Evaluation of Preflo® Modified Starches as New Direct Compression Excipients. I. Tabletting Characteristics

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This investigation evaluated some new (Preflo®) and existing commercially available (Starch 1500, Star Tab) modified starches as direct compression excipients. Preflo® corn starches (CH-10, CH-20, CH-30) and Preflo® potato starches (P-250, PI-10, PJ-20) were evaluated and compared with respect to their pharmaceutical properties such as particle size, density, flowability, friability, and compression properties. Preflo® starches showed a high bulk density and good flowability. Preflo® corn starches and Star Tab formed harder tablets than Preflo® potato starches and Starch 1500. Data from the Athy–Heckel plots indicated that the Preflo® starches are soft materials and, unlike Starch 1500, undergo plastic deformation. Tablets containing acetaminophen were also compressed with the starches and disintegration and dissolution studies were conducted. Starch 1500 tablets disintegrated in 3.5 min, whereas none of the Preflo® starch tablets disintegrated in 30 min. While complete acetaminophen release occurred in 25 min from Starch 1500 tablets, the drug dissolution time from Preflo® starch tablets varied from 4 to 12 hr, indicating a potential use for some of these starches in solid oral modified-release dosage forms.

KEY WORDS: modified starches; tablet diluents; direct compression; compression properties; acetaminophen.

INTRODUCTION

The concept of direct compression utilizing a direct compression diluent has received much attention in the past decade (1–5), although the process has been utilized for the last 25 years. In the process of selecting an excipient as a direct compression diluent, a number of tests such as evaluation of particle size distribution, flowability, density, compressibility, compression parameters, etc., should be performed (6–13). The purpose of this investigation was to evaluate Preflo modified corn and potato starches as direct compression diluents with respect to their physical and tabletting properties and compare them with commercially available direct compression starches, Starch 1500 and Star Tab.

MATERIALS AND METHODS

The materials were used as received from the suppliers. The materials used in this study were Preflo modified waxy corn (pregelatinized, cross-linked, and stabilized) starches CH-10, CH-20, and CH-30 (Roquette Corporation, Gurnee, IL), Preflo modified potato (pregelatinized, cross-linked, and stabilized except for P-250, which was only pregelatinized) starches P-250, PI-10, and PJ-20 (Roquette Corporation, Gurnee, IL), Starch 1500 (Colorcon, Inc., West Point, PA), Star Tab (Crompton & Knowles Corporation, Pennsauken, NJ), glyceryl behenate (Compritol 888, Gattefossé Corporation, Elmsford, NY), and acetaminophen USP (Amend Drug and Chemical Co., Irvington, NJ).

Particle Size Determination

A weighed amount (100 g) of each starch was placed on the first sieve of a nest of U.S. Standard 8-in. stainless-steel sieves (mesh size, 60, 80, 100, 120, 170, 200, 230, 270, 325, and 400) arranged in order of decreasing aperture size. The nest of sieves was clamped onto a Meinzer sieve shaker (Model 18480, CSC Scientific Co., Fairfax, VA) and then subjected to vibrations for 20 min (till no apparent change in weight was observed), at a speed setting of 6 U. After sieving, the amount retained on each sieve was ascertained and the distribution of the particle size was plotted on log-probability axes.

Angle of Repose

The angle of repose (θ) for each powder was determined by placing 30 g (no change in the angle of repose was observed with a greater amount) of the powder in a funnel (with an orifice diameter and a base diameter of 1.0 and 6.5 cm, respectively). The tip of the orifice of the funnel was fixed from the ground horizontal surface and the powder was allowed to flow only under the force of gravity. The angle of repose was calculated from Eq. (1),

$$\tan \theta = \frac{h}{r} \quad (1)$$

where h is the height of the pile of powder and r is the radius of the base of the cone. The angle of repose was calculated from a mean of three determinations.

Scanning Electron Microscopy (SEM)

The powder samples were sputter-coated with gold–palladium alloy (60-nm thickness) and observed under a JEOL scanning electron microscope (Model JSM 840, Dallas, TX) in order to examine their surface characteristics and scanning electron photomicrographs were taken.

