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RESEARCH PAPER

The Effect of Compaction Force and Type of Pregelatinized Starch on the Dissolution of Acetaminophen

C. W. Symecko* and C. T. Rhodes

The University of Rhode Island, Department of Pharmaceutics, Kingston, Rhode Island 02881

ABSTRACT

The influence of four pregelatinized starches—National® 1551, Lycatab®PGS, Pregeflo®M, and Starch 1500®—as binders, on the dissolution of acetaminophen was evaluated in a model wet-granulated system. Systems containing 82% acetaminophen were prepared under the same processing conditions and compacted to three target tablet thicknesses. The dissolution performance was assessed using a point estimate of percent dissolved at 30 min ($\%T_{30}$) as well as dissolution efficiency through 30 min (DE_{30}). All four binders evaluated meet USP requirements for purity. National 1551, Lycatab PGS, and Starch 1500 were not affected by compaction force in terms of dissolution performance. Differences were observed between the fully pregelatinized systems of National 1551 and Lycatab PGS, in comparison to the partially pregelatinized system, Starch 1500. The Pregeflo M starch produced a system with delayed drug dissolution and was influenced by compaction force.

INTRODUCTION

Cornstarch NF has found vast uses in pharmaceutical formulations, as an absorbent in over-the-counter (OTC) powder preparations; as a diluent and disintegrant; and when heated in an aqueous environment, as a binder in tablet formulations. Similar starch functionality has recently been outlined in the food industry with starch being identified as an agent for thickening, coating, binding, imbibing, dusting, molding, stabilizing, coating, gelling, adhesion, and encapsulation (1). Starch suppliers identified the heating of native starch and the subsequent molecular reordering as starch pregelatinization. The resultant product has the ability to form gels in a cold aqueous environment, a characteristic which promotes its usefulness as a binder in the process of wet granulation. By choosing to include a pregelatinized starch, a formulator may decrease produc-

*Present address: Department of Pharmaceutical Process/Technical Development, Hoffmann-La Roche, Inc., Nutley, NJ 07110.

tion time by eliminating the heating of native starch prior to granulation (2,3).

Pregelatinized starches commonly function in solid dosage formulations as binders and diluents. Due to their adhesive properties pregelatinized starches are commonly included in wet-granulated systems as binders. Their function is to aid in interparticulate bond formation during granulation and compaction. The end product formed, tablets, exhibit the benefit of superior mechanical performance (i.e., increased tablet hardness and tensile strength, and a decreased friability).

The current NF monograph for pregelatinized starches is complete as to the purity of the compound but is incomplete as to its functionality. This is exemplified by the inclusion of both partially and fully pregelatinized starches under one monograph (4). Recent attention has been paid to the importance of functionality tests for excipients (5), particularly the pregelatinized starches (6). Excipient functionality would consist of evaluating certain critical physical properties of excipients which are of importance to the integrity of the final dosage form. One example of functionality would be to identify the critical particle size distribution required for a directly compressible matrix which would allow it perform in a reproducible manner as a diluent in a tablet formulation.

In the case of wet-granulated systems, simple excipient functionality (e.g., particle size) may not truly correlate with the success or failure of the final manufactured dosage form. The wet-granulation process itself is used to increase particle size to allow for a more free-flowing, homogeneous, and easier-compressing formulation. In the case of wet-granulated systems, applied functionality would be of more merit in the evaluation of certain NF excipients.

An applied functional evaluation would take into account properties exhibited or imparted by an excipient to a model system (formulation). As part of a complete evaluation for wet-granulated systems, granule properties, events during compaction, and tablet properties would be of benefit for full excipient characterization. It may be of great merit to also evaluate the effect of processing variables on the model system, to identify any effect small changes normally encountered in manufacturing may have on the performance of the excipient studied.

One such processing variable which needs further study is the effect of compaction force. Previously, the effect of compaction force on the dissolution efficiency of tablets prepared using directly compressible excipients has been identified (7). Also, the effect of starch concentration, type of starch, and compaction pressure in double-compressed (dry-granulated) systems has been studied (8,9). An interaction between possible type of tablet disintegrant and compaction pressure was illustrated in both directly compressible and wet-granulated systems (10). In wet-granulated systems, the effect of compaction force on the dissolution performance of two model drugs was identified and an increase in dissolution performance as a function of compaction force was illustrated (11). The aforementioned studies all identify critical interactions between compaction force and one type of formulation variable.

The objective of this evaluation is to identify the effect compaction force has on the dissolution of acetaminophen from tablets prepared by wet granulation using four different brands of pregelatinized starch as binders. The goal is to identify possible functional differences between four brands of pregelatinized starch in the scope of drug release from compressed wet-granulated systems.

