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Effects of shear and pH on starch phosphates prepared by reactive extrusion as a sustained release agent

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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 biocompatibility and biodegradability. This study investigated the effects of different shear and pH conditions on starch extrudates prepared via reactive extrusion to act as an excipient in sustaining drug release. Starches, including waxy corn, common corn, and potato, were used to prepare starch phosphates at a shear rate of 50 or 200 rpm and at pH 9.0 or 11.0. The reaction efficiency of phosphorylation was improved when extruded at 200 rpm. Unmodified starch extrudates exhibited more degradation at 200 rpm with a shorter residence time over those at 50 rpm with a longer residence time. The carbohydrate profiles of starch phosphates showed an increased proportion of high molecular-weight components at 200 rpm, possibly due to an increase in cross-linking reaction at a higher shear rate. Both waxy corn and potato phosphates exhibited an *n* value indicative of anomalous transport, but most common corn phosphates showed an *n* value indicative of Fickian diffusion. Waxy corn phosphates exhibited different rheological properties but similar drug release profiles. Common corn phosphates exhibited rigid gel conformations, and exhibited slower drug release than unmodified ones. Potato starch phosphates exhibited considerable differences in their rheological properties drug release profiles between 50 and 200 rpm with phosphates at 200 rpm showing more fluid-like properties and poor drug release. The results demonstrate that the reaction efficiency of phosphorylation by reactive extrusion and subsequently drug release can be affected by the shear rate and pH for different starch types.

1. Introduction

There is a strong and growing interest in the use of biopolymers in oral drug delivery systems because of their non-toxicity and biodegradability. Starch has been one of the most commonly used excipients in the pharmaceutical industry. Its application, however, has been limited to filler, disintegrant, or binder roles because of its poor free flowing properties, limited stability, and negligible cold-water swelling. Thermally modified or pregelatinized starches have shown some promise as hydrophilic matrix systems (Herman, Remon, & De Vilder, 1989; Mohile, 1986; Sánchez, Torrado, & Lastres, 1995; Yoon, Kweon, & Lim, 2007) because their properties are similar to those of cellulose derivatives, i.e. hydroxypropylmethyl cellulose. Pregelatinized starches have been shown to control the delivery of drugs in oral dosage forms through the formation of an obstructive gel layer (Herman et al., 1989). 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 of ~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).

The physicochemical properties of starch can be markedly altered through chemical modification (Rutenberg & Solarek, 1984). Phosphorylation is known to increase viscosity and water binding capacity of starch (Landerito & Wang, 2005; Liu, Ramsden, & Corke, 1999; Muhammad, Hussin, Man, Ghazali, & Kennedy, 2000). It produces either monostarch phosphates via substitution and/or distarch phosphates via cross-linking, and the type of phosphorylation is governed by reaction conditions. Phosphorylation of starch via reactive extrusion has been investigated by several authors (Chang & Lii, 1992; Landerito & Wang, 2005; Nabeshima & Grossmann, 2001; Salay & Ciacco, 1990; Seker & Hanna, 2005). Reactive extrusion is a more commercially viable process to produce starch phosphates than the conventional oven-heating method due to its low cost, absence of waste, and short reaction time (Chang & Lii, 1992).

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Limited studies (Landerito & Wang, 2005; Seker & Hanna, 2005) have been done to elucidate the effect of various extrusion parameters on the actual phosphorylation of starch and whether these trends differ with the oven-heating method. A recent study (O'Brien, Wang, Vervaet, & Remon, 2008) prepared and compared extruded starch phosphates of different origins, amylose contents, and modification conditions as an excipient in sustaining drug release. It was reported that the phosphorylation efficiency decreased with increasing amylose content for corn starches. The structural features of the hydrogel as modified by the phosphorylation reaction altered the kinetics of drug release from the swellable matrices. Waxy corn phosphate at pH 9.0 as well as common corn and potato phosphates at pH 11.0 was found to exhibit more case-II like diffusion due to a high density of cross-links and stronger chain entanglement. The degree of entanglement among the amylopectin branch chains was important in governing drug release in waxy corn and potato starches.

During extrusion, starch is subjected to high pressure (up to 10^3 psi) (Lai & Kokini, 1990), heat, and shear forces. The extruder can be considered a high-temperature (150–170 °C) short-time (75–200 s) (HTST) bioreactor that can cause gelatinization, melting, and fragmentation of starch (Lai & Kokini, 1991). It can convert starch from a granular and semicrystalline material into a highly viscous, plastic material (Brümmer, Meuser, Lengerich, & Niemann, 2002), which is accompanied by disruption of the crystalline structure of starch molecules and their reduction to smaller sizes (Vasanthan, Yeung, & Hoover, 2001). The main parameters that influence reactions, such as shear forces, residence time, and shear rate, are defined by the geometry of the extruder as well as the processing variables, such as temperature, screw speed, amylose to amylopectin ratio, and moisture content (Lai & Kokini, 1991).

