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Tableting Properties of a Directly Compressible Starch

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Abstract □ Tableting properties of a directly compressible starch are investigated. This starch appears to have many advantages over starch USP with respect to fluidity and compressibility and as such would be useful in direct compression. In addition, compressible starch gives results comparable to USP starch in terms of disintegration time and dissolution rate when used at equivalent levels. The high moisture content of compressible starch does not affect the stability of aspirin when compressed together. Amylose is shown to be the effective component of starch in terms of its disintegrant effect. Doubt is cast on the role of starch grain swelling in tablet disintegration.

Keyphrases □ Starch, directly compressible—tableting properties □ Flow properties—compressible starch □ Dosage forms, compressible starch—high, low drug content □ Stability—directly compressible starch dosage forms □ Dissolution, disintegration—compressible starch tablets

Of the various methods available for the production of tablets, direct compression offers a number of advantages, particularly in regard to ease and economy of manufacture and increased product stability. Since the majority of drugs lack either sufficient bulk, satisfactory compression characteristics, or flow properties, it is necessary to utilize suitable excipients to impart such properties to the tablet formulation. However, the number of filler-binders reported to be useful for direct compression is quite limited. These include spray-dried lactose, anhydrous lactose, microcrystalline cellulose, and amylose (1–5). The need to evaluate new filler-binders is, therefore, obvious. A variety of starch[1] has recently been suggested for use as a filler-binder in direct compression. This starch is claimed to be relatively fluid, and does not require a lubricating agent when compressed alone. The possibility that the directly compressible starch might be a useful filler-binder in direct compression warranted an evaluation of its tableting properties.

A list of typical properties of the compressible starch (6) are summarized in Table I. Chemically, compressible starch does not differ from starch USP.

EXPERIMENTAL

Effect of Environment on Hardness and Disintegration Time—A study of variations in hardness and disintegration time caused by environment was conducted on tablets compressed to a constant thickness by means of a rotary press (Colton model 216) using 1.58 cm. ($^5/_8$-in.) dies and flat-faced punches. The tablets were divided into two groups and stored at a high temperature (60°), and high relative humidity (60% at 40°) for a week and changes in hardness and disintegration time noted. The results are presented in Table II.

Flow Properties—To study the effects of glidants on the fluidity of the compressible starch, two commonly used flow conditioners (pyrogenic silica[2] and hydrated sodium silico-aluminate[3]) were tried. Two-kilogram batches of the glidant and the compressible starch were blended (Patterson-Kelly Twin Shell Blender,

[1] Marketed as Sta-Rx 1500 Starch by A. E. Staley Mfg. Co., Decatur, Ill.

[2] Colloidal silicon dioxide, marketed as Cab-O-Sil by Cabot Corp., Boston, Mass.

[3] Marketed as Zeolex by J. M. Huber Corp., New York, N. Y.

Table I—Typical Properties of Compressible Starch

Cold water solubles	12%
Moisture	12%
Screen analysis	
on No. 8	none
on No. 40	0.2
on No. 80	1.5
on No. 100	0.5
on No. 140	6.0
on No. 170	5.5
on No. 200	11.8
on No. 270	13.0
through No. 270	61.5
Tablet placebo	
hardness	14.0 kg.
friability (wt. loss)	0.07%

model LB 331). No other fillers or lubricants were employed. The blends were then compressed on a rotary tablet machine (Colton model 216) using standard 1.11 cm. ($^7/_{16}$-in.) punches and dies. All settings of die fill and feed frame were held constant. A control batch of the compressible starch was also compressed under identical conditions. One hundred tablet samples were used in determination of weight variation. The results are shown in Figs. 1 and 2, respectively.

Formulations with High-Dose Drugs—Many drugs do not lend themselves to direct compression either due to their compression characteristics or the smallness of their dose. Therefore, one or more filler-binders are added to impart suitable compression characteristics or to increase the bulk of the tablet. When the ratio of drug to filler is small, compressibility is usually a function of the compressibility of the filler alone. Attempts were made to tablet some typical drugs which are known to be difficult to compress directly (5). Efforts were made to use the minimum amount of the filler-binders within the limitations of reasonable tablet size. Drugs chosen for the study included ascorbic acid, sodium sulfathiazole, and sodium *p*-aminosalicylate. The combinations of the drug with the fillers were blended for 15 min. and then directly compressed on a rotary tablet press using 1.11 cm. ($^7/_{16}$-in.) punches and dies. After several trials, the following general formulation for direct compression was found to yield acceptable tablets:

Drug	%
Sodium sulfathiazole, ascorbic acid, sodium *p*-aminosalicylate	60.0
Compressible starch	18.5
Microcrystalline cellulose	18.5
Stearic acid	2.5
Pyrogenic silica	0.5

A crystalline or granular form of the drug was used to improve the flow. The results of direct compression of ascorbic acid have recently been published (7). The characteristics of tablets obtained with the remaining drugs are shown in Table III.