The four excipients—Starch 1500® (S1500), National® 1551 (N1551), Lycatab® PGS (PGS), and Pregeflo® M (PM)—meet current NF specifications for purity. S1500 is considered to be a partially pregelatinized starch and has found uses as an adjunct binder in directly compressible formulations. The other starches—N1551, PGS, and PM—are categorized as fully pregelatinized starches.

EXPERIMENTAL

Materials

The three fully pregelatinized starches—National 1551 (National Starch and Chemical Co., Bridgewater, NJ), Lycatab PGS, and Pregeflo M (Roquette Frères, Lestrem, France)—were used as binders along with a partially pregelatinized starch, Starch 1500 (Colorcon Inc., West Point, PA). The disintegrant, Purity®, 21 (National Starch and Chemical) met USP standards for starch purity. The lubricant, magnesium stearate (Fisher Scientific, Fair Lawn, NJ), was passed over a 20-mesh screen prior to mixing. The active in the model formulation, acetaminophen, was of USP grade (Mallinckrodt Specialty Chemicals Co., St. Louis, MO). All buffer compounds, sodium hydroxide, and potassium phosphate (Sigma Chemicals, St. Louis, MO) were of reagent grade, and the acetaminophen used for the analyti-

cal standard was a USP reference standard (Rockville, MD).

Methods

Starch Evaluation

The four pregelatinized starches—National 1551, Lyacatab PGS, Starch 1500, and Pregeflo M—along with the cornstarch NF, were evaluated for particle shape and surface characteristics using a JEOL scanning electron microscope (JEOL USA, Peabody, MA).

Mixing and Granulating

Acetaminophen, cornstarch NF, and the binder were dry mixed in a Hobart model A-200 mixer (Troy, OH) for 4 min on setting 1. While dry mixing occurred, powder consumption was monitored and recorded every 15 sec. After 4 min the powder was granulated with water using a Masterflex (Cole Parmer, Chicago, IL) peristaltic pump at a flow rate of 60 ml/min. Water was added for 30 sec, then stopped for 1 min to allow for homogeneous wetting of the powder. This procedure was repeated until end point was achieved. During the granulating stages, powder consumption was monitored every 30 sec. The granulation end point was achieved when a 10-point increase in baseline power consumption was reached.

After end point was determined the wet granulates were passed through an 8-mesh screen. The formulations were dried in a Blue M hot air oven (Blue Island, IL) at 50°C on drying trays at a depth of 1 in. for 18 hr. The dried granules were then passed through a Stokes Oscillating Granulator (Stokes–Pennwalt, Warminster, PA) equipped with an 18-mesh screen.

Lubrication

Just prior to compaction, 500 g of granules were mixed with 1% magnesium stearate (prescreened 20 mesh), for 5 min in a Tuburla T2-C mixer (Will A. Bachofen, Basel, Switzerland). At this point in the process the rest of the cornstarch NF was added as this ratio of intragranular:extragranular cornstarch was identified as optimal in terms of tablet friability and disintegration (12).

Compaction

Tablets were compressed on an instrumented Stokes-B2 tablet press equipped with 3/8-in. flat-face tooling. Throughout the entire study only 1 of the 16 stations was set up for compaction. Tablets were compressed to a target weight of 395 mg and to 3 target thicknesses: 4.75, 4.62, and 4.51 mm. Throughout the compaction process maximum compression force was recorded. The average values of 10 compaction events were used to estimate the compaction force at each press setting.

Postcompactional Tablet Tests

Tablet thickness was evaluated using a Mitutoyo hand-held dial calliper (Tokyo, Japan), and tablet hardness was determined using a Erweka Model TBT tablet hardness tester (Milford, CT). The average of 10 tablets was used to estimate tablet thickness and hardness at each press setting.

Dissolution

The official USP dissolution test for acetaminophen tablets was used to evaluate the four formulations in this study. Using the USP Apparatus 2, Distek Dissolution System 2100 (North Brunswick, NJ), 6 stations at 37°C, dissolution was evaluated in a phosphate buffer pH 5.8 with the paddles rotating at 50 rpm. The tolerance limits set in the USP in this monograph state that no less than 80% (Q) dissolve in 30 min (4). These limits were used as the criteria for a passed or failed dissolution evaluation.

Samples of the dissolution media were taken at 5, 10, 15, 30, 60, and 90 min. These samples were filtered using a Gelman Supor Model 450, 0.45-μm membrane filter system (Ann Arbor, MI). Samples of the filtered dissolution media were diluted 25 times in order to obtain ultraviolet (UV) absorbance in the linear region. At a wavelength of 242 nm the absorbance of the samples was compared to that of known concentrations of acetaminophen (USP Reference Standard). All UV analysis was performed on a Hewlett–Packard (Corvallis, OR) Model 8145A diode array spectrophotometer.