The objective of this study was to evaluate the effects of the shear forces in reactive extrusion on the characteristics of starch phosphates and their subsequent use as matrices in sustaining drug release. Starches of different origins, amylose contents, phosphorylation conditions, and extruder screw speeds were compared.

2. Materials and methods

2.1. Materials

Corn starches, including waxy corn (~0% amylose [Amioca]) and common corn (~27% amylose [Melojel]) were obtained from National Starch and Chemical Company (Bridgewater, NJ). Potato starch (~20% amylose) was obtained from AVEBE (Foxhol, Netherlands). Metoprolol tartrate (MPT) was obtained from Esteve Quimica, S.A. (Barcelona, Spain).

2.2. Preparation of starch phosphates

Three native starches, including waxy corn, common corn, 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, 2005) prior to extrusion as described below. Two reaction pHs, 9.0 and 11.0, were selected to produce starch phosphates with different substitution to cross-linking ratios. The reaction pH of 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 (2005). The well-mixed starch was manually fed into the screw. All starch phosphates were processed at 50 rpm or 200 rpm to produce extrudates which had undergone the broadest difference in shear rate available within the extruder. The 50 rpm was chosen for lower shear and longer residence times, whereas the 200 rpm was chosen for its higher shear and shorter residence time. 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. The residence time of starch extrudates was approximated by the addition of a blue food dye to several trial starch mixtures.

Extruded starch phosphates 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. Two samples were prepared for each treatment.

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 (2005).

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. 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.

2.7. 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 were dry mixed in a tumbling mixer (manual mini-Inversina, BiOENGiNEERiNG, Wald, Switzerland) for 15 min. Tablets were compressed using a Carver press eccentric tableting machine (Wabash, IN) fitted with a 13-mm diameter flat punch (Pellet die, Wabash, IN) at a force of 2.5 mT.

2.8. Drug release properties

Dissolution tests on MPT tablets were performed with a Varian 705 DS dissolution apparatus equipped with a VK 8000 automatic sampler (Varian Inc., Palo Alto, CA) 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 (Beckman DU 520, Beckman Coulter, Fullerton, CA), and a standard linear curve of MPT from 10 to 100 μg/mL was established.

2.9. 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.

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.

2.10. Experimental design and statistical analysis

A 3 × 3 × 2 completely randomized design (CRD) with 3 starch types, 2 reaction pHs plus 1 unmodified control, and 2 screw speeds were utilized to evaluate these factors on dissolution properties of MPT. All sample analysis was performed in triplicate. 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 Tukey–Kramer test at the 95% confidence interval.

3. Results and discussion

3.1. Phosphorus content

The starch extrudates prepared at pH 9.0 generally contained similar or higher phosphorus contents when compared with those prepared at pH 11.0 (Table 1). Chang and Lii (1992) and Muhammad et al. (2000) also reported a decrease in phosphorus content with an increase in alkalinity for phosphorylation using the conventional oven-heating method. Among different starch types, waxy corn extrudates had higher phosphorus contents than the other ones. Landerito and Wang (2005) proposed that the branching structure of amylopectin might retain more phosphates for phosphorylation, which might otherwise be distributed to regions where few starch molecules are present. The potato extrudate prepared at pH 11.0 and 50 rpm showed low phosphorus content. It is not clear if the inherent high phosphorus content of potato and/or the specific reaction conditions contributed to the low phosphorylation efficiency

Waxy corn extrudates prepared at 200 rpm contained significantly higher phosphorus content than those prepared at 50 rpm. The extrudates prepared at 200 rpm experienced a shorter residence time of approximately 75 s versus a residence time of approximately 200 s for those prepared at 50 rpm. Despite its shorter residence time, extrusion at 200 rpm had better phosphorylation efficiency than extrusion at 50 rpm for waxy corn starch. However, there was no difference in phosphorus content among common corn extrudates. The lower amylopectin content of common corn may have contributed to the similar phosphorus content at the two screw speed conditions. Among potato extrudates, the slower screw speed produced higher phosphorus content at pH 9.0, but the faster screw speed generated higher phosphorus content at pH 11.0. This suggests that phosphorylation of starch might not be independently affected by the alkalinity of the reaction or the speed of the screw but rather a combination of both factors. The reaction efficiency of phosphorylation at pH 11.0 increased with increasing shear rate from 50 to 200 rpm for potato and waxy corn starches. The phosphorus results suggest that the phosphorylation efficiency can be affected by shear rate within reactive extrusion.

