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Application of cross-linked rice starches as drug delivery matrices in monolithic tablets

Christopher F. Peluso*, Fernanda O. Onofre‡, and Ya-Jane Wang‡‡

ABSTRACT

The sustained release properties of regular and waxy rice starches and their derivatives were studied in tablets. The starches were cross-linked to different levels with epichlorohydrin, and the sustained release properties, swelling power, and rheological characteristics of the matrices prepared were determined. Propranolol hydrochloride was used as a model drug. The sustained release properties of waxy rice starch improved with increasing cross-linking levels, whereas cross-linking had little impact on the functionality of regular rice starch matrices. There was an increase in swelling power for both regular and waxy rice starches as cross-linking levels increased. Both starches showed an increase in the storage modulus when cross-linking was increased, with the regular rice starch matrices showing greater differences among samples. Regular rice starch matrices showed an independence of frequency as cross-linking increased, indicating a “true gel” characteristic, whereas waxy rice matrices behaved as a “weak gel.” Both regular and waxy rice starches displayed a decrease in creep and recovery profiles with an increase in cross-linking level. Waxy rice starch showed potential as a sustained release agent in tablets.

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INTRODUCTION

The recent demand and effort to produce safer drugs has led to an emphasis on how drugs are delivered to the human body. Tablets are a common form of drug administration, and different types of drug release systems can exist in a tablet form. For instance, conventional oral delivery systems promote an immediate and complete drug release in the gastrointestinal tract, whereas sustained delivery systems retard the release of the drug from the pharmaceutical form, providing a more constant blood level of the drug over time (Chien, 1989). A common manner of sustaining drug release is by creating a physical barrier through the formation of a gel matrix, which restricts the movement of the drug inside the tablet and its release to the medium. The mechanism of drug release depends on the matrix used, but is commonly associated with drug diffusion through the matrix and matrix erosion and dissolution into the medium.

Acrylic acid derivatives, hydroxypropylmethyl cellulose (HPMC), and starch have been used as tablet excipients. Starch and HPMC are biodegradable and biocompatible, as opposed to acrylic acid derivatives, but starch forms gel faster than HPMC, which may be a great advantage for matrix formation in tablets. Maize starch has been extensively studied in sustained-release systems, but little work has been done on the sustained-release properties of rice starch.

Swelling power, also known as water-holding capacity, corresponds to the ability of a material to hold water. Swelling power is an important property to determine the potential application of a starch polymer matrix as a pharmaceutical excipient in sustained release systems. Upon swelling, water penetrates into the tablets in fronts, which begin on the outside and move inwards until the whole matrix is swollen (Vlachou et al., 2004). Swelling of the resulting tablet in a liquid medium coupled with erosion of the matrix becomes the main component of drug release for a solvent-activated drug delivery system such as a hydrogel (Chien, 1989). It was reported that rice starch in particular would make an adequate tablet filler/drug carrier mainly due to its fine particle size and similar swelling power when compared with other starches like tapioca and potato (Bos et al., 1987).

Rheology studies the viscoelastic properties of matrices and can more thoroughly describe the microstructure of the gel layer in a tablet (Richardson and Kasapis, 1998). Viscoelasticity is an indication of the overall elastic properties of a viscous or semi-viscous material, such as a gel or swollen tablet, and can be characterized by both strain...
and recovery capacities of a matrix (Tecante, 2001). Different procedures can be used to evaluate the viscoelastic properties of matrices, including frequency sweep and creep/recovery tests. The frequency sweep test is the application of different twisting movement frequencies on the matrix, and the elastic and viscous components of the system can be measured via the storage modulus \(G'\) and the loss modulus \(G''\), respectively. The storage modulus is a way of expressing the potential energy stored in a given system temporarily, whereas the loss modulus is the measurement of the amount of energy lost as heat to cause a flow in the fluid matrix. In order to be considered as a gel, the substance must have a storage modulus greater than the loss modulus, among other properties (Jimenez-Avalos et al., 2005). Tan \(\delta\) is the ratio between \(G''\) and \(G'\), and a reliable way to quantify the relationship between the two moduli. Positive parameters should be obtained for each modulus: tan \(\delta\), creep, and the recovery period (Jimenez-Avalos et al., 2005). In the creep/recovery test, a constant stress is initially applied on the matrix to determine and quantify any deformation that occurs with time. A recovery step follows the creep step, in which the stress is removed and the capacity of the matrix to return to its original state is measured (Jimenez-Avalos et al., 2005). Herman and Remon (1989) reported that the gel strength of hydrated tablets was proportional to the amylose content, with starches lower in amylose having greater gel strength. In addition, the tablets that were low in or free of amylose showed an obstructive gel layer-forming capacity, which was independent of compression force and essential for sustaining the release of a drug from a matrix.