Stability of Moisture-Sensitive Drugs in Direct Compression Formulations—Due to the high concentration of moisture (11–12%) in the compressible starch, a question arises as to the stability of moisture-sensitive drugs, such as aspirin, in the presence of the filler. The aspirin tablets compressed in the previous experiment were used in this experiment. Aspirin tablets containing 20% microcrystalline cellulose were also prepared by direct compression as the 5% moisture content of this filler has also been questioned. Tablets containing 20% cornstarch prepared by slugging were used as a control. The tablets were placed in amber 15-g. (0.5-oz.) square bottles with their caps closed loosely and stored under the following conditions: 40% relative humidity and room temperature (25°); dry heat at 60°; and 75% relative humidity at 60°. For assay, the spectrophotometric method used by Reier was used (8). Dehydrated alcohol was used as a solvent in place of diluted alcohol. The results of this experiment are presented in Table IV.

Table II—Effect of Environment on Hardness and Disintegration Time of Plain Compressible Starch Tablets

Initial		1 Week at 60°		1 Week at 40° and 60% Relative Humidity	
Hardness, s.c.u.[a]	Disintegration Time, sec.[b]	Hardness, s.c.u.	Disintegration Time, sec.	Hardness, s.c.u.	Disintegration Time, sec.
17.6	930	>28	1140	>28	1040
(19.0)[c]	(1.6)[c]	—	(1.52)[c]	—	(1.1)[c]
14.4	795	21.8	880	16.5	771
(18.3)	(0.9)	(16.0)[c]	(0.57)	(19.3)[c]	(0.5)
8.0	655	13.7	691	11.4	650
(21.0)	(2.7)	(10.7)	(0.82)	(19.8)	(1.5)
3.4	509	8.5	500	7.1	480
(20.3)	(1.5)	(17.5)	(2.10)	(13.5)	(1.2)

[a] Strong Cobb units. [b] USP method without disks. [c] ( ) = coefficient of variation based on a sample of 10 tablets.

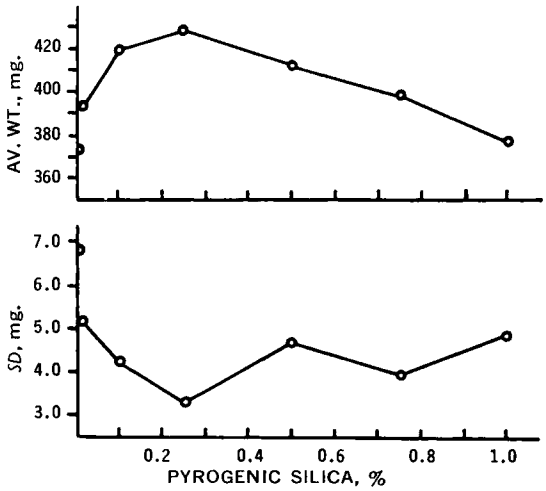

Figure 1—*Effect of pyrogenic silica on the fluidity of compressible starch as evidenced by weight variation.*

Effect of Disintegration and Dissolution—Compressible starch placebos take from 5–15 min. to disintegrate depending upon compression pressure and age. However, it was determined in preliminary experiments that compressible starch could act as a disintegrating agent in lower concentrations. The obvious advantage of utilizing compressible starch made a comparison study of its disintegrating properties of great interest. Tablets were compressed containing 20-mesh aspirin crystals, spray-dried lactose,[4] and unmilled dicalcium phosphate[5] as fillers and 4 and 8% of the following disintegrating agents: cornstarch, USP; compressible starch[1]; amylose[6]; amylopectin[7]; and alginic acid.[8] The addition of 0.75%