3.2. Swelling power

The swelling powers of starch extrudates measured at 37 °C are presented in Table 1. The swelling power of unmodified waxy corn extrudate was slightly greater at 200 rpm than at 50 rpm, presumably due to the increased dextrinization of starch molecules at a higher shear rate (Lai & Kokini, 1991). The formation of low molecular-weight components as well as the disruption of hydrogen bonds between neighboring starch chains would increase the free hydroxyl groups available to associate with water, resulting in an increase in swelling power. Nevertheless, unmodified common corn and potato extrudates displayed similar swelling power at both screw speeds, which was attributed to the presence of amylose. The swelling power of extruded starch phosphates was

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

Starch type	Treatment	Screw speed (rpm)			
		50	200	50	200
		Phosphorus (%)		Swelling power	
Waxy corn	Unmodified	0.01^{a}	0.01^{a}	8.3^{b}	11.6^{a}
	pH 9.0	0.59^{b}	0.65^{a}	20.7^{b}	25.1^{a}
	pH 11.0	0.52^{b}	0.64^{a}	20.4^{b}	29.1^{a}
Common corn	Unmodified	0.03^{a}	0.04^{a}	11.7^{a}	12.3^{a}
	pH 9.0	0.42^{a}	0.32^{a}	13.5^{a}	14.6^{a}
	pH 11.0	0.36^{a}	0.31^{a}	13.8^{a}	13.8^{a}
Potato	Unmodified	0.09^{a}	0.09^{a}	16.0^{a}	16.1^{a}
	pH 9.0	0.51^{a}	0.32^{b}	31.5^{a}	19.6^{b}
	pH 11.0	0.28^{b}	0.41^{a}	25.0^{a}	24.1^{a}

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

mostly influenced by the extent of phosphorylation. 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 shear rates for common corn phosphates. Despite phosphorylation, the limited increase in swelling power in common corn extrudates relative to their unmodified counterparts was attributed to the negative impact of amylose on swelling. Among potato extrudates, the swelling power of the extruded starch phosphates further demonstrated the interaction of phosphorylation and shear rate. The swelling power of potato extrudates at 200 rpm was greater when prepared at pH 11.0 than at pH 9.0, which corresponded to increased phosphorylation. Similarly the swelling power of potato extrudates prepared at pH 9.0 was greater when extruded at 50 rpm than at 200 rpm. For the potato extrudates prepared at pH 11.0, the swelling power was not as affected by the shear rate, despite significantly higher phosphorus content at 200 rpm. It is suspected that the increased phosphorus content at pH 11.0 might be in the form of distarch esters, which limited the swelling power of the resultant potato extrudates.

3.3. Carbohydrate distribution

Representative normalized HPSEC profiles of extruded starch phosphates are shown in Fig. 1. Because of the severe physical disruption and the further substitution and cross-linking from phosphorylation, the chromatograms were not compared statistically but discussed according to the elution time and distribution of the profiles. Unmodified extrudates at 200 rpm were found to elute slightly later than those at 50 rpm. Davidson, Paton, Diosady, and Rubin (1984) indicated that no mechanical degradation of the starch can occur in the section of the extruder filled with solid starch but only in a melted state. They found that the dextrinization of starch was dependent on both the residence time in the fully melted zone and the shear rate induced by the extruder (Davidson et al., 1984). The present results indicate that shear rate was a more dominating parameter than residence time in terms of starch dextrinization. The higher shear rate at 200 rpm, although shorter residence time of approximately 75 s, caused more extensive dextrinization of starch molecules than the lower shear rate at 50 rpm with longer residence time of 200 s. Nonetheless, the overall carbohydrate distributions of the unmodified extrudates were similar between the two rpm levels.

The carbohydrate profiles of phosphorylated starch extrudates were different from their unmodified counterparts and significantly affected by the screw speed. Phosphorylated starch extrudates consisted of a greater proportion of low molecular-weight components than their respective unmodified ones, with common corn extrudates showing the most difference. The increased proportion of low molecular-weight components was attributed to the increased dextrinization of starch phosphates as a result of phosphorylation that decreased gelatinization and promoted swelling. Starch phosphates extruded at 50 and 200 rpm showed similar elution time for their peaks, but their proportions of high and low molecular-weight components differed. Starch phosphates at 200 rpm had a smaller proportion of low molecular-weight components that eluted later than those at 50 rpm. The difference in the proportion of high and low molecular-weight components of starch extrudates indicates that the higher shear rate at 200 rpm improved the cross-linking efficiency for starch phosphates. The increased proportion of high molecular-weight components implies the formation of more cross-linked molecules that possessed larger molecular weights and thus eluted earlier.

