Effects of Drying Process for Amorphous Waxy Maize Starch on Theophylline Release from Starch-Based Tablets

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ABSTRACT: Physical properties and theophylline-release profiles of compressed tablets prepared with amorphous waxy maize starches dried using different methods were examined. A gelatinized waxy maize starch paste (10% solids in water) was either freeze-dried or oven-dried (40 or 105°C) until the moisture content reached to <5%. To form the tablets, the dried amorphous starch powders, either with or without theophylline (3 : 10, w/w), were remoistened to a water content of (17 ± 0.2)%, and compressed into tablets. The drying process applied to the amorphous starch powders affected both the compactness and swelling behavior of the tablets. Although no crystallinity was detected in all the starches tested, X-ray diffraction patterns indicated that starch chains dried at the lower temperature (40°C) are allowed more time to re-associate during the drying process than those dried at the higher temperature (105°C). The freeze-dried starch powders formed tablets characterized by greater compactness and rigidity than was observed in the oven-dried starch samples. The drug release of the tablets prepared with the starch dried at the higher temperature (105°C) occurred at a much slower rate than that of the tablets made with the starch dried at the lower temperature (40°C). The drug release characteristics of the freeze-dried starch tablets were nearly identical to those of the tablets prepared with the starch dried at 105°C. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 105: 1908–1913, 2007

Key words: waxy maize starch; amorphous; compression; swelling; drug release

INTRODUCTION

Pharmaceutical tablets are usually manufactured by molding ingredients containing drug(s) in a compact matrix, from which the release of the drug can be optimally controlled. In such matrices, nondrug components are usually required for the control of tablet swelling and erosion, the factors correlated with the diffusion of drug components. Ordinary drug release from a tablet follows first-order kinetics, whereas the most desirable release profile is achieved, theoretically, in accordance with zero-order kinetics. Unlike nonswellable systems, in which drug release occurs via a leaching mechanism,[1] drug release from a swellable system involves solvent penetration, which is normally coupled with the phase transitions of the components to rubbery states. Upon the exposure of a tablet to gastric liquids, partial hydration occurs, inducing the formation of an outer gel-layer, which normally functions as a control membrane for the process of drug diffusion. Therefore, the physical characteristics of the layer, including erosion rate and viscosity, are important factors in the ultimate drug release profile.[2]

Starch is a natural biopolymer composed principally of amylose and amylopectin, which is widely used, with or without structural modifications. As a matrix polymer in tablets, starch allows the controlled release of a variety of drugs. It has several advantages over synthetic polymers as a release control agent, such as low cost, nontoxicity, biodegradability, and biocompatibility. The morphology and physical properties of the tablets are affected by the degrees to which gelatinization[2] and retrogradation[3] occur in the employed starch. The granular and molecular structures of the constituent starch have been shown to affect matrix formation, thus directly affecting the drug release properties of the tablet. Pregelatinized starch has been identified as a better release-control agent than native and chemically modified starches, as it readily forms an obstructive gel layer on the surface of tablets.[2–7] Waxy starches have been shown to be more effective with regard to the retardation of matrix hydration than are normal starches,[2] due primarily to the fact that the intramolecular hydrogen bonds between the amylopectin chains stabilizing the matrix structure of the tablet.[8]

Moisture functions as a plasticizer for starches, via the augmentation of chain mobility. This enhanced starch chain mobility results in reduction of glass transition temperature (T_g),[5–7] yield stress, the elastic

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modulus,[8,9] and elastic relaxation during the tablet decompaction process.[1] Therefore, the presence of moisture, at appropriate levels, enhances both plastic deformation and compactibility characteristics.[7–10]

In the present study, amorphous waxy maize starch powders prepared using different drying processes, including oven- and freeze-drying, were examined in their morphology and physical characteristics as tablet excipients. We used theophylline, which acts on relaxation of bronchial smooth muscle and lowering blood pressure, as a model drug. At a therapeutic serum concentration of theophylline above 10–20 μg/mL, side effects such as stimulation of central nervous system may occur.[11]

EXPERIMENTAL

Materials

The commercial waxy maize starch was supplied by Samyang Genex (Seoul, Korea) and the anhydrous theophylline was purchased from the Sigma-Aldrich Chemical (St. Louis, MO).

