Mechanism of Action of Starch as a Tablet Disintegrant III

Factors Affecting Starch Grain Damage and Their Effect on Swelling of Starch Grains and Disintegration of Tablets at 37°

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A study was undertaken to determine the effect of the tableting procedure on starch grain swelling and tablet disintegration. The swelling of damaged starch grains in simulated gastric fluid USP is demonstrated. Submersion of starch samples that had been ball milled from 10 to 48 hr. produced increases in grain diameters of 40 to 80 percent. Damage to the grains resulting from compression of pure cornstarch is shown to be insignificant. The effect of compressional force and hardness of tablet ingredients was examined and in each formulation the starch grain damage increased with compressional force. There was no correlation between degree of starch grain damage and hardness of the tablet ingredients. It appeared that the crystalline form of the ingredient may have exerted a greater influence on starch damage than the hardness. There was no correlation between starch damage and stress produced by elastic recovery of the tablet. Contrary to what might be expected, there was an inverse relation between the amount of stress and the degree of starch grain damage for all of the formulations except aspirin. There was no evident relationship demonstrated between disintegration time and starch grain damage. Outside of compressional force, the inherent effect of the tablet ingredient was the only factor that appeared to affect disintegration. The long-accepted swelling mechanism of starch as a tablet disintegrant was not demonstrated in this study. The results of the investigation revealed no measurable correlations between starch grain damage and disintegration or between starch swelling and compressional force.

FROM THE PREVIOUS STUDIES, it does not seem probable that untreated or unmodified starch will swell sufficiently at 37° to cause tablet disintegration (1, 2). If swelling is the primary mechanism whereby starch exerts its disintegrant effect, then this property may be imparted to the starch by the tableting procedure.

Since swelling of the grains may occur reversibly or irreversibly, the effect of each type of swelling on disintegration should be considered. It is known that the starch grains have a limited capacity for absorbing cold water and swelling reversibly (3). When a suspension of starch is subjected to heat or appropriate chemical treatment, the micellar network within the grain is weakened by disruption of hydrogen bonds, and irreversible swelling, or gelatinization, occurs. Irreversible swelling results in partial solubilization of the starch molecules and formation of an adhesive paste. This adhesiveness should tend to hinder rather than promote disintegration. This hindrance was observed by submersing an aspirin tablet containing 10% cornstarch in hot water, which will cause starch to gelatinize. The tablet would not disintegrate and examination of the tablet revealed that the interior was essentially dry. This could indicate formation of a starch paste "sealer" coat around the exterior of the tablet, preventing penetration of water into the tablet.

Cooper and Brecht (4) also suggested starch gelatinization as a possible explanation for the hindrance to disintegration observed when starch is incorporated into a sodium salicylate tablet. Sodium salicylate in aqueous solution causes starch to gelatinize.

The detrimental effect of irreversible swelling on disintegration is further supported by the observation that any substantial amount of pregelatinized starch (*e.g.*, 5%) in the tablet formulation hinders disintegration (5).

From this it would appear that only reversible swelling could exert a favorable effect on disintegration. The literature indicated that reversible swelling results in 5 to 10% increases in grain diameters (5). Assuming that starch grains are spheres, a 10% diameter increase corresponds to a 33.1% volume increase. This volume increase has no relation to tablet disintegration until it can be correlated to the increase it would produce in the tablet volume. The maximum proportion of starch normally used in tablet formulations is 10% by weight. The percent of the total tablet volume occupied by this amount of starch will depend on the density of the other in-

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gredients. The range for densities of tablet formulations is usually from 0.5 to 2.5 Gm./ml. The percent increase in tablet volume (%V) corresponding to a 33.1% starch volume increase may be calculated by:

$$\%V = 0.331 \times 0.1 \times \frac{d_t}{d_s} \times 100$$

where d_t is the density of the tablet formulation, d_s is the density of starch, and the two constants, 0.331 and 0.1, refer to the 33.1% starch volume increase and the 10% by weight starch in the formulation. Based on these conditions, a starch volume increase of 33.1% should produce a tablet volume increase of only 1.1 to 5.5%. Since most tablets probably contain more than 5.5% void space, it seems unlikely that starch grains would produce sufficient strain within the tablet to promote disintegration.

It is known that untreated starch is insoluble in cold water but may absorb 25 to 30% of its weight in water with no appreciable swelling (6). Sjostrom (7) states that if a starch grain is mechanically damaged it will gelatinize in cold water.