Dissolution data were analyzed using an estimator of percent dissolved at 30 min and dissolution efficiency (DE) from 0 to 30 min. Dissolution efficiency was calculated using Eq. (1).

$$DE = \int y dt \div 3000 \quad (1)$$

where DE (dissolution efficiency) is a function of the area under the percent dissolved versus time plot from

0 to time t, divided by the area under the same curve if dissolution was complete and instantaneous (3000). The use and limitations of dissolution efficiency in characterization of dissolution performance have been described previously (13,14). Recent applications of this method in the study of drug release from directly compressible tablets and solid dispersions of polyethylene glycol have been described. (15).

RESULTS AND DISCUSSION

Acetaminophen is a difficult compound to compact into suitable tablets when incorporated into tablet formulations at high percentages. The model system chosen contains acetaminophen at 82% w/w, resulting in a system which is extremely difficult to compact successfully. Its elastic nature provides for a good model to illustrate binding effects of the four brands of pregelatinized starch used in this evaluation.

In order to minimize tablet disintegration effects on drug dissolution, cornstarch NF was used both intra- and extragranularly. This addition provided for effective tablet disintegration which is illustrated by the absence of any lag time in the dissolution profiles for the PGS, N1551, and the S1500 systems. A minor lag time can be observed for the PM system when compacted to the thinnest target, indicating that at this thickness the delay in dissolution may be partially attributed to a prolonged disintegration time.

The differences between cornstarch NF, and partially and fully pregelatinized starches can be identified by evaluating the scanning electron photomicrographs depicted in Figs. 1–5. Figure 1 depicts cornstarch NF at 500× magnification. The starch granules exist as spheres with a very narrow particle size distribution. These granules are "ungelatinized" and consist of a common molecular ordering.

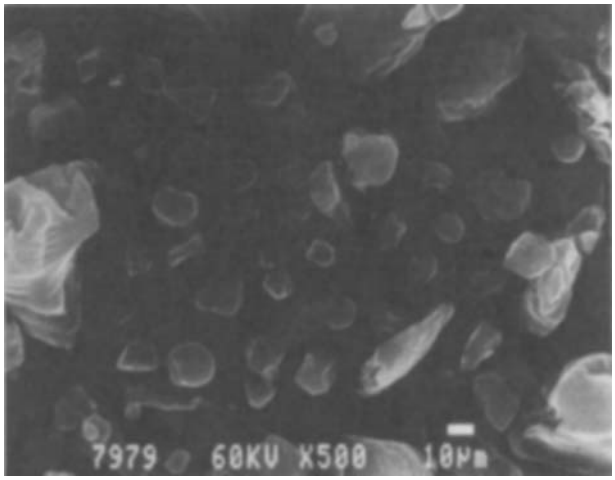

Figure 2. Scanning electron photomicrograph: Starch 1500 (partially pregelatinized starch) (original magnification 500×).

A change in the molecular orientation under heated conditions in an aqueous environment brings about starch gelatinization. For use in pharmaceutical systems these starches are subsequently dried by spray, roller, or extrusion methods. Figure 2 is a scanning electron photomicrograph of a partially pregelatinized starch (S1500) at 500× magnification. Small spherical granules which are ungelatinized, as well as large ruptured granules which are gelatinized, a physical modification, can

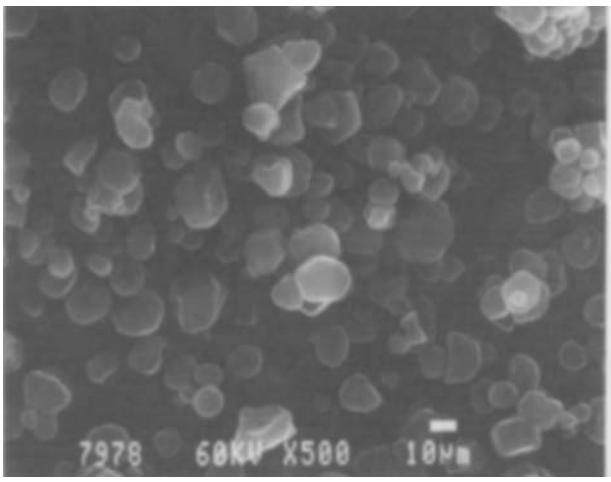

Figure 1. Scanning electron photomicrograph: cornstarch NF (original magnification 500×).

