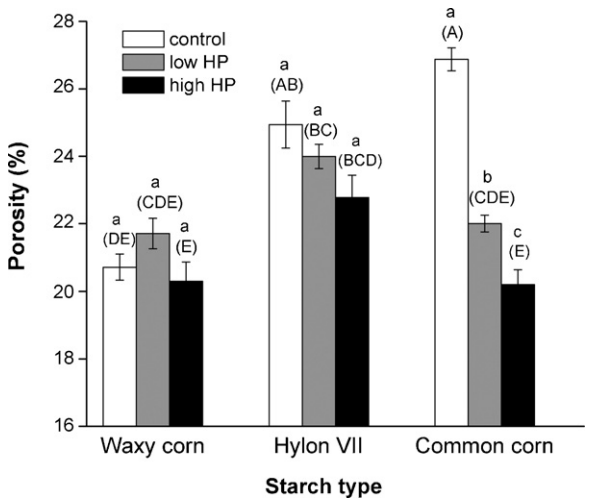

Fig. 6. Tablet porosity of hydroxypropylated starch and their controls. Control: gelatinized only; HP: hydroxypropylation. The lowercase letters represent means comparison by starch type, and the uppercase letters in parentheses represent means comparison across starch types. Means with different letters are statistically different ($P < 0.05$).

viscosity. HP significantly decreased the complex viscosity of amylose-containing starches, but not that of waxy corn starch because of the similar G' and G'' values of hydroxypropylated and control waxy corn starch matrices.

Table 2 lists the recoverable compliance of all starch matrices prepared. HP increased the recoverable compliance of all starch matrices, indicating the formation of a more elastic network structure with improved recovery. In contrast, the controls had stiffer structures with less mobility, which led to less rearrangement of the matrix upon the removal of stress, resulting in lower recovery (Agoub and Morris, 2008).

3.5. Porosity

HP did not change the porosity of waxy corn matrices and only slightly decreased that of Hylon VII ones, but significantly decreased the porosity of common corn matrices (Fig. 6). The porosity of common corn matrices steadily decreased with increasing HP.

The final porosity of a tablet is a result of the compaction process, the porosity under compression, and the elastic recovery after the decompression stage, i.e. stress relaxation (van der Voort Maarschalk et al., 1997; Steendam et al., 2001). The porosity of starch tablets is primarily a function of their stress relaxation (van der Voort Maarschalk et al., 1997; van Veen et al., 2002). Stress relaxation is a result of the release of stored energy in the matrix during compression, which leads to structure expansion and increased porosity (van der Voort Maarschalk et al., 1996). Pregelatinized starch is a viscoelastic material, capable of undergoing plastic deformation and stress relaxation after compression, particularly in the presence of a lubricant such as magnesium stearate, leading to the formation of porous matrices (Rees and Tsardaka, 1994; Rahmouni et al., 2002). In our study, hydroxypropylated matrices showed lower storage modulus with increasing HP (Fig. 3), which may affect their stress relaxation pattern after compression. Matrices with lower storage modulus might have less stress relaxation, and consequently lower porosity. The storage modulus of waxy corn starches did not change with HP, thus resulting in similar porosity in tablets. Rahmouni et al. (2003) reported that tablets prepared with hydroxypropylmethylcellulose (HPMC) and cross-linked amylose (CLA) had lower porosity values than those made with CLA only because HPMC had lower stress relaxation than CLA.

