Sustained Release Properties of Crosslinked and Substituted Starches

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ABSTRACT: High amylose corn, waxy corn, and potato starches were crosslinked (XL) to an optimal degree and then substituted with carboxymethyl (CM) and aminoethyl (AE) groups, and their drug release properties, swelling power, and potential interactions with drugs were investigated. Propranolol hydrochloride, sodium diclofenac and acetaminophen were used as model drugs. High amylose starch required a higher XL degree to achieve good sustained release properties, whereas waxy corn required the least XL. Drug release was more governed by the matrix characteristics than by drug properties, and XL-CM high amylose corn starch displayed a nearly constant drug release for all three drugs tested. Swelling power correlated well with sustained release properties with the better matrices swelling to greater extents. There was a potential interaction between XL-AE-starches and diclofenac as indicated by differential scanning calorimetry. Starches from different sources require different types and degrees of modifications to achieve satisfactory sustained release. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 1558–1565, 2010

Key words: drug delivery systems; polysaccharides; crosslinking; substitution; starch

INTRODUCTION

Starch is widely used in the food industry, and lately the pharmaceutical industry has been exploiting its use as a functional ingredient in different formulations. Starch was initially used as filler and disintegrant,[1] and now assumes more functional roles in pharmaceutical applications such as capsules,[2] coatings,[3] and implants.[4] Starches from different sources vary mainly in their chemical structure and composition (amylose-to-amylopectin ratio), which strongly affects their gel-forming properties and their potential use as sustained release matrices. Amylose is an essentially linear polymer and tends to reassociate to form an insoluble network structure,[5] which leads to poor water holding capacity and unstable gel matrices in its native form. In contrast, amylopectin is a highly branched and large molecular weight polymer, which is less prone to reassociation and thus shows a better water holding capacity.[6]

It has been shown that pregelatinized starches have better sustained release ability than their native counterparts because of their gel-forming ability.[7] Chemical modifications can also be employed to improve the sustained release properties of starch, such as substitution and crosslinking. Crosslinked high amylose starch matrices have been used for high drug loading formulations,[8] which were further substituted with functional groups to confer pH and ionic strength dependency of swelling and drug release.[9,10] Substituted high amylose starch has been studied as gastro-resistant excipient for use in enteric formulations.[11] Starches from other sources have not been as extensively studied.[12-15]

The performance of a sustained release agent is also affected by the type of drug in the formulation. The physicochemical characteristics of the drug influence the performance of the matrix under the particular conditions in use, thus affecting its release from the system. The presence of functional groups in the matrix or in the drug structure allow for intermolecular associations with different neighboring groups, causing potential interactions between adjacent structures in a tablet system via hydrogen bonding, electrostatic interactions, or Van der Waals forces.

The interactions between drug and excipient can affect the stability, chemical nature, and bioavailability of a drug in a matrix, which will ultimately affect the safety and efficacy of the drug *in vivo*.[16,17] Differential scanning calorimetry (DSC) can detect possible interactions between drugs and excipients, and thus potential incompatibilities of components in a mixture.[18]

In this study, derivatives of high amylose corn, waxy corn, and potato starches were prepared by crosslinking at an optimal level and then substituting with carboxymethyl and aminoethyl groups.

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Their sustained release properties were evaluated using propranolol hydrochloride, diclofenac sodium, or acetaminophen in tablets. Swelling power of the starch derivatives was determined, and DSC analyses were conducted to detect the presence of drug–starch interactions.

EXPERIMENTAL

Materials

Waxy corn (AMIOCA) and 70% high amylose corn (Hylon VII) were provided by National Starch and Chemical Company (Bridgewater, NJ). Potato starch was obtained from Tate & Lyle (Decatur, IL). Propranolol hydrochloride and sodium diclofenac were purchased from TCI America (Portland, OR), and acetaminophen, magnesium stearate, epichlorohydrin (ECH), 2-chloroethylamine hydrochloride, and monochloroacetic acid were purchased from Sigma Aldrich (St. Louis, MO), Riedel-de Haën (Seelze, Germany), Acros Organics (Morris Plains, NJ), Alfa Aesar (Ward Hill, MA), and Fisher Scientific (Fair Lawn, NJ), respectively. All other chemicals were of ACS grade.

