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Starch phosphates prepared by reactive extrusion as a sustained release agent

Stephen O'Brien [a], Ya-Jane Wang [a,*], Chris Vervaet [b], Jean Paul Remon [b]

[a] Department of Food Science, University of Arkansas, 2650 N. Young Ave, Fayetteville, AR 72704, USA
[b] Faculty of Pharmaceutical Science, Ghent University, Harelbekestraat 72, B-9000 Gent, Belgium

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ABSTRACT

Characteristics of native starch have limited its application in solid dosage forms as a sustained release agent. There is a growing interest in improving starch functionality for sustained release applications because of its non-toxicity and biodegradability. This study attempted to investigate extruded starch phosphates as an excipient in sustaining drug release. Starches from various botanical sources with different amylose contents, including waxy corn, common corn, Hylon V (~50% amylose), Hylon VII (~70% amylose), and potato, were used to prepare starch phosphates at pH 9.0 or 11.0 using a reactive extrusion method. Phosphorous content was higher for starch phosphates prepared at pH 9.0 than at pH 11.0, and varied with starch type when phosphorylated at pH 9.0. Reactive extrusion produced starch extrudates that upon forming hydrogels were capable of sustaining release of metoprolol tartrate (MPT). The structural features of the hydrogel as modified by the phosphorylation reaction were found to alter the kinetics of drug release from the swellable matrices. The unmodified extrudates formed weaker gels as evidenced by their rheological properties, and showed faster drug release. Waxy corn starch phosphorylated at pH 9.0 as well as common corn and potato starches phosphorylated at pH 11.0 were found to exhibit more case-II-like properties attributed to a high density of cross-links and stronger chain entanglement. Waxy corn starch phosphorylated at pH 9.0 exhibited the lowest degree of drug release. The entanglement among amylopectin molecules and branch chains was suggested to play a role in governing MPT release.

1. Introduction

Starch is one of the most commonly used excipients in the manufacturing of tablets as filler, a disintegrant, or a binder (Visavarungroj & Remon, 1992). Its availability and low cost have allowed it to be integrated into a wide variety of pharmaceutical formulations. However, inferior characteristics of native starches such as poor free flowing properties, stability limitations, and negligible cold-water swelling have limited its application in solid dosage forms as a sustained release agent. Many petroleum-derived products, such as polyethylene glycols or polymethacrylates (Eudragit) as well as the semi-synthetic cellulose derivatives, have shown success in sustaining drug release. Nonetheless, there is a growing interest in improving the functionality of polysaccharides for use in oral drug delivery systems because of their non-toxicity and biodegradability.

Starch consists of two structurally different molecules: amylose, an essentially linear molecule, and amylopectin, a highly branched molecule. Starches from different botanical sources and genetic backgrounds are different in chemical composition and structure. Thermally modified or pregelatinized starches have shown some promise as hydrophilic matrices in sustained release systems (Herman, Remon, & De Vilder, 1989; Mohile, 1986; Sánchez, Torrado, & Lastres, 1995; Yoon, Kweon, & Lim, 2007). Herman et al. (1989) found that as excipients pregelatinized starches controlled the oral delivery of drugs through the formation of an obstructive gel layer. Further work by Herman and Remon (1989) demonstrated that the drug release behavior of pregelatinized starch matrices was mainly governed by the amylose/amylopectin ratio, the degree of gelatinization, and the starch concentration with waxy corn starch, ~0% amylose content, showing the most promising results. Typically the kinetics of drug release from swellable matrices depends on the structural features of the hydrogel and the processes of hydration and swelling of the polymer carrier, with the gel layer formed around the glassy core being the main controlling factor (Michailova, Titeva, & Kotsilkova, 2005; Michailova, Titeva, Kotsilkova, Krusteva, & Minkov, 2001).

Chemically modified starches have also shown promise in the pharmaceutical industry as sustained release matrices. For example, starches substituted with cationic groups-like carboxymethyl (Nabais et al., 2007) or anionic groups-like aminoethyl (Mulhbacher, Ispas-Szabo, Lenaerts, & Mateescu, 2001) or acetate (Pohja, Suihko, Vidgren, Paronen, & Ketolainen, 2004), and starches cross-linked by various agents such as epichlorohydrin have all retarded drug release from solid dosage forms at various levels

* Corresponding author. Tel.: +1 479 575 3871; fax: +1 479 575 6936.
E-mail address: yjwang@uark.edu (Y.-J. Wang).

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(Lenaerts, Dumoulin, & Mateescu, 1991). Little work has been done on the phosphorylation of starch other than several studies evaluating pregelatinized phosphate-cross-linked starch as a binding agent in wet granulation (Visavarungroj, Herman, & Remon, 1990; Visavarungroj & Remon,1990, 1991). The conventional phosphorylation by oven heating produces monostarch phosphates via substitution and/or distarch phosphates via cross-linking, and the type of phosphorylation is governed by reaction conditions. For example, at a reaction pH below 9.0 the terminal phosphate groups of sodium tripolyphosphate (STPP) are protonated and produce monometaphosphates, which can react rapidly with starch hydroxyl groups to produce monostarch phosphates (Lim & Seib, 1993). At a reaction pH above 10, starch ionized hydroxyls can attack the STPP central phosphate to form starch pyrophosphates, which can be further attacked by starch hydroxyl groups to give distarch phosphate (Lim & Seib, 1993). Monostarch phosphates exhibit increased viscosity and water binding capacity (Landerito & Wang, 2005a; Liu, Ramsden, & Corke, 1999; Muhammad, Hussin, Man, Ghazali, & Kennedy, 2000), which would help the formation of a gel barrier to control water penetration and drug diffusion. On the other hand, the formation of distarch phosphates may help maintain the granule integrity when starch is exposed to severe processing conditions such as extrusion. Reactive extrusion has been shown to be a more commercially viable process to produce starch phosphates due to its low cost, absence of waste, and short reaction time (Chang & Lii, 1992).

The aim of this study was to evaluate extruded starch phosphates as an excipient in sustaining drug release. Starches of different origins, amylose contents, and modification conditions were compared to better understand how these factors affect the sustained release properties of the resultant starch phosphates.

2. Materials and methods

2.1. Materials

Commercial starches, including waxy corn (~0% amylose [AMIOCA]), common corn (~27% amylose [MELOJEL]), and two high amylose corn (~50% amylose [Hylon V] and ~70% amylose [Hylon VII]) were gifts from National Starch and Chemical Company (Bridgewater, NJ). Potato starch (~20% amylose) was donated by AVEBE (Foxhol, The Netherlands). Metoprolol tartrate (MPT) was obtained from Esteve Quimica, S.A. (Barcelona, Spain).