3.4. Dissolution properties

The MPT release profiles of starch extrudates are shown in Fig. 2 and release kinetics in Table 2. Error bars were smaller than data point symbols and therefore not shown. The evaluation of MPT release kinetics was based on Peppas' equation, Eq. (1), (Peppas, 1985) as previously defined (O'Brien et al, 2008);

$$M_t/M_\infty = k \times t^n \tag{1}$$

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. 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 profiles of unmodified starch extrudates at both rpm levels exhibited negligible difference. These extrudates exhibited at least 50% drug release within 6, 2.5, and 8 h for waxy corn, common corn, and potato starch, respectively. Both unmodified waxy corn and potato exhibited an n value indicative of anomalous transport, but common corn showed an n value indicative of Fickian diffusion.

Waxy corn phosphates exhibited similar dissolution profiles at both pHs and screw speeds with 50% drug release at approximately 6 h and n values indicative of anomalous transport. The increase in phosphorus content and subsequent swelling power of waxy corn phosphates when extruded at 200 rpm over 50 rpm had a small impact on the ability of their hydrogels to impede drug release.

Common corn phosphates exhibited slower releases of MPT than their unmodified counterparts for both pH. The common corn phosphates extruded at 200 rpm displayed a slower release of MPT at pH 9.0, but a faster release at pH 11.0. At pH 9.0, common corn released 50% drug within 6 h when phosphorylated at 200 rpm but released 50% drug within 3 h when phosphorylated at 50 rpm. Among all common corn phosphates, only the ones by pH 9.0/200 rpm and pH 11.0/50 rpm exhibited n values indicative of anomalous diffusion.

Potato phosphates at 50 rpm displayed considerably slower release rates than those at 200 rpm. The potato phosphate extruded at 50 rpm exhibited 50% drug release within 8.5 h, in comparison with 1.5 h when extruded at 200 rpm. Although their phosphorus contents and swelling powers were similar, the inability of potato phosphate at 200 rpm to impede drug release suggests that the slight increase in cross-linking at the higher shear rate might have a considerable impact on the drug release. The potato phosphates at 50 rpm all exhibited n values signifying anomalous diffusion.

3.5. Rheological studies

Dynamic testing can provide a more explicit and detailed characterization of the gel structure. The rheological properties of starch extrudates were studied in an attempt to understand how the screw speed might affect the gel characteristics of the resulting extruded phosphates. The gel characteristics could then be related to the gel properties of the tablets as an indication of the actual drug release mechanism. 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.

The mechanical spectra of starch extrudates obtained by dynamic oscillatory test are shown in Figs. 3 and 4. The unmodified waxy corn extrudates were shown to be viscoelastic with predominance in fluid behavior because their loss moduli (G'') were greater than their storage moduli (G'), both of which exhibited a dependency on angular frequency (ω). The decreased magnitude

