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Effects of structure and modification on sustained release properties of starches

Fernanda Onofre [a], Ya-Jane Wang [a,*], Andronikos Mauromoustakos [b]

[a] Department of Food Science, University of Arkansas, 2650 N. Young Avenue, Fayetteville, AR 72704, USA
[b] Agricultural Statistics Laboratory, University of Arkansas, Fayetteville, AR 72701, USA

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ABSTRACT

Starches of different sources and compositions were investigated to determine the effect of structure and chemical modification on the sustained release properties of the resultant modified starches. Starches were cross-linked with epichlorohydrin and substituted with carboxymethyl or aminoethyl groups at different levels. Substitution efficiency was overall higher for waxy corn and potato starches than for Hylon VII, and was higher for starches at low cross-linking levels than those at high cross-linking ones. Waxy corn starch displayed better sustained release properties when cross-linked to a lower level, whereas Hylon VII showed better performances when cross-linked to a higher level. Matrices substituted with carboxymethyl and aminoethyl groups at the high level showed better sustained release properties than those substituted at the low level. The proportion and structure of amylose and amylopectin in starches from different botanical sources strongly influenced the level of modification required to produce a satisfactory sustained release matrix.

1. Introduction

Conventional drug delivery formulations promote a fluctuation of drug plasma concentration over time due to a burst drug release from the pharmaceutical form, which is not ideal in a proper pharmacotherapy. Sustained delivery systems offer a better approach to drug therapy because they provide a more constant drug plasma concentration within the therapeutic window (Chien, 1992; Lordi, 1986).

Polymers are often used in sustained release formulations to provide diverse functionality to the formulation in which they are employed (Langer, 1993). Hydrogels are hydrophilic polymers commonly used as sustained release agents in pharmaceutical formulations because of their ability to form a gel network upon swelling, which entraps the drug and acts as a barrier to its release to the surrounding medium. Derivatives of cellulose such as hydroxypropylmethyl cellulose (HPMC), ethylcellulose, and their combinations with other polymers have been extensively studied in sustained release formulations (Levina & Rajabi-Siahboomi, 2004; Vlachou, Naseef, & Efentakis, 2004). More recently, starch and its derivatives have received greater attention for different pharmaceutical applications due to their biodegradability and biocompatibility. Starch-based capsules (Vilivalam, Illum, & Iqbal, 2000), film coatings (Cummings et al., 1996; Milojevic et al., 1996; Siew, Basit, & Newton, 2000), microspheres (Mundargi, Shelke, Rokhade, Patil, & Aminabhavi, 2008), and subcutaneous implants (Désévaux, Dubreuil, Lenaerts, & Girard, 2002) have been studied, and tablet is the most common pharmaceutical form explored.

Starch can be obtained from a variety of sources. Among various commercially available starches, 70% high amylose corn, commonly referred to as high amylose starch, has been extensively studied for its sustained release applications. Mateescu, Lenaerts, and Dumoulin (1995) prepared cross-linked high amylose starch with epichlorohydrin after gelatinization as a sustained-release excipient, and found that matrices cross-linked at lower levels showed better sustained release ability. Lenaerts et al. (2003) prepared a modified high amylose starch by cross-linking with phosphorous oxychloride and substitution with hydroxypropyl groups prior to gelatinization (Contramid®). This modified starch has been extensively characterized for its structural and physicochemical properties, such as amylose polymorphism, substitution degree, swelling, and permeability (Baille, Malveau, Zhu, & Marchessault, 2002; Dumoulin, Alex, Szabo, Cartilier, & Mateescu, 1998; Ispas-Szabo, Ravenelle, Hassan, Preda, & Mateescu, 2000; Le Bail, Morin, & Marchessault, 1999; Lenaerts et al., 1998; Mulhbacher, Ispas-Szabo, & Mateescu, 2004; Mulhbacher & Mateescu, 2005; Rahmouni, Chouinard, Nekka, Lenaerts, & Leroux, 2001; Rahmouni, Lenaerts, & Leroux, 2003; Ravenelle, Marchessault, Légaré, & Buschmann, 2002; Thérien-Aubin, Baille, Zhu, & Marchessault, 2005). Carboxymethyl-substituted high amylose starch also exhibited effective sustained delivery properties (Calinescu, Mulhbacher, Nadeau, Fairbrother, & Mateescu, 2005; Chebli, Cartilier, & Hartman, 2001; Nabais et al., 2007). Nevertheless, starches of different compositions and sources have been limitedly evaluated for their sustained release applications (Michailova, Titeva, Kotsilk-

* Corresponding author. Tel.: +1 479 5753871; fax: +1 479 5756936.
E-mail address: yjwang@uark.edu (Y.-J. Wang).

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ova, Krusteva, & Minkov, 2001; Pringels, Ameye, Vervaet, Foreman, & Remon, 2005; Te Wierik, Eissens, Bergsma, Arends-Scholte, & Lerk, 1997; Te Wierik et al., 1996).

Starch is primarily composed of amylose, an essentially linear polymer, and amylopectin, a highly branched molecule. In addition to the difference in amylose/amylopectin ratio, starches from different sources also vary in their structural characteristics, and consequently their physicochemical properties. In this study, effects of starch composition and source, and modification type on the sustained release ability of the resultant modified starches were investigated.