2.2. Preparation of starch phosphates

Five native starches, including waxy corn, common corn, Hylon V, VII and potato, were used to prepare starch phosphates to contain the maximum phosphorus allowed by regulation, 0.4% (Code of Federal Regulation., 1991). Starch was mixed with sodium tripolyphosphate (STPP), sodium trimetaphosphate (STMP), and sodium sulphate using the dry mixing method (Landerito & Wang, 2005a) described below prior to extrusion. Two reaction pH, 9.0 and 11.0, were selected to produce starch phosphates with different substitution to cross-linking ratios. The reaction pH 9.0 was chosen to promote the formation of phosphate monoesters, whereas pH 11.0 favored the formation of phosphate diesters (Lim & Seib, 1993; Muhammad et al., 2000). Native starches were also extruded under the same conditions in the absence of phosphate salts as controls. Starch (700 g, db) was adjusted to a moisture content of 35% (w/w) prior to the extrusion process. The necessary additional water to reach 35% moisture content was used to dissolve 35 g STPP, 14 g STMP, and 35 g sodium sulphate. The solution was adjusted to pH 9.0 or 11.0 with 5% NaOH and added incrementally to the starch while mixing in a mixer (KitchenAid, St. Joseph, MI). The starch and salt mixture was mixed for 30 min to achieve homogenous mixing.

2.3. Extrusion parameters

A PolyLab laboratory-scale Rheomex twin-screw extruder with intermeshing counter-rotating screws (ThermoHaake, Karlsruhe, Germany) was used in the extrusion process. The barrel has a conical design with three heating zones, a maximum operating temperature of 400 °C and pressure of 7000 kPa. It is equipped with an air–temperature-controllable system and operates at a maximum screw speed of 200 rpm. A 3-mm rod die attached at the end of the extruder barrel was used in this study. The extruder is controlled by a computer system where extrusion parameters are monitored by Polylab monitor software (ThermoHaake).

Phosphorylated starch prepared by reactive extrusion followed the method of Landerito and Wang (2005a). The well-mixed starch was manually fed into the screw at a screw speed of 50 rpm. The temperature zones of the extruder barrel and the die were maintained at 90/102/140/145 °C, where the first, second, and third temperature represented the first, second, and third zone of the barrel, respectively, while the fourth temperature was the temperature of the die.

Phosphorylated starch extrudates were dried at 40 °C for 48 h. Samples were then coarsely ground with a Waring blender prior to being milled with a UDY cyclone sample mill (Fort Collins, CO) equipped with a 0.5-mm screen. The resulting powder was then sieved through a 150-μm Standard Sieve before drying at 40 °C for an additional 48 h to further reduce the moisture content below 2.0% before tableting.

2.4. Phosphorus content

The phosphorus content of starch phosphates was determined spectrophotometrically according to a standard method (CRA., 1999) as described in Landerito and Wang (2005b).

2.5. Swelling power

Swelling power was measured by suspending 40 mg of dry starch in 1.5 ml of deionized water into a microcentrifuge tube. The tube was placed on a heating block at 37 °C for 60 min. The sample was then rapidly cooled to room temperature in an ice-water bath and centrifuged at 10,000g for 5 min. The swelling power was determined by measuring the sediment paste weight divided by its initial dry weight.

2.6. Thermal properties

Thermal properties were assessed by a Perkin-Elmer Pyris-1 differential scanning calorimeter (DSC, Perkin-Elmer Co., Norwalk, CT.). The instrument was calibrated with indium and an empty pan was used for reference. Starch (~10.0 mg, db) was weighed into a stainless steel DSC pan and then moistened with 20.0 μl of deionized water using a microsyringe. The pan was hermetically sealed and allowed to stand for 24 h prior to analysis. The sample was scanned from 25 to 130 °C at 10 °C/min. The onset (T_O), and peak (T_P) gelatinization temperatures and enthalpy (ΔH) were automatically computed.

2.7. X-ray diffraction

X-ray diffraction patterns of starch phosphates were obtained by a Phillips Analytical diffractometer (Philips, Almelo, The Netherlands) with a copper anode X-ray tube. The diffractometer was operated at 27 mA and 50 kV, and the reflection angle (2θ) was

from 5° to 45° at 0.1° step size with a count time of 2 s. A 100% relative humidity chamber was used to equilibrate starch samples for 24 h prior to scanning.

2.8. Carbohydrate distribution

The molecular size distribution and relative proportions of amylose and amylopectin of starch samples were characterized by high-performance size-exclusion chromatography (HPSEC) following the method of Kasemsuwan, Jane, Schnable, Stinard, and Robertson (1995) as modified by Wang and Wang (2000). The HPSEC system (Waters, Milford, MA) consisted of a 515 HPLC pump with an injector of 100 μl sample loop, an in-line degasser, a 2410 refractive index detector maintained at 40 °C, and a series Shodex OHpak columns (KB-802 and KB-804) maintained at 55 °C.

2.9. Tablet formulations

MPT was used as a model drug in this study due to its high water solubility (>1 g/ml at 25 °C). Tablets of extrudates were formulated with 30% MPT and dry mixed in a tumbling mixer (Turbula, T2A, Bachofen, Basel, Switzerland) for 15 min. Tablets were compressed using an eccentric tableting machine (Korsch type, EKO, Frankfurt, Germany) fitted with a 13-mm diameter flat punch at a force of 2.5 mT.

2.10. Drug release properties

Dissolution tests on MPT tablets were performed with a VanKel VK 7000 dissolution apparatus equipped with a VK 8000 automatic sampler (VanKel Technology, Cary, NC) using 900 ml deionized water as the medium and USP Apparatus 2 (paddle). The dissolution medium was maintained at 37 ± 0.5 °C, and the rotation speed was set at 100 rpm. Samples (5 ml) were automatically withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h, and the withdrawn sample was not compensated for with dissolution medium during the testing. Sample concentrations were spectrophotometrically determined at 275 nm (Shimadzu UV-140-02, Kyoto, Japan), and a standard linear curve of MPT from 10 to 100 μg/ml was established.

2.11. Rheological studies

Rheological properties were assessed using an AR 2000 rheometer (TA Instruments, New Castle, DE). The instrument was equipped with a sand-blasted stainless steel parallel-plate geometry (60 mm diameter) to avoid slippage during measurement. All measurements were carried out at 37 °C, a gap size of 1000 μm, and with mineral oil coated around the periphery to prevent evaporation.

