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Comparison of Disintegrant and Binder Activity of Three Corn Starch Products

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Abstract

This study demonstrates the differences obtained when using different corn starch products as both binder and disintegrant in pharmaceutical tablets. Formulations made with Fluftex W, Tablet White and Purity 21 starches were compared. In addition, Avicel PH101 was used in this study as a benchmark component whose properties are well understood.

Four test formulations containing hydrochlorothiazide were prepared by wet granulation. Starch was incorporated in both powder and paste form. All granulations were found to possess similar traits when evaluated based upon geometric mean diameter, particle size distribution, bulk/tap densities, powder flow rate and surface characteristics.

Tablets prepared from these granulations were shown to be similar when evaluated for degree of friability, weight and content uniformity. All starch formulations disintegrated within 30 seconds and produced similar dissolution profiles. Tablets produced with Avicel, however, were found to exhibit significantly longer disintegration times than the starch formulations. In addition, these tablets displayed a dissolution profile that was significantly different than the starch formulations, particularly during the earlier stages of the dissolution process.

When monitoring compression and ejection forces required to produce tablets of the same degree of hardness (≈6kg), Fluftex W and Tablet White granulations were found to use significantly lower forces than the Purity 21 granulation. This may be indicative of Fluftex W and Tablet White's superiority over Purity 21 in terms of binder capacity.

Introduction

Since the introduction of tablets into the pharmaceutical industry, corn starch has been recognized as the one of the most commonly used excipients in the manufacture of tablets (1). The evaluation of starch's disintegrant and binder

activities has been the subject of numerous research publications (2-9). In addition, the means by which starch causes tablets to disintegrate is still an area of interest to many pharmaceutical scientists (3,4,11-13). It is interesting to note, however, that while studies comparing different types of starches have been conducted (3,6,9), no one, as yet, has evaluated the possible differences that may occur when using different brands of the same type of starch. Thus, the purpose of this study is to evaluate the differences in granule and tablet properties that may be obtained when using different brands of corn starch as both binder and disintegrant in the preparation of pharmaceutical tablets.

Materials and Methods

Materials. Fluftex W and Tablet White corn starches were obtained from American Maize-Products Company (Hammond, IN). Purity 21 corn starch was obtained from National Starch and Chemical Company (Bridgewater, NJ). Microcrystalline cellulose (Avicel PH101), hydrous lactose and magnesium stearate were the other excipients used in this study and were received from FMC Corporation (Philadelphia, PA), Mallinckrodt (St. Louis, MO) and Fisher Scientific (Fairlawn, NJ) respectively. The test drug, hydrochlorothiazide, was obtained from Sigma Chemicals Company (St. Louis, MO).

Preparation of Tablets. Four test formulations containing hydrochlorothiazide were prepared by wet granulation (see Table 1). Lactose, hydrochlorothiazide and dry starch, or Avicel PH101, were first blended in an instrumented Kitchen-Aid mixer[1] for 5 minutes. The dry blend was then granulated with the appropriate granulating fluid (starch paste or water) with the power consumption being monitored every 30 seconds. The granulations were sieved through a 6 mesh screen and dryed in a walk-in oven to 1.0% loss on drying. The dried granulations were then sieved through 14 mesh screen and blended with magnesium stearate (40 mesh sieve) in a Turbula[2] mixer at 90 rpm for 3 minutes. Final blends were compressed on an instrumented rotary press[3] equipped with 3/8" flat faced punches to a weight of 400mg and hardness of 6-8kg. Lower punch and ejection forces were monitored during the tableting process.

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1 Model K5-A, Hobart Manufacturing Co., Troy, OH.
2 Model T2C, Will A. Bachofen, Basel Switzerland.
3 Model B-2 Sixteen Station Rotary Tablet Press, Stokes-Penwalt, Warminster, PA.

TABLE 1.

Composition of Tablet Formulations

Material/Formulation	% Weight of Each Material			
	TW	FW	P21	A101
Hydrochlorothiazide	10.0	10.0	10.0	10.0
Avicel PH101	-	-	-	5.0
Dry Starch	4.0 TabletWhite	4.0 Fluftex W	4.0 Purity 21	-
Starch (as 5% paste)	1.0 TabletWhite	1.0 Fluftex W	1.0 Purity 21	-
Magnesium Stearate	0.5	0.5	0.5	0.5
Lactose, hydrous	qs	qs	qs	qs
Distilled water	qs	qs	qs	qs

Granule Evaluation. Each granulation was evaluated for powder flow[4], bulk and tap density[5] and particle size distribution[6]. In addition, scanning electron micrographs were taken at 60x and 600x magnification with a 35° tilt in order to examine surface characteristics of each granulation[7].