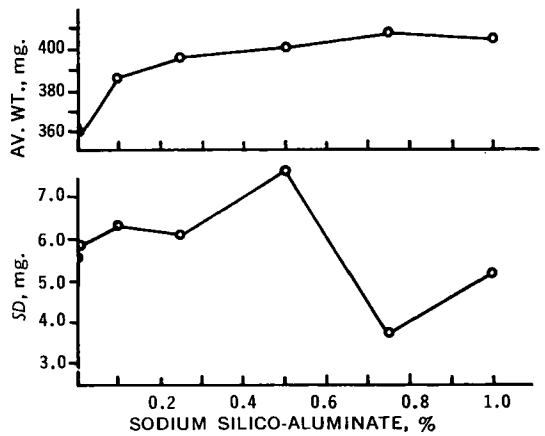

Figure 2—*Effect of sodium silico-aluminate on the fluidity of compressible starch as evidenced by weight variation.*

[4] Lactose USP spray processed, Foremost Dairies, Inc., Burlingame, Calif.
[5] Dicalcium phosphate dihydrate USP Unmilled, Stauffer Chemical Co., Chicago, Ill.
[6] Avebe, Veendam, Holland.
[7] A. E. Staley Manufacturing Co., Decatur, Ill.
[8] Marketed as Landalgine, Edward Mendell Co., Inc., Yonkers, N. Y.

Table III—Characteristics of Some High-Dose Drugs Produced by Direct Compression

Drug	Compressible Starch, %	Cofiller (Microcrystalline Cellulose), %	Stearic Acid, %	Pyrogenic Silica, %	Av. Wt. of Tablet, mg.	Disintegration Time[a]	Hardness, s.c.u.[b]
Aspirin (20 mesh crystals), 80%[c]	20	—	—	—	442 (1.05)[d]	73 sec. (3.9)[e]	8.9 (26.9)[e]
Sodium sulfathiazole (granular), 60%[f]	18.5	18.5	2.5	0.5	383 (1.0)	21 min. (3.0)	8.3 (9.5)
Sodium *p*-aminosalicylate, 60%[g]	18.75	18.75	2	0.5	408 (1.5)	3 min. (2.5)	8.4 (10.0)

[a] USP method without disks. [b] Strong Cobb units. [c] S. B. Penick & Co., New York, N. Y. [d] Coefficient of variation based on a sample of 100 tablets. [e] Coefficient of variation based on a sample of 10 tablets. [f] American Cyanamid Co., New York, N. Y. [g] Miles Laboratories, Elkhart, Ind.

magnesium stearate to the spray-dried lactose and unmilled dicalcium phosphate was necessary for lubrication. Amylose and amylopectin were included in the experiment as they are the two major starch fractions and it was hoped that some knowledge as to the mechanism of action of starch as a disintegrating agent could be gained. Tablets were compressed at two or three hardness levels. The results obtained from the tablets containing 4 and 8% disintegrating agent are shown in Tables V and VI.

In order to make the *in vitro* experiments more meaningful all tablets were formulated to contain 0.1% of amaranth USP. Dissolution tests using the beaker method of Levy and Hayes (9) were carried out and the concentration of amaranth was measured at a wavelength of 520 mμ using a colorimeter (Spectronic 20, Bausch & Lomb, Inc., Rochester, N. Y.). Results obtained from the tablets directly compressed using unmilled dicalcium phosphate are shown in Figs. 3–6.

Table IV—Potency of Aspirin Tablets (Percent) after Storage under Various Conditions

Additive, 20%	100 Days 25°	100 Days 60°	60 Days 60° & 75% Relative Humidity
Starch USP	99.0	93.0	90.6
Compressible starch	99.1	93.1	90.6
Microcrystalline cellulose	99.1	94.5	90.7

Table V—Effect of 4% Disintegrating Agent on Disintegration of Directly Compressed Tablets