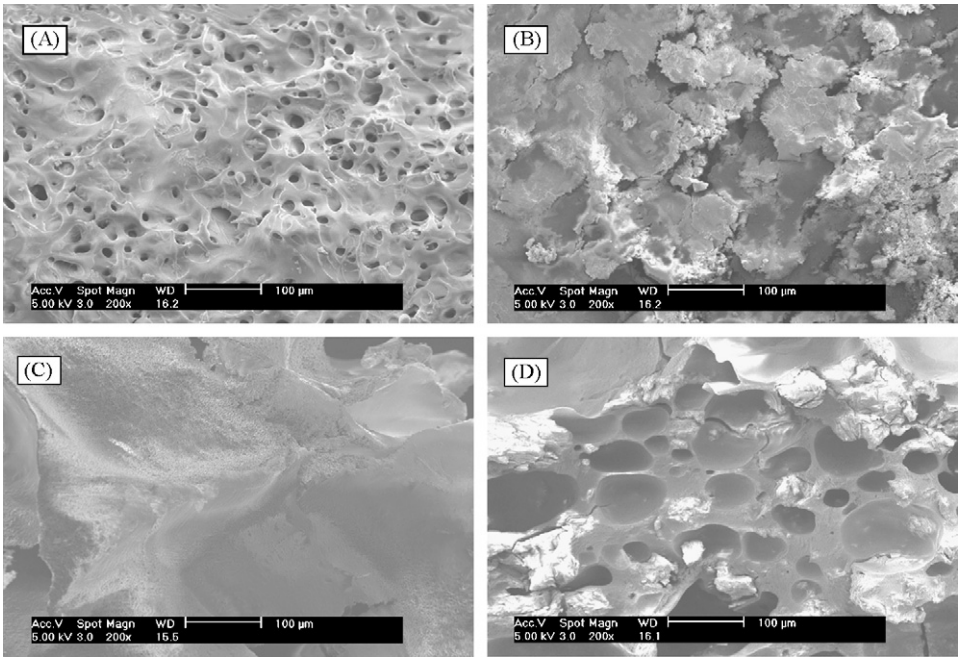

Fig. 7. SEM surface micrographs of swollen waxy corn starch tablets. (a) Control, surface; (b) control, cross-section; (c) high hydroxypropylation, surface; (d) high hydroxypropylation, cross-section.

The formation of more compact and closed matrix structures as a result of HP may contribute to the slower drug release from substituted amylose-containing matrices. Lower porosity was associated with slower drug release (Freiberg and Zhu, 2004) because more closed structures hindered the free movement of drug. An increase in porosity, which resulted in a decrease in tortuosity of the network, allowed for a more free movement of drug (Collins et al., 2007).

3.6. Morphology of swollen tablets

The surface and cross-section micrographs of freeze-dried swollen tablets of controls and highly substituted waxy corn, Hylon VII, and common corn starches are shown in Figs. 7–9, respectively. Micrographs of common corn control tablet are not presented because of its rapid erosion upon immersion in water. The micrographs clearly show that the cross-section structure was different from the surface, which was also reported by Ravenelle et al. (2002) and Thérien-Aubin et al. (2005) and may be attributed to the different impacts that compaction force had on the exterior and interior of tablets during compression.

The unmodified waxy corn starch tablet had a very porous surface with pores smaller than 10 μm (Fig. 7a), whereas its cross-section had a more closed structure with large interparticle voids (Fig. 7b). The hydroxypropylated waxy corn starch tablet had a smooth surface (Fig. 7c) but large voids were observed in its cross-