Tablet Evaluation. Tablet disintegration was evaluated in 35±2°C distilled water[8]. The weight, hardness[9] and friability[10] of the tablets was also evaluated.

Dissolution Profiles. Dissolution profiles of tablets were obtained in 900ml of 0.1N HCl using USP Dissolution Apparatus I[11]. The amount of drug released into the dissolution media was measured via UV spectrophotometry at 254nm wavelength[12].

4 Model PR1200 Tod-loading Balance, Mettler Instrumentation, Hightstown, NJ in tandem with Cole-Parmer Chart Recorder, Chicago, IL.
5 Model EG80; 50K, J.Engelsmann A.-G., Ludwigshafen, Germany.
6 Central Scientific Sieve Shaker, VanKel Industries, Edison, NJ.
7 Model 1200EX Scanning-transmission Electron Microscope, JOEL USA, Peabody, MA.
8 Model 10-911-71B USP Disintegration Apparatus, VanKel Industries, Edison, NJ.
9 Model TBT Hardness Tester, Erweka Apparatebau, Heusenstamm, Germany.
10 Model TA3 Roche Friabilator, Erweka Apparatebau, Heusenstamm, Germany.
11 Model W-112A USP Dissolution Apparatus, VanKel Industries, Edison, NJ.
12 Model 8451A Diode Array UV Spectrophotometer, Hewlett Packard, Palo Alto, CA.

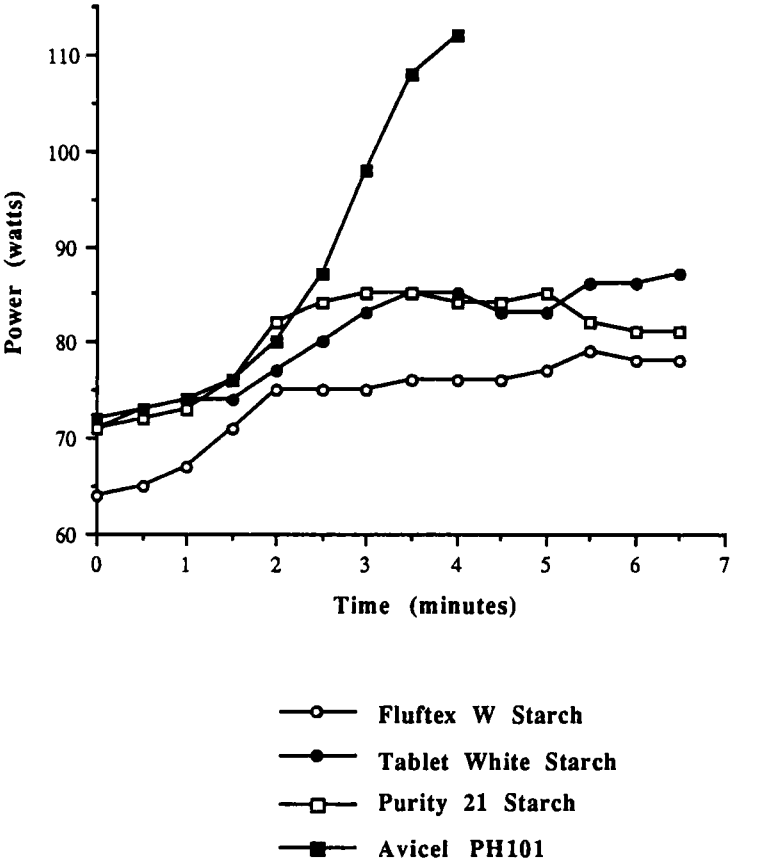

FIGURE 1.

Granulation Power Consumption Profiles

Results and Discussion

Granule Evaluation

a. Power Consumption

Figure 1 illustrates the power consumed by each of the four formulations during the granulation process. The power consumption profile of the Avicel formulation is notably different than that of the starch products. As we know that microcrystalline cellulose differs significantly from starch, this result is certainly not unexpected. Although the Fluftex W granulation appears to have a slightly lower power consumption profile than both the Tablet White and Purity 21

TABLE 2.