Optimization of crosslinking level

The optimal level of crosslinking to achieve satisfactory sustained release properties was determined for each starch type by nonlinear regression modeling. Four levels of crosslinking were prepared for each starch type according to the procedure described by Mulhbacher et al.[8] with slight modification. Seven grams of starch 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 was added, followed by the appropriate amount of ECH depending on the crosslinking level being prepared. Waxy corn starch (WC) was crosslinked at levels 1, 3, 5, and 7% ECH (w/w of starch), high amylose corn starch (Hylon) at levels 9, 12, 15, and 18% ECH, and potato starch at levels 1, 4, 7, and 10% ECH. Crosslinking of Hylon matrices at degrees lower than 9% ECH did not provide satisfactory sustained release (preliminary results, data not shown). The mixture was stirred at 50°C for 40 min, and neutralized to pH 5–6 with 3*M* acetic acid. Starch was precipitated with 1 × vol. 85% acetone, followed by washing with 2 × ½ vol. 70% acetone, 1 × vol. 85% acetone, and 1 × vol. pure acetone. The modified starch was then dried at 40°C overnight, ground using a Cyclone Sample Mill (UDY Corporation, Fort Collins, CO), and passed through a 75-μm sieve.

Preparation of crosslinked and substituted starches

Starches were prepared according to the procedure described by Mulhbacher et al.[8] with slight modification. Thirty-five grams of starch was mixed with 100 mL of deionized water and stirred at 50°C for 20 min. Thereafter, 120 mL of 1.5*M* NaOH was added, followed by the appropriate amount of ECH that was previously optimized for each starch type, and the mixture was stirred at 50°C for 40 min. Thereafter, 35 g monochloroacetic acid dissolved in 30 mL of water was added and stirred at 50°C for 1 h for carboxymethylation, or 43 g chloroethylamine were added and stirred at 70°C for 1 h for aminoethylation while maintaining the pH ~ 10 with 20% (w/v) NaOH. After the substitution reaction was completed, the medium was neutralized to pH 5–6 with 3*M* acetic acid, and starch was precipitated and washed with acetone as previously described. Each modified starch was prepared in duplicate. The carboxyl content of carboxymethylated (CM) starches was determined according to the procedure described by Kuakpetoon and Wang,[19] and the nitrogen content of aminoethylated (AE) starches was determined by the micro-Kjeldahl method.[20]

Dissolution studies

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

Drug release was evaluated using an Apparatus II[21] dissolution instrument (Varian, Cary, NC). Tablets were immersed in 900 mL of deionized water at 37.5°C for 24 h at a paddle rotation speed of 50 rpm. Samples were taken without medium replacement, and drug release was measured using a spectrophotometer (Beckman Coulter, Fullerton, CA). Propranolol hydrochloride was used as the model drug in the optimization of crosslinking level. Propranolol hydrochloride, diclofenac sodium, and acetaminophen were used as model drugs in evaluating crosslinked and substituted starches. Drug release was measured in a spectrophotometer with wavelengths of 290 nm for propranolol, 276 nm for diclofenac, and 243 nm for acetaminophen. All analyses were performed in triplicate.

Swelling power

The swelling power of unmodified and modified starches was determined according to the procedure of O'Brien et al.[22] with slight modifications. Forty milligrams of starch was weighed into a 2-mL micro-centrifuge tube, and 1.5 mL of DI water was added. The starch was allowed to swell in a 37.5°C heating block for 1 h, and then the tube was

immediately placed in an ice bath to cool down. The tube was centrifuged in a micro-centrifuge (Eppendorf Centrifuge 5415D, Germany) at 12,000 × g for 10 min. The excess water was carefully removed and the tube containing the remaining gel was weighed. The swelling power was calculated as:

$$\text{Swelling power (g/g)} = \frac{\text{gel weight (g)}}{\text{dry starch weight (g)}}$$

Three measurements were done for each starch sample.