Starch (~350 mg, db, 10% w/w) was weighed and moistened with 3.5 ml of deionized water and allowed to stand for 24 h prior to analysis. Steady shear flow studies were made at a shear rate ($\dot{\gamma}$) from 0.03 to 10 s^{-1}, where shear stress (σ) and viscosity (η) were recorded.

Dynamic tests (or small amplitude oscillatory shear) were conducted via two steps: (1) strain sweeps at constant frequency 1.0 Hz to determine the maximum deformation attainable by a sample in the linear viscoelastic range, and (2) frequency sweeps at a constant deformation (1% strain) within the linear viscoelastic range. Starch (~175 mg, db, 5% w/w) was weighed and moistened with 3.5 ml of deionized water and allowed to stand for 24 h prior to analysis. The mechanical spectra were obtained by recording the G′, G″, $|\eta^*|$ as a function of frequency from 0.06 to 62.81 *rad*/s, where G′ is the storage modulus and related to the elastic behavior of the material, G″ is the loss modulus and related to the fluid behavior of the material, and $|\eta^*|$ is the complex viscosity which describes the flow behavior of the material.

2.12. Experimental design and statistical analysis

A 5 × 2 completely randomized design (CRD) with 5 starch types and 2 reaction pH was utilized to evaluate these factors on dissolution properties of MPT. All analyses were performed in duplicate and error bars represented a single standard deviation. The data was statistically analyzed and power law regressions produced by the JMP program (Version 7.1, SAS Software Institute, Inc. Cary, NC). All significant differences were reported using the Student's *t*-test at the 95% confidence interval.

3. Results and discussion

3.1. Phosphorus content

The level of phosphorylation was chosen according to Lim and Seib (1993); nevertheless the resultant phosphorus from phosphorylation was significantly greater in the present study (Table 1) than their results. The high temperature and pressure in extrusion promoted more efficient incorporation of phosphorus, agreeing with previous works (Chang & Lii, 1992; Landerito & Wang, 2005a). Among phosphorylated samples, the extrudates prepared at pH 9.0 generally contained a higher phosphorus content than those prepared at pH 11.0, with the exception of Hylon VII. Muhammad et al. (2000) reported a similar trend of decreasing phosphorus content with increasing reaction alkalinity using the conventional oven heating method. Phosphorus content increased with decreasing amylose content for corn starch phosphates prepared at pH 9.0. Landerito and Wang (2005a) proposed that the branching structure of amylopectin might retain more phosphates in the crystalline region for phosphorylation. Nevertheless, this trend was not observed for the samples prepared at pH 11.0, which favored the formation of distarch phosphates. The results confirm that the degree of phosphorylation was affected by reaction conditions in addition to starch composition and structure. Considerably low phosphorylation efficiency was observed for potato starch when its indigenous phosphorus was taken into account. It is not clear if the inherent high phosphorus content and/or the B-type crystalline structure of potato starch had an impact on the phosphorylation reaction.

3.2. Swelling power

The mechanism of water uptake and drug release by the gel matrix is strongly affected by the structural features of the network. Therefore, the swelling power, i.e. water absorption capacity,

Table 1
Phosphorus content (%) and swelling power of starch extrudates at 37 °C.

Starch type		Treatment		
		Unmodified	pH 9.0	pH 11.0
Waxy corn	Phosphorus content (%)	0.01c	0.43a	0.29b
	Swelling power	7.55b	20.56a	21.43a
Common corn	Phosphorus content (%)	0.02b	0.41a	0.33a
	Swelling power	14.10a	15.56a	15.87a
Hylon V	Phosphorus content (%)	0.02b	0.32a	0.30a
	Swelling power	3.25c	4.94a	3.94b
Hylon VII	Phosphorus content (%)	0.04b	0.27a	0.27a
	Swelling power	3.61a	3.62a	4.00a
Potato	Phosphorus content (%)	0.07b	0.32a	0.29a
	Swelling power	14.22c	31.30a	20.88b

Note: Means of two measurements followed by a common letter in the same row within the same property are not significantly different ($p > 0.05$).

is important in understanding how modification affects drug release of these starch matrices. The swelling power values measured at 37 °C are listed in Table 1. The swelling powers of the starch matrices increased after phosphorylation at both pH with waxy corn showing the most increase and Hylon VII the least. Only waxy and potato starch with ~0% and 20% amylose content, respectively, were significant. The extrusion conditions and the introduction of negatively charged phosphate groups diminished the hydrogen bonding among adjacent molecules, which allowed greater water penetration and swelling. No significant differences in swelling power were noted between phosphorylation conditions for corn starches, but potato starch phosphorylated at pH 9.0 displayed a significantly greater swelling power than at pH 11.0. Although all starches had significantly higher phosphorus contents after phosphorylation, the limited increase in swelling power for amylose-containing corn starch phosphates relative to their unmodified counterparts suggests that amylose counteracted the effects of phosphate monoesters that would increase the swelling power.

3.3. Thermal properties

The gelatinization properties of phosphorylated and unphosphorylated starch extrudates are summarized in Table 2. The majority of the ordered structure in all starch types was disrupted by extrusion as evidenced by their diminished endotherms. No endotherm was observed for waxy corn starch, denoting that its ordered structure was completely disrupted. All remaining corn starches exhibited two endotherms, whereas potato starch exhibited only one endotherm. The low temperature endotherm was assumed to be from a mixture of residual ordered structure and retrograded amylopectin, and the high temperature endotherm was from retrograded amylose (Chanvrier, Uthayakumaran, Appelqvist, Gidley, Gilbert, & Lopez-Rubio, 2007). Although the results were not all statistically significant, the pH 11.0 extrudates generally exhibited slightly higher onset and peak temperatures, whereas unmodified extrudates had a slightly higher enthalpy value for the low temperature endotherm. The absence of the high temperature endotherm in potato starch, presumably from retrograded amylose, was attributed to the large molecular weight of potato amylose that was not as easy to re-associate during the extrusion condition (Takeda, Hizukuri, Takeda, & Suzuki, 1987; Takeda, Shirasaka, & Hizukuri, 1984).

Table 2
Thermal properties of starch extrudates.