Granulation Properties

Property/Formulation	TW	FW	P21	A101
Bulk Density (g/ml)	0.4717	0.4902	0.4296	0.4464
Tapped Density (g/ml)	0.5814	0.6097	0.5682	0.5814
Compressibility Index (%)	11.87	17.65	18.52	23.21
Powder Flow (g/sec)	*10.79 (1.22)	11.28 (1.28)	11.72 (1.33)	11.45 (1.11)
Geometric Mean Diameter (μm)	500.11	424.89	481.04	403.99

* - Mean (Coefficient of Variation %)

granulations, more replicates are needed to determine whether this difference is of statistical significance.

b. Granulation Densities

Table 2 lists the properties of the four granulations including their granulation densities and derived property, Compressibility Index. Compressibility Index is an indicator of the granulation's flowability and is calculated as follows:

$$CI = 1 - (V_{tap}/V_{bulk})$$

where CI = compressibility index
V_{tap} = volume of tapped powder
V_{bulk} = volume of bulk powder

Granulations having CI's less than 15% usually exhibit good flow tendencies while those with a CI value greater than 25% most likely have poor flowability. The Tablet White granulation gave the lowest, and thus, presumably the best, CI values. However, when evaluating this data it is important to keep in mind that replicates of the bulk and tap densities were not performed and the differences noted may actually be insignificant.

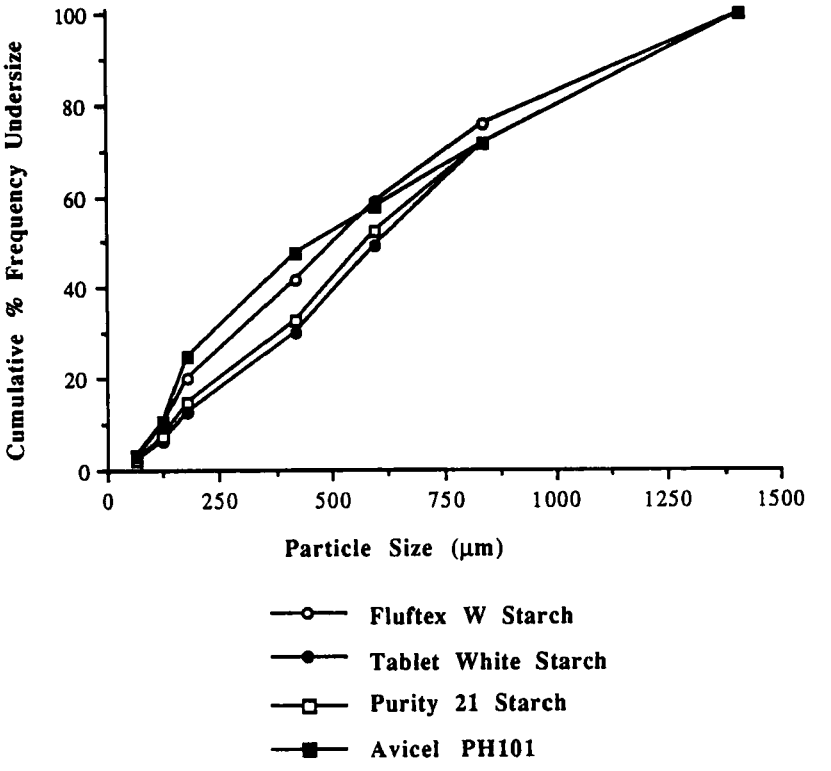

FIGURE 2.

Granulation Cumulative Frequency Plots

c. Powder Flow

Powder flow through a 1.2cm orifice was monitored for each granulation. Triplicate measurements revealed no significant differences between the four granulations in terms of their powder flow. As each granulation was prepared using the same method, this result is not necessarily remarkable.

d. Sieve Analysis

Figure 2 illustrates the results obtained from the sieve analysis of the four granulations. The particle size distributions do not appear to differ significantly from one granulation to the next. This can be attributed to the fact that all granulations were prepared by the same method. The geometric mean diameters of each four granulations ranged from 400-500μm with Avicel having the smallest

diameter and Tablet White Starch the largest. Although this same trend is noted for CI values, the range in particle size does not appear to have affected powder flow (see Table 2).

e. Scanning Electron Micrographs

Each granulation was examined at 60x and 600x magnification with a 35° tilt using a JOEL 1200EX scanning electron microscope. Figures 3a-d are micrographs taken at 60x magnification. No significant differences in surface and shape characteristics of these granules appear to exist when examined at 60x magnification. On the other hand, at the 600x magnification level (Figures 4a-d) the starch particles can clearly be seen in all of the granulations prepared with starch (see arrows). The presence of these intact starch particles is most notable in the Tablet White granulation (Figure 4b). As starch particles primarily undergo elastic deformation, one might expect the intact starch particles to adversely affect the binding properties of the granulation (13). However, as will be discussed further on in this paper, the Tablet White granulation was able to be compressed to sufficient hardness without use of excessive compression forces.