Compression Pressure[a]	Disintegration Time, sec. Control	Starch USP	Comp. Starch	Amylose	Amylopectin	Alginic Acid
Dicalcium Phosphate Tablets						
Low 4	>5000 (N.C.)[b]	222 (47.6)[c]	63 (4.9)[c]	83 (16.9)[c]	>5000 (N.C.)	35 (3.2)[c]
Med. 8	>5000 (N.C.)	192 (33.4)	60 (2.4)	42 (2.6)	>5000 (N.C.)	31 (2.1)
High 12	>5000 (N.C.)	126 (10.7)	50 (2.4)	61 (6.1)	>5000 (N.C.)	29 (1.8)
Aspirin Tablets						
Low 3	>5000 (N.C.)	6 (N.C.)	4 (N.C.)	4 (N.C.)	2200 (294)[c]	
High 5	>5000 (N.C.)	6 (N.C.)	22 (N.C.)	8 (N.C.)	3290 (222)	
Spray-Dried Lactose Tablets						
Low 4	690 (18.8)[c]	607 (23.7)[c]	440 (10.5)[c]	820 (60.1)[c]	2100 (76)[b]	
High 8	830 (18.8)	645 (48.0)	500 (8.9)	830 (31.3)	1850 (450)	

[a] Strong Cobb units. [b] N.C. = Not calculated. [c] Standard deviation based on a sample of six tablets.

Table VI—Effect of 8% Disintegrating Agent on Disintegration of Directly Compressed Tablets

Compression Pressure[a]	Disintegration Time, sec. Control	Starch USP	Comp. Starch	Amylose	Amylopectin	Alginic Acid
Dicalcium Phosphate Tablets						
Low 4	>5000 (N.C.)[b]	154 (25.4)[c]	128 (14.2)[c]	138 (14.7)[c]	>5000 (N.C.)	23 (1.8)[c]
Low 8	>5000 (N.C.)	58 (10.6)	64 (9.2)	95 (5.0)	>5000 (N.C.)	23 (2.1)
High 12	>5000 (N.C.)	30 (4.5)	68 (9.6)	113 (17.2)	>5000 (N.C.)	22 (2.1)
Aspirin Tablets						
Low 3	>5000 (N.C.)	~2 (N.C.)	14 (N.C.)	8 (N.C.)	>5000 (N.C.)	
Med. 5	>5000 (N.C.)	~2 (N.C.)	17 (N.C.)	8 (N.C.)	>5000 (N.C.)	
Spray-Dried Lactose Tablets						
Low 4	690 (18.8)[c]	420 (28.8)[c]	360 (11.8)[c]	540 (53.4)[c]	3700 ((764)[c]	
High 8	830 (18.8)	390 (28.8)	360 (17.3)	570 (13.4)	3400 (868)	

[a] Strong Cobb units. [b] N.C. = Not calculated. [c] Standard deviation based on a sample of six tablets.

DISCUSSION

Compressible starch exhibits a fairly high degree of cohesiveness and maintains satisfactory compressibility upon addition of several commonly used active ingredients. By itself, it is self-lubricating and self-disintegrating. However, when active ingredients are added which are not self-lubricating, addition of an auxiliary lubricant is needed. The use of alkaline stearate lubricants noticeably decreases the hardness of tablets containing compressible starch.

Compressible starch can be compressed into tablets with a relatively wide range of hardnesses. As can be seen from Table II, an increase in tablet hardness usually occurs in plain tablets during the first week of storage at elevated temperatures, and is accompanied by a loss of weight due to a loss of moisture. If the compressibility of starch can be partially attributed to hydrogen bonding, this bonding would be strengthened as drying occurs.

This increase in hardness is reflected in an increase in disintegration time for the elevated temperature samples which is not evident in the room temperature samples. The increase in disintegration time does not appear to be of a serious nature.

The tablets stored at 40° and 60% relative humidity also exhibited a loss in weight, averaging around 3%. The tablets tended to harden slightly but there was little or no effect on disintegration time. As expected, the tablets tended to swell slightly in a humid environment which was evidenced by a slight increase in thickness.

Although compressible starch is free-flowing and forms tablets with a fairly uniform weight, its fluidity is still not adequate for high-speed compression. The results in Fig. 1 show that pyrogenic silica definitely improves fluidity and this effect is evident in increased die fill. As the concentration of the pyrogenic silica is increased from 0.01 to 1%, the standard deviation gradually decreases, reaching a minimum at 0.25% and then rising again.