The objectives of this study were: 1) to investigate the effects of starch composition and cross-linking on the sustained-release properties of rice starch tablets, and 2) to characterize and correlate the properties of the matrices with their drug-release abilities.

**MATERIALS AND METHODS**

*Materials.* Waxy rice (Remyline AX-DR) and regular rice (Remy DR) starches were obtained from A&B Ingredients, Inc. (Fairfield, N.J.). Propranolol hydrochloride was obtained from TCI America (Portland, Ore.), magnesium stearate from Riedel-de Haën (Seelze, Germany), epichlorohydrin (ECH) from Acros Organics (Morris Plains, N.J.), and sodium sulfate from EMD Chemicals, Inc. (Gibbstown, N.J.). All other chemicals used were of ACS grade.

*Cross-linking Reaction.* Both waxy and regular rice starches were cross-linked at levels 0.01, 0.05, and 0.1% epichlorohydrin (w/w of starch). Forty grams of starch were combined with 6 g of anhydrous sodium sulfate and 100 mL of deionized water in a 1-L reaction vessel. The pH was adjusted to 12 with 10% NaOH, and the proper amount of ECH was added. The mixture was then covered and stirred at room temperature for 48 h. Afterwards 100 mL of deionized water was added, followed by 50 mL of 20% NaOH to gelatinize the cross-linked starch. The paste was then neutralized to pH 6 with 6 N HCl. The starch was precipitated with 400 mL 85% acetone (v/v), followed by washing 5 × 400 mL 50% ethanol to remove salts, 400 mL 70% acetone, and 400 mL pure acetone. The precipitate was separated into small pieces, dried in a 40°C oven for 2 days, and ground in a Cyclone Sample Mill (UDY Corporation, Fort Collins, Colo.) equipped with a 75-μm sieve. A control of each starch was prepared as described without the cross-linking step. All modified starches and controls were prepared in duplicate.

*Preparation of Tablets.* A manual mixer (Inversina, Bioengineering AG, Wald, Switzerland) was used to homogeneously mix the modified starch (69% w/w) and propranolol hydrochloride (30% w/w) for 10 min. Magnesium stearate was then added (1% w/w) as lubricant, and the mixture was mixed for an additional 1 min. The tablets were prepared by compressing a premeasured amount of 500 mg of the mixture at 2.0 MP using a 13-mm die (Carver, Wabash, Ind.) with a hydraulic press (Carver, Wabash, Ind.).

*Drug-release Properties.* Drug release properties were studied using a dissolution Apparatus II (paddle) (USP, 2005) instrument (Varian Inc., Cary, N.C.). The medium was 900 mL of deionized water at 37.5°C to simulate human body temperature. The use of the water medium served as a screening process. The tablet was immersed in the water for 24 h using a paddle rotation speed of 50 rpm. Five-mL samples were removed over the course of the time period (0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24 h) with no medium replacement. The concentration of propranolol hydrochloride in the aliquot sample was measured using a spectrophotometer (Beckman Coulter, Fullerton, Calif.) at 290 nm. Triplicate measurements were performed for each starch.

*Swelling Power.* Swelling power of the modified starches was determined by adding 40 mg of starch sample to 1.5 mL of deionized water in a pre-weighed 2-mL microcentrifuge tube. The tube was vortexed for 5 s, placed in a preheated heat block at 37.5°C for 1 h, and then cooled in an ice-water bath to room temperature. The tube was then centrifuged at 12,000 × g for 10 min, and water was removed from the tube using a dropper. The swelling power was calculated by dividing the weight of the paste by the dry weight of the starch sample. Each starch was measured at least in triplicate.