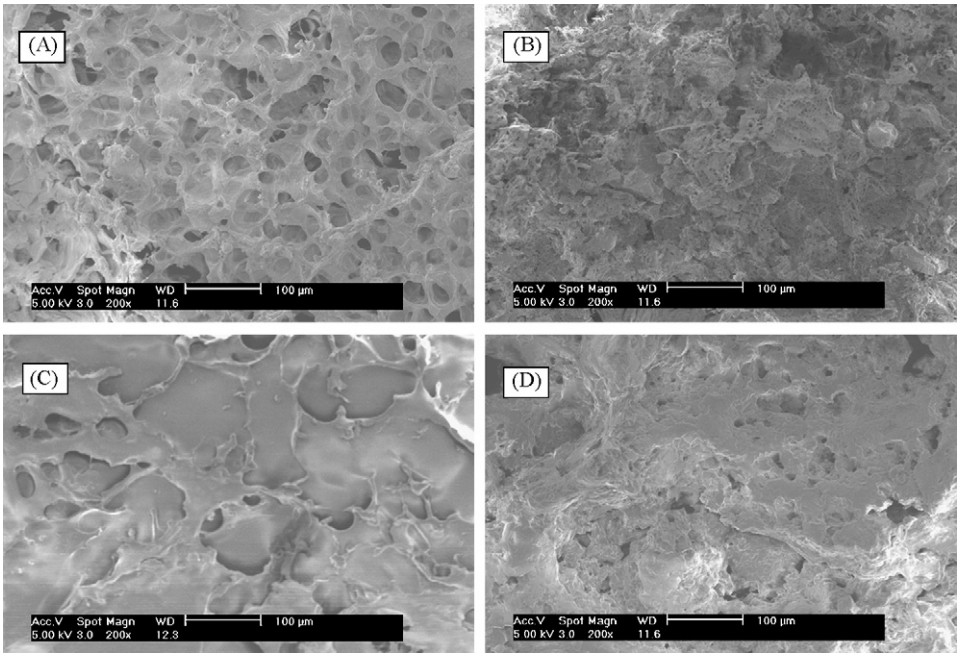

Fig. 8. SEM surface micrographs of swollen Hylon VII tablets. (a) Control, surface; (b) control, cross-section; (c) high hydroxypropylation, surface; (d) high hydroxypropylation, cross-section.

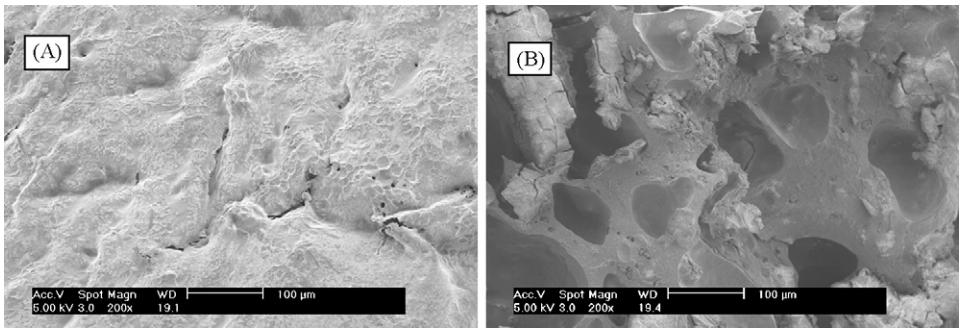

Fig. 9. SEM surface micrographs of swollen common corn starch tablets. (a) High hydroxypropylation, surface; (b) high hydroxypropylation, cross-section.

section (Fig. 7d). It is evident that control and hydroxypropylated waxy corn starches had different pore size distributions, which could not be shown from porosity results (Fig. 6) because porosity was the average of different pore sizes. Furthermore, starch matrices may rearrange upon swelling, showing different morphological appearances.

The Hylon VII control tablet had a porous surface (Fig. 8a), and a rough, uneven cross-section with many voids (Fig. 8b), which was also observed in tablets of cross-linked Hylon VII starch (Moussa et al., 1998). The hydroxypropylated Hylon VII tablet had a slightly smoother surface (Fig. 8c), and a smoother cross-section with smaller voids (Fig. 8d) than the control. Hydroxypropylated common corn starch tablets had a smooth and closed surface (Fig. 9a) but a cross-section with large voids (Fig. 9b).

HP led to the formation of more compact, closed tablet surfaces for all starch types. Furthermore, the cross-section of hydroxypropylated tablets was smoother and had fewer voids than the controls. The formation of more closed structures may be a result of higher water holding capacity of hydroxypropylated matrices, which led to an approximation of chains and reduction of intermolecular space. Furthermore, the more compact structure of hydroxypropylated matrices was also suggested by the previous porosity results, particularly in amylose-containing starches. This reduction in pore size and smooth matrix structure may play an important role in delaying drug release.