Density, Porosity, and Percentage Compressibility

The powder was gently poured into a 100-cm^3 graduated cylinder to a total volume of 90 cm^3. The bulk density was computed using Eq. (2).

$$\text{Density} = \frac{\text{Weight (g)}}{\text{Volume (cm}^3\text{)}} \quad (2)$$

For ultimate tap density, the cylinder was tapped over a

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0.5-in. vertical drop, using a Vanderkamp Tap Density Tester (Model 10705, VanKel Industries, Inc., Edison, NJ), until no measurable change in the volume was observed. Equation (2) was used to calculate the ultimate tap density. True density was determined using a multivolume pycnometer (Model 1305, Micromeritics Instrument Corporation, Norcross, GA). At least three readings were taken for each density determination and the mean value was computed.

Porosity of the powders was calculated from the density data using Eq. (3).

$$\text{Percentage Porosity} = \left[1 - \frac{\text{Bulk Density}}{\text{True Density}}\right] \times 100 \quad (3)$$

The percentage compressibility of the powders was calculated using Carr's index (14) as shown in Eq. (4).

$$\%\ \text{Compressibility} = \left[1 - \frac{\text{Bulk Density}}{\text{Ultimate Tap Density}}\right] \times 100 \quad (4)$$

Tablet Compression

In the first compression study, the starches were compressed to form tablets (300 mg) on an instrumented high-speed rotary press (Model HT-AP18SS-U/I.b., Elizabeth-Hata International, Inc., North Huntingdon, PA) at a press speed of 30 rpm using ⅜-in. standard concave punches and dies without lubricant or other excipients at different compression forces of 500, 1000, 1500, 2000, and 2500 kg. The relative density of the plain starch tablets was determined from the geometric parameters, the weights of the tablets, and the true density of the starches.

In a second study, the starches were blended initially with 20% acetaminophen USP (a poorly compressible drug as the active ingredient) for 10 min in a twin-shell blender (Model LB-2636, Patterson-Kelly Co., Inc., East Stroudsburg, PA). Compritol 888 (0.25%, w/w) was subsequently added as a lubricant to the starch–drug mixture and blended for an additional 5 min in the twin shell blender. The mixture was then compressed to form tablets (300 mg) on the Elizabeth-Hata high-speed rotary press at 1000- and 2000-kg compression force using ⅜-in. standard concave punches and dies (area of the punch, 0.7126 cm^2).

Physical tests such as weight variation, thickness, diameter, crushing force (PharmaTest Tablet test system, Model TDH/PTB, Scientific Instrument and Technology Corporation, Englishtown, NJ), and friability (Erweka friabilator TA3, Erweka Instrument Corporation, Heusenstamm, West Germany) were carried out on a random sample of 20 tablets from each batch.

Disintegration and Dissolution

A disintegration apparatus (Erweka Disintegration Apparatus ZT2, Chemical and Pharmaceutical Industry Co., Inc., New York) complying with the specifications of the USP was used for disintegration studies. The disintegration medium used was water maintained at 37 ± 0.5°C. The test was conducted on six acetaminophen tablets compressed at 2000 kg from each starch.

Drug dissolution from various starch–acetaminophen tablets compressed at 2000 kg was determined with a USP XXII Dissolution Type II apparatus (Vanderkamp Six Spindle Dissolution Apparatus, VK-6010, VanKel Industries, Inc., Edison, NJ) at 50 ± 1 rpm. The dissolution medium was 900 mL of distilled, degassed water maintained at 37 ± 0.5°C. The samples were analyzed for drug using a UV spectrophotometer (Spectronic 601, Milton Roy Co., Rochester, NY) at 242 nm.

RESULTS AND DISCUSSION

Particle Size Distribution

The particle size distributions of all starches were plotted on log-probability axes. The geometric mean diameters, d_g, were calculated from the graphs as the particle size corresponding to 50% cumulative percentage weight. The geometric standard deviations, σ_g, were calculated from the graphs as particle size at 50% divided by particle size at 16% undersize. The geometric mean diameter, the geometric standard deviation and the correlation coefficient for all the starches are listed in Table I. The geometric mean diameter values, d_g, lie between 50 and 65 μm for all Preflo starches. Starch 1500 and Star Tab have larger geometric mean diameters (88 and 90 μm, respectively) than the Preflo starches. According to the USP definitions of powders based on the

