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Characterization and Performance of a New Direct Compression Excipient for Chewable Tablets: Xylitab®

Lisa E. Morris, Jeffrey C. Moore, and Joseph B. Schwartz

Department of Pharmaceutics, Philadelphia College of Pharmacy and Science, Philadelphia, Pennsylvania 19104

ABSTRACT

Xylitab® is a commercially available direct compression form of xylitol. Two grades of this material, Xylitab 200 and Xylitab 100, were evaluated for compaction, flow, lubrication requirements, and dilution potential. As expected, the products required lubrication for tableting, and a level of 0.5% magnesium stearate and 0.5% stearic acid was found to give the best performance. Compaction profiles were generated using both an instrumented single-punch press and a rotary tablet press. Tablets up to hardness values of 20 Kp were obtained on the single-punch press; the maximum hardness values on the rotary press was 11 Kp. Flow behavior on the tablet presses was excellent as shown by tablet weight uniformity data with less than 1% RSD values. Further evaluation by Heckel analysis showed that both products exhibit brittle and viscoelastic behavior, and undergo elastic recovery primarily in the die. To test dilution potential, powdered acetaminophen was selected as a severe test material. Under these conditions, 20% drug still produced an acceptable tablet, but hardness values were reduced as expected. With a directly compressible grade of acetaminophen, a complete chewable formulation was successfully produced using Xylitab 200 as the main direct compression excipient and sweetening agent. Xylitab exhibits acceptable properties as a direct compression chewable tablet excipient and warrants further study.

INTRODUCTION

Chewable tablets continue to be a popular dosage form. But a major disadvantage with chewing a tablet is that most drugs leave a bitter aftertaste. This has prompted the investigation into sweetening and flavoring agents which will mask unpleasant aftertastes and create a pleasant taste of their own.

Xylitol (American Xyrofin, Inc., Schaumburg, IL) is currently used as a bulk sweetener in the food industry. Xylitab®, a direct compression form of xylitol (1), is commercially available in three grades (Xylitab 100, 200, and 300) as a granulated excipient. Xylitab 100 is granulated with 3% polydextrose, and Xylitab 200 with 1.5% sodium carboxymethylcellulose. Xylitab 300 is granulated solely with xylitol and is intended for use with other directly compressible pharmaceutical excipients. Xylitol has the same sweetness as sugar and is the sweetest sugar alcohol (2,3). In addition, xylitol provides the highest negative heat of solution of any sugar alcohol (2,3). The resulting significant cooling effect can aid in masking bitter tastes (2,3). Xylitol has demonstrated cariostatic effects which make it an attractive alternative sweetener for sugar-free products (4,5). These properties make Xylitab a potential excipient for chewable tablets.

A direct compression excipient must exhibit good flow and compressible characteristics. If it has no inherent lubricating properties, as with most diluents, other additives must be present to prepare a satisfactory tablet. The purpose of this paper is to evaluate Xylitab's performance as a direct compression excipient for flowability, lubrication requirements, compaction, and dilution potential.

MATERIALS AND METHODS

All tablets were prepared by the conventional method of direct compression. To insure a uniform particle size, the excipient and drug were completely passed through a No. 12 mesh screen prior to processing. The lubricant(s) were completely passed through a No. 20 mesh screen and bolted onto the mixture. Each batch of excipient and lubricant(s) was blended for 5 min in a Patterson–Kelly Twin Shell Blender. When a drug was included in the formulation, a 10-min mixing time with drug and Xylitab was performed prior to the lubrication step.

Physical Properties

Micromeritic measurements were performed on the two Xylitab grades to characterize the excipients. The mean particle size was determined from sieve analysis on a Model RX-24 Portable Sieve Shaker (Tyler, Mentor, OH) using No. 16, 20, 30, 50, 80, and 100 mesh screens. The bulk density measurement was performed by filling a 50-g sample through a funnel into a 100-ml graduated cylinder. The tapped density was carried out using a Vanderkamp Tap Density Tester (Van-Kel Industries, Inc., Chatham, NJ) in 50 tap intervals until a constant volume was maintained. The true density was measured using a helium micropycnometer (Quantachrome, Syosset, NY).