4. Conclusions

HP markedly improved the sustained release ability of Hylon VII and common corn starches in both water and simulated GI conditions, but had a negative impact on waxy corn matrices in water. HP increased the water holding capacity of all starches, impeded the binding of α-amylase to starch, and resulted in more fluid-like matrices with decreased tablet porosity and smoother and more closed tablet structures. These characteristics likely contributed to a protection against α-amylase hydrolysis, thus retarding drug release from hydroxypropylated matrices under simulated GI conditions. HP was shown to be an effective way to improve the sustained release properties of amylose-containing corn starches.

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References

Agoub, A.A., Morris, E.R., 2008. Particulate rheology and acid-induced gelation of oxidised cellulose. Carbohydr. Polym. 71, 416–427.
Almdal, K., Dyre, J., Hvidt, S., Kramer, O., 1993. Towards a phenomenological definition of the term 'gel'. Polym. Gels Netw. 1, 5–17.
Alvarez-Manceñido, F., Landin, M., Lacik, I., Martínez-Pacheco, R., 2008. Konjac glucomannan and konjac glucomannan/xanthan gum mixtures as excipients for controlled drug delivery systems. Diffusion of small drugs. Int. J. Pharm. 349, 11–18.
Chebli, C., Cartilier, L., Hartman, N.G., 2001. Substituted amylose as a matrix for sustained-drug release: a biodegradation study. Int. J. Pharm. 222, 183–189.
Chung, H.-J., Shin, D.-H., Lim, S.-T., 2008. *In vitro* starch digestibility and estimated glycemic index of chemically modified corn starches. Food Res. Int. 41, 579–585.
Clark, A.H., Ross-Murphy, S.B., 1987. Structural and mechanical properties of biopolymers gels. Adv. Polym. Sci. 83, 57–192.
Collins, J.H.P., Gladden, L.F., Hardy, I.J., Mantle, M.D., 2007. Characterizing the evolution of porosity during controlled drug release. Appl. Magn. Reson. 32, 185–204.
Désévaux, C., Dubreuil, P., Lenaerts, V., Girard, C., 2002. Tissue reaction and biodegradation of implanted cross-linked high amylose starch in rats. J. Biomed. Mater. Res. 63, 772–779.
Dumoulin, Y., Alex, S., Szabo, P., Cartilier, L., Mateescu, M.A., 1998. Cross-linked amylose as matrix for drug controlled release. X-ray and FT-IR structural analysis. Carbohydr. Polym. 37, 361–370.
Freiberg, S., Zhu, X.X., 2004. Polymer microspheres for controlled drug release. Int. J. Pharm. 282, 1–18.
Herman, J., Remon, J.P., 1989. Modified starches as hydrophilic matrices for controlled oral delivery. II. In vitro drug release evaluation of thermally modified starches. Int. J. Pharm. 56, 65–70.
Hoover, R., Zhou, Y., 2003. In vitro and in vivo hydrolysis of legume starches by α-amylase and resistant starch formation in legumes—a review. Carbohydr. Polym. 54, 401–417.
Hsu, S., Lu, S., Huang, C., 2000. Viscoelastic changes of rice starch suspensions during gelatinization. J. Food Sci. 65, 215–220.
Jeong, K.J., Panitch, A., 2009. Interplay between covalent and physical interactions within environment sensitive hydrogels. Biomacromolecules 10, 1090–1099.
SAS, 2008. JMP 8.0. SAS Institute Inc., Cary, NC, USA.
Johnson, D.P., 1969. Spectrophotometric determination of the hydroxypropyl group in starch ethers. Anal. Chem. 41, 859.
Le Bail, P., Morin, F.G., Marchessault, R.H., 1999. Characterization of a crosslinked high amylose starch excipient. Int. J. Biol. Macromol. 26, 193–200.
Luyten, H., van Vliet, T., Walstra, P., 1992. Comparison of various methods to evaluate fracture phenomena in food materials. J. Texture Stud. 23, 245–266.
Martinez, M.A.R., Gallardo, J.L.-V., de Benavides, M.M., López-Duran, J.D.G., Lara, V.G., 2007. Rheological behavior of gels and meloxicam release. Int. J. Pharm. 333, 17–23.
Mateescu, M.A., Lenaerts, V., Dumoulin, Y., 1995. Use of cross-linked amylose as a matrix for the slow release of biologically active compounds. U.S. Patent 5,456,921, 10 October.
Milojevic, S., Newton, J.M., Cummings, J.H., Gibson, G.R., Botham, R.L., Ring, S.G., Stockham, M., Allwood, M.C., 1996. Amylose as a coating for drug delivery to the colon: preparation and in vitro evaluation using 5-aminosalicylic acid pellets. J. Control. Rel. 38, 75–84.
Moussa, I.S., Lenaerts, V., Cartilier, L.H., 1998. Effect of some physical parameters on the swelling properties of cross-linked amylose matrices. Int. J. Pharm. 173, 35–41.
Mulhbacher, J., Ispas-Szabo, P., Lenaerts, V., Mateescu, M.A., 2001. Cross-linked high amylose starch derivatives as matrices for controlled release of high drug loadings. J. Control. Rel. 76, 51–58.
Mulhbacher, J., Ispas-Szabo, P., Mateescu, M.A., 2004. Cross-linked high amylose starch derivatives for drug release. II. Swelling properties and mechanistic study. Int. J. Pharm. 278, 231–238.
Nabais, T., Brouillet, F., Kyriacos, S., Mroueh, M., Amores da Silva, P., Bataille, B., Chebli, C., Cartilier, L., 2007. High-amylose carboxymethyl starch matrices for oral sustained drug-release: *in vitro* and *in vivo* evaluation. Eur. J. Pharm. Biopharm. 65, 371–378.