Tablet Evaluation

a. Disintegration Time

Table 3 is a summary of the tablet properties of each of the formulations. All formulations, save Avicel, produced tablets which disintegrated within 30 seconds in 35±2°C distilled water. Although the Avicel granulation produced tablets whose disintegration times were significantly longer than those tablets prepared from the starch granulations, these differences were not found to exist between the individual starch granulations.

b. Friability

All granulations produced tablets having acceptable levels of friability which were below the industry standards of 0.8% (14). In addition, the levels of friability for each formulation do not statistically differ from one another at both the 99 and 95% confidence intervals.

c. Weight Variation

All formulations produced tablets that fell within the USP <731> specifications for weight uniformity. At a level of $p = 0.01$, the degree of weight variation between tablets made from different formulations was not of statistical significance. This is in good agreement with the results obtained from powder flow analysis of these formulations.

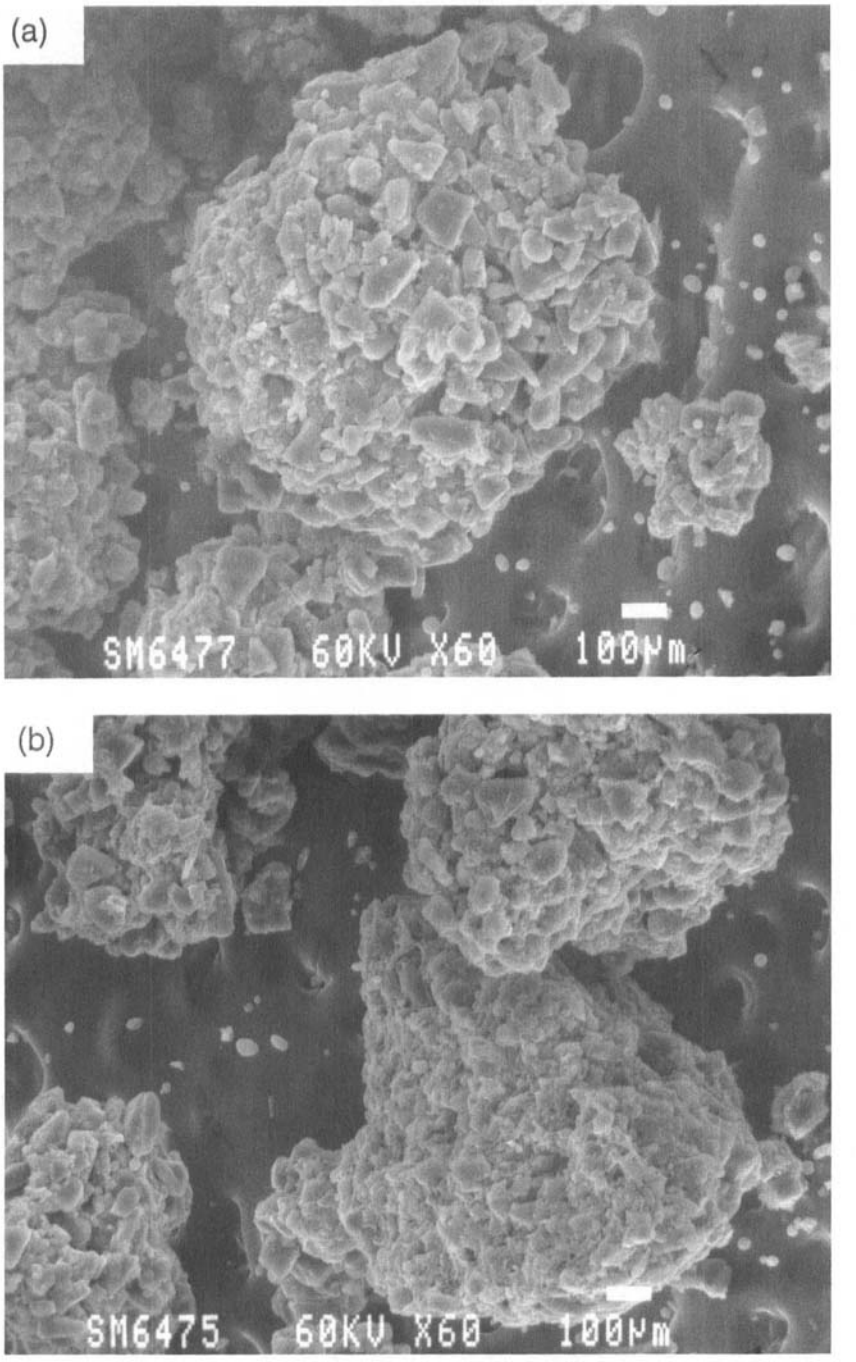

FIGURE 3a-d.