Preparation of amorphous starch

A starch suspension in water (total 100 g, 10% starch solids, w/w) was pasted by heating for 15 min in a boiling water-bath, with mechanical stirring. The paste was then transferred to a glass dish (20 cm diameter), and dried in a convection oven (40 or 105°C) or freeze-dried to a moisture content of $\leq$5%. The dried starch products were then ground into powder (Grinder, Woonam, Korea), and sieved with a 300 μm-mesh screen. To prepare the theophylline-containing amorphous starch products, a starch suspension (10% solids, w/w) containing theophylline (3% solids, w/w) was pasted and dried in accordance with the above-described procedure.

Preparation of tablets

Dried starch powders were remoistened to (17 $\pm$ 0.2)% by storing in a humidity chamber (25°C, 75% relative humidity), then compressed into flat-faced tablets (300 mg, 13 mm diameter) with a hydraulic press (Dongjin, Seoul, Korea) at 60 kN (holding time 1 s). The tablets were then dried overnight in a convection oven at 105°C, and stored in a desiccator until analyzed in their morphology, physical properties, and drug release profiles.

MEASUREMENTS

Moisture content

The moisture contents of the amorphous starch powders were determined by drying the powders in a convection oven, for 24 h at 130°C.

X-ray diffraction

The long-range molecular arrangements of the amorphous starch powders were evaluated using an X-ray diffractometer (Rigaku, D/MAX-IIIA, Japan), at 40 kV and 30 mA, with Nickel-filtered Cu-Kα. Scattered radiation intensities were measured in a range between 3 and 40° (2θ) at 1°/min intervals.

Tablet morphology

Tablets prepared with the starch powders dried under different conditions were fractured, and vertical sections of the tablets were observed via a scanning electron microscopy at an accelerating voltage of 5 kV (JOEL, JSEM 5410LV System, Japan).

Crushing strength

The crushing strength of the dried tablets was determined using an Instron Mechanical Tester (Instron Engineering, Canton, MA). The crushing strength was calculated according to the following equation[7]:

$$\sigma = 2P/\pi Dt \quad (1)$$

in which σ, D, t, and P represent crushing strength (kg/cm^2), tablet diameter (mm), tablet thickness (mm), and applied force (kg), respectively.

Water uptake

The dried tablets were immersed in distilled water (30 mL) at room temperature, and the weight gain of the tablets was measured at 10-min intervals. Water uptake was expressed as percentage of weight increase, on the basis of the initial dry weight.[9] The thickness of the gel layer on the surfaces of the swollen tablets was also determined, by using a light microscopy (D-490ZOOM, Olympus, Japan).

Drug release

Theophylline release testing was conducted in a USP dissolution testing system (Woojoo Sci., Korea) at 100 rpm and 37°C in 0.05M phosphate buffer (pH 6.8). The resulting theophylline concentrations in buffer solution were determined by using a spectrophotometer at 268 nm. The kinetics for the theophylline release was determined in accordance with the following equation[10]:

$$M_t/M_\infty = kt^n \quad (2)$$

in which M_t/M_∞ was the fraction of the drug released at time t, and k represents the kinetic drug release constant. In the present study, the values of k and n were

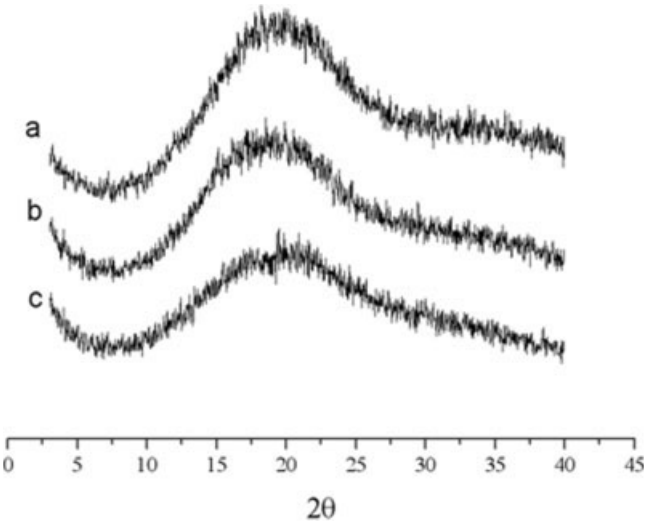

Figure 1 X-ray diffraction patterns of amorphous waxy maize starches dried under different conditions: (a) oven-dried at 40°C; (b) oven-dried at 105°C; (c) freeze-dried.

determined via regression analysis, at a confidence level of 95%. All measurements were conducted in triplicate.