Lubricant Requirements

The type and level of lubricant was varied to determine the effect for each Xylitab grade. The excipient was blended with magnesium stearate (Mallinckrodt, St. Louis, MO) alone, stearic acid (Ruger Chemical Co., Inc., Irvington, NJ) alone, or with a mixture of the two lubricants at a 0.5%, 1%, and 2% total lubricant level. Room conditions were monitored to control temperature at a range of 70°–80°F and relative humidity at $<60\%$. The blends were compressed on an instrumented single stroke tablet press (Manesty F-3) using a 7/16 in. flat, beveled edge tooling set.

Each blend was evaluated for compactibility and lubrication effect. A compaction profile was generated using the average tablet hardness and the average maximum upper punch force. The compactibility of the excipients was evaluated by the shape of the compaction profile and the force at maximum tablet hardness.

The upper punch forces were monitored using a piezoelectric transducer and acquired by a digital oscilloscope. At least four forces (1000 to 8000 pounds) were targeted for the studies. Fifteen maximum upper punch force outputs were averaged at each target force. The tablet weight was targeted to 550 mg. The weights of five tablets and the corresponding tablet hardness values were averaged.

To determine effective lubrication, the occurrence of punch face sticking, die wall sticking, capping upon ejection, and lamination during hardness testing were observed during or following compression. A variation in tablet weight indicated poor flow of the blend or an accumulation of the material along the die wall, causing lower punch sticking.

Compaction on a Rotary Tablet Press

The most effective lubricant determined for each grade of Xylitab compressed on the single-punch press was used as the optimal lubrication for further studies. The compactability and suitability of the lubrication level for each blend were compared on an instrumented rotary tablet press. A compaction profile was generated using the average tablet hardness and the average maximum compression force. A compaction profile for each Xylitab blend was generated using 7/16 in. deep concave tooling.

Four tooling stations were installed on the rotary press (Manesty Betapress). Both the precompression and compression forces were monitored by strain gauges and acquired by a data acquisition computer system (SMI, Pittstown, NJ). Precompression force was not applied to the material. The hardness was targeted to a maximum value and four ranges below the maximum were collected. Five turret revolutions were averaged for each tooling station. Five runs or 25 force values were averaged. The tablet weight was targeted to 550 mg. The weights of five tablets and the corresponding tablet hardness values were averaged.

Deformation Behavior

The deformation behavior of the two grades with optimal lubrication was studied on an instrumented single-punch tablet press using 7/16 in. flat faced tooling. The upper punch movement was measured using a linear variable differential transformer (LVDT). The corresponding upper punch pressure generated in the die was monitored with a piezoelectric transducer. The output from the instrumentation was acquired by a data acquisition computer system (6).

The data conversion and analysis system converted the upper punch movement to powder densification [ln (1/porosity)] based on the tablet weight and true density of the powder (6). The Heckel plot [ln(1/porosity] versus upper punch pressure) representing powder densification in the die was used to interpret the deformation behavior of the materials (6–11). The densification plots for the two grades at the same tablet hardness (11–14 Kp) were compared. Each densification plot was isolated into six phases of compression and decompression, based on the upper punch movement in the die (6). A material's deformation behavior was then described by the densification and pressure changes occurring in the regions.

Dilution Potential

To test dilution potential, powdered acetaminophen (Monsanto Co., St. Louis, MO) was selected as a severe test material. Each Xylitab grade was diluted with 10%, 20%, 30%, and 40% drug. Sorbitol (ICI Ruger, Irvington, NJ), a widely used polyol, in the form of a crystalline powder served as a control. The optimal lubrication was added to each blend. The compactability and suitability of the lubrication level was evaluated for each blend. Compression was performed on the same instrumented single punch press using 7/16 in. flat beveled edge tooling.

RESULTS AND DISCUSSION

Physical Properties

The mean particle size, bulk and tapped densities, and true density of Xylitab 100 and Xylitab 200 are listed in Table 1. The two grades have similar bulk, tapped, and true densities. The particle size distributions for Xylitab 100 and Xylitab 200 are presented in Fig. 1. Xylitab 200 has a 17% larger mean particle size than Xylitab 100. The majority of particles range in size between 170 and 300 μm.