DSC analyses

Five mg of modified starch, drug, or their physical mixture (30% drug, 69% starch, and 1% magnesium stearate) was hermetically sealed in a stainless steel pan and heated from 25 to 300°C at a heating rate of 5°C/min using a DSC (Pyris-1, Perkin-Elmer, Norwalk, CT). The instrument was calibrated with indium and an empty pan was used as reference. All analyses were performed in duplicate.

Statistical analyses

The amount of drug released at 4 h was used as a criterion for comparison of the response caused by different crosslinking degrees on drug release. A nonlinear regression model was fit to the data, and the crosslinking level that promoted the lowest drug released at 4 h of dissolution was chosen as the optimum level for each starch type. Means comparison was done using the Tukey-Kramer HSD test. The analyses were performed using JMP 7.0.2,[23] and significance was reported using an α level of 0.05.

RESULTS AND DISCUSSION

Crosslinking level optimization

Figure 1 shows that propranolol release over time was affected by the crosslinking degree (cld) for each type of starch studied. For Hylon matrices [Fig. 1(a)], all cld markedly decreased the drug release rate up to cld 15, after which the release rate slightly increased. Dumoulin et al.[24] reported a similar trend of improved sustained drug release from high amylose starch with increasing cld only to a certain level, after which a further increase in crosslinking increased the rate of drug release. On the other hand, crosslinking had little or negative effect on WC. WC with cld 1 and 3 displayed similar rates of drug release as the noncrosslinked control up to 12 h [Fig. 1(b)]. Higher crosslinking degrees (cld 5 and 7) resulted in significantly faster drug release. For potato starch, lower crosslinking degrees (especially cld 4) reduced the drug release rate to the most extent, whereas cld 10 showed a release rate comparable to the control [Fig. 1(c)].

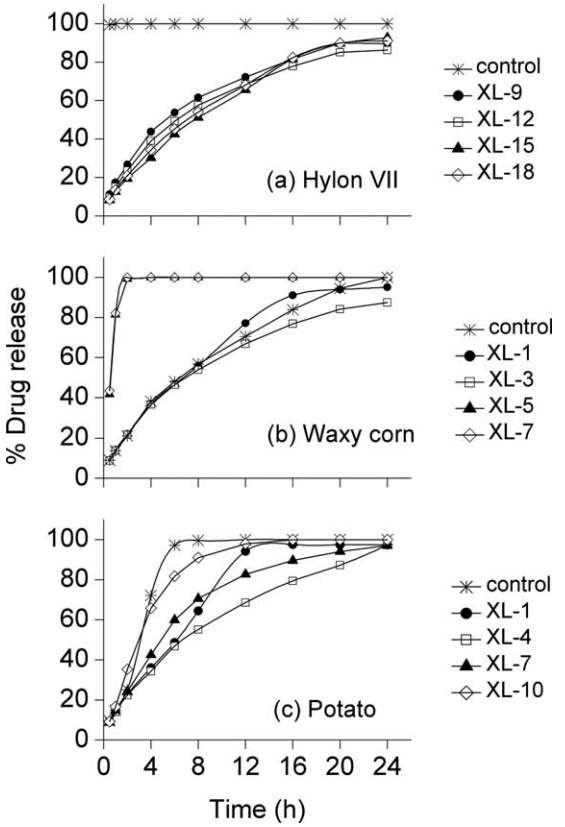

Figure 1 Propranolol hydrochloride release from high amylose corn (Hylon VII) (a), waxy corn (b), and potato (c) starches crosslinked at different degrees. The numbers on the legend correspond to the crosslinking degree used (epichlorohydrin, w/w of starch), with the control being unmodified.

The results showed that excessive crosslinking was detrimental to the formation of a good hydrogel and consequently to its sustained release properties for all starches. Dumoulin et al.[24] and Ispas-Szabo et al.[25] reported that the decrease in the sustained release properties of highly crosslinked high amylose starches was attributed to excessive stiffness and lack of movement of the crosslinked starch chains, which hindered their reassociation into a more organized matrix capable of sustaining drug release. The similar behavior observed in WC and potato matrices in the present study may be explained by the same mechanism.