RESULTS AND DISCUSSION

X-ray diffraction

The X-ray diffraction patterns demonstrated that all the waxy maize starch powders used as tablet excipients were amorphous (Fig. 1). The drying of the starch paste to a moisture content of <5% required an extensive period of time, and was dependent on both the drying methods and temperatures used. During these periods, retrogradation of the constituent starch could occur.

Although none of the starch samples evidenced long-range crystallinity on X-ray diffraction, all starch samples displayed broad diffraction peaks, thereby indicating the presence of molecular rearrangements among the amorphous starch chains. When a drying temperature of 40°C was applied, the required drying period was much longer than when a temperature of 105°C was applied. Therefore, a longer period of time provided more chance for the amylopectin chains to re-associate. On the basis of the detected peak heights, the degree of chain association appeared to be greater when the starch paste was dried at a lower temperature (40°C). The freeze-dried starch sample exhibited the smallest peak, indicating a lesser degree of association than was observed in the oven-dried starch samples. This was attributed to the restriction of chain mobility conferred by freezing.

Tablet morphology

Vertical sections of the tablets prepared with the amorphous starch samples evidenced different appearances on SEM, in accordance with the applied drying methods. The tablets prepared with the freeze-dried starch sample appeared more uniform and concrete-like than those with the oven-dried starch samples (Fig. 2). However, no significant differences were observed between the two oven-dried tablets prepared at different temperatures.

Freeze-drying hindered the re-association of starch chains, and thus yielded the starch powders with a relatively lower density but a larger surface area. We assume that these morphological differences might allow the freeze-dried starch for a high degree of interparticulate bonding while the starch powders were compressed into tablets. Therefore, the bonding among the starch particles during the physical compression resulted in the formation of a compact and uniform tablet matrix.

Crushing strength

The drying conditions applied in the preparation of amorphous starch samples affected the physical strength of the resultant compressed tablets (Fig. 3). In

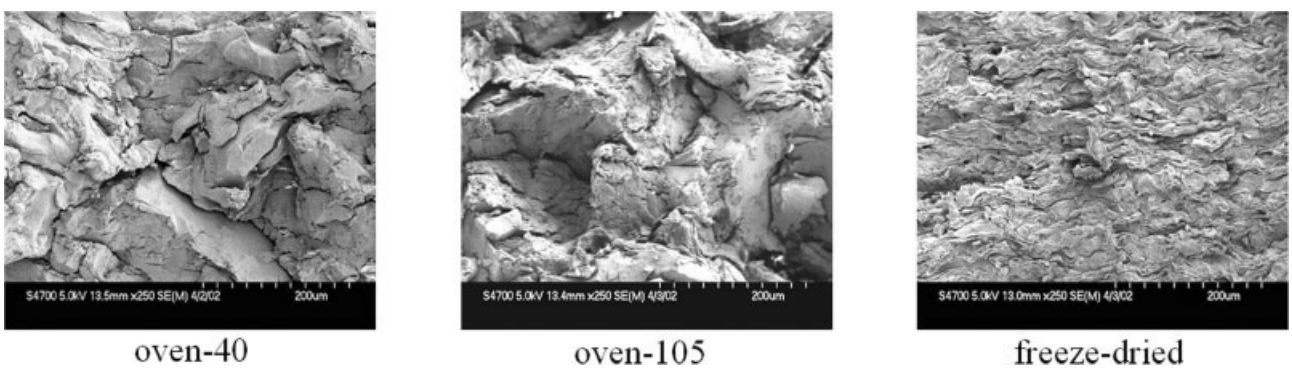

Figure 2 Scanning electron micrographs of vertical sections inside tablets compacted from amorphous waxy maize starches dried under different conditions.