Scanning Electron Micrographs at 60x Magnification and 35° tilt: (a) Fluftex W Starch; (b) Tablet White Starch; (c) Purity 21 Starch and (d) Avicel PH101 Granulations

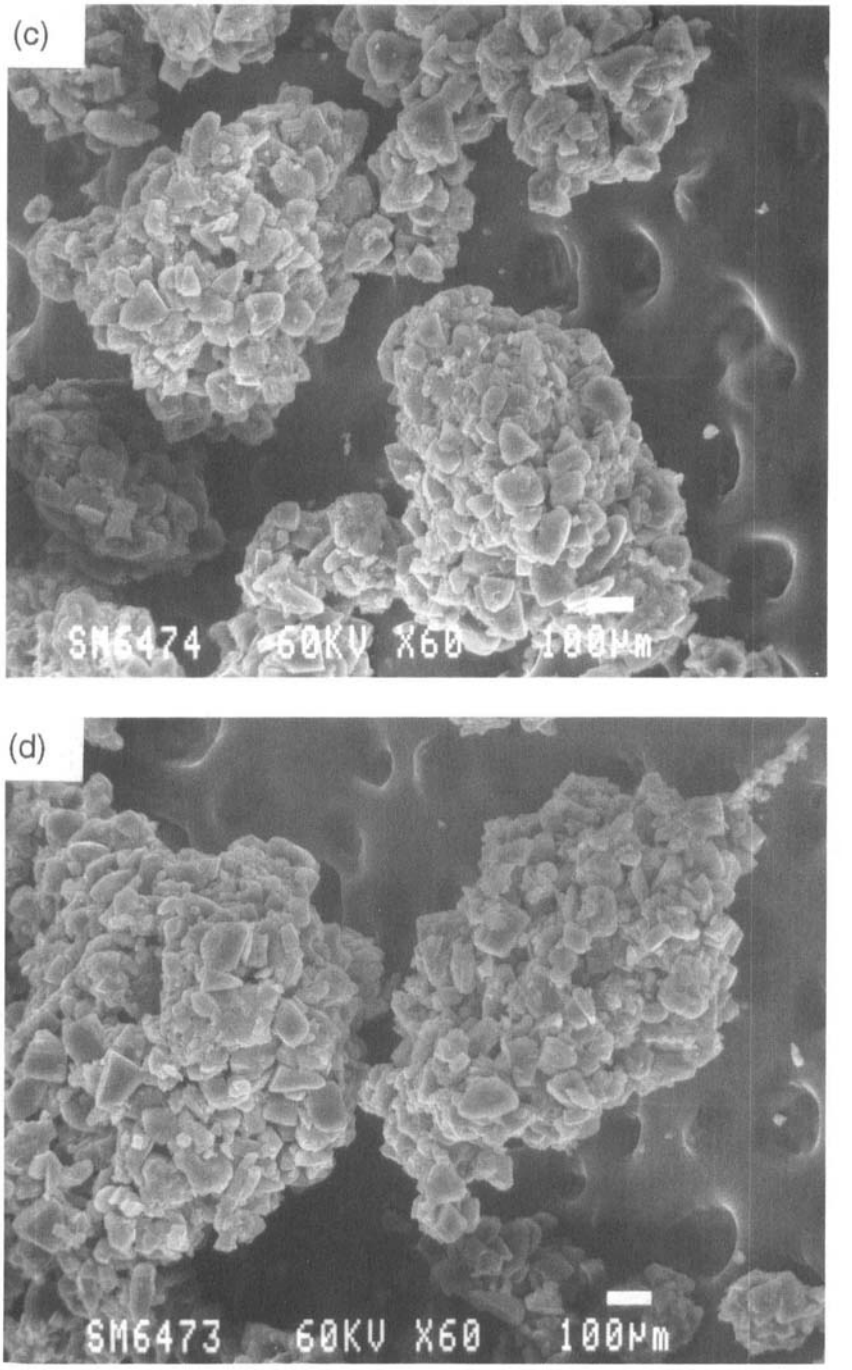

FIGURE 3. Continued