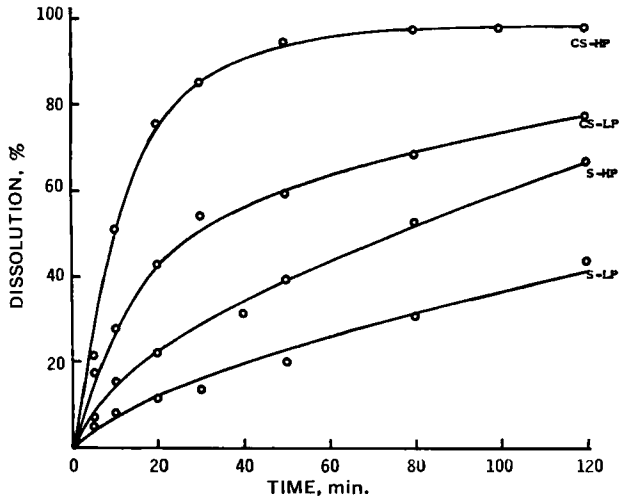

Figure 3—*Effect of compression pressure on dissolution of amaranth from directly compressed calcium phosphate tablets containing 4% starch or compressible starch. Key: CS = compressible starch; S = starch USP; HP = high pressure (12 s.c. units); LP = low pressure (4 s.c. units).*

Simultaneously with the decrease in standard deviation, the average weight of tablets reaches its peak at the 0.25% level of the glidant and then tends to taper off as the concentration of the glidant is increased. As expected, the change in tablet hardness parallels the change in tablet weight. The additions of the glidant beyond the 0.25% level caused no further increase in tablet weight but rather resulted in a decrease. Standard deviation showed uniform improvement over the control of all concentrations of the glidant. These results are almost identical to those obtained by Augsburger and Shangraw in work with microcrystalline cellulose and illustrate again the relatively low concentrations of pyrogenic silica needed for optimum fluidity (10). Gold *et al.* have also shown that optimum glidant concentration is less than 0.5% (11). The continued use of higher concentrations in industry may be due to tradition or lack of proper blending of the glidant. Tablet granulations with a larger particle size might even require a lower concentration. However, in most cases where glidants have been used, their effects are masked by the presence of lubricants needed for die ejection.

The effect of sodium silico-aluminate on the fluidity of the compressible starch follows a somewhat different pattern. As the concentration of the glidant is gradually increased, the fluidity is progressively improved and seems to reach an optimum level at a concentration of 0.75% of the sodium silico-aluminate and then levels off.

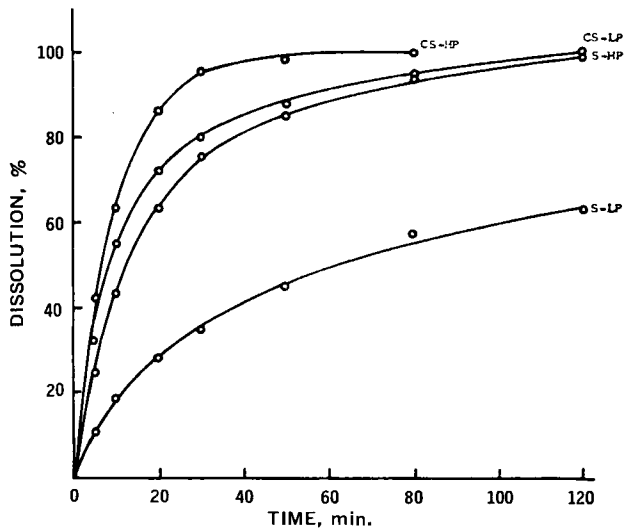

Figure 4—*Effect of compression pressure on dissolution of amaranth from directly compressed dicalcium phosphate tablets containing 8% starch or compressible starch. Key: CS = compressible starch; S = starch USP; HP = high pressure (12 s.c. units); LP = low pressure (4 s.c. units).*