2. Experimental

2.1. Materials

Waxy corn and 70% high amylose corn (Hylon VII) were gifts from National Starch and Chemical Company (Bridgewater, NJ). Potato starch was obtained from Tate & Lyle (Decatur, IL). Sodium benzoate and propranolol hydrochloride were purchased from Mallinckrodt Baker Inc. (Phillipsburg, NJ) and TCI America (Portland, OR), respectively. Magnesium stearate was obtained from Riedel-de Haën (Seelze, Germany). Epichlorohydrin (ECH) was obtained from Acros Organics (Morris Plains, NJ), 2-chloroethylamine hydrochloride was purchased from Alfa Aesar (Ward Hill, MA), and chloroacetic acid was purchased from Fisher Scientific (Fair Lawn, NJ). All other chemicals were of ACS grade.

2.2. Experimental and treatment design

Six factors with two or three levels each were tested and listed in Table 1. The combinations of levels to be tested were determined using a fractional factorial design in a completely randomized fashion. Forty-eight treatment combinations were generated and tested.

2.3. Preparation of cross-linked and carboxymethyl (CM)-substituted starches

Starches were modified according to the procedure described by Mulhbacher, Ispas-Szabo, Lenaerts, and Mateescu (2001) with slight modifications. The amount of starches used in this study was half of the amount of Hylon VII used in the original procedure by Mulhbacher et al. (2001) because of high viscosity encountered upon gelatinization. Starch (7 g Hylon VII, 7 g waxy corn, or 6 g potato) was mixed with 34 mL of deionized water and stirred at 50 °C for 20 min in a water bath. Thereafter, 47 mL of 1.5 M NaOH were introduced into the medium, followed by epichlorohydrin (ECH) (3 g or 16 g ECH per 100 g starch for low and high level of cross-linking, respectively). The mixture was stirred at 50 °C for 40 min, and then an appropriate amount of monochloroacetic acid was added (1:1 w/w acid:starch for the high-level, and 1:2 w/w acid:starch for the low-level substitution), while maintaining the pH at 10–11 with 15% (w/w) NaOH at 50 °C for 1 h. Then, the pH was neutralized to 6 with 3 M acetic acid, and the starch was precipitated with 1× vol. 85% acetone, followed by washing twice with ½ vol. 70% acetone, 1× vol. 85% acetone, and finally 1× vol. pure acetone. The precipitate was dried at 40 °C overnight, ground using a Cyclone Sample Mill (UDY Corporation, Fort Collins, CO), and passed through a 75-μm-sieve. The carboxyl content of CM-substituted starches was determined according to the procedure described by Kuakpetoon and Wang (2001).

2.4. Preparation of cross-linked and aminoethyl (AE)-substituted starches

The procedure to prepare AE-starches was similar to that of CM-starches (Mulhbacher et al., 2001) with modifications. The starch was first cross-linked as described above, and an amount of chloroethylamine equivalent to 1.2× the starch weight was dissolved in water and added to the medium. The reaction was carried out at 70 °C for the high-level substitution and at 50 °C for the low-level substitution for 1 h while maintaining the pH at 9–10 with 10% NaOH solution. The mixture was neutralized, precipitated and washed with acetone solutions, ground and sieved as previously described. The nitrogen content of the AE-substituted starches was determined by the Micro-Kjeldahl method (AACC, 1997).

2.5. Dissolution studies

Modified starch and drug (20% or 50% of tablet weight of sodium benzoate or propranolol hydrochloride) were mixed in a mini-manual mixer (Inversina, Bioengineering AG, Wald, Switzerland) for 10 min. Then, magnesium stearate (1% weight of tablet) was added as a lubricant to the mixture and mixed for an additional min. Tablets were prepared by compressing 500 mg of the mixture at 2.5 MT for 5 s using a 13-mm die (Carver, Wabash, IN) with a hydraulic press (Carver, Wabash, IN).

Drug release was evaluated using an Apparatus II (USP, 2005) dissolution instrument (Varian Inc., Cary, NC). Tablets were immersed in 900 mL of deionized water at 37.0 °C for 24 h at a paddle rotation speed of 50 rpm. Samples were taken without replacements, and drug release was measured using a spectrophotometer (Beckman Coulter, Fullerton, CA) at 290 nm for propranolol hydrochloride and 225 nm for sodium benzoate.

2.6. Statistical analyses

A repeated measures analysis of drug release over 24 h was conducted (time points were free of alias to each other), and the main effects of the factors and their two-way interactions were determined. All the analyses were conducted using JMP 7.0.2 (SAS, 2007). Significance is reported using an α level of 0.05.

3. Results and discussion

3.1. Substitution efficiency

Table 2 lists the substitution levels of CM and AE in different treatments. For CM substitution, efficiency was overall higher in waxy corn (0% amylose), followed by potato (~20% amylose), and Hylon VII (~70% amylose), which followed the order of increasing

Table 1
Factors and levels of each factor studied.

Factors	Levels			Number of levels
Drug type	Sodium benzoate	Propranolol hydrochloride		2
Starch type	Waxy corn	Hylon VII	Potato	3
Cross-linking degree (g ECH/100 g starch)	3	16		3
Substitution type	Carboxymethyl (CM)	Aminoethyl (AE)		2
Substitution level	High	Low		2
Drug loading (w/w)	20%	50%		2

Table 2
Efficiency of carboxymethyl (CM)- and aminoethyl (AE)-substitution*.