A possible explanation for swelling occurring in starch grains incorporated into a tablet is in a report on the compressional behavior of potato starch. Fuhrer (8) reported that the grains are deformed plastically under the pressure and suggested that at a suitable degree of deformation the stability of the grains is lowered so that they may swell in water at room temperature.

EXPERIMENTAL

Since no substantial evidence was found by changing the chemical environment to support the hypothesis that starch effects tablet disintegration through swelling, this study was planned to demonstrate the effect of damage on starch grain swelling and to determine the influence of the tableting procedure and tablet ingredients on starch grain damage and tablet disintegration.

Since the nature of the tablet constituents may affect swelling, the addition of an ingredient to cornstarch was studied. The following general formula was used for the tablet formulations:

Active ingredient	10.00 Gm.
Cornstarch[1]	0.75 Gm.

The materials chosen as the ingredient in the formulations were aspirin, talc, calcium carbonate, calamine, sodium chloride, and sucrose. Aspirin was selected because of its widespread use and because of its use in previous disintegration studies. Talc, calcium carbonate, and calamine were selected to include materials of varying hardness, because hardness may influence the degree of damage imposed on the starch grains during tableting. Mohs' hardness scale values for these three materials are: talc, 1; calcium carbonate, 3; and calamine, 5 (9). Sucrose and sodium chloride were included to determine the effect of water-soluble substances and their crystalline structure on starch damage. Tablets of pure cornstarch were included as controls.

The force of compression used in the tableting procedure influences void space, disintegration time, and may influence starch grain damage. These factors were studied and comparisons among them were made to determine what significance could be attributed to each factor.

The extent of elastic recovery after compression for each of the formulations and for pure cornstarch was investigated. The greater the elastic recovery of the tablet after release of pressure, the greater is the stress within the tablet. This stress might affect starch grain damage.

Procedure for Preparation and Examination of Tablets—The tablet formulations were mixed in a mortar and then compressed as a powder in a Carver laboratory press model B[2] using standard, flat-faced, stainless steel punches and die of $^3/_8$ in. diameter.

The die and lower punch were fixed at a definite position throughout the experiment and the powder was manually placed in the die and leveled with the top. This procedure gave uniform weights for the tablets from a particular formulation.

Tablets of each formulation were prepared using varying compressional forces. The individual tablets were measured for thickness and diameter with a vernier caliper and weighed. Utilizing the tablet dimensions and weights, the percent void space (% e) was calculated by:

$$\%\ e = \left(1 - \frac{d_b}{d_t}\right) \times 100$$

where

$$d_b = \frac{W}{V}$$

and

$$d_t = \frac{10.75\ \text{Gm.}}{10.00\ \text{Gm.}/d_i + 0.75\ \text{Gm.}/d_s}$$

where d_b and d_t are the bulk density and true density of the formulation, d_i is the density of the ingredient (10, 11), d_s is the density of starch, W is the weight of the tablet in Gm., and V is the volume of the tablet in cm.^{3}.

Procedure for Determination of Disintegration Time—The disintegration time for each tablet in simulated gastric fluid USP (SGF) at 37° was determined using a modification of the USP disintegration apparatus, so that only one tablet was disintegrated at a time and the time required for all the granules to pass through the 10-mesh screen determined. The disintegration times reported represent an average of five determinations.

Procedure for Production and Determination of Starch Grain Damage—Sandstedt and Mattern (12) state that starch grains are easily damaged by pressure, shear, or strain such as that applied by grinding procedures. Damage to the grains was effected by ball milling in a 1-quart porcelain ball mill using 0.5-in. diameter porcelain balls and a single tier roller mill.[3] Samples were removed at various time intervals and the extent of damage to the starch grains was determined.

[1] Marketed as Melojel (MJ) by National Starch and Chemical Corp.

[2] Fred S. Carver, Inc., Hydraulic Equipment, Summit, N.J.

[3] Phipps and Bird, Inc., catalog No. 62-502.

A qualitative method suggested by Schoch (5) consisted of suspending the starch in water and examining the grains under a polarizing microscope. Schoch states that severe damage gives grains which swell in cold water and hence show no polarization cross. Lesser degrees of damage result in a darkened area at the center of the grain when viewed under normal light.