Table 1

Physical Properties of Xylitab 100 and Xylitab 200

Materials	Mean Particle Size (mm)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	True Density (g/cm^3)
Xylitab grade 100	219	0.566	0.637	1.4994
Xylitab grade 200	257	0.552	0.610	1.4817

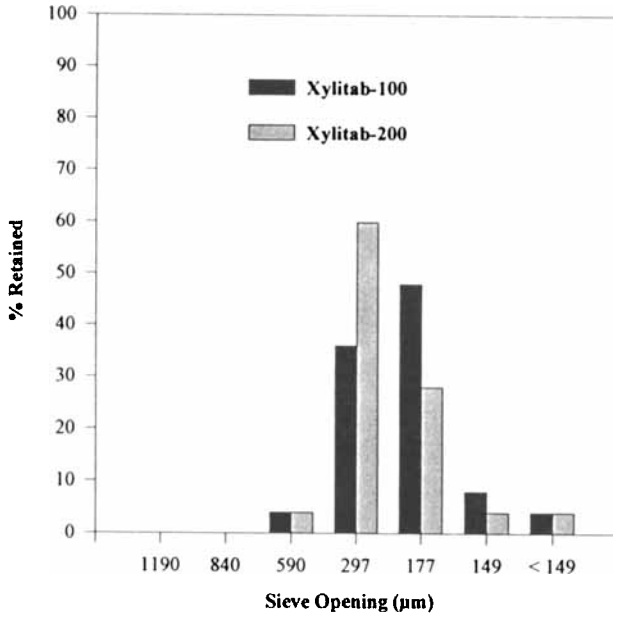

Figure 1. Particle size distributions for Xylitab 100 and 200.

Lubricant Requirements

Direct compression of each grade of Xylitab with 1% magnesium stearate resulted in varying degrees of die wall and punch face sticking. The observation persisted after reducing room humidity from 65% to 35%, indicating the need for lubricant optimization. Xylitab 100 was consistently more sensitive to lubricant type and level than Xylitab 200. Figures 2 and 3 represent selected compaction profiles for the lubricated batches of Xylitab 100 and 200.

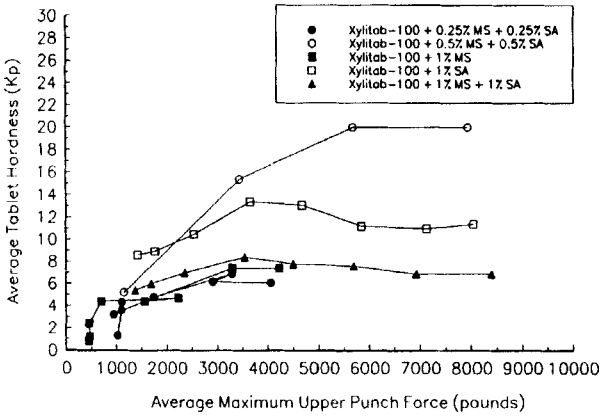

Figure 2. Compaction profile for Xylitab 100 at a 0.5%, 1%, and 2% total lubricant level. MS = magnesium stearate SA = stearic acid.

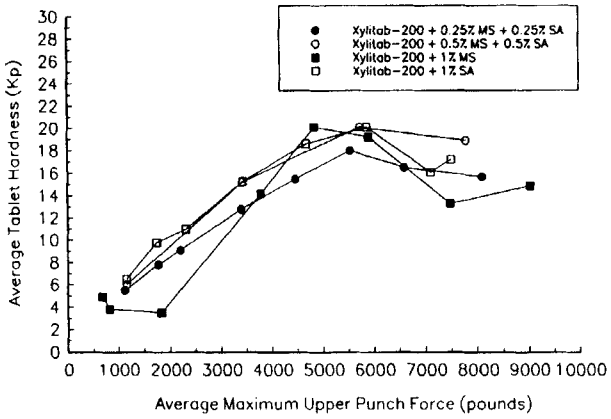

Figure 3. Compaction profile for Xylitab 200 at a 0.5% and 1% total lubricant level.

Magnesium Stearate Alone

A 1% level of magnesium stearate was combined with each grade. Die wall sticking during compression and capping/lamination during hardness testing* were observed for each grade, but at different force ranges. These observations are evident on the compaction profiles as reduced hardness values, as seen in Figs. 2 and 3. At all force ranges, the Xylitab 100 formulation had extensive die wall and punch face sticking.

Extensive die wall sticking causes the lower punch to mechanically stick in the die, resulting in poor weight control and variable force output. The erratic hardness values result in a nonlinear compaction profile as shown in Fig. 2. The maximum hardness obtained was 7.4 Kp at 3295 lb of force. Softer tablets occurred from 1560 to 4224 lb of force.