Starch	Cross-linking level (g ECH/100 g starch)	Substitution level	Carboxyl content (% as is)	Nitrogen content (% as is)
Waxy corn	3	High	0.68 ± 0.03	1.28 ± 0.03
Waxy corn	3	Low	0.22 ± 0.01	1.25 ± 0.02
Waxy corn	16	High	0.21 ± 0.01	1.25 ± 0.01
Waxy corn	16	Low	0.20 ± 0.01	1.07 ± 0.04
Hylon VII	3	High	0.22 ± 0.01	1.32 ± 0.03
Hylon VII	3	Low	0.19 ± 0.01	0.76 ± 0.00
Hylon VII	16	High	0.12 ± 0.01	1.15 ± 0.03
Hylon VII	16	Low	0.10 ± 0.02	1.03 ± 0.00
Potato	3	High	0.37 ± 0.01	1.44 ± 0.06
Potato	3	Low	0.20 ± 0.01	1.20 ± 0.06
Potato	16	High	0.26 ± 0.01	1.28 ± 0.04
Potato	16	Low	0.15 ± 0.01	0.99 ± 0.04

* Mean ± standard error of two measurements.

amylose content, and was generally higher in starches cross-linked at degree 3 (3 g ECH/100 g starch) than at degree 16 (16 g ECH/100 g starch) at the same level of substitution. The efficiency of CM-substitution in the present study was lower than those reported by Mulhbacher et al. (2001, 2004) and Mulhbacher and Mateescu (2005), which was attributed to dilution of the reaction medium. As previously mentioned, the amount of starch was reduced to half in order to decrease the viscosity for effective mixing, particularly for waxy corn, potato, and starches cross-linked to the high level. It has been demonstrated that a decrease in starch concentration led to a decrease in substitution efficiency, which was attributed to a decrease in the chance of starch molecules to come in contact with the reagent from the addition of large amounts of water (Jeon, Viswanathan, & Gross, 1999; Khalil, Hashem, & Hebeish, 1990; Khalil, Hashem, & Hebeish, 1995; Song, He, Ruan, & Chen, 2006). The presence of a large amount of water may also promote hydrolysis instead of esterification of monochloroacetic acid. Hebeish and Khalil (1988), Bhattacharyya, Singhal, and Kulkarni (1995), and Rakhmatullin, Emelyushin, and Gavrilov (1999) reported that aqueous alkaline media favored the hydrolysis of monochloroacetic acid into its glycolate form, reducing the substitution efficiency.

For AE substitution, the overall substitution efficiency was similar in waxy corn and potato starches, but slightly lower in Hylon VII. As in CM substitution, AE-substituted starches with the high cross-linking degree had a lower substitution efficiency. The formation of cross-links might interfere with the subsequent substitution reaction by reducing the availability and/or accessibility of hydroxyl groups, consequently decreasing the substitution efficiency.

The effect of starch composition on reaction efficiency has been reported (Kuakpetoon & Wang, 2008; Landerito & Wang, 2005). A decrease in reaction efficiency was associated with increasing amylose content in various starches. Hylon VII had the lowest efficiency when compared with waxy corn, common corn, 50% high amylose corn, and potato starches for phosphorylation and oxidation. The low reaction efficiency for high amylose starches was speculated to be related to the linear nature of amylose, which is not capable of entrapping the reagent as well as the branched structure of amylopectin. This branched structure of amylopectin may retain more reagents for reaction. It is important to note that these findings were based on granular reaction. In this study, starch was pregelatinized prior to chemical modification, thus the conformation and interaction of starch molecules may also contribute to their differences in reaction efficiency.

Gelatinization of starch leads to the formation of a molecular dispersion of amylose and amylopectin in the medium. When packed in the granule, these macromolecules are interdispersed and associated with each other into semi-crystalline structure. However, upon gelatinization and release of the macromolecules to the solution, they become incompatible and immiscible due to their distinct natures (Kalichevsky & Ring, 1987). Jane, Xu, Radosavljevic, and Seib (1992) reported that cross-linking of granular starch resulted in cross-linking of amylose and amylopectin molecules, whereas cross-linking of pregelatinized starch resulted in cross-linking of only amylose or only amylopectin but not between them. Amylose and amylopectin possess different properties that lead to their immiscibility, such as differences in molecular size and branching structure (Tolstoguzov, 2003). Amylose exists in an amorphous state in starch granule but becomes crystalline from self-association after dissolved in solution because of its linear structure. In comparison, amylopectin is present in a semi-crystalline state in granules but becomes less organized when dissolved in solution and then undergoes slower self-association than does amylose (Tolstoguzov, 2003). The strong self-association of amylose molecules might reduce their accessibility to reagents, while the less ordered amylopectin molecules were more receptive to modification, leading to higher reaction efficiency.

3.2. Effect of drug type on drug release

Overall drug release profiles for sodium benzoate and propranolol hydrochloride were significantly different ($P < 0.05$), regardless of starch type, modification, or drug loading (Fig. 1). The release of sodium benzoate was fast, and the profiles were similar for all starches (data not shown). The release of propranolol hydrochloride, on the other hand, varied considerably with starch matrices.