Table I. Physical Properties of All Starches

Starch	Geometric mean diameter d_g (μm)	Geometric standard deviation σ_g	Correlation coefficient of particle size distribution	Angle of repose (deg), mean ± RSD	Bulk density (g/cm^3), mean ± RSD	Ultimate tap density (g/cm^3), mean ± RSD	True density (g/cm^3), mean ± RSD	Percentage compressibility	Percentage porosity
CH-10	50	1.31	0.99	32 ± 0.10	0.53 ± 0.02	0.72 ± 0.00	1.49 ± 0.00	27	64
CH-20	52	1.30	0.97	27 ± 0.03	0.51 ± 0.01	0.73 ± 0.01	1.48 ± 0.00	30	66
CH-30	54	1.29	0.97	31 ± 0.03	0.58 ± 0.01	0.84 ± 0.01	1.49 ± 0.00	31	61
P-250	50	1.33	0.98	36 ± 0.04	0.53 ± 0.02	0.69 ± 0.01	1.51 ± 0.00	24	65
PI-10	65	1.31	0.96	25 ± 0.04	0.51 ± 0.01	0.66 ± 0.01	1.47 ± 0.00	23	65
PJ-20	57	1.36	0.98	28 ± 0.02	0.53 ± 0.01	0.70 ± 0.01	1.48 ± 0.00	25	64
Starch 1500	88	1.42	0.99	22 ± 0.07	0.65 ± 0.01	0.88 ± 0.00	1.48 ± 0.00	27	56
Star Tab	90	1.52	0.97	22 ± 0.08	0.42 ± 0.02	0.59 ± 0.00	1.49 ± 0.00	30	72

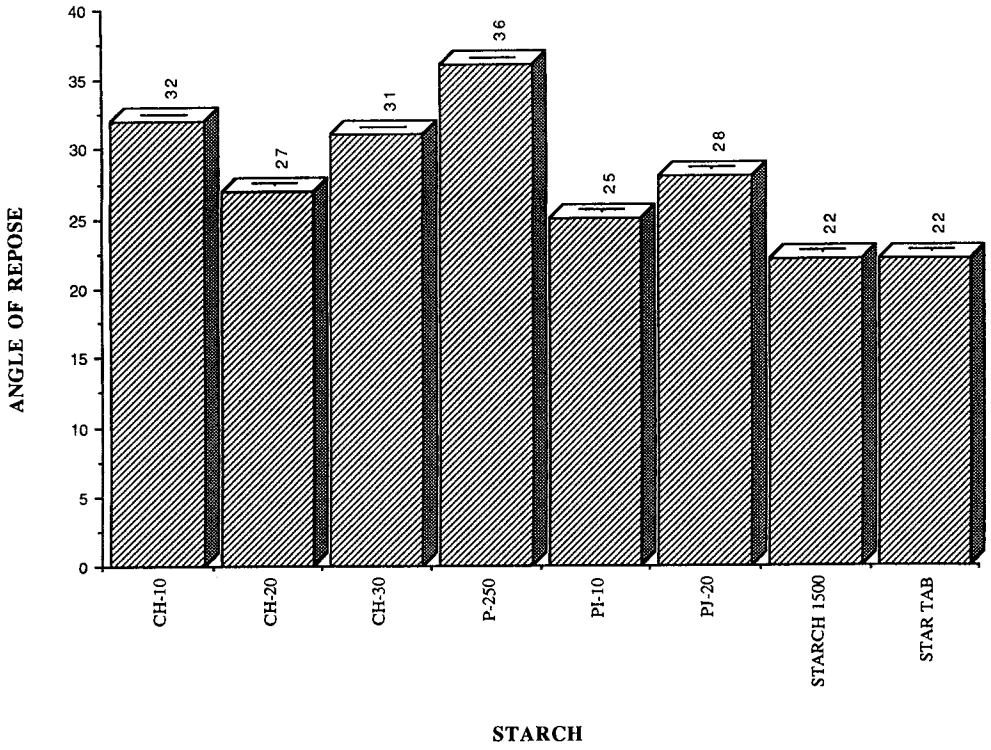

Fig. 1. Angle of repose of all starches (mean ± RSD).

particle size, the Preflo starches can be defined as fine to very fine powders.

Angle of Repose

The angle of repose of a powder is affected by the particle size distribution and it usually increases with a decrease in particle size (15). The values of angle of repose (Fig. 1) obtained for the starches are consistent with the particle size distribution data. Based on the particle size distribution data, Star Tab, Starch 1500, and Preflo PI-10, which have a larger particle size than the other Preflo® starches, exhibited smaller angle of repose values. Moreover, evidence gathered from the SEM showed that the Star Tab and Starch 1500 particles are more spherical in shape, whereas the Preflo starches are smooth, flattened particles with angular edges. Hence, a smaller angle of repose value for Star Tab and Starch 1500 was observed compared to the Preflo® starches. However, the angles of repose of all starches (except P-250) are well below the range of 34 to 48° (15) seen for most pharmaceutical powders and indicate good flowability for the Preflo® starches.