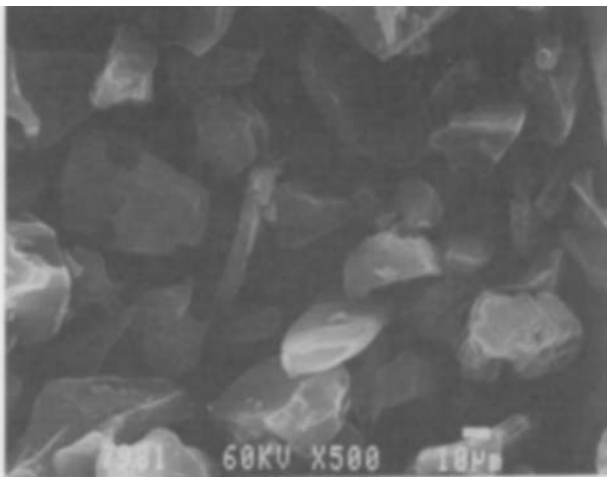

Figure 3. Scanning electron photomicrograph: National 1551 (fully pregelatinized starch) (original magnification 500×).

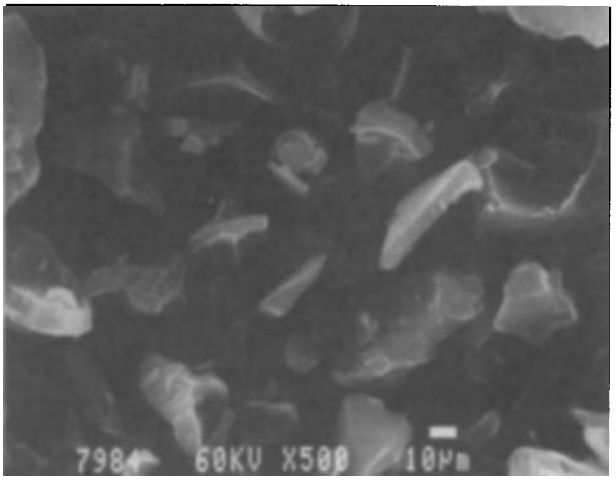

Figure 4. Scanning electron photomicrograph: Lycatab PGS (fully pregelatinized starch) (original magnification 500×).

be observed in the micrograph. Since S1500 has both unmodified starch granules and physically ruptured starch granules, it is considered as a partially pregelatinized starch.

The fully pregelatinized starches can be observed in Fig. 3 (N1551), Fig. 4 (PGS), and Fig. 5 (S1500). These starches have no trace of ungelatinized or unruptured starch granules. The fully pregelatinized starches have particles of very irregular shape. The micrographs show that N1551 and PM have similar shapes and size distributions. The PGS product appears to have particles which are twice the size of the other starch brands.

The compaction and the tablet data for the systems investigated are presented in Tables 1–4. Tablet weight

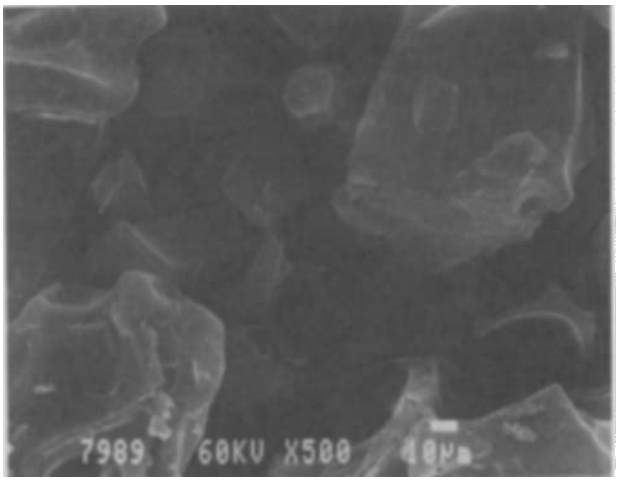

Figure 5. Scanning electron photomicrograph: Pregeflo M (fully pregelatinized starch) (original magnification 500×).

and thickness values for all systems fell close to the target weight of 395 mg and thicknesses of 4.75, 4.62, and 4.51 mm, respectively. These small variations would be expected when compacting tablets on a rotary tablet press like the one used in this study.

Tablet hardness, a measure of the binder's ability to hold the tablet together through interparticulate bonding and to withstand the strains of decompaction, ranged from 3–4 kg for the lower compaction forces to 4–6 kg when the systems were compacted to the thinnest target. PM may provide for better tablet bonding when exposed to higher compaction forces as indicated by the highest tablet hardness response at the tablet thickness of 4.55 mm.