The amount of drug released at 4 h for each crosslinking degree was selected for each starch type, and a nonlinear regression model was fit to the data to determine the cld that would result in the lowest rate of drug release. The clds that would release the least amount of drug in 4 h for Hylon and potato starch matrices were 15 and 4, respectively. Although there was no difference between the control and clds 1 and 3 at 4 h of dissolution for WC, cld 1 was

TABLE I
The Nitrogen and Carboxyl Contents (%, db) of Modified Starches

Starch	Nitrogen content (%, db)	Carboxyl content (%, db)
Hylon XL-AE	1.73 ± 0.03	–
Hylon XL-CM	–	0.98 ± 0.00
Waxy corn XL-AE	1.70 ± 0.11	–
Waxy corn XL-CM	–	1.05 ± 0.02
Potato XL-AE	1.97 ± 0.03	–
Potato XL-CM	–	0.59 ± 0.03

Hylon, high amylose corn starch; XL-AE, crosslinked and aminoethylated; CM, crosslinked and carboxymethylated. Results are mean ± standard error of two measurements.

chosen as the optimal level because it resulted in a less eroded gel matrix after 24 h of dissolution (personal observation). The results indicate the important role of starch amylose-to-amylopectin ratio in determining the optimal cld for sustained drug release. WC (nearly 0% amylose) required slight crosslinking to function as a good sustained release matrix; potato starch (around 20% amylose) required an intermediate cld; Hylon VII (~70% amylose) required a high degree of crosslinking to achieve similar functionality. The trend demonstrates that the higher the amylose content, the higher the crosslinking degree required to sustain drug release for starches that are gelatinized prior to modification, agreeing with previous results.[15] The need for a large quantity of crosslinking reagent at the gelatinized starch state to form a good sustained release matrix, especially in amylose-containing starches, was attributed to the presence of dispersed, random structure upon gelatinization. It was necessary to use extensive crosslinking to hold chains together to create a well-connected structured matrix. The linear nature of amylose required much more covalent bonding than did the highly branched amylopectin, which is capable of forming extensive intermolecular interactions.

Substitution efficiency

Table I presents the substitution degrees of the 6 modified starches. The reaction efficiency of aminoethylation was higher than carboxymethylation, and substitution levels were similar for Hylon VII and WC starches. Potato starch had a slightly higher nitrogen content, but a lower carboxymethyl content. It is not clear if the inherently high phosphate content in potato starch affected the substitution efficiency. The substitution levels obtained in the present study were higher than those reported in other studies.[9,10] Starches with higher carboxyl and aminoethyl contents were initially prepared, but showed very poor sustained release properties (data not shown). Therefore, they were not further studied and discussed in this study.

Dissolution studies

Propranolol hydrochloride, acetaminophen, and diclofenac sodium are drugs with different solubilities and structural characteristics. Propranolol hydrochloride has a high solubility in water, and behaves as a weak base under its p*K*a of 9.45.[26] Diclofenac sodium is poorly soluble in water, and behaves as a weak acid (p*K*a ~4).[27] Acetaminophen is fairly soluble in water, and possesses a very weak acidic hydrogen on its aromatic ring and also an amide group on its side chain with a p*K*a of 9–10.[28]

Dissolution profiles of propranolol from unmodified and modified starch matrices are displayed in Figure 2(a). Hylon-XL-CM, Hylon-XL-AE, unmodified WC (control), and WC-XL-AE exhibited slower rates of drug release, whereas the others exhibited markedly faster release rates. Among all matrices, Hylon-XL-CM had the slowest rate of propranolol release, and performed better than Hylon-XL only [Fig. 1(a)]. The introduction of carboxyl groups