Table II. Compression Properties of Plain Starch Tablets

Compression property	Compression force (kg)	CH-10	CH-20	CH-30	P-250	PI-10	PJ-20	Starch 1500	Star Tab
Thickness (mm)	500	5.02	5.36	5.18	5.48	5.37	5.38	4.76	4.97
	1000	4.67	4.81	4.66	5.09	4.99	4.95	4.33	4.29
	1500	4.37	4.53	4.43	4.70	4.67	4.57	4.26	4.08
	2000	4.29	4.42	4.33	4.66	4.57	4.43	4.23	4.05
	2500	4.27	4.35	4.28	4.56	4.52	4.36	4.24	4.16
Percentage friability	500	0.8	10.2	1.9	32.2	100[a]	23	1.4	0.2
	1000	0.0	0.2	0.0	0.3	4.3	1.4	0.4	0.0
	1500	0.0	0.0	0.0	0.0	0.7	0.1	0.0	0.0
	2000	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0
	2500	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0
Relative density	500	0.66	0.62	0.65	0.57	0.63	0.61	0.74	0.70
	1000	0.75	0.71	0.75	0.65	0.69	0.70	0.84	0.85
	1500	0.82	0.77	0.80	0.72	0.76	0.77	0.86	0.91
	2000	0.85	0.81	0.83	0.74	0.79	0.82	0.86	0.93
	2500	0.86	0.82	0.84	0.77	0.80	0.83	0.86	0.92

[a] All the tablets broke up.

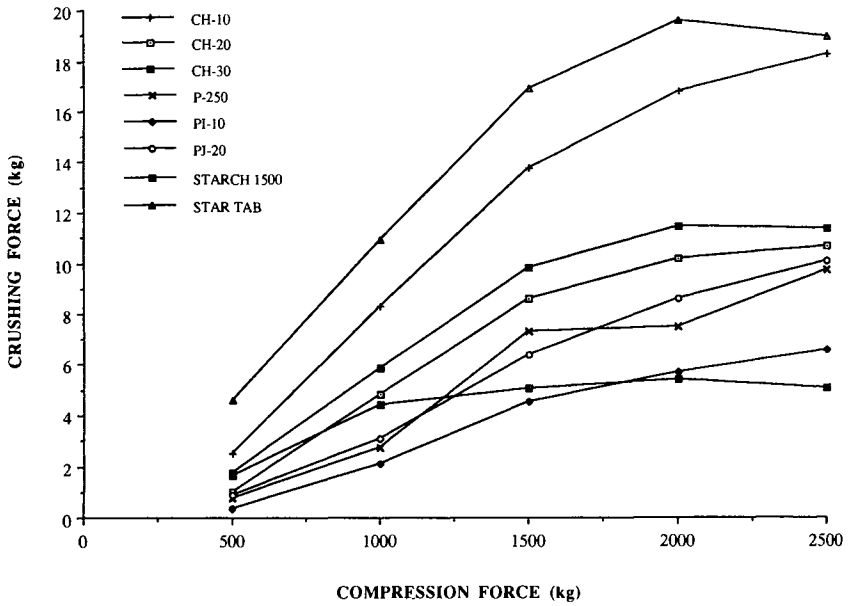

Fig. 2. Effect of compression force on the crushing force of plain starch tablets.

Density, Porosity, and Percentage Compressibility

The bulk density of a powder partially describes its packing behavior. Higher bulk density is advantageous in tabletting because of a reduction in the fill volume of the die. The density, porosity, and percentage compressibility values for all the starches are shown in Table I. The bulk and tap density values of all the Preflo® starches were between those of Starch 1500, which exhibited the highest bulk density (0.65 g/cm^3) and tap density (0.88 g/cm^3), and those of Star Tab, which had the lowest bulk density (0.42 g/cm^3) and tap density (0.59 g/cm^3). The bulk density values of the Preflo® starches were similar to one another due to the similarities in their particle size distribution. However, the tap density values of the Preflo® corn starches were significantly ($P < 0.001$) higher than those of Preflo® potato starches. These differences might be due to different particle shape as observed in SEM photomicrographs and differing percentage of fines as determined by the particle size analysis, both of which significantly affect the packing arrangement of particles. The true densities of all the starches were found to be similar and the values ranged from 1.47 to 1.51 g/cm^3 as shown in Table I.