The experimental design, a 4 × 3 factorial, used to evaluate dissolution performance, can be observed in Table 5. The two dissolution parameters, $\%T_{30}$, and DE_{30}, were chosen to correspond with the time limit for dissolution outlined in the acetaminophen tablet monograph in the USP/NF which states that 80% of Q label amount must be dissolved in 30 min for a successful test. The parameter $\%T_{30}$ allows for a one time point (30 min) comparison while DE_{30} provides for a complete comparison of all time points (0, 5, 10, 15, and 30 min) prior to and including the point required in the USP.

The dissolution profiles of the four systems can be observed in Figs. 6–9. Of the three fully pregelatinized starches evaluated—N1551, PGS, and PM—only PM was shown to be affected by compaction force. This effect is illustrated by the different and decreasing dissolution response for the three target tablet thicknesses studied. The dissolution profiles of the other two fully pregelatinized starches, PGS and N1551, are identical with 100% dissolved before 20 min at all thicknesses and compaction forces investigated. The dissolution profile of the partially pregelatinized starch, S1500, as seen in Fig. 9, indicated no effect of compaction force on dissolution performance; however, a minor difference was observed in the time to reach 100% dissolved, with this system taking 30 min.

The dissolution responses at the compaction forces investigated can be observed in Table 6. For both dissolution responses, $\%T_{30}$ and DE_{30}, PGS and N1551 provided wet-granulated systems which performed equally well in terms of drug release. This was identified by the same Scheffe grouping. The partially pregelatinized starch, S1500, which falls in the same USP monograph as N1551 and PGS, resulted in a system with different drug release characteristics than the fully pregelatinized starches. This was identified by a different Scheffe grouping than the first two brands. PM produced the slowest system in terms of drug release.

Table 1

Compaction and Tablet Responses: National 1551

	Target Tablet Thickness		
	A	B	C
Tablet thickness (mm)[a]	4.72	4.60	4.55
	(0.01)	(0.02)	(0.01)
Tablet weight (mg)[a]	395.9	392.8	398.4
	(4.4)	(3.9)	(2.8)
Tablet hardness (kg)[a]	3.07	4.12	4.92
	(0.31)	(0.21)	(0.17)
Maximum compaction force (kN)[a]	9.94	14.27	20.92
	(0.31)	(0.77)	(0.77)

[a]Mean of 10 determinations; standard deviation in parentheses.

Table 2

Compaction and Tablet Responses: Pregeflo M

	Target Tablet Thickness		
	A	B	C
Tablet thickness (mm)[a]	4.78	4.66	4.55
	(0.02)	(0.03)	(0.04)
Tablet weight (mg)[a]	397.7	395.8	390.4
	(4.7)	(3.3)	(5.4)
Tablet hardness (kg)[a]	3.97	5.57	6.15
	(0.45)	(0.67)	(0.34)
Maximum compaction force (kN)[a]	9.06	11.58	16.46
	(0.30)	(0.79)	(0.82)

[a]Mean of 10 determinations; standard deviation in parentheses.

Table 3

Compaction and Tablet Responses: Lycatab PGS

	Target Tablet Thickness		
	A	B	C
Tablet thickness (mm)[a]	4.72	4.62	4.55
	(0.04)	(0.03)	(0.04)
Tablet weight (mg)[a]	387.6	394.1	389.8
	(4.1)	(10.4)	(1.5)
Tablet hardness (kg)[a]	3.17	4.57	5.37
	(0.20)	(0.44)	(0.43)
Maximum compaction force (kN)[a]	10.13	14.46	17.82
	(0.57)	(0.63)	(0.84)

[a]Mean of 10 determinations; standard deviation in parentheses.

Table 4

Compaction and Tablet Responses: Starch 1500

	Target Tablet Thickness		
	A	B	C
Tablet thickness (mm)[a]	4.75	4.60	4.50
	(0.03)	(0.04)	(0.04)
Tablet weight (mg)[a]	401.5	394.9	400.0
	(4.7)	(7.6)	(4.0)
Tablet hardness (kg)[a]	4.15	5.20	5.90
	(0.21)	(0.33)	(0.21)
Maximum compaction force (kN)[a]	10.72	14.19	17.81
	(0.68)	(0.76)	(0.91)

[a]Mean of 10 determinations; standard deviation in parentheses.

Table 5

Experimental Design

	Binder											
	National 1551[a]			Pregeflo M[b]			Lycatab PGS[b]			Starch 1500[c]		
Target tablet thickness (mm)	A: 4.75	B: 4.62	C: 4.51	A: 4.75	B: 4.62	C: 4.51	A: 4.75	B: 4.62	C: 4.51	A: 4.75	B: 4.62	C: 4.51

R = binder × thickness × binder thickness
$R_1 = \%T_{30}$
$R_2 = DE_{30}$

[a]Registered trademark of National Starch and Chemical Co.
[b]Registered trademark of Roquette Frères.
[c]Registered trademark of Colorcon, Inc.