Xylitab 200 had extensive die wall sticking only at forces less than 1827 lb. At forces greater than 1827 lb, tablet hardness increased in proportion to the applied force. A maximum hardness of 20.1 Kp was obtained at 4839 lb. As force was increased to a level of 9025 lb, the hardness gradually reduced to 13–14 Kp. At

*It is noted that tablet capping and/or lamination during compaction and ejection represents an unacceptable situation, and this was rarely observed. When the same phenomenon occurs only during hardness testing, it serves as a warning of softer tablets, but the tablets may be acceptable. When the compaction profile exhibits a reduction of tablet hardness at higher forces, there is usually a correlation.

forces from 7478 to 9025 lb, a reduction in hardness was found. This resulted in a parabolic shaped profile as shown in Fig. 3. Magnesium stearate alone, at a 1% level, was not an effective lubricant for either grade.

Stearic Acid Alone

A 1% level of stearic acid was combined with each grade. No die wall sticking occurred with either grade during the compaction study. Both grades showed softer tablets at compression forces greater than 5800 lb. The shape of the compaction profiles is different from that of the magnesium stearate study as shown in Figs. 2 and 3.

Xylitab 100 was more sensitive to lubricant type, in terms of its effect on tablet strength and lubrication. With stearic acid alone, punch face sticking was observed with Xylitab 100 from 1421 to 2539 lb of force. At this force range, tablets as hard as 8–10 Kp were produced. A maximum hardness of 13.4 Kp was obtained at 3648 lb of force. As more force was applied, the hardness plateaued to 11 Kp. A 1% level of stearic acid reduced die wall sticking and improved tablet strength, appearing to be a more effective lubricant for Xylitab 100 than magnesium stearate alone.

The compaction profile for Xylitab 200 shows that hardness increased in proportion to the applied force. The hardness peaked to 20.1 Kp at 5858 lb of force. Capping upon ejection was observed from 7095 to 7502 lb of force, resulting in a decreased tablet strength of 16–17 Kp. As compared to the magnesium stearate study, sticking was eliminated when combining Xylitab 200 with stearic acid. While the tendency for the tablets to cap upon ejection was affected by the lubricant type, the maximum tablet strength for Xylitab 200 was not affected by the lubricant type.

Combinations of Magnesium Stearate and Stearic Acid

The lubricants were combined in a 1:1 ratio to total a 0.5%, 1%, and 2% lubricant level. The compaction performance of each Xylitab was optimal at the 1% combined lubricant level. Extensive die wall and punch face sticking were observed at all forces for Xylitab 100 in conjunction with a 0.5% combined lubricant, resulting in poor weight control, variable force output, and a maximum tablet hardness of 6.9 Kp. No capping/lamination during hardness testing was observed at this lubricant level. As represented in Fig. 2, the erratic hardness values results in a nonlinear compaction profile similar to the profile for 1% magnesium stearate alone.

The 0.5% combined lubricant level was more effective for Xylitab 200. No die wall sticking was observed. Punch face sticking did occur at forces less than 1100 lb. Figure 3 shows that, as more force is applied, hardness increases in proportion to the force. A maximum tablet hardness of 18 Kp was obtained at 5535 lb of force. At forces greater than 6500 lb, a decrease in tablet strength to 16 Kp resulted.

Xylitab 100 combined with a 2% combined lubricant level was a less effective lubricant and resulted in weaker tablet strengths. Punch face sticking was observed from 1375 to 3531 lb of force. The hardness peaked to 8.4 Kp at 3531 lb of force. The compaction profile, represented in Fig. 2, shows that as more force was applied, the hardness plateaued to 6–7 Kp. At forces greater than 4500 lb, softer tablets were observed.

The combined level of 0.5% magnesium stearate and 0.5% stearic acid was found to give the best performance for both grades of Xylitab and was the optimal lubrication for the remaining studies. Each grade of Xylitab produced a maximum tablet hardness of 20 Kp peaking at 5700 lb of force. Die wall and punch face sticking were not observed at this lubricant level. Although capping/lamination was observed during hardness testing at forces greater than 7000 lb, no apparent change in hardness was measured.