The percentage porosity values (Table I) were lowest (56%) for Starch 1500, while Star Tab showed the highest porosity (72%). This was because Starch 1500 had the highest bulk and tap density, and Star Tab showed the lowest bulk and tap density.

The percentage compressibility (Table I) calculated from the density data showed a higher compressibility (27% to 30%) for the Preflo® corn starches and Star Tab (30%) and lower values (22% to 24%) for Preflo® potato starches and Starch 1500 (26%), which is consistent with the crushing force data discussed in the next section. In spite of the good flowability of all the starches as suggested by the angle of repose values, the Carr's indexes indicate a poor flow potential for all the starches. This incongruity between the angle of repose and the Carr's index values may be due to the fact that Carr's index is a one-point determination and does not reflect the ease or speed with which cohesion occurs (16).

Tablet Compression

The thickness, friability, and relative density of the tab-

Table III. Calculated Values from Athy-Heckel Plots

Starch	Slope (k) $\times 10^4$	Intercept (A)	Correlation coefficient (r)	Yield pressure P_y (kg/cm^2)	D_0	D_a	D_b
CH-10	3.31	0.92	0.97	3020.6	0.35	0.60	0.25
CH-20	2.77	0.83	0.98	3613.3	0.35	0.57	0.22
CH-30	2.79	0.94	0.97	3588.8	0.39	0.61	0.22
P-250	2.16	0.74	0.98	4620.6	0.35	0.52	0.17
PI-10	2.35	0.87	0.98	4247.3	0.35	0.58	0.23
PJ-20	3.06	0.77	0.98	3262.7	0.36	0.54	0.18
Starch 1500	2.13	1.37	0.84	4700.3	0.44	0.75	0.31
Star Tab	4.87	1.11	0.91	2051.8	0.28	0.67	0.39

Table IV. Compression Properties of Acetaminophen Tablets

Compression property	Compression force (kg)	CH-10	CH-20	CH-30	P-250	PI-10	PJ-20	Starch 1500
Crushing force (kg)	1000	1.03	1.55	1.11	0.37	0.25	0.30	1.25
	2000	4.46	3.25	4.05	1.90	0.65	0.98	2.71
Thickness (mm)	1000	4.73	4.62	4.71	5.10	5.20	4.90	4.44
	2000	4.46	4.55	4.51	4.66	4.65	4.48	4.34
Percentage friability	1000	6.7	4.0	19.6	100[a]	100[a]	100[a]	18.1
	2000	0.4	0.7	0.4	2.2	100[a]	45.4	1.1

[a] All the tablets broke up.

lets compressed from all starches without lubricant or other excipients at different compression forces (500, 1000, 1500, 2000, and 2500 kg) are shown in Table II. Figure 2 shows an increase in crushing force with increasing compression force, except for Starch 1500 and Star Tab, which show a slight decrease in crushing force at 2500-kg compression force. Starch 1500, being a viscoelastic material, showed a decrease in crushing force at 2500 kg, because at higher compression forces a greater proportion of the total deformation is elastic and, therefore, recoverable (17,18). Moreover, Starch 1500 and Star Tab containing larger particles than Preflo® starches might have undergone fragmentation at 2500-kg compression force, creating new surfaces incapable of bonding during the brief compression stage, which increased the elastic rebound and decreased the crushing force (17). Among the Preflo® starches, CH-10 showed the highest slope and greatest crushing force, while PI-10 showed the lowest crushing force value. The thickness values of tablets of all Preflo® starches decreased with increasing compression force (Table II). However, there was an increase in thickness at 2500-kg compression force for Starch 1500 and Star Tab after a decreasing pattern in thickness up to 2000 kg (Table II), indicative of the elastic rebound as mentioned above. Generally, the Preflo® corn starches formed harder compacts than Preflo® potato starches at each compression force. At the higher compression forces, Star Tab gave extensive sticking problems and caused minor damage to the tablet press during the compression cycle. Hence, Star Tab was excluded from the compression studies with acetaminophen to prevent possible damage to the tablet press.