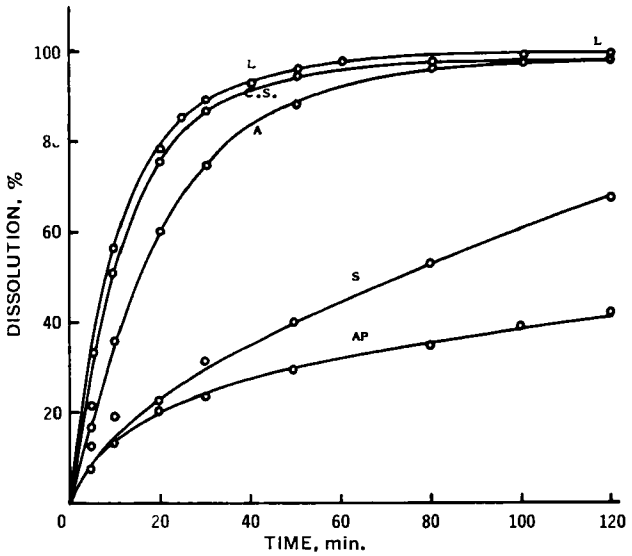

Figure 5—*Effect of 4% disintegrating agent on dissolution of amaranth from directly compressed dicalcium phosphate tablets. Key: L = alginic acid; CS = compressible starch; A = amylose; S = starch USP; AP = amylopectin.*

The difference between the two glidants as reflected in the above-mentioned parameters may be explained on the basis of the smaller effective particle size of the pyrogenic silica. The fact that beyond a concentration of 0.25% of pyrogenic silica and 0.75% of sodium silico-aluminate tablet weights decreased, may be due to an increase in bulk volume of the mixtures. If the glidants do adhere to particle surfaces rather than fill in void spaces, as suggested by Augsburger and Shangraw, then the effect would be to increase the particle diameter and thus, to increase the bulk volume (10).

It is possible to obtain acceptable tablets by combining the compressible starch with other filler-binders commonly employed in direct-compression, such as microcrystalline cellulose, spray-dried lactose, anhydrous lactose, and a commercially available direct-compression granulation.[9] As would be expected, combinations of

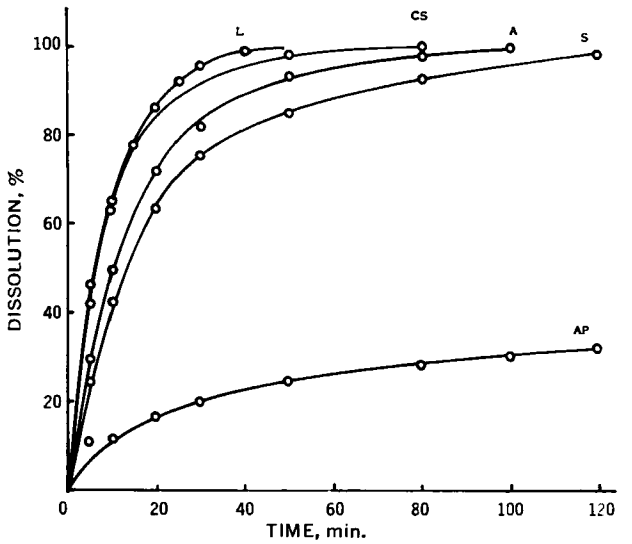

Figure 6—*Effect of 8% disintegrating agent on dissolution of amaranth from directly compressed dicalcium phosphate tablets. Key: L = alginic acid; CS = compressible starch; A = amylose; S = starch USP; AP = amylopectin.*

[9] Marketed as Encompress by Edward Mendell Co., Yonkers, N. Y., contains dicalcium phosphate dihydrate (89%), starch (7.5%), magnesium or calcium stearate (1%), and microcrystalline cellulose (2.5%).

compressible starch with either microcrystalline cellulose or the direct-compression granulation required no lubrication. While the compressible starch is antiadherent in regard to punches and dies, it is not a lubricant and requires additional lubrication when diluted with as little as 5–10% of a nonlubricated filler, such as spray-dried lactose or anhydrous lactose.

Although magnesium stearate is known to soften all tablets, tablets containing compressible starch seem to be particularly sensitive. It was impossible to obtain filler tablets with adequate hardness when a concentration of 0.5% magnesium stearate was exceeded. Even at a concentration of 0.5%, flexibility in hardness levels is limited. Stearic acid and hydrogenated vegetable oil[10] generally allowed for a wider range of tablet hardnesses, even though they had to be used in higher concentrations. Talc did not prove to be an effective lubricant in any blend.

Although aspirin is routinely tableted by slugging to avoid hydrolysis, the anhydrous nature and simplicity of the direct compression process would appear to be ideally suited for manufacturing aspirin tablets. The results in Table III show that it is possible to obtain acceptable tablets of aspirin by direct compression. As in the case with slugging, no lubricant is necessary.