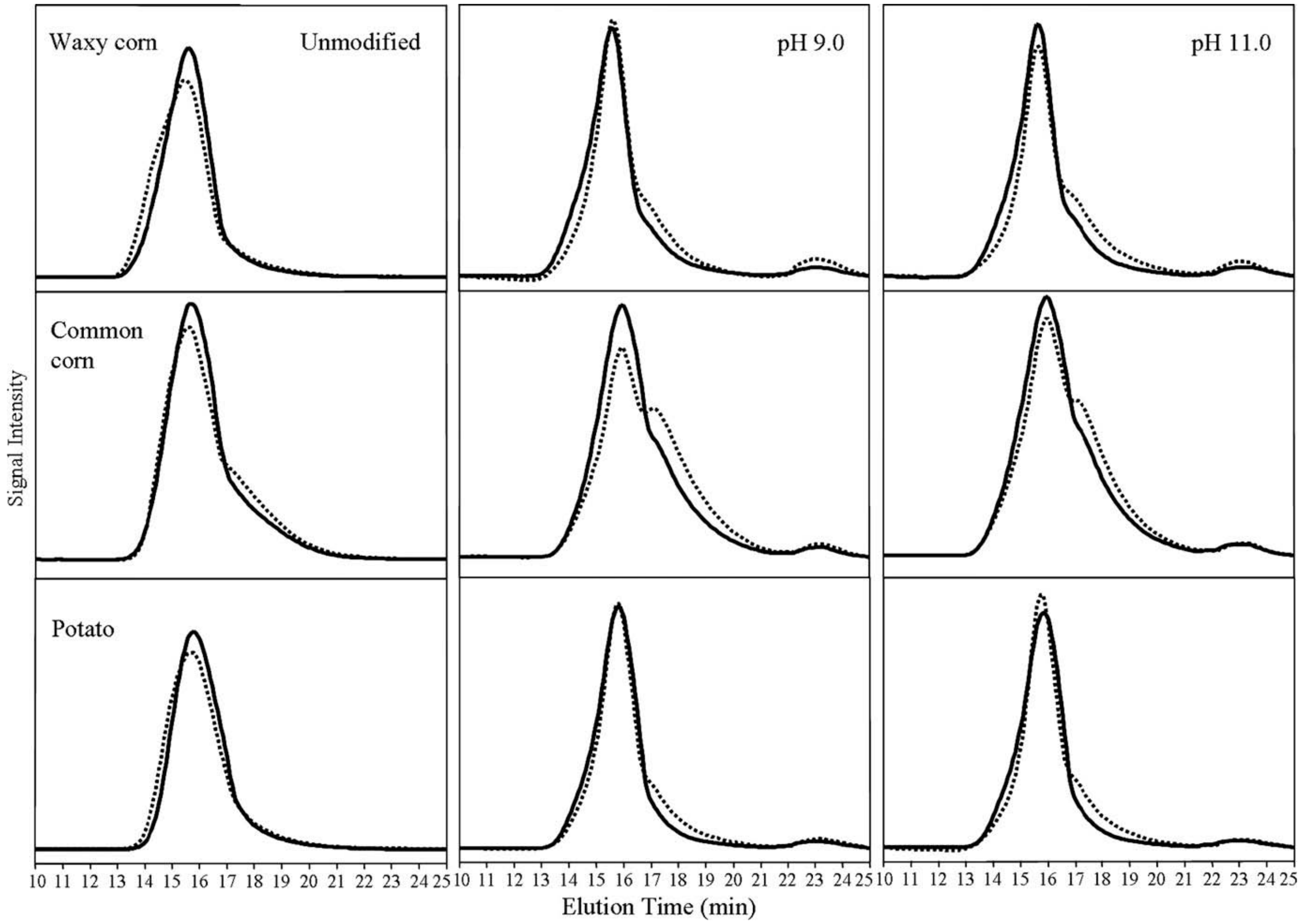

Fig. 1. HPSEC chromatograms of 50 rpm (dotted line) and 200 rpm (solid line) starch extrudates.

of the dynamic moduli for the unmodified waxy corn extrudate at 200 rpm indicates that its structure was more fluid-like than its counterpart at 50 rpm. Regardless of rpm, the dependency of the dynamic moduli with angular frequency suggests that the hydrogel structure of the unmodified waxy corn extrudates was influenced by a translational motion of chains and not a rigid structure (Tecante, 2001). Both waxy corn phosphates at pH 9.0 and 11.0 by 50 rpm were found to have a stronger gel structure because G′ was significantly greater than G″, indicating increased chain entanglement (Tecante, 2001). The relative independence of the dynamic moduli with regard to ω shows that a strong network structure, which could be described as a 'true' or a 'strong' gel, was maintained. Both waxy corn phosphates at pH 9.0 and at pH 11.0 by 200 rpm were found to have viscoelastic properties with more viscous fluid-like behavior than their counterparts. The dependency of the dynamic moduli on ω indicates that the samples at 200 rpm did not exhibit as strong a gel as those at 50 rpm. Furthermore, the trend of the complex viscosity, $|\eta*|$, in both waxy corn starch phosphates showed a strong non-Newtonian shear-thinning behavior under the condition tested (Fig. 4). The extrudates at 50 rpm showed an increase in intensity and dependency on frequency. The plots of modified waxy corn extrudates and potato extrudates at 200 rpm exhibited a slight curvature at higher ω, which is characteristic of starch suspensions, showing higher viscosities in that region (Tecante & Doublier, 1999). The $|\eta*|$ indicate that the shear rate of 200 rpm reduced the non-Newtonian shear-thinning properties of waxy corn phosphates, presumably from increased cross-linking at 200 rpm as supported by the carbohydrate distribution profiles (Fig. 1). The slightly larger n of the modified waxy extrudates at 200 rpm suggests that the differences in their gel structures is not of sufficient magnitude to dictate differences in their drug release properties because of the considerable entanglement associated with amylopectin branch chains.

All common corn extrudates were shown to be viscoelastic with predominance in the solid behavior attributable to their greater G′ than G″. The relative independence of G′ and G″ from ω for all common corn phosphates indicates the gels were capable of maintaining a network structure. The similar intensity and shape of their dynamic profiles suggest similar interactions of their networks despite the phosphorylation reaction. The similarities among the unmodified and phosphorylated starches regardless of the screw speed indicate the strong impact of amylose on gel properties. The independence of ω over 3 logarithmic scales suggests that the solid-like behavior was of a more rigid structure. The common corn phosphates at 50 rpm were also shown to have dynamic moduli of a greater magnitude, thus more solid behavior, than at 200 rpm. The common corn phosphates also all showed a strong non-Newtonian shear-thinning behavior from their $|\eta*|$. Common corn phosphates had rigid structures, but the dominating role of amylose limited the ability of some common corn phosphates to better sustain drug release.