Drug release from a matrix is affected by many factors, such as diffusivity of the drug from the matrix to the solvent, porosity and tortuosity of the matrix, and swelling ability and erosion susceptibility of the matrix (Lidner, Möeckel, & Lippold, 1996). The size of the drug molecule also plays a role in its transport through a matrix. Zhao, Wang, and Zhang (2007) described that drugs can be transported out of a matrix via (1) movement through the free volume of the cavities of the matrix, or (2) jumping between the cavities due to the wriggling or movement of the matrix polymer chains. On the other hand, the diffusion mechanism for larger drug molecules is mainly governed by the polymer wriggling phenomenon of the matrix. Sodium benzoate is considerably smaller than propranolol hydrochloride, therefore its diffusion from starch matrices might be less influenced by the matrix and more dominated by its transport through cavities. In contrast, the properties of the matrices might have more influence on propranolol hydrochloride release, therefore matrices showed different release behaviors.

Because of the significant differences in release profiles between sodium benzoate and propranolol hydrochloride, all statistical analyses were conducted according to drug type.

3.3. Starch type and cross-linking effect on drug release

Fig. 2 presents the averaged propranolol release profiles observed for different starches, regardless of the modifications performed. Starch type was found to play a major role in controlling drug release. Potato starch displayed better sustained release of propranolol hydrochloride, whereas Hylon VII released propranolol rapidly, and waxy corn starch showed an intermediate release. The potential of potato starch as a sustained release agent has been reported by Te Wierik et al. (1996, 1997), in which potato starch that was enzymatically degraded by pullulanase and α-amylase and subsequently retrograded showed good sustained release ability in simulated gastrointestinal conditions. The sustained release

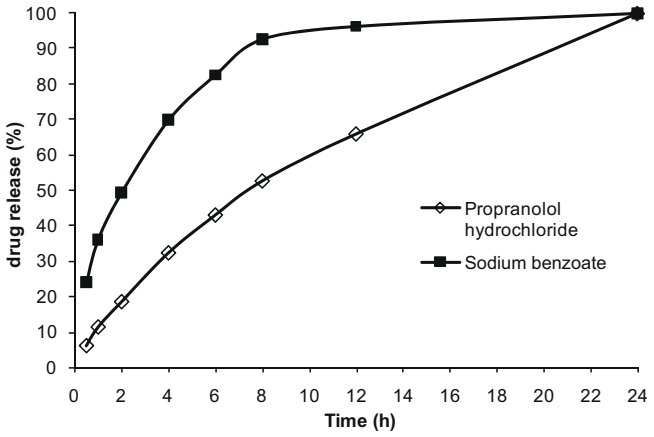

Fig. 1. Overall release profiles of sodium benzoate and propranolol hydrochloride from starch matrices.

property of pregelatinized waxy starch has been demonstrated by Herman, Remon, and De Vilder (1989) and Herman and Remon (1989), in which corn starches with varying amounts of amylose (0%, 25%, and 70%) were evaluated. These starches were thermally treated by spray drying, extrusion, or drum drying, resulting in partial or complete gelatinization, without prior chemical modification. They observed that fully gelatinized starches, particularly waxy corn starch, exhibited good sustained release properties.

A significant interaction between starch type and cross-linking degree ($P < 0.001$) was noted (Table 3). The amylose content in corn starch predominantly determined the cross-linking level required to produce a satisfactory matrix for achieving sustained release of drugs. A higher level of cross-linking was required for Hylon VII, whereas a low cross-linking level was favored for waxy corn starch in order to slow the release of propranolol (Fig. 3). Because waxy corn starch consists of nearly 100% amylopectin, the highly branched structure of amylopectin may promote extensive interaction among amylopectin molecules and form a strong and viscous matrix capable of sustaining drug release. In contrast, the essentially linear nature of amylose could not support the formation of a network structure unless amylose molecules were linked together through extensive cross-linking as in Hylon VII in the present reaction conditions. On the other hand, there was no remarkable difference in sustained release properties of potato starch when cross-linked at different levels. It is suspected that the large molecular weight of amylose and amylopectin in potato

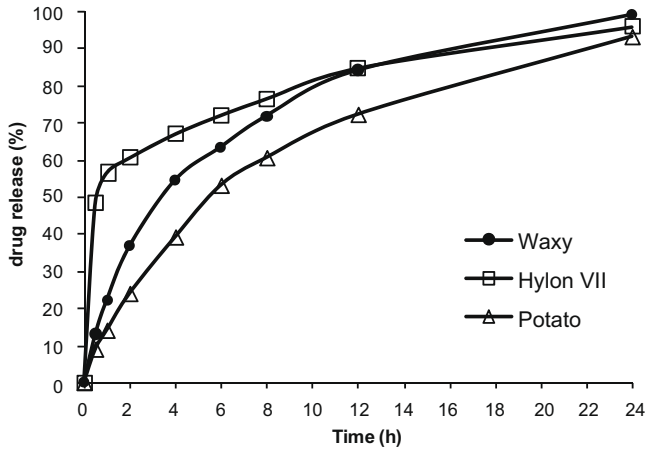

Fig. 2. Overall propranolol hydrochloride release by different starch matrices.

(Takeda, Hizukuri, Takeda, & Suzuki, 1987; Takeda, Shirasaka, & Hizukuri, 1984) may help the formation and stabilization of matrix structure and at the same time better adapt its conformation to the presence of cross-links.