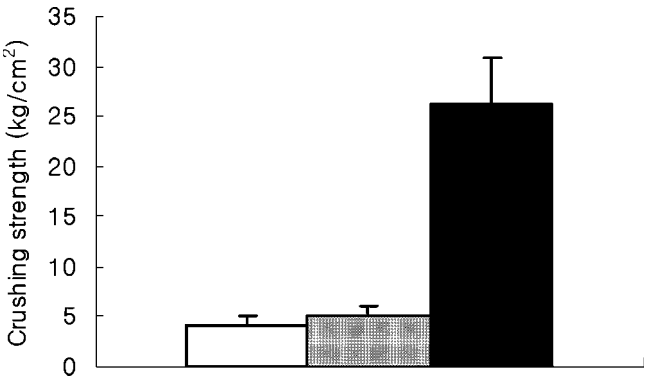

Figure 3 Effects of drying conditions of amorphous waxy maize starches on the crushing strength of tablets: □ oven-dried at 40°C; ■ oven-dried at 105°C; ■ freeze-dried, ($n = 3$, mean ± S.D.).

comparison to starch samples prepared via oven-drying, the freeze-dried starch samples yielded tablets that evidenced significantly higher resistance to mechanical crushing. The temperature at which the oven-dried samples were processed, however, did not appear to have a significant effect on the strength of the resulting tablet. These results are consistent with the SEM observations (Fig. 2). It also suggests that the physical strength of the compressed tablets is principally dependent on interparticular bonding occurring during the formation of tablets, and to a lesser degree on chain association occurring during the drying of the amorphous starches.

Water uptake

For a sustained release of drug, polymers in tablet matrices should swell fast and form a viscous gel layer.[12] Tablet swelling occurs following the penetration of a solvent into the tablet via surface pores. The penetrating water initially forms a gel-layer on the surface of the tablet, which ultimately mediates the drug diffusion characteristics of the tablet. The morphology of the gel components substantially affects tablet compactness and porosity, both of which are primary factors with regard to solvent penetration and drug release rates.[13–15]

The drying methods applied to the amorphous starch paste were shown to influence substantially the water uptake characteristics of the tablets (Fig. 4). The swelling profiles of the tablets prepared with the oven-dried starches prepared at different temperatures (40 and 105°C) were similar, whereas the freeze-dried starch tablets exhibited much lower water penetration levels (Fig. 4). As was revealed by the microscopic data (Fig. 2), the high levels of interparticular bonding occurring in the freeze-dried starch samples might inhibit the penetration of water into the tablets. Moreover, the tablets constructed from the freeze-dried starch manifested plateau during the water exposure period (270 min). This suggests that the water penetration profile of these tablets follows a near zero-order kinetic pattern.

The gel layers formed by water penetration could be readily observed in a light microscopy (Fig. 5). The thickness of the layers, measured under the microscope, increased gradually with continued water penetration (Fig. 6). The tablets constructed from the freeze-dried starch manifested a markedly reduced gel thickness, as compared with the oven-dried starch tablets. This tendency was consistent with the water penetration data, in which the freeze-dried starch tablets were shown to absorb less water than the oven-dried starch tablets (Fig. 4). The gel thickness of the freeze-dried starch tablets increased for the first 40 min of immersion in water, but remained unchanged (Fig. 6). However, as is indicated in Figure 4, the penetration of water into the freeze-dried starch tablets continued for up to 5 h of water immersion. This demonstrates that the water absorbed through the gel layer continued to diffuse inside the tablets. This phenomenon was caused by the differences in the morphology of tablet matrix (Fig. 2).

Drug release

As the drying methods were shown to influence final tablet morphology and water penetration profiles, it was also expected that the drug release profiles of the tablets also proved dependent on the drying method applied. As shown in Figure 7, the drug release profile was, indeed, affected by the drying process. However, the profiles of the tablets were somewhat different from the results in crushing strength and water penetration. Drug release from the tablets prepared with the starch oven-dried at 105°C was nearly identical to