Onofre, F., Wang, Y.-J., Mendez-Montealvo, G., submitted for publication. Sustained release properties of cross-linked corn starches with varying amylose contents in monolithic tablets. Starch/Stärke.
Pal, J., Singhal, R.S., Kulkarni, P.R., 2002. Physicochemical properties of hydroxypropyl derivative from corn and amaranth starch. Carbohydr. Polym. 48, 49–53.
Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.
Rahmouni, M., Chouinard, F., Nekka, F., Lenaerts, V., Leroux, J.C., 2001. Enzymatic degradation of cross-linked high amylose starch tablets and its effect on in vitro release of sodium diclofenac. Eur. J. Pharm. Biopharm. 51, 191–198.
Rahmouni, M., Lenaerts, V., Massuelle, D., Doelker, E., Johnson, M., Leroux, J.-C., 2003. Characterization of binary mixtures consisting of cross-linked high amylose starch and hydroxypropylmethylcellulose used in the preparations of controlled release tablets. Pharm. Dev. Technol. 8, 335–348.
Rahmouni, M., Lenaerts, V., Massuelle, D., Doelker, E., Leroux, J.-C., 2002. Influence of physical parameters and lubricants on the compaction properties of granulated and non-granulated cross-linked high amylose starch. Chem. Pharm. Bull. 50, 1155–1162.
Ramkumar, D.H.S., Bhattacharya, M., 1996. Relaxation behavior and the application of integral constitutive equations to wheat dough. J. Texture Stud. 27, 517–544.
Ravenelle, F., Marchessault, R.H., Légaré, A., Buschmann, M.D., 2002. Mechanical properties and structure of swollen crosslinked high amylose starch tablets. Carbohydr. Polym. 47, 259–266.
Rees, J.E., Tsardaka, K.D., 1994. Some effects of moisture on the viscoelastic behavior of modified starch during powder compaction. Eur. J. Pharm. Biopharm. 40, 193–197.
Roper, H., 1996. Applications of starch and its derivatives. Carbohydr. Eur. 15, 14–21.
Shi, X., BeMiller, J.N., 2000. Effect of sulfate and citrate salts on derivatization of amylose and amylopectin during hydroxypropylation of corn starch. Carbohydr. Polym. 43, 333–336.
Steendam, R., Frijlink, H.W., Lerk, C.F., 2001. Plasticization of amylodextrin by moisture. Consequences for compaction behavior and tablet properties. Eur. J. Pharm. Sci. 14, 245–254.
Te Wierik, G.H.P., Eissens, A.C., Bergsma, J., Arends-Scholte, A.W., Lerk, C.F., 1997. A new generation of starch products as excipient in pharmaceutical tablets. II. High surface area retrograded pregelatinized potato starch products in sustained-release tablets. J. Control. Rel. 45, 25–33.