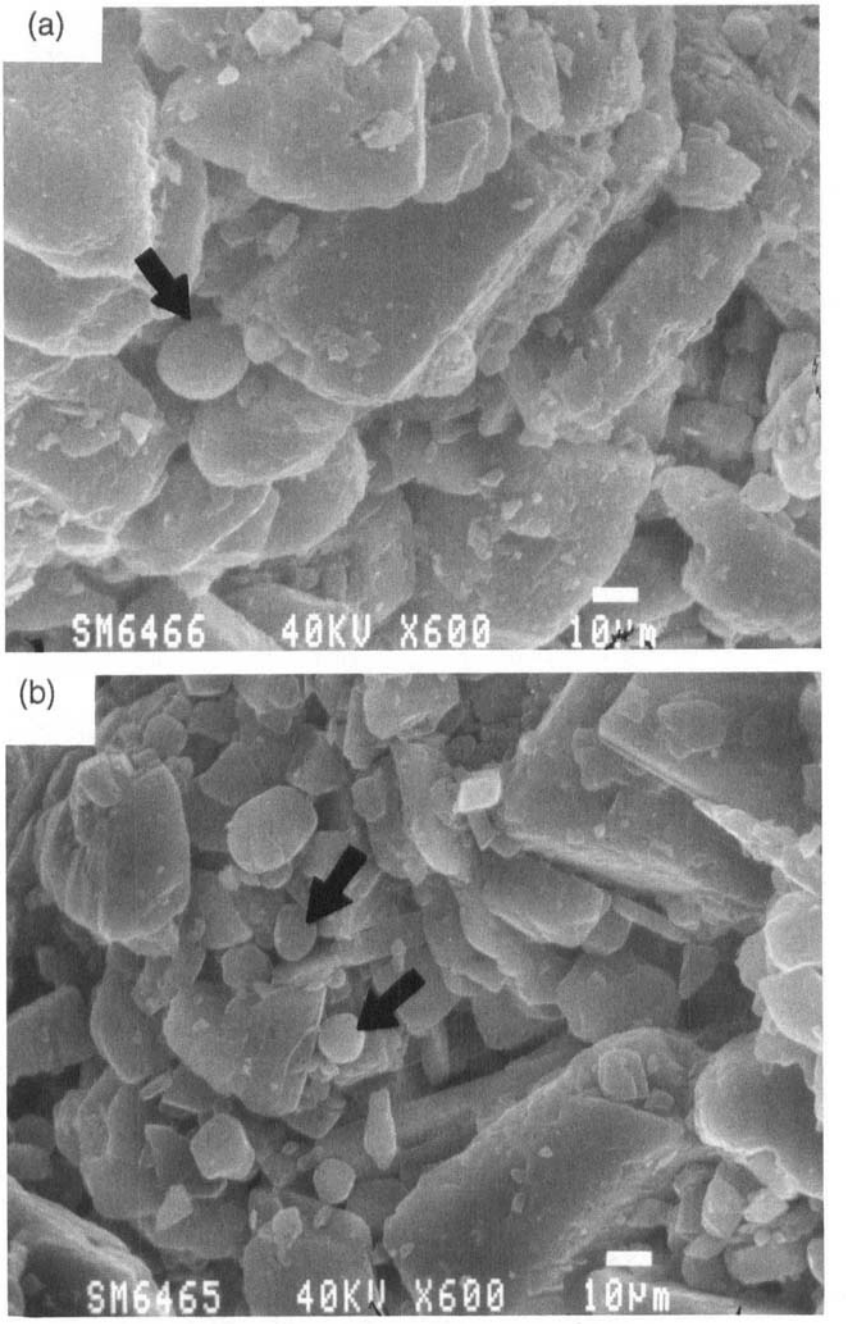

FIGURE 4a-d.

Scanning Electron Micrographs at 600x Magnification and 35° tilt: (a) Fluftex W Starch; (b) Tablet White Starch; (c) Purity 21 Starch and (d) Avicel PH101 Granulations