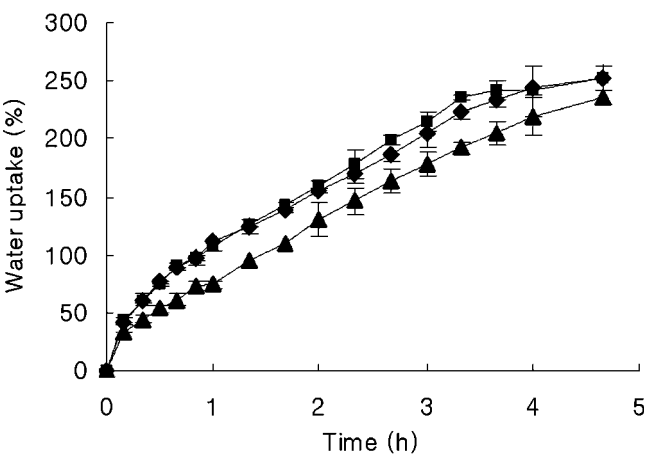

Figure 4 Effects of drying conditions of amorphous waxy maize starches on the water uptake of tablets: ◆ oven-dried at 40°C; ■ oven-dried at 105°C; ▲ freeze dried, ($n = 3$, mean ± S.D.).

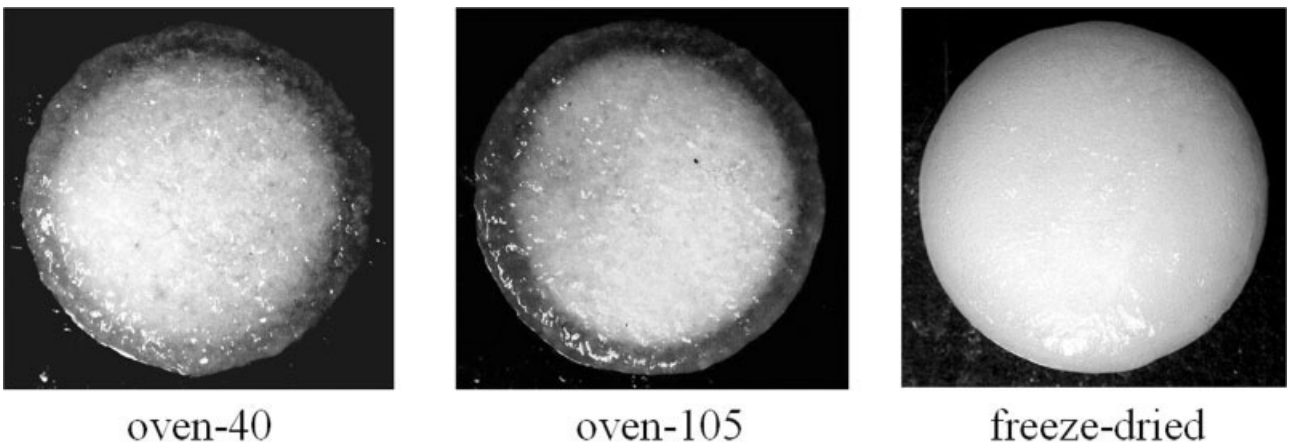

Figure 5 Photographs of swollen tablets compacted with amorphous waxy maize starches.

that observed with the freeze-dried starch tablets (Fig. 7). However, the tablets prepared from the 40°C oven-dried starch exhibited markedly faster release than that of the tablets constructed from the starch dried at 105°C.

With regard to the findings of the kinetic study (Table I), the tablets constructed of the starch oven-dried at 105°C exhibited a higher n value and lower k value than did the freeze-dried starch tablets. Therefore, overall release was slower in the oven-dried starch tablets than in the freeze-dried starch tablets. The higher n value indicates that the release from the tablet more closely follows zero-order kinetics. Therefore, in terms of drug release profile, the oven-dried starch with heat was slightly more favorable than the freeze-dried starch.