Thérien-Aubin, H., Baille, W.E., Zhu, X.X., Marchessault, R.H., 2005. Imaging of high-amylose starch tablets. 3. Initial diffusion and temperature effects. Biomacromolecules 6, 3367–3372.
Thérien-Aubin, H., Zhu, X.X., Ravenelle, F., Marchessault, R.H., 2008. Membrane formation and drug loading effects in high amylose starch tablets studied by NMR imaging. Biomacromolecules 9, 1248–1254.
2003. U.S. Pharmacopeia/National Formulary (USP 26-NF 21). United States Pharmacopeial Convention, Inc., Rockville, MD, p. 2155–2156.
van der Voort Maarschalk, K., Zuurman, K., Vromans, H., Bolhuis, G.K., Lerk, C.F., 1997. Stress relaxation of compacts produced from viscoelastic materials. Int. J. Pharm. 151, 27–34.
van der Voort Maarschalk, K., Zuurman, K., Vromans, H., Bolhuis, G.K., Lerk, C.F., 1996. Porosity expansion of tablets as a result of bonding and deformation of particulate solids. Int. J. Pharm. 140, 185–193.
van Veen, B., van der Voort Maarschalk, K., Bolhuis, G.K., Visser, M.R., Zuurman, K., Frijlink, H.W., 2002. Pore formation in tablets compressed from binary mixtures as a result of deformation and relaxation of particles. Eur. J. Pharm. Sci. 15, 171–177.
Vilivalam, V.D., Illum, L., Iqbal, K., 2000. Starch capsules: an alternative system for oral drug delivery. Pharm. Sci. Technol. Today 3, 64–69.
Vlachou, M., Naseef, H., Efentakis, M., 2004. Image analysis studies of dimensional changes in swellable hydrophilic polymer matrices. Polym. Adv. Technol. 15, 683–689.
Wang, Y.-J., Wang, L., 2000. Effects of modification sequence on structures and properties of hydroxypropylated and crosslinked waxy maize starch. Starch/Stärke 52, 406–412.
Wischmann, B., Blennow, A., Madsen, F., Jørgensen, K., Poulsen, P., Bandsholm, O., 2005. Functional characterisation of potato starch modified by specific in planta alteration of the amylopectin branching and phosphate substitution. Food Hydrocolloid 19, 1016–1024.
Wurzburg, O.B., 1986. Introduction. In: Wurzburg, O.B. (Ed.), Modified Starches: Properties and Uses. CRC Press, Boca Raton, pp. 3–16.
Yoneya, T., Ishibashi, K., Hironaka, K., Yamamoto, K., 2003. Influence of cross-linked potato starch treated with $POCl_3$ on DSC, rheological properties and granule size. Carbohydr. Polym. 53, 447–457.
Yoon, H.-S., Kweon, D.-K., Lim, S.-T., 2007. Effects of drying process for amorphous waxy maize starch on theophylline release from starch-based tablets. J. Appl. Polym. Sci. 105, 1908–1913.
Zhang, L.-M., Yang, C., Yan, L., 2005. Perspectives on: strategies to fabricate starch-based hydrogels with potential biomedical applications. J. Bioact. Compat. Polym. 20, 297–314.