The results suggest that the formation of a satisfactory sustained-release matrix is strongly influenced by both the proportion and the structural characteristics of amylose and amylopectin, which determine the nature of the resultant matrix structure, gel strength, and viscoelastic properties from their interactions after hydration. The structural characteristics of starch pastes and gels are also affected by starch concentration, amylose/amylopectin proportion, gelatinization degree, and gelatinization method and conditions (Bagley & Christianson, 1982; Michailova et al., 2001). Michailova et al. (2001) demonstrated that the addition of pregelatinized waxy corn starch to HPMC suppressed the polymer mobility of the mixture, decreasing hydration and subsequent gel diffusivity and drug release. The highly branched structure of amylopectin led to the formation of extensive intra- and inter-molecular hydrogen bonding, causing molecular constraints that decreased polymer mobility and hydration capacity. Ispas-Szabo et al. (2000) demonstrated the influence of crystallinity of high amylose starch matrix in drug release in a tablet formulation. They reported that moderate crystallinity or a more balanced ratio between order/disorder of starch chains led to better sustained release because both crystalline and amorphous structures were involved in network formation upon swelling.

3.4. Effects of substitution type and level on drug release

Substitution type and level showed a significant interaction over time ($P = 0.0061$) (Table 3). Fig. 4A displays the drug release of AE-and CM-starches at low and high levels of substitution. The overall release profiles of both substitutions at the high level were similar, with AE-starches substituted at the low level showing faster release. The substituents may contribute to stabilization of the matrix through the formation of hydrogen bonding with starch hydroxyl groups. Most of the carboxylic groups in CM-starches were in the non-ionized form at pH ~4 of the dissolution medium, which would favor hydrogen bonding between CM and hydroxyl groups. In the case of AE-starches, although the amino groups are fully protonated and positively charged at pH ~4, the strong hydrogen bonding between amine and hydroxyl groups might play a more dominant role in stabilizing the resultant matrix than the charge effect. Hydrogen bonding was suspected to be a major contributor to the stabilization from both substituents; therefore, an increase in the level of substitution was associated with a slower release rate. Dumoulin et al. (1998) and Ispas-Szabo et al. (2000) also reported hydrogen bonding as being important in molecular interactions in starch tablets. Mulhbacher et al. (2001) also reported a better performance of starch matrices substituted at a higher level than those substituted at a lower level.

Table 3
Main effects and interactions among factors*.

Effect	*P*-value (Univar H–F Epsilon)
Starch type	<0.0001
Cross-linking degree	<0.0001
Substitution type	<0.0001
Substitution level	<0.0001
Drug loading	<0.0001
Starch type × cross-linking degree	<0.0001
Substitution type × substitution level	0.0061
Starch type × substitution type	0.0029
Starch type × drug loading	0.0033

* Data for propranolol hydrochloride release.

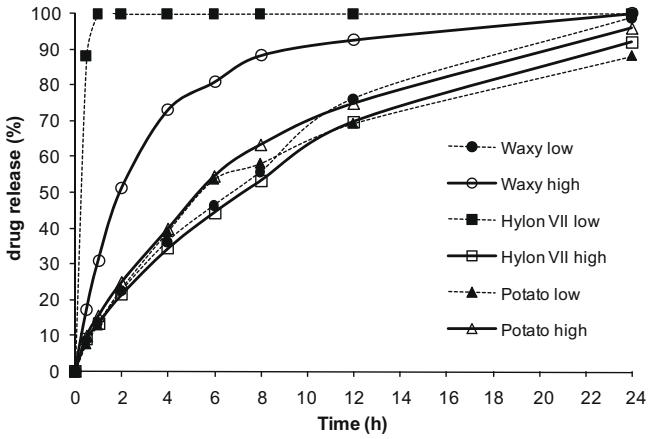

Fig. 3. Propranolol release profiles of different starch matrices cross-linked in different degrees. Low, cld 3; High, cld 16.

The charge effect of the substituents might have been more pronounced if the level of substitution was higher because the concentration of ionized groups in the polymer would be of a larger magnitude. More charged groups in the polymer might contribute to a decrease in hydrogen bonding and an increase in ionic interactions among starch chains and between starch and drug molecules. In addition, the charge effect could be more evident if different pH were used, such as slightly alkaline phosphate buffer as the dissolution medium. Such condition would likely promote ionization of carboxylic groups as well as protonation of amino groups, and the charge effect, if existent, may have been better detected. The pH effect on the behavior of starch matrices and drug release has been reported by Mulhbacher et al. (2004) and Mulhbacher and Mateescu (2005). In these studies, the swelling of CM-cross-linked Hylon VII matrices increased with increasing pH and decreased with increasing ionic strength of the medium, while drug diffusion decreased with increasing swelling. In contrast, the diffusion of drugs and swelling power of cross-linked-only Hylon VII, acetylated-cross-linked Hylon VII, and AE-cross-linked Hylon VII matrices were not affected by different ionic strength and pH conditions, indicating that these matrices were stable regardless of the surrounding environment, and the charge effect was not a major factor for their behavior.

Another significant interaction was found between substitution type and starch type ($P = 0.0029$) (Table 3). CM-substituted waxy corn and potato starches had clearly better sustained release trend than their AE-substituted counterparts (Fig. 4B). However, this trend was not observed in Hylon VII. The type of substitution had little influence on drug release profile of Hylon VII.