Table 6

Dissolution Responses

	$\%T_{30}$[a]			DE_{30}[a]			Scheffe Grouping[b]
	A	B	C	A	B	C	
Lycatab PGS	99.06	100.12	96.84	0.87	0.87	0.86	a
	(1.58)	(1.97)	(0.86)	(0.01)	(0.02)	(0.01)	
National 1551	97.12	96.75	96.79	0.88	0.87	0.87	a
	(0.81)	(0.73)	(1.56)	(0.01)	(0.01)	(0.02)	
Starch 1500	92.87	90.05	90.23	0.88	0.77	0.78	b
	(3.05)	(8.47)	(3.32)	(0.01)	(0.03)	(0.03)	
Pregeflo M	83.56	70.87	61.38	0.72	0.65	0.59	c
	(3.04)	(3.94)	(5.99)	(0.01)	(0.02)	(0.03)	

[a]Target tablet thicknesses: A = 4.75; B = 4.62; C = 4.51.
[b]Same grouping indicates no significant difference.

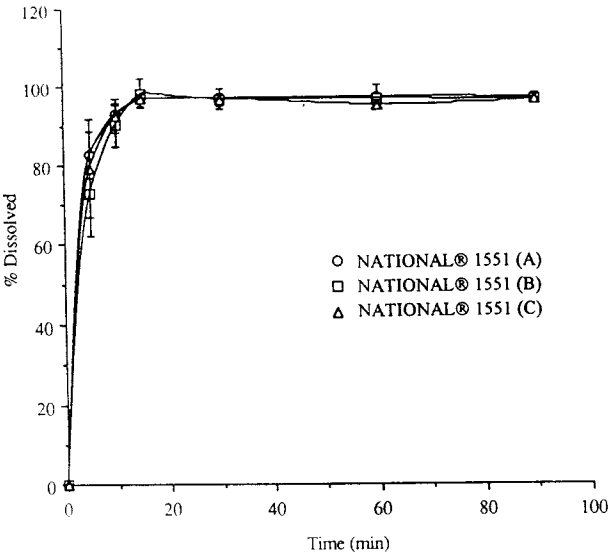

Figure 6. Dissolution profiles of National 1551.

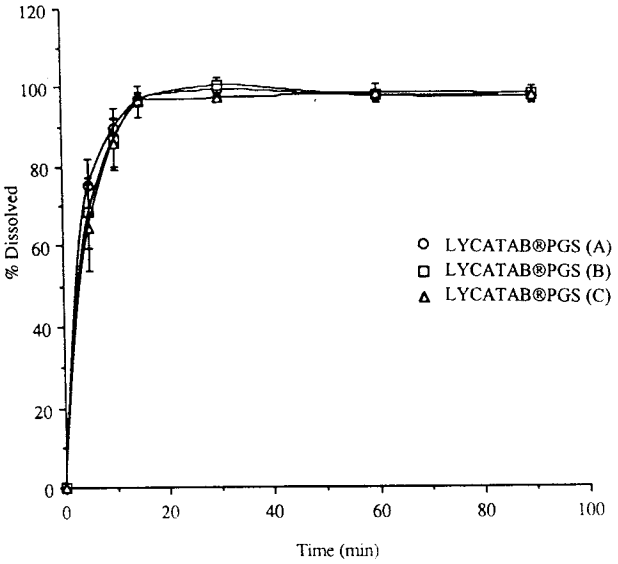

Figure 8. Dissolution profiles of Lycatab PGS.

This system was also the most affected by compaction force, with $\%T_{30}$ values ranging from 83 to 61 and DE_{30} values ranging from 0.70 to 0.59. The other starches were not affected by compaction force, as indicated by only small changes in dissolution values.

The same effect can be observed graphically in the compaction force versus $\%T_{30}$ relationship depicted in Fig. 10. The N1551 and PGS have a similar effect on drug dissolution over the range of compaction forces investigated and show no influence of compaction force on the drug release from the formulation. The partially pregelatinized starch, S1500, produced a system with a lower percent dissolved at 30 min, but like the PGS, and N1551, it was not influenced by compaction force. A clear influence of compaction force on the dissolution performance of the PM system, as measured by $\%T_{30}$,