Starch type	Endotherm	Thermal properties	Unmodified	pH 9.0	pH 11.0
Waxy corn	I	T_O	–	–	–
		T_P	–	–	–
		ΔH	–	–	–
	II	T_O	–	–	–
		T_P	–	–	–
		ΔH	–	–	–
Common corn	I	T_O	57.4a	57.2a	58.0a
		T_P	64.2a	63.6a	65.1a
		ΔH	1.25a	0.94a	0.82a
	II	T_O	118.6a	119.8a	121.2a
		T_P	126.1a	127.6a	129.8a
		ΔH	1.88a	2.17a	1.87a
Hylon V	I	T_O	56.0a	56.8a	59.6a
		T_P	64.6a	66.0a	67.9a
		ΔH	4.28a	2.84b	2.64b
	II	T_O	113.7b	119.4a	119.0a
		T_P	121.6a	127.4a	127.8a
		ΔH	2.53a	2.37a	2.82a
Hylon VII	I	T_O	56.0a	56.4a	58.9a
		T_P	64.6b	69.9a	70.8a
		ΔH	2.93a	2.44a	2.10a
	II	T_O	116.8a	119.0a	120.5a
		T_P	123.6b	127.1ab	130.2a
		ΔH	2.40a	2.13a	2.53a
Potato	I	T_O	56.4a	59.0a	58.2a
		T_P	69.7a	70.8a	70.9a
		ΔH	2.47a	1.74a	1.84a
	II	T_O	–	–	–
		T_P	–	–	–
		ΔH	–	–	–

Note: Means of two measurements followed by a common letter in the same row within the same property are not significantly different ($p > 0.05$).

3.4. X-ray diffraction

Starch crystalline structure was increasingly disrupted by extrusion with decreasing amylose content (Fig. 1). Waxy corn and potato starches exhibited no diffraction peaks after extrusion, while common corn, Hylon V, and VII retained low intensity peaks. Common corn, Hylon V, and VII still displayed a A-type pattern with weak peaks at 11°, 15°, and 18° (Zobel, 1964), agreeing with the DSC results that there was some crystalline structure not destroyed by extrusion in these starches. In addition, phosphorylation lowered the intensity of these peaks in starch phosphates, indicating that the incorporation of phosphates weakened the crystalline structure. The greater melting of starch crystallites from the extrusion process contributed to the higher swelling power of phosphorylated starches. The higher swelling power of phosphorylated starches was ascribed to the greater melting of starch crystallites through the imbibing of moisture during the extrusion process. The minor differences found in both the DSC and X-ray diffractograms do not contradict the considerable differences in swelling power because the predominating force of disrupting starch crystallinity was from the mechanical disruption of the molecular bonds by the intense shear fields within the extruder rather than from high moisture gelatinization (Lai & Kokini, 1990).

3.5. Carbohydrate distribution

Representative normalized HPSEC profiles of unmodified, pH 9.0, and 11.0 starch extrudates are shown in Fig. 2. The unmodified extrudates were found to have a larger proportion of high molecular-weight components and a smaller proportion of low molecular-weight fraction than phosphorylated ones, suggesting more degradation for starch phosphates. Dextrinization is known to become a predominant mechanism of starch fragmentation during low-moisture and high-shear extrusion such as in this study (Lai & Kokini, 1991). Therefore, the more extensive degradation of starch phosphates was attributed to their increased swelling that rendered them more susceptible to shear and heat. The typical mechanism of dextrinization within an extruder is limited degradation of amylopectin, which nevertheless greatly decreases in overall molecular size as evidenced in the present chromatograms (Lai & Kokini, 1991). The HPSEC profiles of unmodified and phosphorylated extrudates became closer to each other with increasing amylose content, presumably from less degradation with decreasing amylopectin content and/or improved granule integrity from increased amylose content (Lai & Kokini 1990). There was slight difference between pH 9.0 and 11.0 extrudates, but the trend was not clear.

3.6. Dissolution properties

The MPT release profiles of extruded waxy corn, common corn, and potato starch phosphates and their unmodified counterparts are shown in Fig. 3 and release kinetics in Table 3. Tablets of

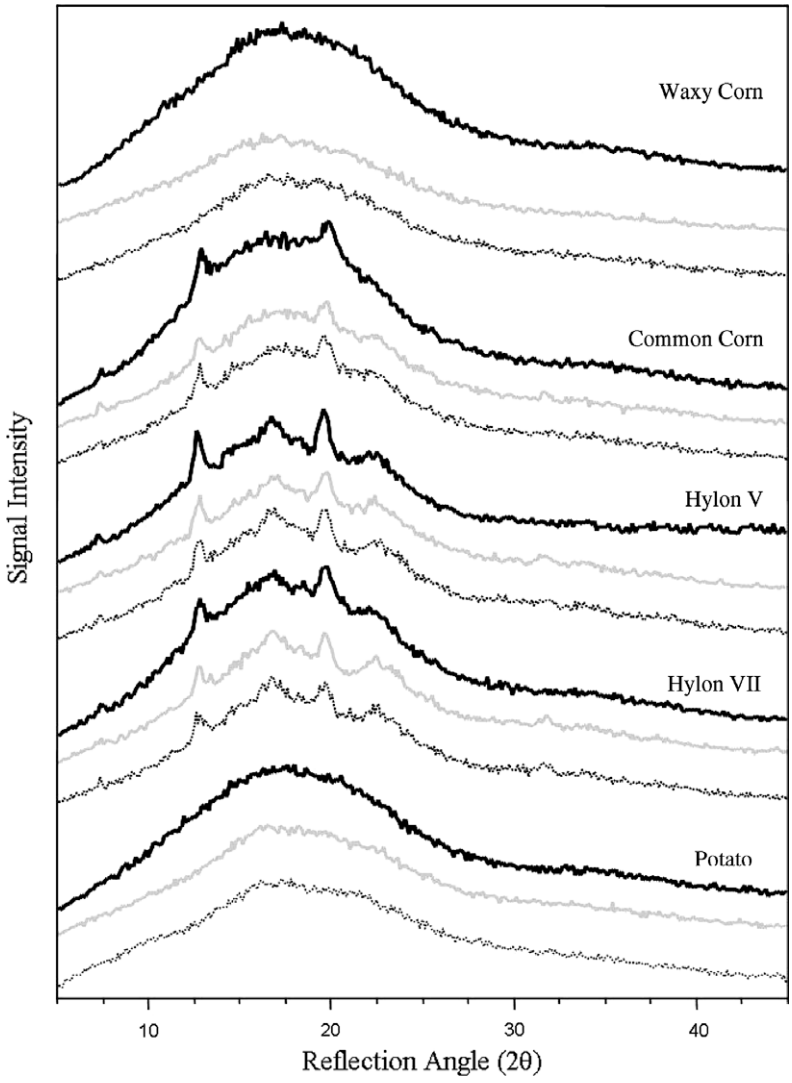

Fig. 1. X-ray diffraction patterns of unmodified starch extrudates (———) as well as starch extrudates phosphorylated at pH 9.0 (———) and pH 11.0 (- - -).

extruded and phosphorylated Hylon V and VII phosphates completely disintegrated in less than 30 min; therefore, their results are not shown, and they were not studied for other properties. The rapid disintegration of extruded Hylon V and VII phosphates was attributed to their limited swelling from their high amylose contents. A much higher phosphorylation level would be required to counteract the restricted swelling from amylose for Hylon V and VII to achieve sufficient swelling and function as satisfactory hydrogel systems.