Compaction on a Rotary Tablet Press

Figure 4 represents the compaction profiles for the Xylitab grades lubricated with the optimal lubricant, 0.5% magnesium stearate and 0.5% stearic acid, compressed on a single-stroke and a rotary tablet press. The

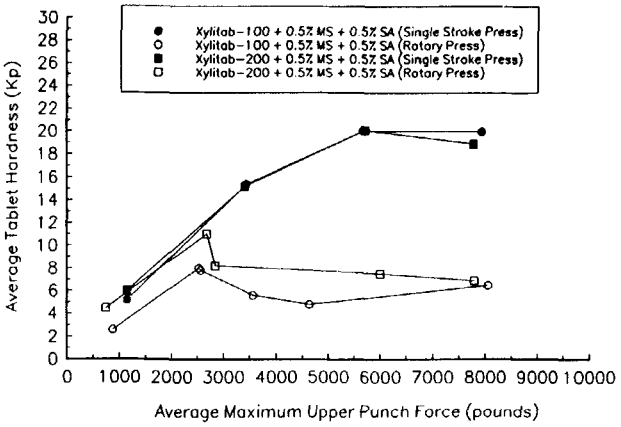

Figure 4. Compaction profile for each Xylitab grade combined with 0.5% magnesium stearate and 0.5% stearic acid compressed on a single-stroke and a rotary tablet press.

rotary press speed was three times the speed of the single-stroke press. Flow behavior on the tablet presses was excellent as shown by tablet weight uniformity data with less than 1% RSD values. The shape of the compaction profile and the force at maximum tablet hardness is different for the excipients and the press type.

On the rotary press, Xylitab 100 produced a maximum tablet hardness of 8 Kp at 2500 lb of force, while Xylitab 200 produced a maximum tablet hardness of 11 Kp at 2700 lb of force. As shown in Figure 4, a reduction in hardness at the higher force ranges was observed. The different profiles for single-stroke and rotary presses suggests that Xylitab has a time-dependent mechanism in its deformation behavior.

Deformation Behavior

Figure 5 represents the densification in the die versus upper punch pressure plot for Xylitab 100 and 200 combined with the optimal lubricant level. The tableted blends have similar weights and hardness values in the range of 11–14 Kp. The shape and magnitude of the densification with pressure is different for the two blends. To evaluate the difference between the two materials, the densification–pressure plot was separated into six regions of compression and decompression (6). The following is a summary of the analysis in each region.

The initial fill density for both grades is comparable to its bulk density. This indicates the blends have good flow properties as described by the fill densification region in Figure 5. From analysis of the densification and pressure changes in compression phase I, the yield pressure for Xylitab 100 was 66 MPa and for Xylitab 200 was 57 MPa. Both Xylitab grades have large fracture propensities describing a brittle material which fractures in the die. The plastic deformation mechanism is reflected in the different compaction profiles for single-punch and rotary presses (speed of compaction).

During the second phase of compression, both excipients further densify in a short amount of time (20 to 80 msec) and achieve more densification to pressure reduction. This indicates the materials undergo some plastic flow during compression and appear to be viscoelastic. Xylitab 200 was more viscoelastic than Xylitab 100 when combined with the optimal lubrication.

During the decompression phases, the two grades undergo elastic recovery, primarily in the die. The low out-of-die elastic recovery (6% to 8%) is reflected in the capping tendency during hardness testing only at very high forces (>7000 pounds).

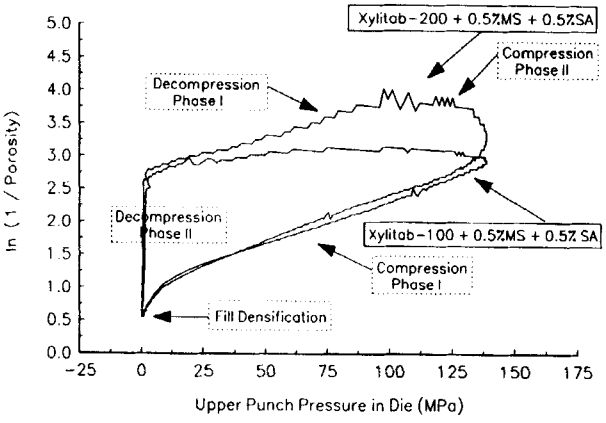

Figure 5. The densification vs. upper punch pressure in the die for each Xylitab grade combined with 0.5% magnesium stearate and 0.5% stearic acid compressed to the same tablet hardness range of 11–14 Kp.

Dilution Potential

The two Xylitab grades differed significantly in terms of their dilution potential with powdered acetaminophen (poorly compressible model drug). When combined with the optimal lubricant, Xylitab 200 could be successfully diluted with 20% drug. Maximum tablet hardness, as expected was reduced to 8.5 Kp at 3800 lb of force. When blended with greater than 20% drug, flow and weight control problems were encountered. Conversely, die wall sticking and weight control difficulties were observed at drug dilutions of 10% and 20% with Xylitab 100. At 10% dilution a maximum hardness value of 2 Kp was obtained for Xylitab 100.