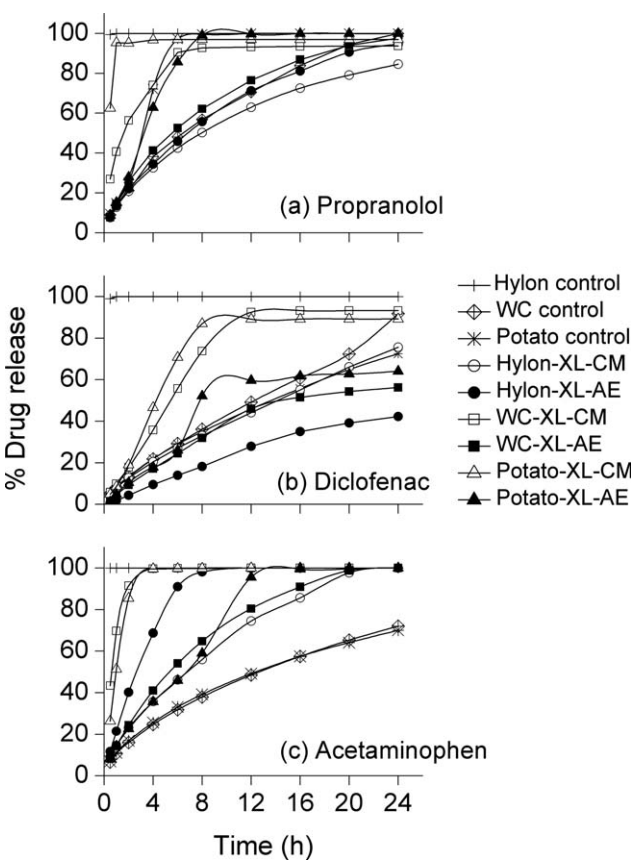

Figure 2 Dissolution profiles of propranolol hydrochloride (a), diclofenac (b), and acetaminophen (c) from modified starches tablets. WC, waxy corn starch; XL-AE, crosslinked and aminoethylated; XL-CM, crosslinked and carboxymethylated; control, unmodified.

slowed the release of propranolol, mostly after 12 h, presumably by strengthening and thus stabilizing the Hylon-XL matrix. It has been reported that carboxyl groups can interact with each other via hydrogen bonding and form dimers,[29] which might help hold starch chains together and slow drug release. Potato-XL-CM and WC-XL-CM matrices, nevertheless, released propranolol much faster than their unmodified controls. With the exception of Hylon-XL-AE matrices, other AE-substituted starches performed similarly to their respective controls, suggesting that AE groups neither destabilized nor improved their matrices. Hylon-XL-AE, on the other hand, showed a much slower release than its unmodified control, and behaved similarly to Hylon-XL-CM matrix. The release profiles of propranolol suggest that the nature of starch matrix was the determinant factor for a satisfactory sustained release agent, and possible interactions between the different substituents and the drug seemed to play a minor role in affecting the performance of the matrices.

The overall release rate of diclofenac was slower than that of propranolol [Fig. 2(b)], which was attributed to the lower solubility of diclofenac under the conditions of this study. Diclofenac sodium is slightly soluble in water, and its solubility is strongly affected by the pH of the medium because its carboxyl group behaves as a weak acid.[27] Efentakis et al.[30] and Sriamornsak and Kennedy[31] reported that drugs of higher solubility facilitate water penetration into the matrix as a result of an increase in osmotic pressure inside the tablet, thus increasing drug release. In this study, the release of diclofenac from all XL-AE-matrices was incomplete, with less than 60% diclofenac released in 24 h. Furthermore, the swollen tablets were morphologically different from the others after 24 h (personal observation). The tablets of XL-AE-starches and diclofenac swelled to a much greater extent than other formulations tested, had a very dense texture, and did not erode after 24 h, which were not noted for XL-AE-starch formulations with propranolol or acetaminophen. The sudden release of diclofenac from potato-XL-AE matrices around 6 h was due to cracking of the tablet. This interesting behavior of XL-AE-matrices could be attributed to an attractive ionic interaction between AE groups and the carboxyl group in diclofenac. Sipos et al.[32] reported possible interactions between ammonium groups of ammonio methacrylate copolymer backbone and diclofenac sodium. The presence of strong ionic attractions among these groups may have prevented the drug from being released, despite the extensive swelling of the tablet.

Bettini et al.[33] reported that the release of low solubility drugs from swellable matrices is mainly by solid particle transportation from the core across the swollen polymer outwards. The presence of undissolved particles would affect the integrity of the swollen matrix, thus promoting its erosion. However, erosion of XL-AE-starch matrices was not observed, which suggests that these matrices possessed a strong polymeric structure capable of withstanding erosion forces. In contrast, all XL-CM-matrices were completely or almost completely eroded after 24 h. Hylon-XL-CM and potato control showed a virtually constant rate of release of diclofenac, with less than 80% of drug released in 24 h. In addition to Hylon-XL-CM, Hylon-XL-AE matrix also released diclofenac in a quasi zero order fashion, but only $\sim$ 40% of drug was released after 24 h.