The tablets compressed at 500 kg (except Star Tab) exhibited poor ($\geq$0.8%) friability. Friability was also poor for PI-10 and PJ-20 tablets (4.3 and 1.4%, respectively) compressed at 1000 kg. However, all starches exhibited excellent friability for tablets compressed at 1500, 2000, and 2500. The weight variation tests were satisfactory for each of the tablet batches and complied with the USP XX test limits (<7.5% difference from the mean for 300-mg tablets).

Typical Athy-Heckel plots (19,20) were constructed from the compression data of the starches. The correlation coefficients, values of slope k (i.e., the reciprocal of yield value), and the intercept A (i.e., related to the movement of the particles during the initial stages of compression) obtained from the Athy-Heckel plots are shown in Table III. The correlation coefficients indicate the linearity of the plot. Table III also shows the value for yield pressure (P_y), the relative apparent density (D_0), the total densification due to the filling of the die and particle rearrangement (D_a), and the density contribution from individual particle movement and rearrangement (D_b). The values obtained for Preflo® starches from the Athy-Heckel plots show good correlation coefficients (0.97–0.98), indicating that compression is occurring by plastic deformation. However, lower correlation coefficients for Starch 1500 and Star Tab (0.84 and 0.91, respectively) due to the nonlinearity of the Athy-Heckel plots indicate a mechanism other than (or in addition to) plastic deformation occurring, especially at higher compression forces as noted earlier.

The yield pressure values for Preflo® starch tablets were lower than those of Starch 1500 tablets as shown in Table III. Star Tab was the softest material, more plastic and easily compressible even at low compression forces. Star Tab and Preflo® corn starches were softer materials than Preflo® potato starches and Starch 1500, hence the former made better and harder tablets. Starch 1500 was the hardest material and formed the softest tablets.

The D_a values for the starches were greater than the D_b values, indicating that more densification is occurring by deformation, rather than by particle rearrangement and movement (21). The high D_a value for Starch 1500 may be due to its larger particle size compared to other starches. The D_a value for Star Tab, which was less than Starch 1500 but greater than Preflo® starches, also agreed well with particle size distribution data. The values of intercept A indicate a greater movement of particles during the initial stages of compression for both Starch 1500 and Star Tab compared to all the Preflo® starches. This may be due to the spherical shape and the large particle size distribution of the two commercially available starches. The particle sizes of all the Preflo® starches were smaller than Starch 1500 and Star Tab. Moreover, the Preflo® starch particles were flat and irregular as noted from the SEM.

Acetaminophen tablets compressed with all starches (except Star Tab as noted earlier) at 1000 and 2000 kg were evaluated for thickness, diameter, crushing force, friability, and weight variation. The values for these studies are listed in Table IV. Acetaminophen was chosen as the model drug because of its poor cohesivity and poor fluidity, which makes it a difficult drug to compress into a tablet. The crushing force values obtained for the acetaminophen tablets compressed with the different starches at 1000 and 2000 kg were lower than the corresponding values obtained for plain starch tablets. This was expected, due partly to the lubricant effect of Compritol 888 and to the softening effect of the poorly compressible drug acetaminophen, which acts as a physical barrier between the bonding surfaces of the

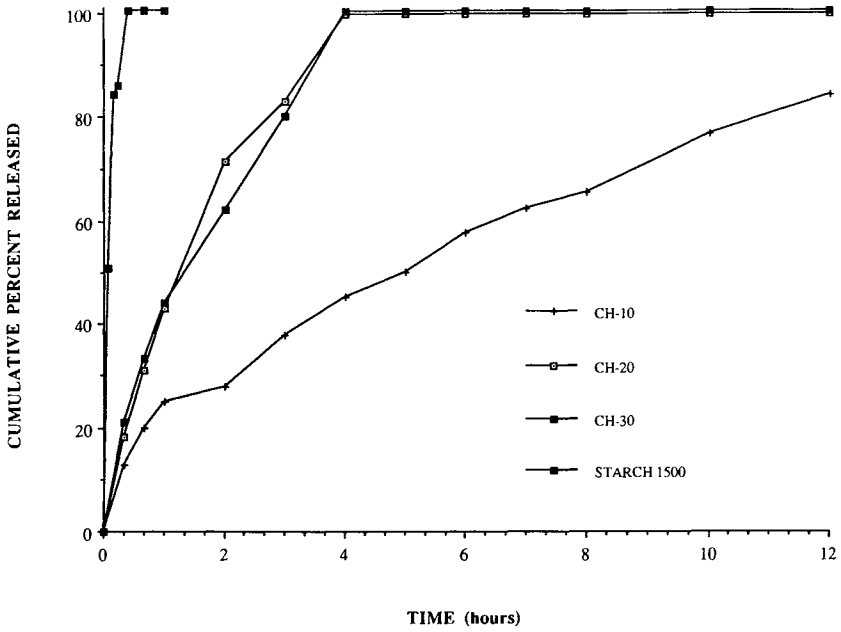

Fig. 3. Release of acetaminophen from Preflo® corn starch tablets and Starch 1500 tablets.

starches. Only the Preflo® corn starches formed fair tablets at 2000 kg. The Preflo potato starches and Starch 1500 formed poor tablets at both 1000 and 2000 kg.