*Rheological Characterization.* A tablet was immersed in 5 mL deionized water in a plastic petri dish (3.6 cm dia.), placed in a pre-heated water bath and maintained at 37°C.
on a hot plate. The tablet was immersed in the water for 15 min to promote water absorption and swelling of the matrix. The excess water was removed from the petri dish with a disposable pipette and the swollen tablet was placed on the bottom plate of an AR 2000 rheometer (TA Instruments, New Castle, Del.) at 25°C to prevent dehydration. A 40-mm sandblasted plate was used, and a frequency sweep followed by a creep test was performed on each sample. A frequency sweep of 1-100 Hz was performed at 0.2% strain. Four parameters were recorded as a function of frequency: storage modulus (G'), loss modulus (G''), tan δ (G''/G'), and complex viscosity (η*). Upon completion of the frequency test, a creep test was performed. A stress of 1.2 Pa was applied to the tablet, and the compliance (J(t)) was measured for 3 min. The stress was then removed and the recovery was measured for another 3 min. Instantaneous compliance (J(0)), the slope of the linear region of the compliance curve, and recoverable compliance (the difference between maximum compliance and final compliance) were recorded. All tests were done in six replicates.

Statistical Methods. Standard error and standard deviation were calculated among each type of sample for comparison. The calculations were used to ensure the precision of replicate trials for each concentration of starch tablet.

RESULTS AND DISCUSSION

Drug Release

Cross-linking did not dramatically change the sustained release properties of regular rice starch (Fig. 1A), but affected the rate of drug release from waxy rice starch matrices when compared with the control (Fig. 1B). Cross-linking to a low level (0.01%) did not change the drug-release properties of waxy rice starch, but cross-linking to intermediate (0.05%) and high levels (0.1%) led to a decrease in the rate of drug release. It can also be observed that the overall rate of drug release from waxy rice matrices was significantly lower than that from regular rice matrices.

Tables made with regular rice starches showed more erosion than those made with waxy rice starches (personal observation). After 24 h, waxy rice tablets usually had a core remaining, while regular rice tablets were completely dissolved in the medium. These remaining cores likely entrapped some drug, accounting for the incomplete drug release observed in waxy rice starches. Overall, the findings of this study showed an improvement in the sustained release properties of waxy rice starch with an increase in the cross-linking level.

Swelling Power

Overall, cross-linking led to an increase in swelling power as the cross-linking level increased for both starch types, although the swelling power of waxy rice cross-linked to the lowest level was similar to the control (Fig. 2).

There was a correlation between the swelling power of waxy rice matrices and their sustained release properties. The sustained-release ability of waxy rice matrices increased with an increase in the cross-linking level, and that was accompanied by an increase in the swelling power of the matrix. This correlation was not very clear for regular rice matrices in this study because all the matrices showed similar drug-release properties.

Rheological Properties

Frequency Sweep Test. In all starches, G' was greater than G'' for the frequency sweep test, which was indicative of the predominantly elastic behavior of the matrices (Fig. 3).

The G' values increased as cross-linking increased in regular rice starch (Fig. 3A). On the other hand, the G' values for all cross-linked waxy rice starches were similar and slightly higher than those of the unmodified control, particularly at higher frequencies (Fig. 3B). Cross-linked regular rice starches showed an independence of frequency at lower frequencies, and the 0.1% cross-linked regular rice starch was independent of frequency for a wider range of frequencies. Matrices with less frequency dependence possess “true gel” characteristics (Almdal et al., 1993). This frequency independence was not observed in waxy rice starches, suggesting that amylopectin structure contributes to the frequency dependence in starch gels. Matrices that are more frequency dependent are considered to be “weak gels” or viscous fluids (Clark and Ross-Murphy, 1987). Furthermore, G' values of regular rice starches were higher than those of waxy rice samples, and than their corresponding G'' values by around 10×. In waxy rice starches, G' was higher than G'', but the difference was smaller than 10×.

Both regular and waxy rice samples showed an increase in tan δ with decreasing frequency (Fig. 4). Regular rice samples (Fig. 4A) showed smaller and more similar tan δ values for different cross-linking degrees, indicating that the changes in both G' and G'' for different cross-linking levels were in the same order of magnitude for different frequencies. Meanwhile, for waxy rice starch (Fig. 4B), the control and 0.01% cross-linked starches showed a steep increase in tan δ with a decrease in frequency, indicating a more significant change in G' when compared to G'' for the frequencies studied. These results showed that the elastic component of waxy rice samples was more affected by cross-linking than the viscous component. On the other hand, waxy rice starches with higher cross-linking levels did not show a drastic change in tan δ values, indicating a more uniform change in both moduli with frequency.