3.5. Effect of drug loading on drug release

Drug loading showed a significant interaction with starch type ($P = 0.0033$) (Table 3). Matrices with low drug loading (20%) released the drug at a slower rate than matrices with high drug loading (50%) for the same starch type (Fig. 5). Drug loading had a great impact on release profile of waxy corn and potato matrices, but limited impact on Hylon VII. Hylon VII matrices were capable of holding higher drug loadings better than waxy corn and potato matrices, although the average propranolol release profile of Hylon VII was faster than those of waxy corn and potato. The potential of cross-linked high amylose starch to be used in high drug loading formulations has also been reported by Mulhbacher et al. (2001). The presence of drug among starch molecules likely disturbed the entanglement of chains, thus resulting in weaker network structure and subsequently increased susceptibility to erosion (Bettini et al., 2001) in waxy and potato matrices. Because the network structure in Hylon VII was mostly formed by the cross-links instead of hydrogen bonds only the stronger bonding of cross-links may allow for higher drug loadings. Lenaerts et al. (1998) reported that high amylose starch matrices were little affected by formulation variables such as tabletting pressure and geometry, and showed little variability and consistent performance between subjects and no influence from food in an *in vivo* study.

4. Conclusions

Cross-linked and substituted starches displayed different sustained release profiles of propranolol hydrochloride in the formu-

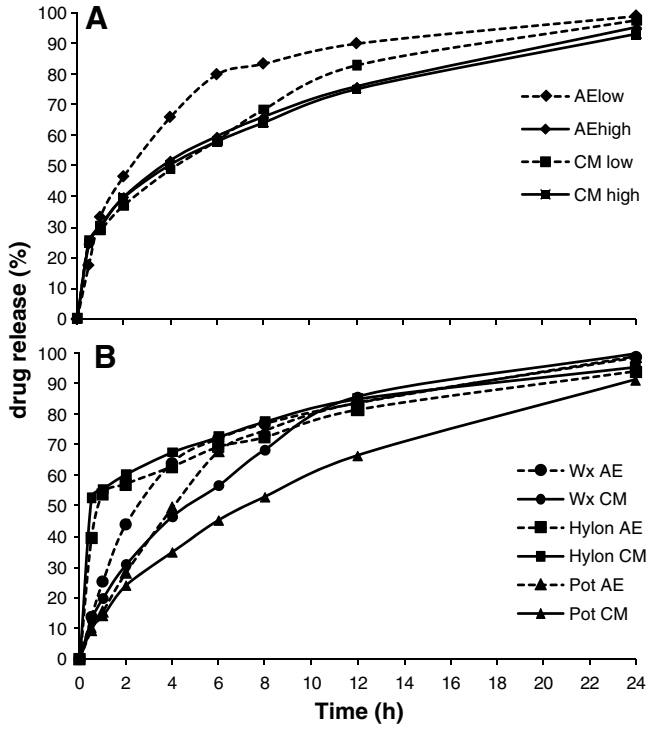

Fig. 4. Overall propranolol release profiles of modified starches. (A) Effect of substitution type and level. (B) Effect of starch type and substitution type. AE, aminoethyl-substituted starches; CM, carboxymethyl-substituted starches; Low, low-level substitution; High, high-level substitution; Wx, waxy corn starch; Hylon, Hylon VII starch; Pot, potato starch.

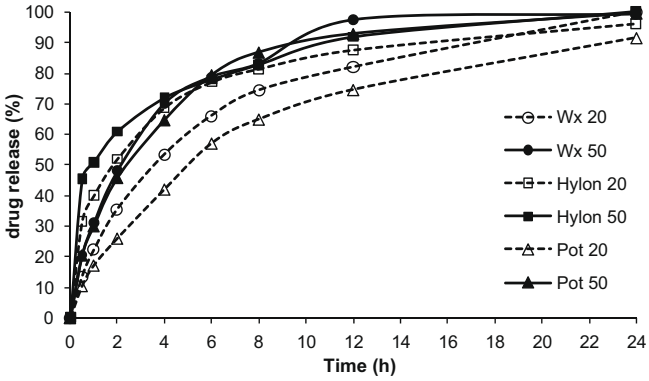

Fig. 5. Overall propranolol release profiles of starch matrices with different drug loadings. Wx, waxy corn starch; Hylon, Hylon VII starch; Pot, potato starch; 20, 20% drug loading (w/w of tablet); 50, 50% drug loading (w/w of tablet).

lations evaluated. Substitution efficiency was overall higher in waxy corn and potato starches, but lower in Hylon VII. Potato starch exhibited an overall better sustained release, followed by waxy and Hylon VII. Drug release was strongly influenced by the degree of cross-linking and starch type. Hylon VII performed better at a higher degree of cross-linking, while waxy starch performed better at a low degree of cross-linking. A significant interaction between substitution type and level was found, but substitution type and level were not the determining factors for the sustained release properties of these starch matrices. This study demonstrates that modified starches from different sources showed different sustained release properties. The type of modification required to produce good sustained release matrices was strongly affected by starch composition and structural characteristics as well as the type of drug used.

References

American Association of Cereal Chemists (AACC). (1997). Approved methods of the American Association of Cereal Chemists. Method 46–13.

Bagley, E. B., & Christianson, D. D. (1982). Swelling capacity of starch and its relationship to suspension viscosity – effect of cooking time, temperature, and concentration. *Journal of Texture Studies, 13*, 115–126.

Baille, W. E., Malveau, C., Zhu, X. X., & Marchessault, R. H. (2002). NMR imaging of high-amylose starch tablets. 1: Swelling and water uptake. *Biomacromolecules, 3*, 214–218.