As shown by the X-ray diffraction patterns (Fig. 1), when the starch paste was dried at a lower temperature (40°C), the starch chains had a better chance to re-associate, due to the extended drying period. However, starch chain association did not result in significant differences in the water penetration characteristics or physical strength of the tablets (Figs. 3 and 4). Rather than the starch chain association, the interparticulate bonding induced during the tablet compaction provided the physical strength and integrity of the tablets. However, the substantially increased stability of theophylline in the tablets showed that the heat (thermal drying at 105°C) did, in fact, result in some changes in the tablets. One possible explanation was that the thermal energy allowed the drug components to interact with starch molecules. Additionally, it was hypothesized that the less degree for chain association during drying allowed the starch chains to be more available for the interaction with drug components. The theophylline should be transformed to its hydrate form while being thermally dissolved in the starch pastes. During the drying process afterward, the dissolved theophylline became solids, likely in its glassy structure rather than in monohydrate crystals because of the high viscosity of the starch pastes. However, it is apparent that the morphology

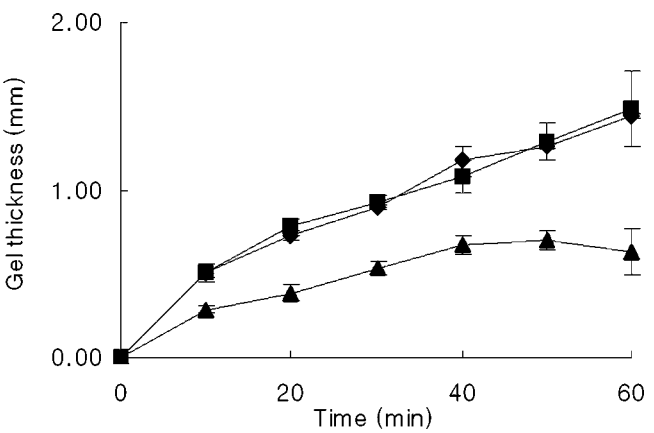

Figure 6 Effects of drying conditions for the starches on the gel thickness of swollen tablets: ◆ oven-dried at 40°C; ■ oven-dried at 105°C; ▲ freeze-dried, ($n = 3$, mean ± S.D.).

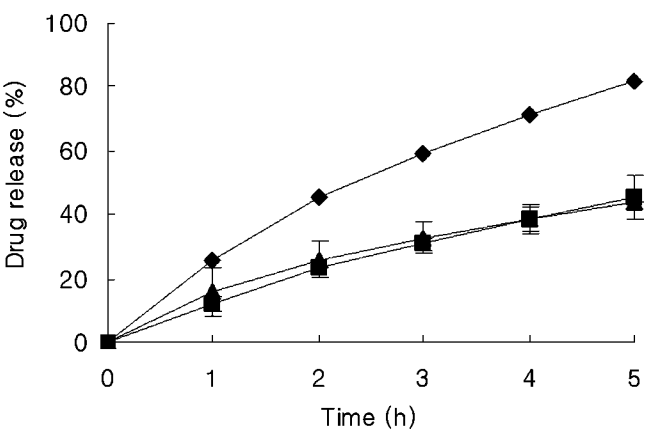

Figure 7 Effects of drying conditions for the starches on theophylline release profiles: ◆ oven-dried at 40°C; ■ oven-dried at 105°C; ▲ freeze-dried, ($n = 3$, mean ± S.D.).

TABLE I
Kinetic Parameters for Drug Release from Tablets Made from Amorphous Waxy Maize Starches Dried under Various Conditions (n = 3, mean ± S.D.)

	Drug release		
Treatments	$k(h^{-n})$	n	r
Oven-dried (40°C)	26.57 ± 2.19	0.72 ± 0.10	0.9967
Oven-dried (105°C)	12.66 ± 0.97	0.81 ± 0.04	0.9971
Freeze-dried	16.01 ± 2.20	0.65 ± 0.09	0.9956

of the drug solids, which can be changed according to the drying process, affects the physical properties and release profile of the tablets. Further studies should be followed in terms of the morphology of the drug and the starch-drug interactions.

CONCLUSIONS

The drying procedure applied for the preparation of amorphous starch powders to be used as tablet excipients was found to affect the morphology and drug release profiles of the compressed tablets. Oven-drying allows for a greater extent of starch re-association during the drying process than does freeze-drying. However, freeze-dried starch yields tablets with greater compactness and more uniform matrices, as a result of the greater degree of interparticulate bonding during tablet formation. This enhanced matrix rigidity also enhanced the stability of the drug (theophylline in this study) within the tablets, thus retarding its release when immersed in water. However, similar drug release effects could be achieved by oven-drying with heat. Thus, any possibility in the existence of thermally induced interactions between starch and drug components should be considered.

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