Sorbitol, when combined with the optimal lubricant, did not exhibit die wall or punch face sticking or capping/lamination during hardness testing. Maximum tablet hardness of 23.5 Kp was observed at 7359 lb of force. When diluted with 10% powdered acetaminophen a maximum tablet hardness of 26 Kp was obtained at 7979 lb. However, dilutions with greater than 10% drug resulted in poor flow characteristics, loss of weight control, and variable force output.

APPLICATIONS OF XYLITAB

Combining Xylitab with Microcrystalline Cellulose

Xylitab 100 was combined with 49.5% microcrystalline cellulose (Avicel® PH102, FMC Corp., Princeton,

NJ) and the optimal lubricant level to evaluate their compatibility. Lower punch face sticking was observed from 4747 to 7763 lb of force. No capping/lamination during hardness testing was observed. The maximum tablet hardness was 29.4 Kp at 7763 lb of force. The addition of microcrystalline cellulose eliminated any capping/lamination tendency and improved tablet strength.

Xylitab 200 was combined with 49% microcrystalline cellulose, 1% colloidal silicon dioxide (Cab-O-sil®, Cabot, Tuscola, IL) and the optimal lubricant level to evaluate their compatibility. No die wall or punch face sticking, and no capping/lamination during hardness testing were observed. The maximum tablet hardness was 30 Kp at 7926 lb of force.

Tooling Set Effects

Xylitab 100 and 200, each combined with the optimal lubricant level, were compressed in three different tooling set sizes and shapes. Both grades exhibited changes in behavior with different tooling images. Figures 6 and 7 represent the compaction profiles for Xylitab 100 and Xylitab 200 in the different tooling sets, respectively. Using a 7/16 in. deep concave tooling set, 550 mg was targeted for tablet weight. The maximum tablet hardness for Xylitab 100 was 19.1 Kp at 5435 lb of force and 15.7 Kp at 3305 lb of force for Xylitab 200. Die wall and punch face sticking were not observed for either grade. Softer tablets were observed at forces greater than 5400 lb for Xylitab 100, and greater than 5800 lb for Xylitab 200.

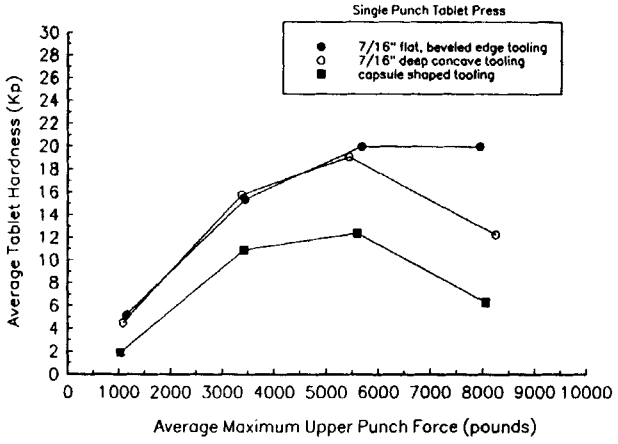

Figure 6. Compaction profile for Xylitab 100 combined with 0.5% magnesium stearate and 0.5% stearic acid compressed in different tooling set sizes and shapes targeting a 550-mg tablet weight.

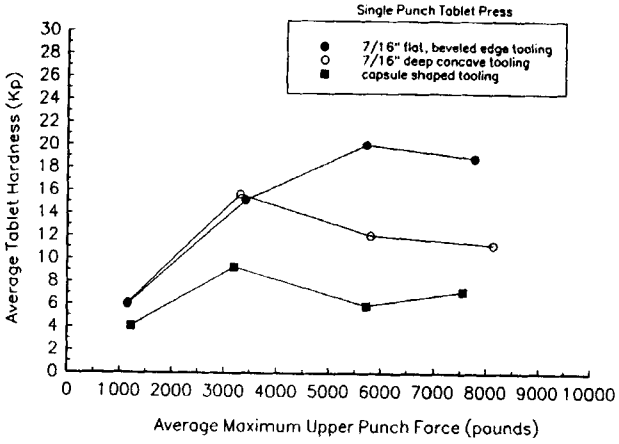

Figure 7. Compaction profile for Xylitab 200 combined with 0.5% magnesium stearate and 0.5% stearic acid compressed in different tooling set sizes and shapes targeting a 550-mg tablet weight.