If the damage is severe enough that the paracrystalline structure of the grain is disrupted, the unswollen grain should also lose its polarization cross. Lesser degrees of damage resulting in less disruption of the paracrystalline nature of the grain should allow passage of proportional amounts of polarized light. In order to eliminate the possibility that reversible swelling in water may affect the polarization characteristics of starch, glycerin was used as the slurrying medium, since starch does not swell in glycerin (13).

The percent damage of the various samples removed from the ball mill was calculated from observation of the polarization crosses of 200 grain. Each grain was assigned a weighted degree of damage, dependent on the number of quadrants within the polarization cross which presented a darkened appearance. For example, if the polarization cross contained two quadrants which exhibited a darkened appearance, the grain was assigned a degree of damage of 0.5. Since it was not possible to determine the absolute extent of a darkened area within the cross, these percentages reflect only a relative degree of damage, which is useful for comparison of samples.

The effect of pressure on starch swelling was determined from tablets of pure cornstarch (MJ). The tablets were prepared on a Carver press utilizing various compressional forces. The tablets were slurried in SGF and in glycerin, and swelling was determined on 100 grains' diameters from each sample, using the procedure described previously (1).

Procedure for Determination of Starch Grain Damage in Tablets—The starch grain damage produced by tableting of the different formulations was determined by examination of 200 grains under the polarizing microscope using the procedure described previously. Two tablets of each formulation prepared at each pressure were used for preparation of the slurries. The procedure for preparation of the slurries was modified, because the starch as a tablet constituent was not available for direct slurrying. The aspirin tablets were slurried in absolute ethyl alcohol, which dissolved the aspirin. The alcohol was decanted and the residual starch grains were slurried in glycerin. Talc, calamine, sucrose, and sodium chloride tablets were disrupted in absolute ethyl alcohol to release the starch for preparation of slurries. Glacial acetic acid was used to effect release of starch from calcium carbonate tablets. Glycerin, absolute ethyl alcohol, and glacial acetic acid were used because these liquids have no effect on starch swelling.

Procedure for Determination of Elastic Recovery—The elastic recovery after compression for each formulation was determined on a Carver press. The powder was placed in the die and the distance the upper punch moved to produce each pressure was measured by dial micrometers attached to the upper punch.

After the maximum pressure had been applied and released, the micrometer reading for the tablet at zero was determined. The tablet thickness was measured with a vernier caliper immediately after removal of the tablet from the die in order to exclude any creep recovery. The sum of these two values minus the micrometer reading at each pressure gave the tablet thickness under pressure. By comparison of the final tablet thickness with the tablet thickness while under pressure, the elastic recovery could be determined.

The elastic recovery for the pure cornstarch tablets was determined by the same procedure at each pressure level studied, instead of only at the maximum pressure applied.

TABLE I—EFFECT OF STARCH GRAIN DAMAGE AND TIME ON MEAN GRAIN SIZES OF CORNSTARCH (MJ) IN SIMULATED GASTRIC FLUID

Ball Mill Time, hr.	% Damage	Time in SGF, min. 0	5	30
0	1.1	6.13[a]	6.41	6.22
1	15.8	5.43	7.08	6.87
2	14.8	5.61	6.27	6.25
3	18.0	5.58	7.18	6.44
4	17.1	5.74	7.58	7.17
5	18.4	5.95	6.64	7.28
10	41.6	5.59	7.10	8.07
15	44.7	6.50	7.79	7.48
20	50.8	6.52	7.53	7.79
36	67.6	7.18	8.37	8.77
48	82.8	6.91	12.24	12.53

[a] Mean grain sizes in scale divisions, one scale division = 1.8 μ.

RESULTS AND DISCUSSION

Investigation of Relationships Among Compressional Force, Starch Grain Damage, and Starch Swelling—Since the compressional force may damage the starch grains, the effect of damage on swelling of starch grains was first studied. Cornstarch (MJ) grains were damaged by ball milling and samples were removed after various time intervals up to 48 hr. and the degree of damage determined by observation of 200 grains under the polarizing microscope. The samples were also examined for the effect of damage on swelling in SGF in a 3 × 12 full factorial experiment. The damage determinations and the mean grain sizes are shown in Table I. The analysis of variance showed that the degree of damage and submersion time both produced significant differences in grain diameters at the 1% level. Duncan's multiple range test (14) for the time effect shows that the grain diameters of unsubmerged starch are significantly different from those of submerged starch, with no difference being demonstrated between the two submersion times. Duncan's multiple range test for the damage effect shows a significant difference between the samples ball

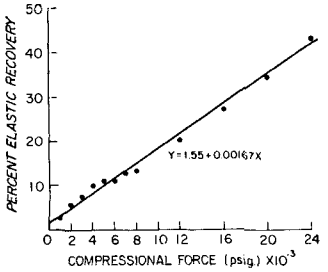

Fig. 1—Effect of compressional force on percent elastic recovery of cornstarch (MJ).