The evaluation of MPT release kinetics was based on Peppas' equation (Peppas, 1985):

$$M_t/M_\infty = k \times t^n \quad (1)$$

where M_t/M_∞ is the fraction of drug released at time t, k is a constant incorporating structural and geometric characteristics of the dosage form, and n is the release exponent indicative of the mechanism of drug release.

The Peppas' power law (1985) was employed to provide insight into the subsequent evaluation of MPT release kinetics. This equation is a generalization of two apparently independent mechanisms of drug transport, Fickian diffusion and case-II transport. Fickian diffusion describes diffusion governed by Fick's law, whereas case-II transport describes diffusion governed solely by the rate of polymer chain relaxation. A release exponent (n) below 0.45 indicates Fickian diffusion, above 0.89 indicates case-II transport, and between indicates anomalous transport for a cylindrical geometry (Ritger & Peppas,1987a, 1987b). The power law can only give limited insight into the exact release mechanism of the drug since the equation assumes constant diffusivities and constant dimensions of the device during drug release. Nonetheless in many cases, the use of a simple empirical or semi-empirical model is sufficient.

The profiles of waxy corn extrudates exhibited at least 50% drug release at 8 h. Waxy corn extrudates prepared at pH 9.0 exhibited the lowest degree of drug release, whereas there was no difference between the unmodified and pH 11.0-phosphorylated waxy corn extrudates, which released MPT at a faster rate. For all waxy starch hydrogels, their values of n were within the anomalous diffusion range of 0.45–0.89. The waxy corn phosphate prepared at pH 9.0 had the highest value of 0.61, indicating that it was more strongly governed by case-II transport than the other treatments. Nonetheless the unmodified waxy corn release profile was not considerably different from the phosphorylated ones, suggesting that extrusion alone can produce an effective hydrogel matrix with waxy corn starch.

The profiles of common corn extrudates exhibited at least 50% drug release at 4 h with the unmodified common corn exhibited significantly faster release. The n values of common corn extru-

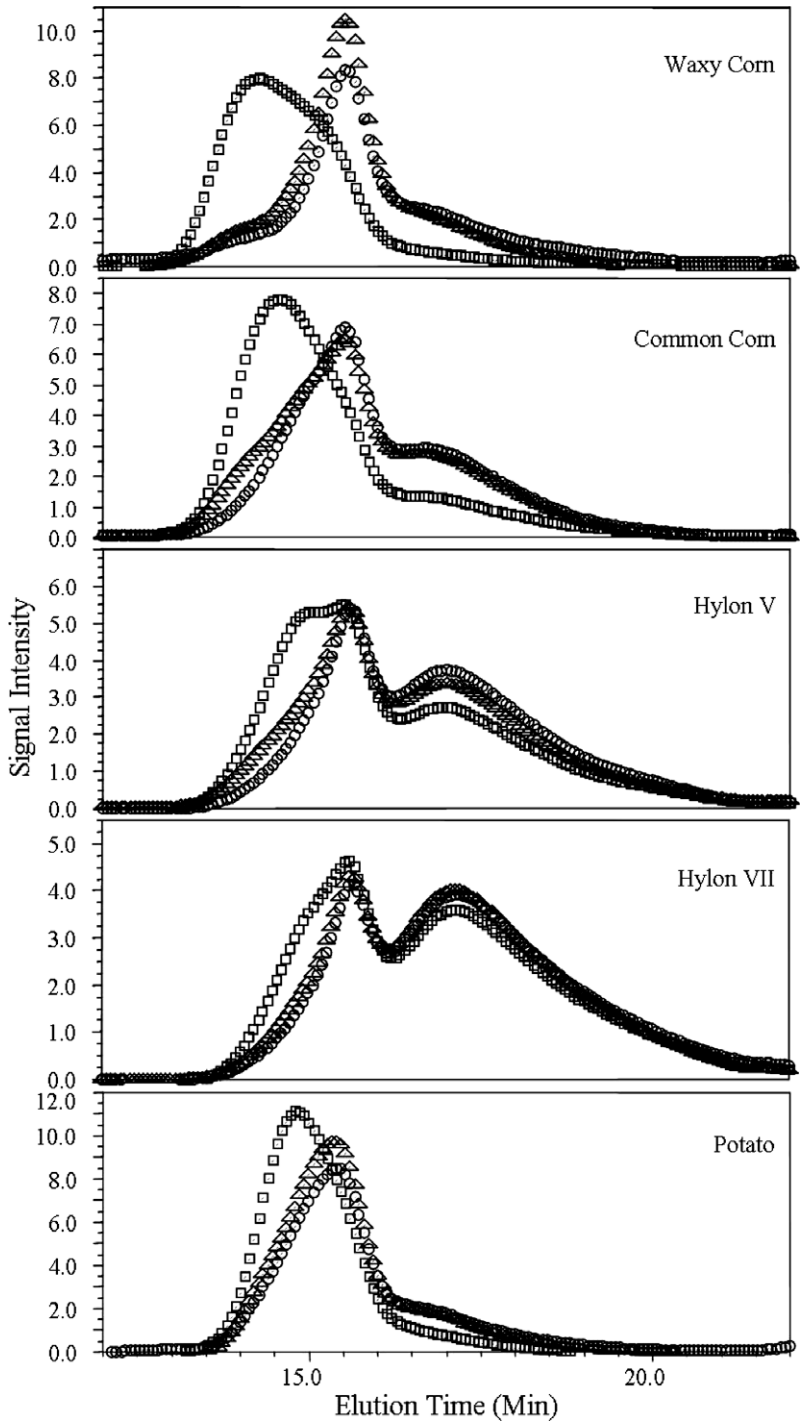

Fig. 2. HPSEC chromatograms of unmodified starch extrudates (□) as well as starch extrudates phosphorylated at pH 9.0 (△) and pH 11.0 (○).

dates were below 0.45, which is indicative of diffusion controlled drug release. The higher *n* value (0.43) of common corn modified at pH 11.0, however, suggests that this modification condition may counteract more the limited swelling from amylose than the other conditions for common corn starch.