Overall, the viscosity, |η*|, of regular rice matrices was
higher than that of waxy rice ones, showing the importance of amylose and amylopectin to the properties of each starch (Fig. 5). Regular rice starch matrices cross-linked to 0.01 and 0.05% levels and the control showed similar profiles with small variation over different frequencies. However, regular rice starch cross-linked to 0.1% showed a steady increase in viscosity with a decrease in frequency, displaying a shear thinning behavior (Fig. 5A). All waxy rice matrices showed fairly constant complex viscosity profiles throughout the frequency range tested (Fig. 5B). Cross-linking of rice amylopectin did not have a strong impact on the complex viscosity of waxy rice starches.

Overall, the frequency data showed that the G’ modulus was lower for starches with lower amylose content. These results imply that the matrices of regular rice starches had a more elastic nature, whereas waxy rice matrices showed a more pronounced, viscous modulus. This more prominent fluidity of waxy rice matrices was supported by the complex viscosity data, which showed lower values for these matrices when compared to those of regular rice.

**Creep Test.** Figure 6 displays the creep and recovery profiles of all starch matrices, and Table 1 lists the creep-test parameters calculated from the data. Overall, the same trend was observed in both regular (Fig. 6A) and waxy (Fig. 6B) rice starch matrices. Cross-linking led to a drastic decrease in compliance, with starches cross-linked to the highest level showing the lowest compliance. Furthermore, it could be observed that waxy rice matrices showed higher creep and recovery compliance over time when compared to regular rice matrices, indicating the importance of amylose for the behavior of the starch matrices.

From Table 1, it can be observed that cross-linking decreased both the instantaneous compliance and slope of the creep curve for both waxy and regular rice matrices, indicating the formation of a more organized matrix with increasing cross-linking for both starch types. Viscosity increased with increasing cross-linking for both starch types, with higher viscosity values being attributed to the higher amylose content of regular rice in all cases. Furthermore, the recoverable compliance decreased as cross-linking was increased for both starch types, probably as a result of an increase in organization and stiffness of the cross-linked samples. Overall, the two starch types showed the same trends but with different magnitudes.

**SUMMARY**

*In vitro* drug release tests showed that waxy rice starch tablets had better sustained-release capacity than regular rice starch, and this ability improved with increasing cross-linking levels. Cross-linking did not have a significant effect on the sustained-release ability of regular rice matrices. Overall, the amylose/amyllopectin ratio in rice starch seemed to have played a significant role in the sustained-release properties of rice starch matrices. Similar trends were observed for the effect of cross-linking on the swelling power and rheological properties of both rice starches. Increasing cross-linking levels led to an increase in swelling power and a decrease in elasticity, accompanied by an increase in organization, stiffness, and viscosity of the matrix. In the case of amylopectin-rich waxy rice starch, an increase in viscosity and organization of the matrix was desired to improve its sustained-release properties, which was followed by an increase in the swelling power and water-holding capacity of the matrix, forming a better gel to sustain drug release. On the other hand, the sustained-release properties of amylose-containing rice starch matrices were not strongly affected by cross-linking, and the changes observed by swelling power and rheological characterizations did not result in different drug-release abilities. It is possible that the high amount of amylose in regular rice played a more dominant role in the sustained-release capacity than did the modifications performed in this study.

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**LITERATURE CITED**


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Fig. 1. Drug release profiles from regular rice (A) and waxy rice (B) starches. The percentages are the cross-linking levels prepared.

Fig. 2. Swelling power of regular and waxy rice starches. The percentages are the cross-linking levels prepared. The error lines represent the standard error for each cross-linked sample.
Fig. 3. G' and G'' values by frequency for regular (A) and waxy (B) starch matrices. The percentages are the cross-linking levels prepared.

Fig. 4. Tan δ as a function of frequency for regular (A) and waxy (B) rice starch matrices. The percentages are the cross-linking levels prepared.

Fig. 5. Complex Viscosity |η*| by frequency for regular (A) and waxy (B) rice starch matrices. The percentages are the cross-linking levels prepared.
Fig. 6. Creep and recovery profiles of regular (A) and waxy (B) rice starch matrices. The percentages are the cross-linking levels prepared.

Table 1. Creep and recovery parameters of regular and waxy rice starch matrices.

<table>
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<th>Starch type</th>
<th>Cross-linking level (%)</th>
<th>Instantaneous compliance $J_0$ (Pa)</th>
<th>Slope</th>
<th>Viscosity $\eta_0$ (Pa.s)</th>
<th>Recoverable compliance $1/\eta$ (1/Pa)</th>
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