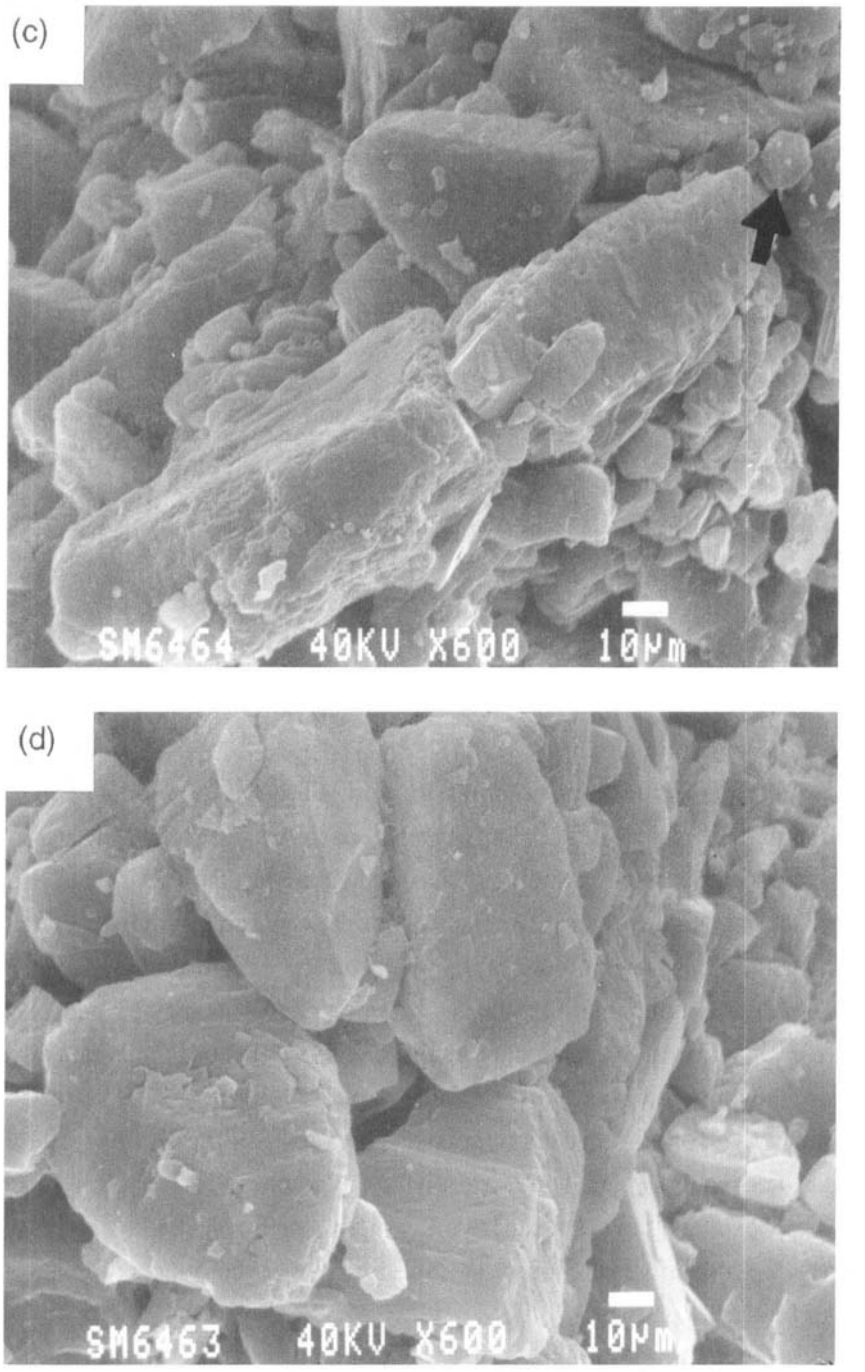

FIGURE 4. Continued

TABLE 3.

Tablet Properties

Property/Formulation	TW	FW	P21	A101
Disintegration Time (minutes)	0.50	0.58	0.57	2.16
Friability (%)	0.706	0.536	0.521	0.611
Weight Variation (%)	1.033	0.719	1.207	0.868
Compression Force (kN)	*19.605 (2.17)	18.353 (3.99)	23.457 (4.36)	20.175 (2.56)
Ejection Force (N)	405.1 (3.27)	365.6 (4.72)	540.9 (4.12)	495.9 (1.93)

* - Mean (Coefficient of Variation %)

d. Compression Force

Table 4 lists the mean compression forces required to produce tablets of the same degree of hardness (≈6kg) and the corresponding Student-Newman-Keul's multi-comparison groupings (significance level of p = 0.01). Different SNK groupings signify that differences exist between granulations. From this table it is shown that the amount of compression force required for Fluftex W is significantly lower than that for all other granulations. This may be indicative of Fluftex W superiority over the other granulations in terms of binder capacity. In addition, the amount of compression force required for Purity 21 is significantly higher than that for all other granulations. The Tablet White and Avicel PH101 granulations, on the other hand, are given the same SNK grouping and thus require approximately the same degree of compression force.

This may be indicative of Fluftex W superiority over the other granulations in terms of binder capacity.

e. Ejection Force

In Table 5 we can see that the differences in compression forces required are translated over into the ejection forces produced during the manufacture of

TABLE 4.