In trying to directly compress a number of high-dose drugs including ascorbic acid, sodium sulfathiazole, and sodium *p*-aminosalicylate, a general formula containing 60% of drug and equal parts of compressible starch and microcrystalline cellulose has been found to be generally adequate. Two to three percent stearic acid or hydrogenated vegetable oil were needed for lubrication but this concentration can be lowered if the drug is nonadherent. In any such work, it is important to maximize the fluidity, compressibility, and lubricability of the drug itself by proper choice of its physical properties.

The stability of aspirin tablets was investigated by employing accelerated aging tests. The decomposition of aspirin due to hydrolysis was comparable for the three fillers used. As can be seen from Table IV, little difference in aspirin stability can be noted regardless of storage conditions or type of starch. As expected, the fastest rate of decomposition occurred at 75% relative humidity. It appears that although the compressible starch contains 12% moisture, this moisture is not readily available for decomposition of the active ingredient. There would, therefore, appear to be no reason to avoid the use of this filler due to its moisture content. The overall aspirin stability was found to correspond closely to that reported previously by Leeson and Mattocks (12).

The effect of different disintegrating agents on directly compressed tablets are summarized in Tables V and VI. A number of conclusions are obvious from reviewing these data.

1. Both amylose and compressible starch (and alginic acid where tested) give disintegration times comparable to starch USP.

2. The water-soluble amylopectin is not effective as a disintegrating agent and significantly retards disintegration of the water-soluble spray-dried lactose tablets.

3. Starch USP, compressible starch, amylose, and alginic acid are more effective as disintegrating agents when used with insoluble fillers or drugs.

4. Disintegration times of aspirin tablets were so rapid that it is not possible to determine significant differences between disintegrating agents.

5. In regard to disintegrating properties, compressible starch was generally equivalent to or better than starch USP in the dicalcium phosphate and spray-dried lactose tablets. This was particularly true in tablets containing only 4% disintegrating agent.

6. The fact that amylose, which does not swell in water, is as effective as starch as a disintegrating agent, leads one to believe that the swelling of starch grains which contain only 24% of amylose has nothing to do with the mechanism of tablet disintegration by starch. Ingram and Lowenthal (13) have come to similar conclusions with more elaborate experiments. Disintegration can more logically be attributed to intermolecular hydrogen bonding which is formed during compression and suddenly released in the presence of excess moisture. A similar mechanism has been proposed for microcrystalline cellulose (4).

As dicalcium phosphate tablets gave a range of disintegrating times based on type of disintegrating agent and tablet hardness, this filler was chosen for further evaluation in the form of dissolution. At a concentration of 4% the superiority of compressible starch suggested in the disintegration tests is clearly shown. In addition, it can readily be seen that dissolution is significantly more rapid from tablets compressed at a higher pressure. Increase of disintegrant concentration to 8% improves dissolution but the compressible starch still out-performs the USP starch.

Comparison of dissolution from tablets containing various disintegrating agents shows alginic acid and compressible starch to give similar dissolution patterns at both concentration levels. Amylose was always superior to starch USP, particularly at the 4% level. Amylopectin proved to have no better effect on dissolution than it did on disintegration. Aging effects on dissolution are still to be determined. It is not important to show that compressible starch is better than starch USP as a disintegrating agent. Taking into consideration the other attributes of compressible starch, it would appear that the establishment of the fact that it is equivalent to starch USP is sufficient to warrant its consideration in direct compression tableting.

SUMMARY AND CONCLUSIONS

1. Compressible starch can be blended and directly compressed in combination with other filler-binders commonly employed in direct compression. However, it is generally recommended that a glidant such as 0.25% pyrogenic silica be employed to maximize fluidity.

2. Although compressible starch is nonadherent in respect to punches and dies, the addition of a lubricant becomes necessary when even small proportions of adherent drugs are introduced. Magnesium stearate noticeably softens compressible starch tab'ets and should not be used in concentrations greater than 0.5%.

3. The presence of moisture in the compressible starch does not appear to adversely affect the stability of a moisture-sensitive drug such as aspirin.

4. Compressible starch would appear to have many advantages over starch USP in that it is much more effective as a dry binder yet gives equivalent or faster disintegration and dissolution times.

5. The disintegrating effects of compressible starch and amylose would seem to offer sufficient evidence to place serious doubt on the role of starch grain swelling in tablet disintegration.

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[10] Marketed as Sterotex by Capital City Products Co., Columbus, Ohio.