The profiles of potato extrudates also exhibited at least 50% drug release at 8 h. The trend of the potato drug release profiles followed that observed previously in the common corn extrudates. Potato extrudates prepared at pH 11.0 exhibited the lowest degree of drug release followed closely by those prepared at pH 9.0. Unmodified potato exhibited an approximate 10% higher release at 8 h than the modified potato starch matrices. All potato hydrogels had *n* values within the anomalous diffusion range of 0.45–0.89. The *n* values of the potato corn extrudates prepared at pH 11.0 and 9.0 (0.57 and 0.56, respectively) indicate that they were more governed by case-II transport than their unmodified counterpart.

3.7. Rheological studies

Dynamic testing is commonly utilized to provide a more explicit and detailed characterization of the gel structure. The rheological

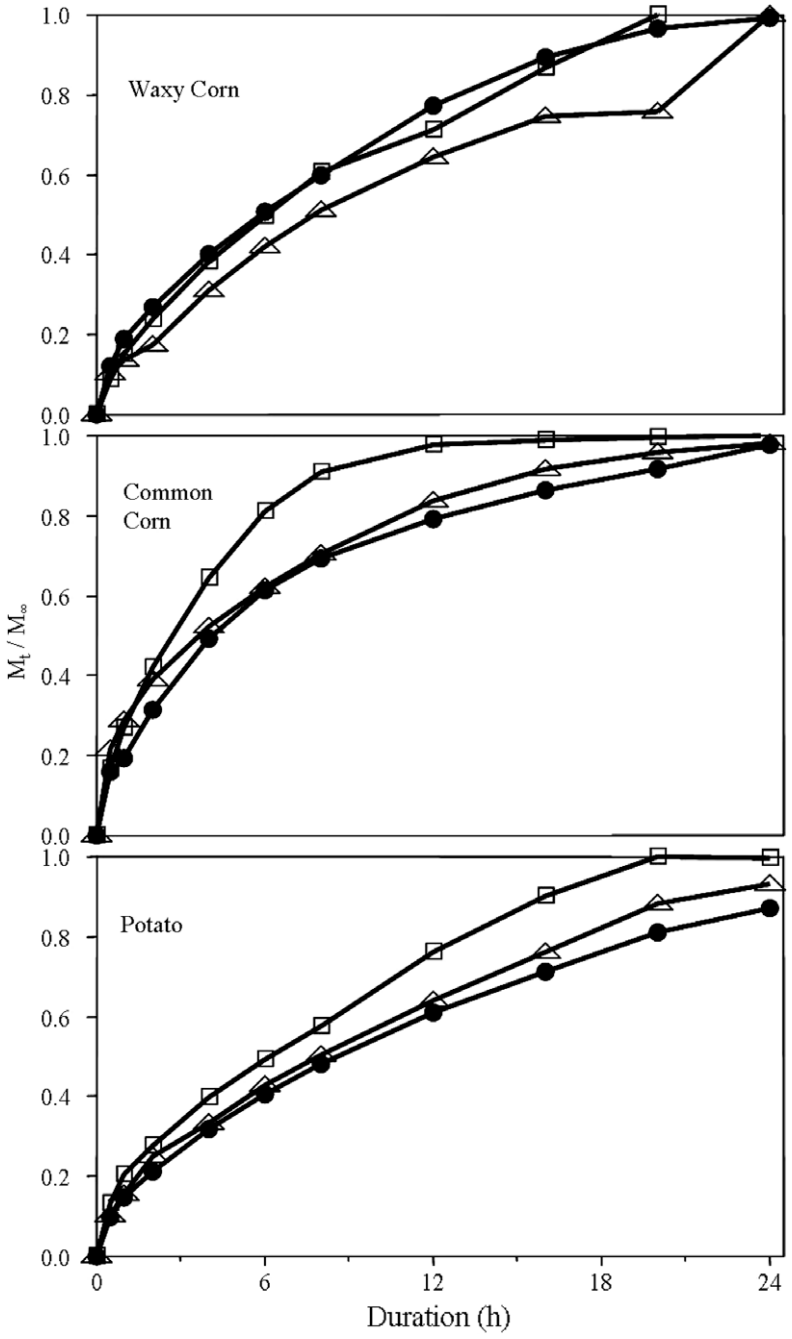

Fig. 3. Drug release profiles unmodified starch extrudates (□) as well as starch extrudates phosphorylated at pH 9.0 (△) and pH 11.0 (○).

Table 3
Release kinetics (k and n) of MPT from starch extrudates.

Starch type	Parameters	Treatment		
		Unmodified	pH 9.0	pH 11.0
Waxy corn	k (h^{-n})	0.18	0.14	0.20
	n	0.57	0.61	0.52
	r^2	0.99	0.99	0.99
Common corn	k (h^{-n})	0.37	0.31	0.26
	n	0.35	0.38	0.43
	r^2	0.93	0.99	0.98
Potato	k (h^{-n})	0.20	0.16	0.15
	n	0.53	0.57	0.56
	r^2	0.99	0.99	0.99

properties of waxy corn, common corn, and potato starches were studied in attempting to relate their gel characteristics to the gel properties of the tablets as an indication of the actual drug release mechanism. Within the concentrations studied, Hylon V and VII could not form a homogeneous dispersion; therefore, their rheological results are not shown. The kinetics of drug release from the swellable matrices is proposed to be governed by the structural features of the hydrogel of which the gel layer formed around the glassy unhydrated core of the tablet. When plotted in a $\log(\sigma)$ vs. $\log(\dot{\gamma})$ scale, the yield stress (σ_0) parameter was estimated by two power law regressions with one starting at low stresses and following constant slope and the second one beginning at the end of the test and going backwards. The σ_0 value was recorded as their intersection and reported in terms of σ. The parameters

Table 4
Yield stress, σ_0, (Pa) and zero viscosities, η_0, (Pa*S) of starch extrudates (10% w/w) at 37 °C.