Bettini, R., Catellani, P. L., Santi, P., Massimo, G., Peppas, N. A., & Colombo, P. (2001). Translocation of drug particles in HPMC matrix gel layer: Effect of drug solubility and influence on release rate. *Journal of Controlled Release, 70*, 383–391.

Bhattacharyya, D., Singhal, R. S., & Kulkarni, P. R. (1995). A comparative account of conditions for synthesis of sodium carboxymethyl starch from corn and amaranth starch. *Carbohydrate Polymers, 27*, 247–253.

Calinescu, C., Mulhbacher, J., Nadeau, E., Fairbrother, J. M., & Mateescu, M. A. (2005). Carboxymethyl high amylose starch (CM-HAS) as excipient for *Escherichia coli* oral formulations. *European Journal of Pharmaceutics and Biopharmaceutics, 60*, 53–60.

Chebli, C., Cartilier, L., & Hartman, N. G. (2001). Substituted amylose as a matrix for sustained-drug release: A biodegradation study. *International Journal of Pharmaceutics, 222*, 183–189.

Chien, Y. W. (1992). Concepts and system design for rate-controlled drug delivery. In Y. W. Chien (Ed.), *Novel drug delivery systems* (pp. 1–42). New York, NY: Marcel Dekker.

Cummings, J. H., Milojevic, S., Harding, M., Coward, W. A., Gibson, G. R., Botham, R. L., Ring, S. G., Wraight, E. P., Stockham, M. A., Allwood, M. C., & Newton, J. M. (1996). In vivo studies of amylose- and ethylcellulose-coated [^{13}C] glucose microspheres as a model for drug delivery to the colon. *Journal of Controlled Release, 40*, 123–131.

Désévaux, C., Dubreuil, P., Lenaerts, V., & Girard, C. (2002). Tissue reaction and biodegradation of implanted cross-linked high amylose starch in rats. *Journal of Biomedical Materials Research, 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. *Carbohydrate Polymers, 37*, 361–370.

Hebeish, A., & Khalil, M. I. (1988). Chemical factors affecting preparation of carboxymethyl starch. *Starch/Starke, 40*, 147–150.

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. *International Journal of Pharmaceutics, 56*, 65–70.

Herman, J., Remon, J. P., & De Vilder, J. (1989). Modified starches as hydrophilic matrices for controlled oral delivery. I: Production and characterization of thermally modified starches. *International Journal of Pharmaceutics, 56*, 51–63.

Ispas-Szabo, P., Ravenelle, F., Hassan, I., Preda, M., & Mateescu, M. A. (2000). Structure-properties relationship in cross-linked high-amylose starch for use in controlled drug release. *Carbohydrate Research, 323*, 163–175.

Jane, J., Xu, A., Radosavljevic, M., & Seib, P. A. (1992). Location of amylose in normal starch granules. I. Susceptibility of amylose and amylopectin to cross-linking reagents. *Cereal Chemistry, 69*, 405–409.

Jeon, Y.-S., Viswanathan, A., & Gross, R. A. (1999). Studies of starch esterification: Reactions with alkenyl-succinates in aqueous slurry systems. *Starch/Starke, 51S*, 90–93.

JMP 7.0.2. (2007). SAS Institute Inc. Cary, North Carolina, USA.

Kalichevsky, M. T., & Ring, S. G. (1987). Incompatibility of amylose and amylopectin in aqueous solution. *Carbohydrate Research, 162*, 323–328.

Khalil, M. I., Hashem, A., & Hebeish, A. (1990). Carboxymethylation of maize starch. *Starch/Starke, 42*, 60–63.

Khalil, M. I., Hashem, A., & Hebeish, A. (1995). Preparation and characterization of starch acetate. *Starch/Starke, 47*, 394–398.

Kuakpetoon, D., & Wang, Y.-J. (2001). Characterization of different starches oxidized by hypochlorite. *Starch/Starke, 53*, 211–218.

Kuakpetoon, D., & Wang, Y.-J. (2008). Locations of hypochlorite oxidation in corn starches varying in amylose content. *Carbohydrate Research, 343*, 90–100.

Landerito, N. A., & Wang, Y.-J. (2005). Preparation and properties of starch phosphates using waxy, common, and high-amylose corn starches. I. Oven-heating method. *Cereal Chemistry, 82*, 215–264.

Langer, R. (1993). Polymer-controlled drug delivery systems. *Accounts of Chemical Research, 26*, 537–542.

Le Bail, P., Morin, F. G., & Marchessault, R. H. (1999). Characterization of a crosslinked high amylose starch excipient. *International Journal of Biological Macromolecules, 26*, 193–200.

Lenaerts, V., Beck, R. H. F., Van Bogaert, E., Chouinard, F., Höpcke, R., & Désévaux, C. (2003). Cross-linked high amylose starch for use in controlled-release pharmaceutical formulations and processes for its manufacture. US Patent Office, Pat. No. 6 607 748.

Lenaerts, V., Moussa, I., Dumoulin, Y., Mebsout, F., Chouinard, F., Szabo, P., Mateescu, M. A., Cartilier, L., & Marchessault, R. H. (1998). Cross-linked amylose starch for controlled release of drugs: Recent advances. *Journal of Controlled Release, 53*, 225–234.

