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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