The unmodified potato extrudates were shown to be viscoelastic with predominance in solid behavior because their G′ values were greater than G″. There were no significant differences in the dynamic moduli of the unmodified potato between 50 and 200 rpm. The potato phosphates by 50 rpm exhibited similar visco-

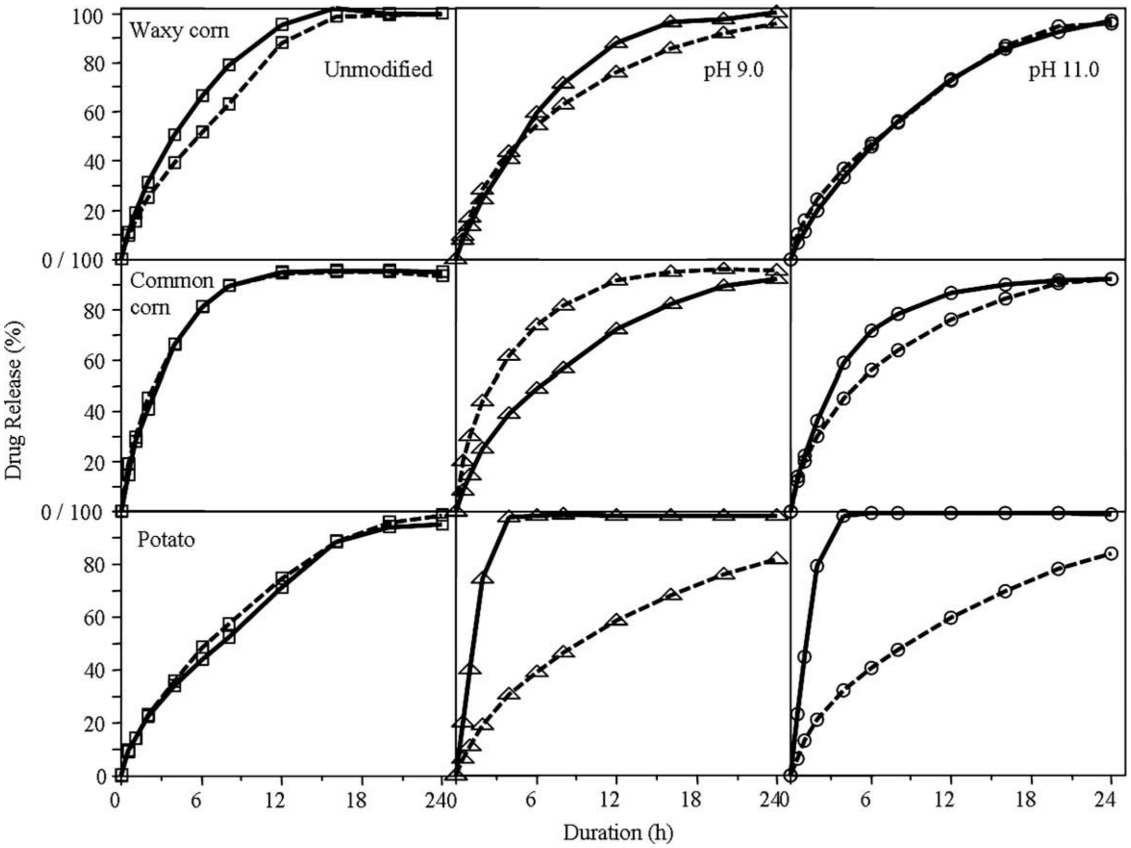

Fig. 2. Drug release profiles of 50 rpm (dotted line) and 200 rpm (solid line) starch extrudates.

Table 2
Release kinetics (*k* and *n*) of MPT and starch extrudates.

Starch type	Parameters	Screw speed (rpm)					
		50	200	50	200	50	200
		Unmodified		pH 9.0		pH 11.0	
Waxy corn	k (h^{-n})	0.2	0.27	0.21	0.21	0.17	0.15
	n	0.54	0.46	0.49	0.52	0.56	0.6
	r^2	0.97	0.95	0.99	0.97	0.99	0.99
Common corn	k (h^{-n})	0.39	0.37	0.37	0.18	0.24	0.32
	n	0.31	0.34	0.33	0.53	0.46	0.37
	r^2	0.93	0.92	0.96	0.99	0.99	0.95
Potato	k (h^{-n})	0.17	0.16	0.14	0.22	0.15	0.21
	n	0.58	0.59	0.58	0.55	0.56	0.59
	r^2	0.99	0.99	0.99	0.84	0.99	0.84