Using a 4/16 × 12/16 in. capsule-shaped tooling set, 550 mg was targeted for tablet weight. Extensive die wall sticking was observed at forces less than 1000 lb for Xylitab 100 and at all force ranges for Xylitab 200, resulting in poor weight control and variable force output. The maximum tablet hardness for Xylitab 100 was 12.5 Kp at 5588 lb of force. Xylitab 200 had a maximum tablet hardness of 9.3 Kp at 3192 lb of force. Softer tablets were observed at forces greater than 5500 lb for Xylitab 100, and greater than 5700 lb for Xylitab 200. Capping upon ejection occurred at forces greater than 5500 lb for Xylitab 100, but only at 5700 lb for Xylitab 200.

Using a 1/4 in. flat, beveled edge, scored upper tooling set, 200 mg was targeted for tablet weight. Figure 8 represents the compaction profiles for Xylitab 100 and 200 using this tooling image. The maximum tablet hardness for Xylitab 100 was 15.2 Kp at 5983 lb of force, and 16.2 Kp at 8100 lb of force for Xylitab 200. Die wall and punch face sticking were not observed for either grade. No capping/lamination during hardness testing was observed for Xylitab 100 but was observed at forces greater than 5500 lb for Xylitab 200. Capping upon ejection occurred at 3400 lb of force for both grades.

Acetaminophen Chewable Tablets

Xylitab 200 was combined with 21% granulated, direct compression grade acetaminophen (Mallinckrodt,

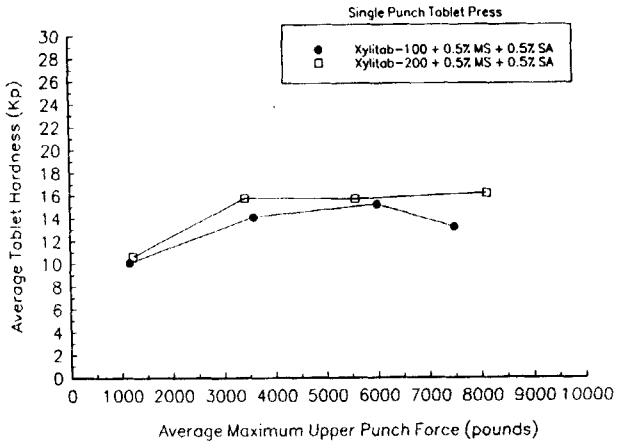

Figure 8. Compaction profile for the Xylitab grades combined with 0.5% magnesium stearate and 0.5% stearic acid compressed in 1/4-in. flat, beveled edge, scored upper tooling targeting a 200-mg tablet weight.

St. Louis, MO) to evaluate its performance as the main direct compression excipient and bulk sweetening agent in a chewable tablet formulation. Table 2 represents a formulation compressed on a single-stroke press, using a 12/32 in. round, flat beveled edge, scored tooling set. Xylitab 200 produced an acceptable tablet and aided in masking the bitter taste of acetaminophen.

CONCLUSIONS

Xylitab exhibits acceptable properties as a direct compression chewable tablet excipient and warrants further study. The level of 0.5% magnesium stearate and 0.5% stearic acid was found to give the best performance for both Xylitab grades in terms of flowability, lubrication requirements, and compaction. Flow behavior on the tablet presses was excellent as shown by tablet weight uniformity data with less than 1% RSD values. The dilution potential for Xylitab 200 with powdered acetaminophen was successful to a level as high as 20%. The plastic deformation mechanism of the two blends is reflected in the different compaction profiles for single-stroke and rotary presses (speed of compaction). Further evaluation by Heckel analysis showed that both products exhibit brittel and viscoelastic behavior, and undergo elastic recovery primarily in the die. A chewable acetaminophen formulation was successfully produced using Xylitab 200 as the main direct compression excipient and bulk sweetening agent.

Table 2

Direct Compression Chewable Tablet Formulation

Materials	mg/tablet	% w/w
Xylitab grade 200	278.0	74.73
Acetaminophen, direct compression grade	80.0	21.51
Cherry flavor	7.6	2.04
Citric acid	3.8	1.02
Stearic acid	0.9	0.24
Magnesium stearate	0.9	0.24
Aspartame	0.8	0.22

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