SNK Evaluation of Tablet Compression Force

Formulation	Mean Compression Force (kN)	SNK Grouping
Fluftex W	18.35	A
Tablet White	19.60	B
Avicel PH101	20.16	B B
Purity 21	23.46	C

TABLE 5.

SNK Evaluation of Tablet Ejection Force

Formulation	Mean Ejection Force (N)	SNK Grouping
Fluftex W	365.6	A
Tablet White	405.1	B
Avicel PH101	495.9	C
Purity 21	540.9	D

these tablets. Again, the ejection forces for Fluftex W tablets were the lowest followed by Tablet White and Avicel PH101, with Purity 21 producing the highest ejection forces. Low force of ejection is desirable as it prevents wear and tear on both the tablet press and tooling. The low ejection force exhibited by the Fluftex W formulation may be due to the low compression force required or it may be attributable to some inherent lubricity of this product on its own. Further experiments at varying compression levels are necessary to determine the precise cause of the relatively low force of ejection required for the Fluftex W formulation.

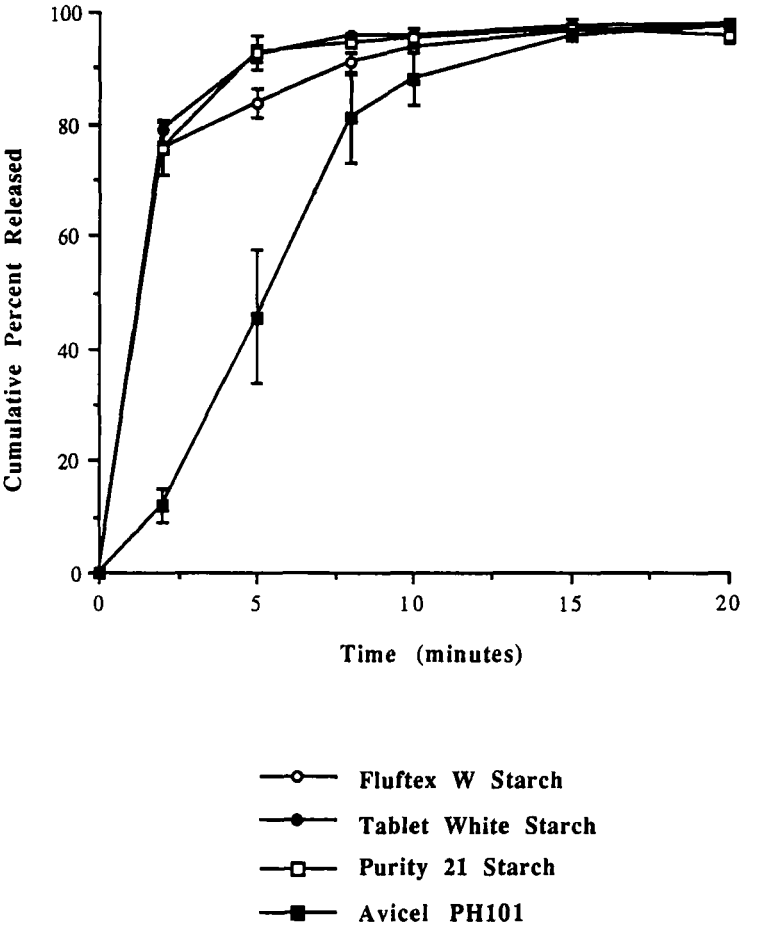

FIGURE 5.

Dissolution Profiles - 900ml 0.1N HCl, USP Apparatus I

Dissolution Profiles

Figure 5 shows the dissolution profiles obtained from tablets produced by each of the four formulations. Tablets produced from the Avicel granulation were found to have significantly (level of $p = 0.01$) lower amounts of hydrochlorothiazide released at the two and five minute time points when compared with tablets produced from the starch formulations. This result was expected, as these tablets were also found to have significantly longer

disintegration times. No significant differences in dissolution profiles were found between those tablets produced from the different starch products.

Conclusions

This study demonstrates that some differences do indeed exist between different corn starch products. These differences are primarily seen as varying degrees of binder capacity for the different products as displayed by compression and ejection forces. Fluftex W starch appears to be the most effective of the three corn starch products evaluated. It is possible that the processing of the corn starch may affect its binding capacity. For instance, Tablet White starch undergoes a bleaching phase during its processing and has shown signs of being less effective as a binder than Fluftex W starch which has not been treated with bleach. Perhaps the bleaching affects, to a small extent, the binding properties of the starch. Further studies designed to specifically evaluate the effects of processing of starch products may provide some interesting results.

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