elastic solid-like behavior as their unmodified counterparts, whereas those by 200 rpm exhibited viscoelastic properties predominated by fluid-like behavior with G″ > G′ in some frequency. Similar to waxy corn phosphates, the dynamic moduli dependency on ω dictates that the gel of potato extrudate at 200 rpm was governed predominately by the translational motion of the macromolecules and not a rigid gel structure (Tecante, 2001). Potato extrudates displayed a strong non-Newtonian shear-thinning behavior according to their $|\eta^*|$, except for the phosphates at 200 rpm. The similarity of the $|\eta^*|$ for the unmodified potato extrudates indicated their similar gel structures at the different rpm levels. The considerable differences in magnitude between potato phosphates at 50 and 200 rpm confirm the differences in their gel structures. The potato phosphates at 50 rpm show a significantly stronger gel network than those at 200 rpm. Newtonian fluid behavior of potato phosphates at 200 rpm agreed with the dynamic moduli data, implying the dominance of fluid-like characteristics, presumably from increased cross-linking. Previous carbohydrate profiles showed that the higher shear rate at 200 rpm improved the cross-linking efficiency for starch phosphates. The drug release and rheological properties of potato phosphates seemed to be strongly affected from the increased cross-linking as compared with those of common corn phosphates, which might be attributed to the B-type crystalline structure or large molecular-weight of amylose and amylopectin in potato starch. The significantly slower drug release profiles of the potato phosphates at 50 rpm suggest that the differences in their gel structures was a dominating factor governing drug release.

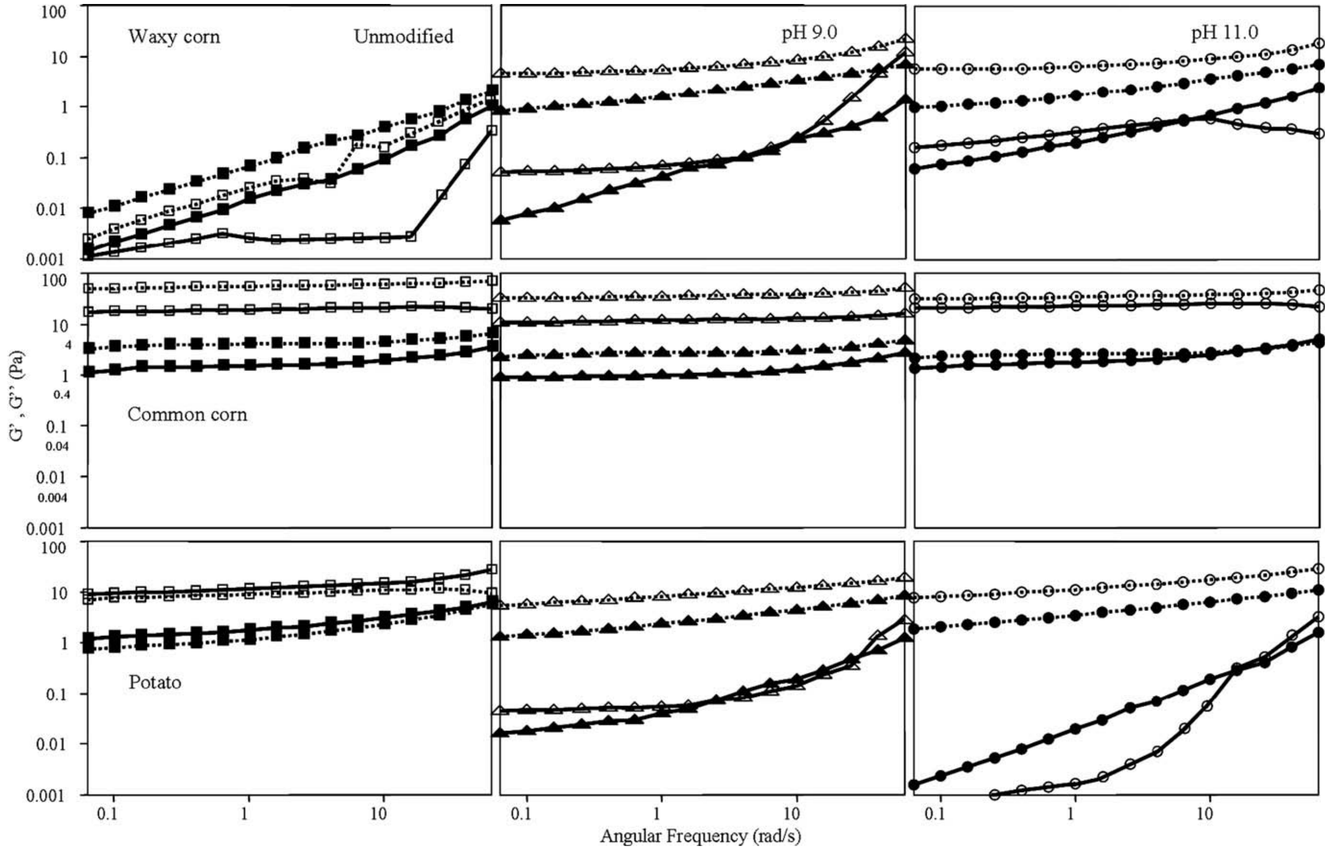

Fig. 3. Mean values for the mechanical spectrum of dynamic moduli of 50 rpm (dotted line) and 200 rpm (solid line) starch extrudates. G′ the open symbols and G′′ the closed symbols.