The release of acetaminophen from all XL-substituted starches was faster than that of propranolol or diclofenac [Fig. 2(c)]. Acetaminophen has poor compaction properties because of its strong elastic deformation,[34,35] which may accelerate drug release. In addition, the substitutions performed in the present study may further destabilize the matrix, resulting in overall faster drug release. WC and potato controls, however, displayed good sustained release profiles. The lack of substituents in these matrices may have resulted in a better compacted tablet, which led to better sustained drug release. Similar to the other two drugs, Hylon control showed an immediate release. Hylon-XL-CM matrix again showed a fairly constant drug release, with 100% of drug released in 20 h. WC-XL-AE and Hylon-XL-CM showed similar dissolution profiles, having the slowest drug release rates among modified starches.

Although the sustained release properties of the matrices prepared varied slightly with drug type, which was attributed to the intrinsic properties of the drugs, the overall performances of the starch matrices were primarily governed by the matrix characteristics. Hylon-XL-CM matrices showed excellent sustained release ability for all three drugs, particularly a near zero-order release of diclofenac and acetaminophen. Hylon-XL-AE matrices, however, performed better than or similar to the crosslinked only matrix (XL-15) [Fig. 1(a)] with propranolol or diclofenac, but not with acetaminophen. On the other hand, modified WC and potato starch performed inferior to their respective unmodified controls, with the exception of WC-XL-AE in diclofenac release. The introduction of substitutents to WC and potato starch strongly destabilized the matrices, thus leading to a fast drug release. The results suggest that crosslinking alone sufficiently improved the functionality of WC and potato matrices as sustained release agents, as shown in Figure 1(b,c).

Swelling power

The swelling power of modified and unmodified starches is presented in Figure 3. Hylon matrices

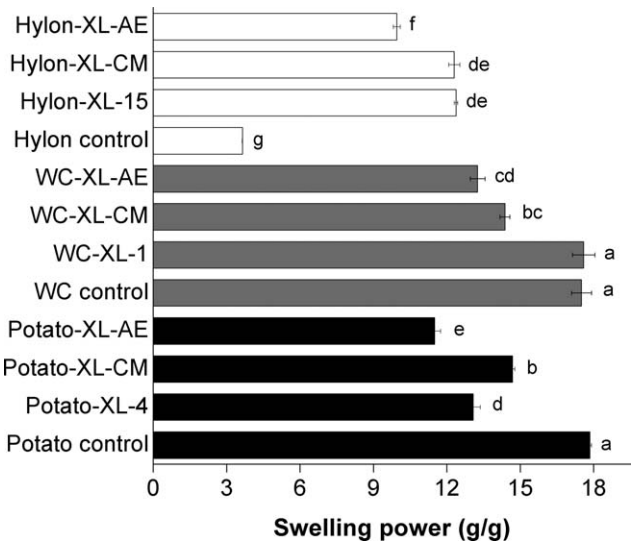

Figure 3 Swelling power of modified and unmodified starches. WC, waxy corn starch; XL-AE, crosslinked and aminoethylated; XL-CM, crosslinked and carboxymethylated; XL, crosslinked only; control, unmodified. The bars represent the standard error of three measurements. Different letters correspond to statistically different means ($P < 0.05$).

had lower swelling power than potato and WC ones, which clearly reflected their differences in chemical composition and structure. The linear structure of amylose promotes reassociation, thus limiting water holding and swelling. In contrast, the branched structure of amylopectin helps trap water and form a stronger hydrogel.[6] The swelling power of potato starch was similar to or slightly lower than that of WC. The presence of phosphate groups in potato starch may render it more hydrophilic,[6] therefore, the swelling power of potato starch was closer to that of WC even though potato starch consists of 22% amylose.[36]

The influence of optimal crosslinking on the swelling power varied with starch type. For Hylon matrices, the extensive crosslinking (cld 15) significantly increased the swelling power. The crosslinks may hinder the reassociation of amylose molecules and subsequently expelling of water from the matrix, thus allowing for the formation of a hydrogel with improved water holding capacity. The crosslinking had little impact on the swelling power of WC, presumably because of the low level of crosslinking. On the other hand, crosslinking significantly decreased the swelling power of potato starch. Crosslinking may hinder the mobility of amylopectin chains, thus negatively affecting their capability of entrapping water in the matrix.