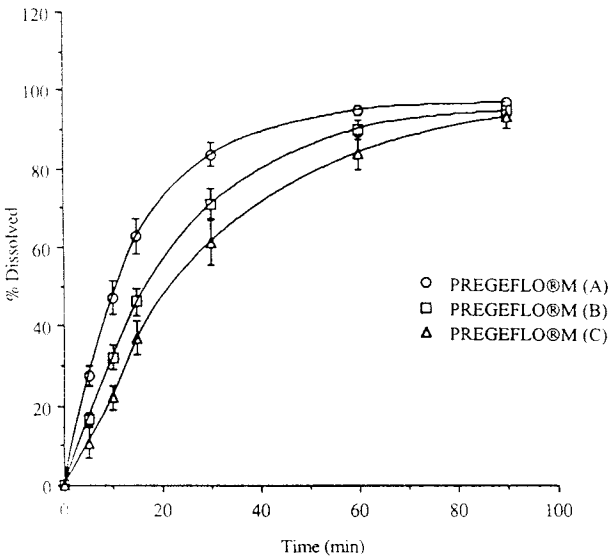

Figure 7. Dissolution profiles of Pregeflo M.

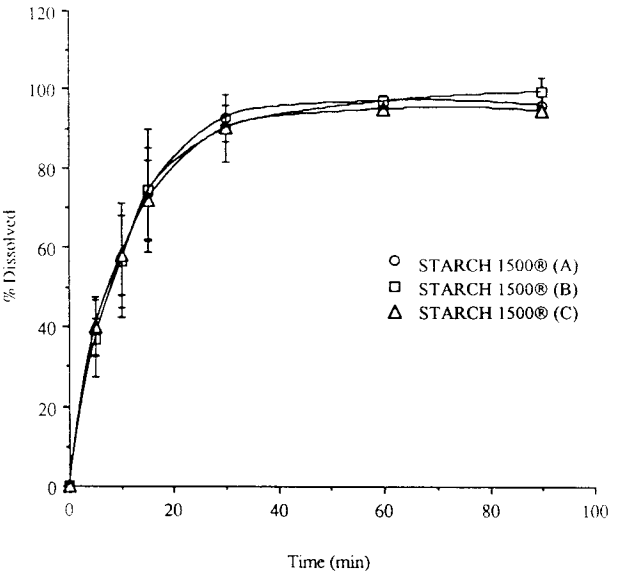

Figure 9. Dissolution profiles of Starch 1500.

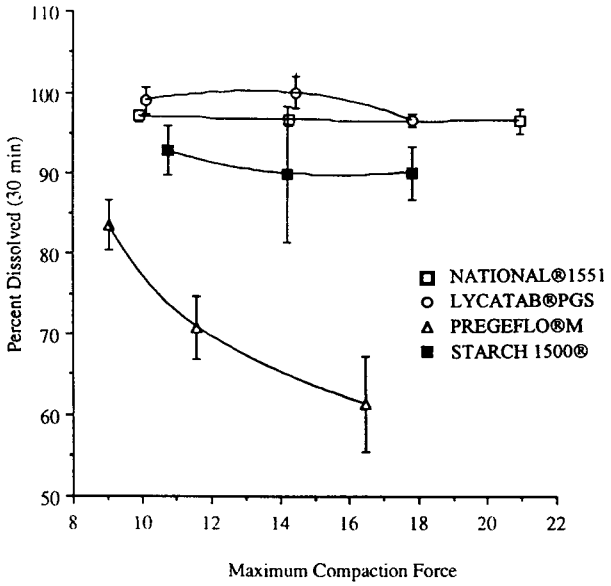

Figure 10. Maximum compaction force vs. percent dissolved (30 min).

can be observed over the range of forces used in this study.

The effect of tablet hardness on dissolution performance was also identified and can be observed in Fig. 11. For the three pregelatinized starches—N1551, PGS, and S1500—all of which meet USP/NF specifications, a different effect of compaction force on tablet hardness was found; however, tablets produced in similar hardness ranges had only minor variations in dissolution performance. In this relationship, PM was found to influence dissolution over the range of tablet hardnesses identified.

To obtain an estimate of total dissolution performance as a function of compaction force and tablet hardness, DE_{30} was plotted as a function of compaction force and tablet hardness; see Figs. 12 and 13, respectively. When evaluating dissolution efficiency, dissolution performance—which was similar when only comparing $\%T_{30}$—is shown to be different when time all points, 30 min and earlier, are used. This is illustrated by the differences in DE_{30} for N1551, PGS, and S1500 above 14 kN and at hardnesses above 5 kg. A delay in dissolution performance as measured by DE_{30} was observed for the PM system as a function of compaction force and tablet hardness.