Starch type		Treatment		
		Unmodified	pH 9.0	pH 11.0
Waxy corn	σ_0 (Pa)	0.05	8.66	0.51
	η_0 (Pa*S)	0.5	703.0	26.3
Common corn	σ_0 (Pa)	4.36	4.63	7.40
	η_0 (Pa*S)	256.5	314.0	382.0
Potato	σ_0 (Pa)	1.91	4.26	9.35
	η_0 (Pa*S)	64.4	181.9	228.1

of zero viscosity, η_0, were also estimated from the plateau region at low $\dot{\gamma}$ as a function of η (data not shown) using a horizontal line from the steady shear flow.

The results from the steady shear flow (Table 4) demonstrate different estimated yield stress (σ_0) values. The σ_0, an indication of rigidity, is the threshold point at which network structure is broken down and the material begins to flow. The modified starch extrudates were all found to have greater σ_0 values over their unmodified counterparts, indicating that the phosphorylation reaction strengthened the gel network. The greater point of σ_0 of the waxy corn extrudate treated at pH 9.0 (8.66) over the other waxy corn samples (0.05 and 0.51) reveal that the gel network could withstand a higher strain before flow began. This result suggests that the extruded waxy corn phosphate prepared at pH 9.0 had a more rigid network, presumably from increased cross-linking than the one prepared at pH 11.0, which was not expected according to their reaction conditions. The extruded potato and common corn phosphates prepared at pH 11.0 exhibited greater σ_0 values (9.35 and 7.40, respectively) than their counterparts (4.26 and 4.63, respectively) prepared at pH 9.0 as expected. When comparing with the dissolution results, the starches with stronger gel networks exhibited slower drug releases for their respective starch types. Moreover, common corn was found to have lower drug release profiles then the other starches despite their rigid gels. It is proposed that amylose prevented adequate entanglement of amylopectin branched chains, resulting in a more porous network structure for MPT to diffuse out in common corn starches.

The zero viscosity (η_0) is often called first Newtonian viscosity and can be described as the plateau value in a graph of log (η) vs. log($\dot{\gamma}$), and its estimates are listed in Table 4. The η_0 was taken to be the plateau at the beginning of the graph. The extruded starch phosphates exhibited greater resistance to flow than their unmodified counterparts regardless of starch type. These results indicate that phosphorylation caused starch flow to be impeded despite the ability of the resultant starch to imbibe a greater amount of water as evidenced by its higher swelling power. The η_0 of the extrudates exhibited a similar trend as their σ_0 values, where the extruded waxy starch phosphorylated at pH 9.0 was higher than the one phosphorylated at pH 11.0, and extruded common corn and potato starches phosphorylated at pH 11.0 were higher than the ones phosphorylated at pH 9.0. It was found that the resistance of starch extrudates to flow negatively correlated with drug release. For waxy corn and potato starches, the strength of the gel network was found to be an important factor dominating the release of MPT. Michailova et al. (2001) reported that it was the amylopectin inter- and intra-molecular interactions that reduced gel layer diffusivity and decreased drug release in pregelatinized waxy starch matrices mixed with hydroxypropylmethyl cellulose (HPMC).

The mechanical spectra of waxy corn, common corn, and potato starch samples obtained by dynamic oscillatory test are shown in Fig. 4. The unmodified waxy corn extrudate was shown to be viscoelastic with predominance in fluid behavior because its loss modulus (G″) was greater than its storage modulus (G′), both of which exhibited a dependency on angular frequency (ω). This relationship reveals that the behavior of this matrix was strongly governed by a translational motion of the macromolecules (Tecante, 2001). The predominance of G′ over G″ for the extruded waxy corn starch phosphates suggests considerably more chain entanglement resulting in a stronger hydrogel as well as the predominance of viscoelastic solid-like behavior (Tecante, 2001). Furthermore, the increase in magnitude of the storage modulus, G′, for the extruded waxy corn phosphates indicates an increase in the strength of the gel structure (Agoub & Morris, 2008) due to phosphorylation. The waxy corn phosphorylated at pH 9.0 exhibited considerably higher G′ than the one phosphorylated at pH 11.0. The general independence of the dynamic moduli with regard to ω for the waxy corn extrudate phosphorylated at pH 9.0 shows that a strong network structure was maintained, which could be described as a 'true' or a 'strong' gel. Nevertheless, the increase in G′ and G″ has been attributed to an increase in cross-link density (Elbert, Pratt, Lutolf, Halstenberg, & Hubbell, 2001) and supports similar conclusions from the steady shear flow study (Table 4). Furthermore, the trend of the complex viscosity $|\eta^*|$ (Pa*s) in all starch extrudates showed a strong non-Newtonian shear-thinning behavior under the condition tested (Fig. 4). The modified waxy corn extrudates exhibited a considerable increase in intensity and decreased dependency on frequency with the waxy corn extrudate phosphorylated at pH 9.0 exhibiting the greatest increase over their unmodified counterpart. These results indicate that phosphorylation through reactive extrusion increased the non-Newtonian shear-thinning properties of waxy corn starch. The intensities of these trends further confirm the trends of σ_0, η_0, and dynamic moduli, indicating that waxy corn extrudate phosphorylated at pH 9.0 had the strongest network structure followed by the one phosphorylated at pH 11.0 and the unmodified counterpart.

All common corn extrudates were shown to be viscoelastic with predominance in the solid behavior attributable to their greater G′ than G″ due to chain entanglement. The relative independence of G′ and G″ from ω for the common corn extrudates indicates the gels were capable of maintaining a network structure, while the similar intensity and shape of their dynamic profiles suggest similar interactions of their networks. The independence of ω over 3 logarithmic scales further suggests the typical solid-like behavior of common corn extrudates adopting a rigid conformation. The modification of the extrudates did not alter their dynamic moduli nor $|\eta^*|$ values, further confirming the strong impact of amylose on gel properties. The magnitude of the dynamic moduli of the common corn extrudates followed the order of pH 11.0 > pH 9.0 > unmodified. The same trend was also observed in the swelling power, σ_0, and η_0 data.