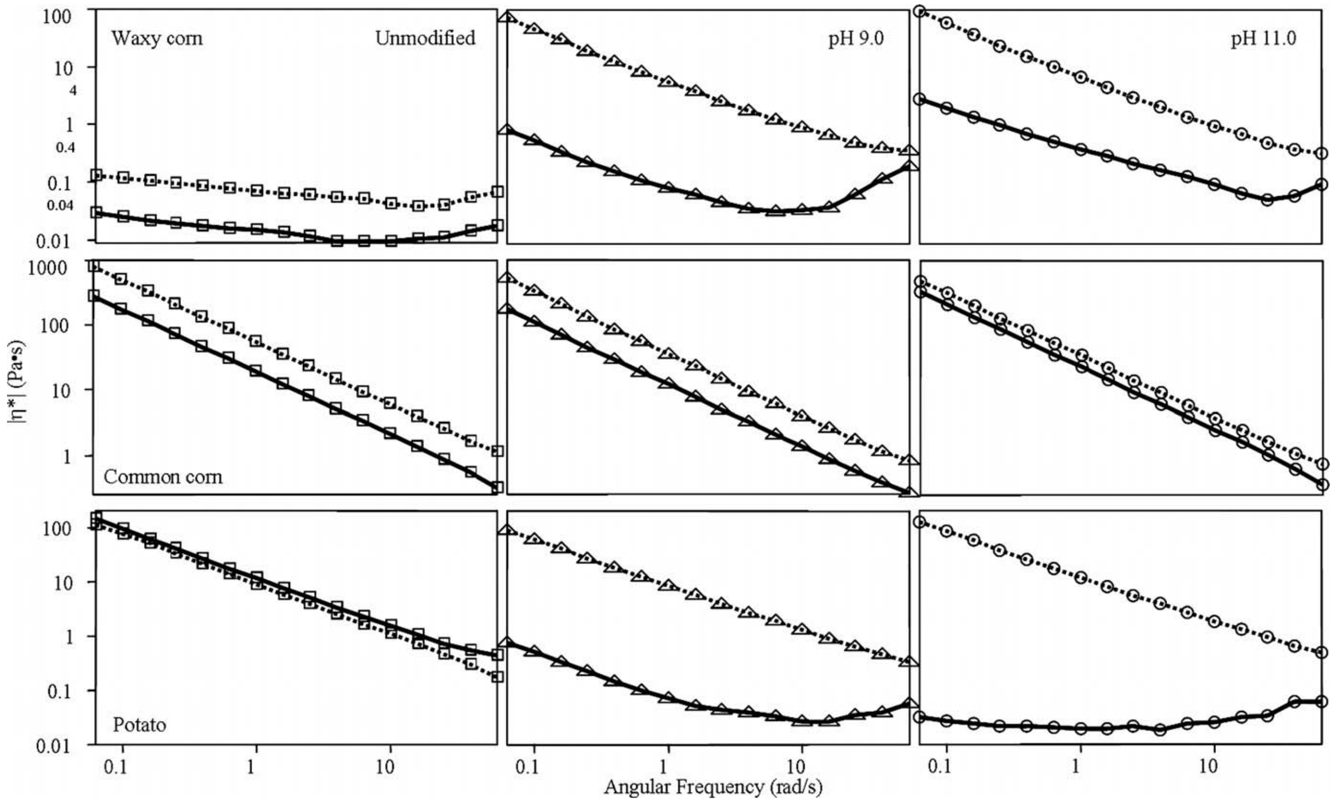

Fig. 4. Mean values for complex viscosity (|η∗|) of 50 rpm (dotted line) and 200 rpm (solid line) starch extrudates.

4. Conclusions

This study found that the reaction efficiency of phosphorylation by reactive extrusion can be affected by the shear rate for different starch types. The reaction efficiency of potato starch was found to decrease at pH 9.0 and increase at pH 11.0 when the shear rate was increased. The swelling power of the starch phosphates was found to be mostly influenced by the extent of phosphorylation. Moreover, the cross-linking efficiency was found to increase at the screw speed of 200 rpm over 50 rpm. The shear rate starch experienced during phosphorylation was found to govern the extent of degradation of starch molecules over the residence time. The ability of starch extrudates to slow drug release was strongly affected by the composition and structure of starch. The extrusion parameters had limited impact on the drug release of waxy corn phosphates because waxy corn starch consists of only amylopectin, whose network structure and subsequently drug release seemed to be less affected by phosphorylation .In contrast, the drug release and rheological properties of common corn and potato extrudates was affected by the amylose component and phosphorylation. A strong gel network structure was preferred for the sustained release of drug.

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