Levina, M., & Rajabi-Siahboomi, A. R. (2004). The influence of excipients on drug release from hydroxypropyl methylcellulose matrices. *Journal of Pharmaceutical Sciences, 93*, 2746–2754.

Lidner, D. W., Möeckel, J. E., & Lippold, B. C. (1996). Controlled release of drugs from hydrocolloid embeddings. *Pharmazie, 51*, 263–272.

Lordi, N. G. (1986). Sustained release dosage forms. In L. Lachman, H. A. Lieberman, & J. L. Kanig (Eds.), *The theory and practice of industrial pharmacy* (pp. 430–456). Philadelphia, PA: Lea & Febiger.

Mateescu, M. A., Lenaerts, V., & Dumoulin, Y. (1995). Cross-linked material for controlled release of biologically active compounds. US Patent Office, Pat. No. 5 618 650.

Michailova, V., Titeva, S., Kotsilkova, R., Krusteva, E., & Minkov, E. (2001). Influence of hydrogel structure on the processes of water penetration and drug release from mixed hydroxypropylmethyl cellulose/thermally pregelatinized waxy maize starch hydrophilic matrices. *International Journal of Pharmaceutics, 222*, 7–17.

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. *Journal of Controlled Release, 38*, 75–84.

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. *Journal of Controlled Release, 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. *International Journal of Pharmaceutics, 278*, 231–238.

Mulhbacher, J., & Mateescu, M. A. (2005). Cross-linked high amylose starch derivatives for drug release. III: Diffusion properties. *International Journal of Pharmaceutics, 297*, 22–29.

Mundargi, R. C., Shelke, N. B., Rokhade, A. P., Patil, S. A., & Aminabhavi, T. M. (2008). Formulation and in-vitro evaluation of novel starch-based tableted microspheres for controlled release of ampicillin. *Carbohydrate Polymers, 71*, 42–53.

Nabais, T., Brouillet, F., Kyriacos, S., Mroueh, M., da Silva, P. A., Bataille, B., Chebli, C., & Cartilier, L. (2007). High-amylose carboxymethyl starch matrices for oral sustained drug-release: *In vitro* and *in vivo* evaluation. *European Journal of Pharmaceutics and Biopharmaceutics, 65*, 371–378.

Pringels, E., Ameye, D., Vervaet, C., Foreman, P., & Remon, J. P. (2005). Starch/Carbopol spray-dried mixtures as excipients for oral sustained drug delivery. *Journal of Controlled Release, 103*, 635–641.

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. *European Journal of Pharmaceutics and Biopharmaceutics, 51*, 191–198.

Rahmouni, M., Lenaerts, V., & Leroux, J.-C. (2003). Drug permeation through a swollen cross-linked amylose starch membrane. *S.T.P. Pharma Sciences, 13*, 341–348.

Rakhmatullin, R. R., Emelyushin, R. E., & Gavrilov, V. I. (1999). Kinetics and mechanism of reaction of sodium arsenite with chloroacetic acid in aqueous alkalis. *Russian Journal of General Chemistry, 69*, 1389–1390.

Ravenelle, F., Marchessault, R. H., Légaré, A., & Buschmann, M. D. (2002). Mechanical properties and structure of swollen crosslinked high amylose starch tablets. *Carbohydrate Polymers, 47*, 259–266.

Siew, L. F., Basit, A. W., & Newton, M. (2000). The potential of organic-based amylose-ethylcellulose film coatings as oral colon-specific drug delivery systems. *AAPS PharmSciTech, 1*, E22.

Song, X., He, G., Ruan, H., & Chen, Q. (2006). Preparation and properties of octenyl succinic anhydride modified early *Indica* rice starch. *Starch/Starke, 58*, 109–117.

Takeda, Y., Hizukuri, S., Takeda, C., & Suzuki, A. (1987). Structures of branched molecules of amylose of various origins, and molar fractions of branched and unbranched molecules. *Carbohydrate Research, 165*, 139–145.

Takeda, Y., Shirasaka, K., & Hizukuri, S. (1984). Examination of the purity and structure of amylose by gel-permeation chromatography. *Carbohydrate Research, 132*, 83–92.

Te Wierik, G. H. P., Bergsma, J., Arends-Scholte, A. W., Boersma, T., Eissens, A. C., & Lerk, C. F. (1996). A new generation of starch products as excipient in pharmaceutical tablets. I: Preparation and binding properties of high surface area potato starch products. *International Journal of Pharmaceutics, 134*, 27–36.

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. *Journal of Controlled Release, 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.

Tolstoguzov, V. (2003). Thermodynamic considerations of starch functionality in foods. *Carbohydrate Polymers, 51*, 99–111.

United States Pharmacopeia/National Formulary (USP) (USP28-NF23). (2005).

Vilivalam, V. D., Illum, L., & Iqbal, K. (2000). Starch capsules: An alternative system for oral drug delivery. *Pharmaceutical Science Technology Today, 3*, 64–69.

Vlachou, M., Naseef, H., & Efentakis, M. (2004). Image analysis studies of dimensional changes in swellable hydrophilic polymer matrices. *Polymers for Advanced Technologies, 15*, 683–689.

Zhao, Z.-J., Wang, Q., & Zhang, L. (2007). Size effect on competition of two diffusion mechanisms for drug molecules in amorphous polymers. *Journal of Physical Chemistry B, 111*, 13167–13172.