When carboxymethylation was performed after crosslinking, the swelling power of Hylon matrices remained the same as their crosslinked only counterpart, whereas that of WC and potato matrices decreased and increased, respectively. On the other hand, when aminoethylation was performed, the swelling power significantly decreased for all three starch types. The incorporation of substituents on starch molecules could affect the interaction between water and starch. Both CM and AE groups are strongly influenced by pH because of their ionic nature.[37] Under the pH 3–4 used for swelling power and dissolution studies, CM groups are mostly protonated, and thus hydrogen bonding is prevalent over ionic interactions. The dimerization of CM groups via hydrogen bonding might behave similarly to crosslinks, therefore the swelling power of XL-CM-matrices was similar to that of XL-matrix for the same starch type. For XL-AE-starches, the amino groups are fully protonated at pH 3–4, and the repulsive electrostatic interaction among neighboring groups may destabilize the network structure, thus resulting in lower swelling power. This weakened structure caused by cationization of starch was also observed by Liu et al.[38]

Swelling power was found to correlate well with drug release profile. In most formulations studied, better sustained drug release was associated with higher swelling power values, particularly within the same starch type. Meanwhile, a dramatic increase in the swelling power of modified Hylon matrices resulted in a significant improvement in their sustained release properties for both CM- and AE-matrices. Nevertheless, other factors such as matrix integrity in the presence of drug, drug-starch interaction, and erosion susceptibility also modulate the drug release from a tablet, and should be taken into consideration as well when explaining drug release from the starch matrices.

DSC analyses

Figure 4 displays the DSC profiles of WC-XL-AE, WC-XL-CM, drugs, and their physical mixtures. Hylon and potato starches and their derivatives exhibited similar trends, and therefore are not shown.

A clear endothermic melting peak was observed for individual drugs, with sodium diclofenac having the highest melting temperature [Fig. 4(c,d)]. For modified starches alone, a major exothermic peak was noted at temperatures above 200°C. This transition was proposed to originate from the rearrangement of amylose and amylopectin molecules. It has been reported that under high temperatures above the glass transition, starch molecules can undergo conformational transitions that create new physical junctions among adjacent chains stabilized by hydrogen bonding, which is an exothermic process.[39,40] The same peak was also detected at a similar temperature range when analyzing native and thermally