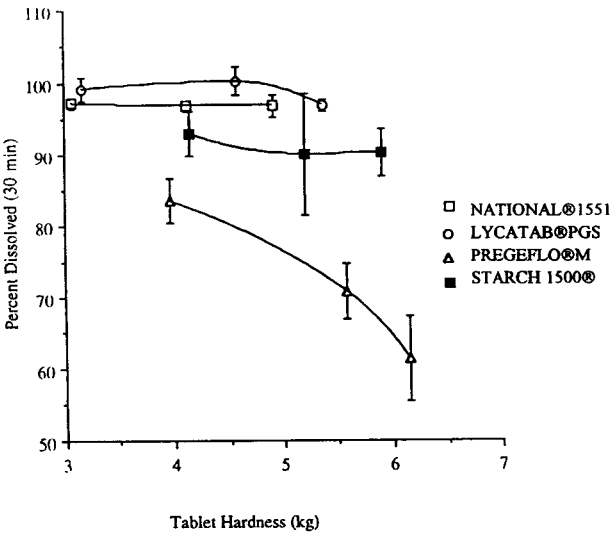

Figure 11. Tablet hardness vs. percent dissolved (30 min).

CONCLUSION

This study illustrates functional differences between four pregelatinized starches—National 1551, Lycatab PGS, Pregeflo M, and Starch 1500—all of which meet current USP/NF standards for purity. In the model acetaminophen system evaluated, the responses of $\%T_{30}$ and DE_{30} were shown to be influenced by compaction force for Pregeflo M, and even though the Starch 1500 system was not affected by compaction force, it did influence dissolution performance of acetaminophen in

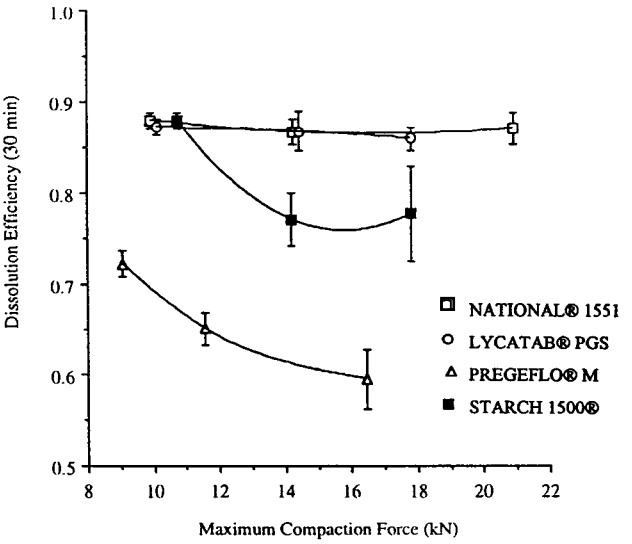

Figure 12. Maximum compaction force vs. dissolution efficiency (30 min).

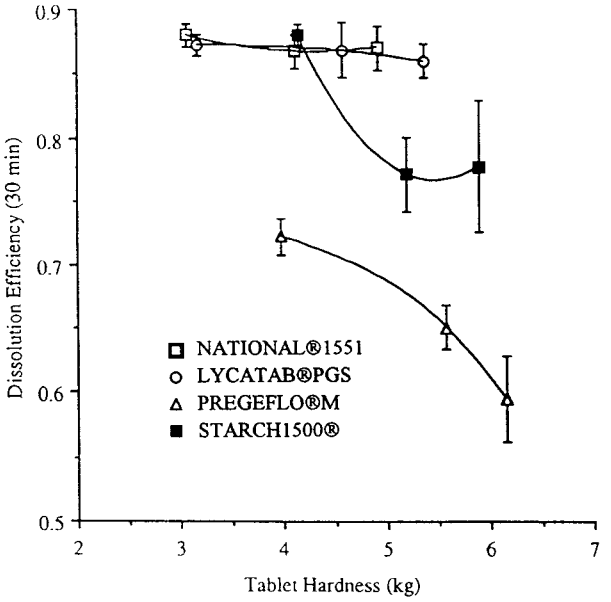

Figure 13. Tablet hardness vs. dissolution efficiency (30 min).

the model system studied. In an immediate-release tablet prepared by wet granulation, both National 1551 and Lycatab PGS would provide a system with the best dissolution performance and also would not be influenced by compaction force. Minor delays in dissolution performance were observed in the system prepared using the partially pregelatinized starch, Starch 1500, but these delays were not increased under high compaction forces. The dissolution data presented show the importance of functionally relevant compendial specifications for pregelatinized starches. The current compendial specifications may completely address the purity of pregelatinized starches, but as to their performance as binders and effect on drug release from compresssed tablets, the fully pregelatinized starches—National 1551 and Lycatab PGS—produced systems with different properties than the partially pregelatinized Starch 1500 system. This study illustrates the importance of both chemical purity, as currently identified in the USP/NF, and functionality of pharmaceutical excipients in overall compendial standardization with goals in international compendial harmonization.

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