The weights of all the tablets compressed at 1000 and 2000 kg were within the USP XX specified limits. However, only tablets compressed with Preflo corn starches at 2000 kg had a friability less than 0.8%. Other starches compressed at 2000 kg and all starches compressed at 1000 kg exhibited poor friability (Table IV).

Disintegration and Dissolution

The disintegration time of the acetaminophen tablets compressed at 2000 kg was greater than 30 min for all Preflo starches and was 3.5 min for Starch 1500, indicating that the Preflo starches behaved as poor disintegrants.

The dissolution of acetaminophen from tablets compressed at 2000 kg with the different starches showed wide variability (Figs. 3 and 4). The Starch 1500 tablets disinte-

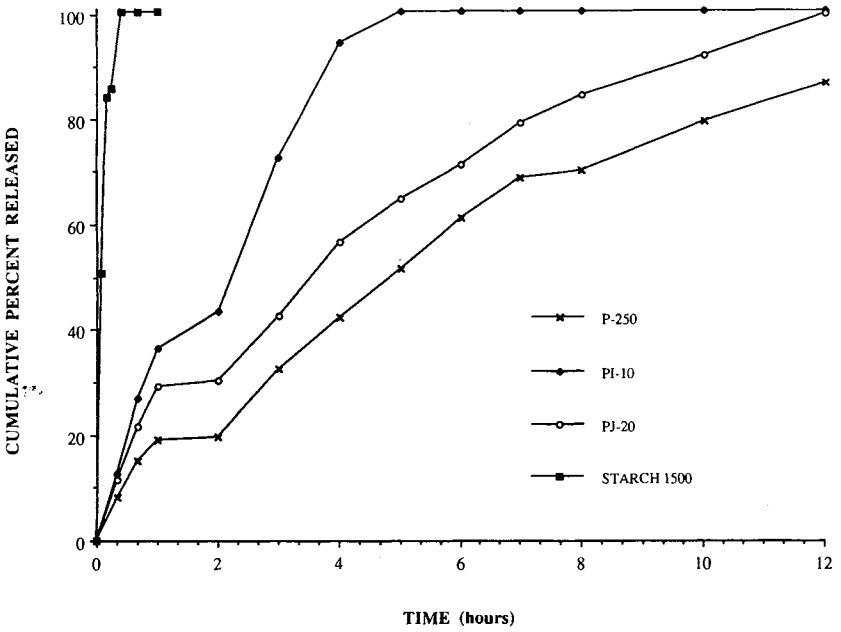

Fig. 4. Release of acetaminophen from Preflo® potato starch tablets and Starch 1500 tablets.

grated within 10 min and released all the drug in 25 min. Complete acetaminophen release occurred for CH-20 and CH-30 (4 hr), PI-10 tablets (5 hr), and PJ-20 tablets (12 hr). However, complete release of acetaminophen from CH-10 and P-250 tablets did not occur within the 12 hr of study. None of the Preflo potato starch tablets and CH-10 tablets disintegrated even after 12 hr, although a few fragments from the periphery were seen floating in the dissolution medium. The CH-20 and CH-30 tablets disintegrated in 3 hr.

The disintegration and dissolution studies show that the Preflo® starches have very poor disintegration properties compared to Starch 1500. However, the poor disintegration property of these starches combined with its ability to release drug for a prolonged time period makes them worthy candidates as direct compression diluents for sustained release formulations.

In conclusion, all the Preflo® starches exhibited good flowability. The Preflo® corn starches made harder tablets than Starch 1500. The Preflo corn starches compressed with 20% (w/w) acetaminophen displayed acceptable tablet compression properties, compared with the commercial Starch 1500. The Preflo® starches showed poor disintegration properties, but the dissolution profiles have indicated a sustained-release potential, which is being investigated.

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