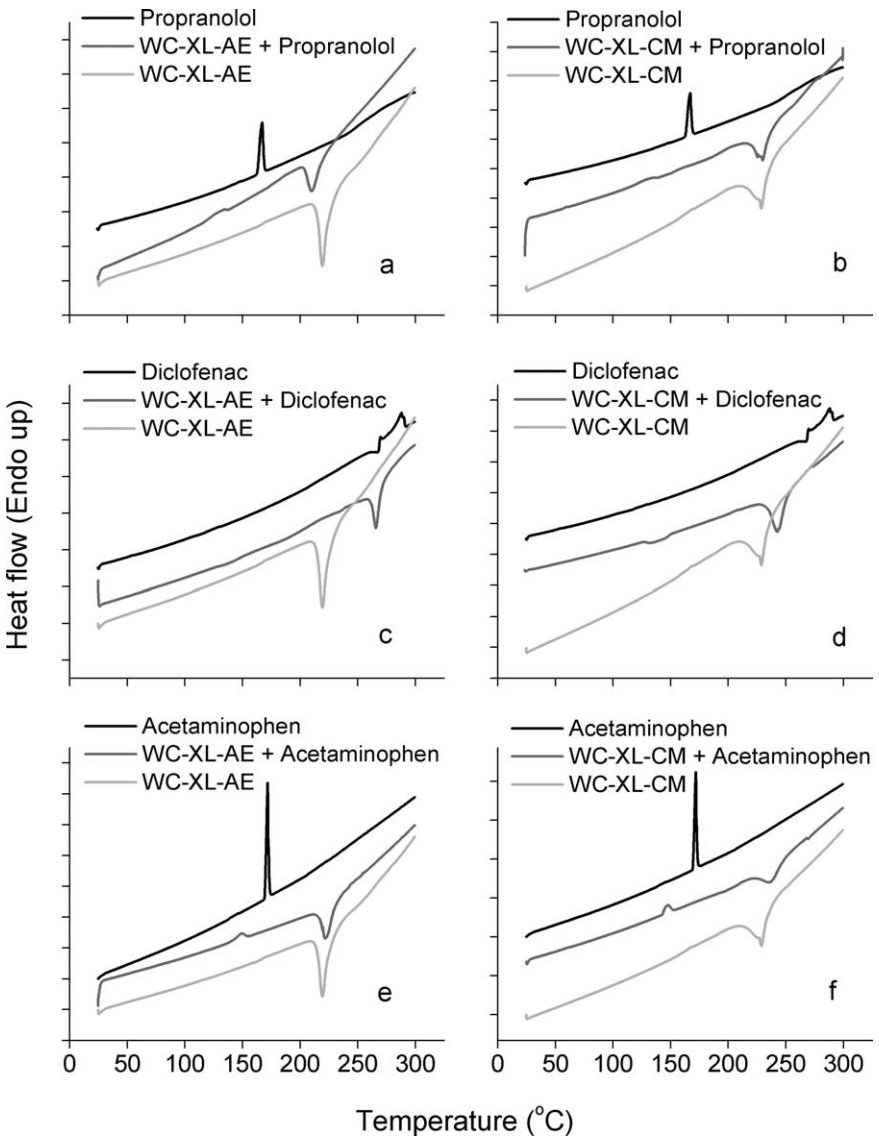

Figure 4 DSC profiles of drugs [propranolol (a,b), diclofenac (c,d), and acetaminophen (e,f)], modified waxy corn starches, and their physical mixtures. WC, waxy corn starch; XL-AE, crosslinked and aminoethylated; XL-CM, crosslinked and carboxymethylated.

gelatinized starches (data not shown). Therefore, this transition was not a result of the gelatinization method or modifications performed in this study, but a transition in amylose and amylopectin conformations at such high temperatures.

When the physical mixtures of drug, starch, and magnesium stearate were analyzed by DSC, the melting peak of the drug shifted to a lower temperature for all three drugs studied. Smith[41] reported that there may be shifts in temperature and peak characteristics upon a simple mixing of the individual components, and these changes thus do not necessarily indicate any interactions between the components. The purity of the drug diminishes when mixed with other components, causing a decrease in its melting temperature. The early melting phenomenon of the three drugs could likely be due to the simple mixing of components, and was therefore not considered as an indication of interaction.

However, for the mixtures containing XL-AE-starches and diclofenac, there was a dramatic shift of the exothermic starch peak [Fig. 4(c)], the peak being delayed by $\sim 50^{\circ}C$ for all starch types. This phenomenon was not as pronounced for any other mixtures. This delay suggests that the transition in the conformation of starch chains was hindered in the presence of diclofenac, which might be due to a strong association between the negatively charged groups in diclofenac and aminoethyl groups of starch, possibly by hydrogen bonding or electrostatic interaction. This association could likely be related to the markedly slower release of diclofenac from the XL-AE matrices observed in the dissolution study.

CONCLUSIONS

The degree of crosslinking was mainly affected by the amylose-amylopectin ratio of the starch. The higher the amylose content, the more extensive the gelatinized starch had to be crosslinked in order to produce a matrix with satisfactory sustained release properties. Hylon-XL-CM matrix showed virtually zero-order release for all three drugs tested. There was a correlation between swelling power and drug release, with starch matrices of higher swelling powers showing better sustained release properties. There was a potential interaction between diclofenac sodium and AE-starches based on the incomplete drug release, atypical morphology of the swollen tablets, and DSC analyses of their physical mixture. This study demonstrates that the functionality of modified starches is governed by the starch composition, which would affect their behavior in different formulations. Therefore, starches from different sources or genetic backgrounds may require different types and extents of modification to achieve satisfactory sustained drug release.

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