The unmodified potato extrudate was shown to be viscoelastic with a weak gel state as G′ was marginally greater than G″. The dependency of G′ on ω suggests that the matrix was influenced by the translational motion of the chains, although not as significant as unmodified waxy corn. Phosphorylation increased the viscoelastic solid-like behavior of the extrudates as evidenced by an increase in G′ from greater chain entanglement. The magnitude of $|\eta^*|$ also confirmed the greater gel strength of the phosphorylated potato extrudates compared with their unmodified counterpart. The increased gel structure of the modified starches led to the decreased drug release through a combination of increased chain entanglement and cross-linking. The differences in the dynamic moduli between potato extrudates phosphorylated at pH 9.0 and 11.0 were negligible, suggesting similarities in the interaction of their networks. The close proximity of potato extrudates phosphorylated at pH 9.0 and 11.0 also agree with their η_0 values. These similarities in gel characteristics explain their similar anomalous drug release

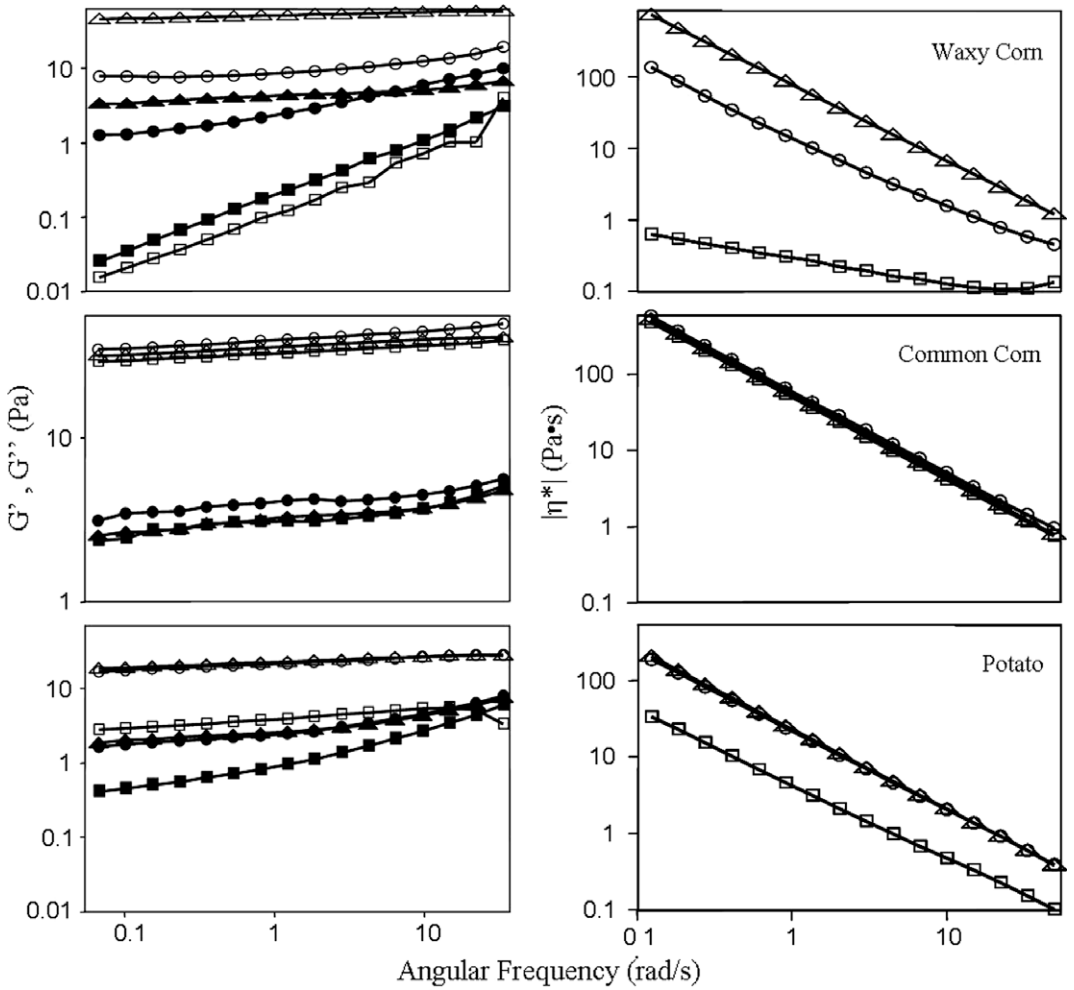

Fig. 4. Mean values for the mechanical spectrum of dynamic moduli of unmodified (□), pH 9.0 (△), and pH 11.0 (○) starch extrudates at 37 °C. G′ the open symbols and G″ the closed symbols.

mechanisms for potato extrudates phosphorylated at pH 9.0 and 11.0 (0.57 and 0.56, respectively). The magnitude of the dynamic moduli followed the order of pH 11.0 > pH 9.0 > unmodified for potato extrudates, a similar trend as in common corn extrudates. The increase in the dynamic moduli was also proposed to be due to an increase in cross-link density at more alkaline phosphorylation conditions. Similar to the other starch types, the gel strength negatively correlated with drug release in potato extrudates. The potato extrudate phosphorylated at pH 9.0 was found to have a similarly strong network structure with that of pH 11.0 followed by their unmodified counterpart with n values of 0.56, 0.57, and 0.53, respectively. The similar dissolution profiles of the potato extrudates support that amylopectin branch chains played an important role in mediating MPT release. Nonetheless, the n values of the phosphorylated potato extrudates suggest that the release of MPT was predominately governed by chain relaxation over their unmodified counterpart, presumably from increased amylopectin entanglement and cross-linking from the phosphorylation.

4. Conclusions

Reactive extrusion was shown to produce starch extrudates, which upon forming a hydrogel were capable of sustaining the release of MPT. There were limited differences in release profiles of modified when compared with the unmodified. The starch phosphates prepared at pH 9.0 generally had higher phosphorus contents than those prepared at pH 11.0, and the phosphorylation efficiency decreased with increasing amylose content. The structural features of the hydrogel as modified by the phosphorylation reaction altered the kinetics of drug release from the swellable matrices. In general, the unmodified extrudates show lower values in swelling power, σ_0, η_0, G′, G″, $|\eta^*|$, as well as moduli dependence on frequency and higher drug release compared with their modified counterparts for each starch. Waxy corn phosphorylated at pH 9.0 as well as common corn and potato phosphorylated at pH 11.0 was found to exhibit more case-II-like properties due to a high density of cross-links and stronger chain entanglement. Waxy corn starch phosphorylated at pH 9.0 exhibited the lowest degree of drug release among the treatments. This study also demonstrated that the structural characteristics of the gel matrices as described rheologically can provide insight into the mechanism of drug diffusion. The entanglement among amylopectin molecules and branch chains was suggested to play a role in governing MPT release in waxy corn and potato starches. In comparison, amylose was found to hinder the entanglement of the amylopectin molecules and branch chains in common corn starch, thus resulting in a more porous network and subsequently faster drug release.

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