TABLE II—EFFECT OF PRESSURE ON PERCENT STARCH GRAIN DAMAGE

Pressure, psig	Ingredient					
	Aspirin	Calcium Carbonate	Calamine	Talc	NaCl	Sucrose
2000	12.8[a]	16.5	13.9	8.0	31.5	22.4
4000	17.4	28.5	18.8	12.1	59.4	50.4
6000	16.9	35.0	26.1	14.0	56.6	53.8
8000	19.2	38.1	27.5	15.1	68.1	56.3

[a] Percent damage.

TABLE III—EFFECT OF PRESSURE ON PERCENT VOID SPACE

Pressure, psig	Ingredient					
	Aspirin	Calcium Carbonate	Calamine	Talc	NaCl	Sucrose
2000	2.3[a]	38.2	6.2	17.7	7.6	12.6
4000	0.3	29.9	1.6	15.9	3.8	9.6
6000	0.1	27.8	0	13.9	2.9	6.5
8000	0	24.0	0	10.5	3.4	8.8

[a] Percent void space.

milled for 48 hr. and the samples ball milled for 36 hr. or less. This means more than two-thirds of the starch grains had to be damaged before there was a statistically significant increase in swelling.

To determine the extent of swelling produced by various compressional forces, a 3 × 8 full factorial experiment was designed. Cornstarch (MJ) tablets were prepared on a Carver press using 0.5-in. flat-faced punches and mean grain sizes determined in SGF after 5 and 10 min. submersion. The mean grain sizes of the starch grains were determined from a glycerin slurry to include unsubmerged starch (zero time) as a basis for comparison. Eight pressures between 0 and 5000 psig were investigated. The analysis of variance of the mean grain sizes revealed no significant differences among the variables investigated.

Using 0.5-in. diameter punches, the maximum compressional force used in the previous experiment (5000 psig) corresponds to an actual pressure of 25,480 p.s.i. Because the actual pressures produced in tableting may vary over a wide range depending on the punch sizes that are used, cornstarch samples subjected to an extremely high compressional force were investigated for evidence of damage. Tablets of cornstarch were prepared on a Carver press utilizing $^3/_8$-in. diameter flat-faced punches and compressional forces of 500 and 24,000 psig, which correspond to actual pressures of 4530 and 217,440 p.s.i., respectively. The percent starch grain damage as determined from glycerin slurries, were 7.8% for the tablet prepared at 500 psig and 5.5% for the tablet prepared at 24,000 psig.

The results of the elastic recovery determinations for cornstarch are shown in Fig. 1. Cornstarch exhibited a high degree of elastic recovery when subjected to high compressional forces. The strain produced by this elastic recovery showed no apparent correlation to starch grain damage as indicated by the above data.

From the observations of strain in starch tablets after subjected to pressure and the extent of starch grain damage produced by pressure, along with the observations in the experiment on pressure and swelling, it seems that starch grains are not significantly damaged by the forces involved during and after compression.

Effect of Tableting Procedure on Starch Properties and Tablet Disintegration—Since starch grain damage resulting from compression of cornstarch alone was shown to be insignificant and when a high percent of starch grains are damaged there is an increase in swelling, the combined effect of other tablet ingredients and compression on starch grains was investigated. If these variables could be related to starch grain damage and hence swelling, this could be considered indirect evidence for a swelling mechanism for tablet disintegration.

Effect of the Hardness of an Added Ingredient and Compressional Force on Tablet Properties—To determine how the added ingredient and force of compression affect such properties as disintegration time and void space in the tablet and damage to the starch grains, tablets were compressed over a pressure range of 2000 to 8000 psig. In each formulation the percent void space decreased[4] and the degree of starch grain damage increased with compressional force. The ingredient apparently had no effect on the proportionality of these relationships, but only on the degree to which they occur. Variation in the degree of starch damage among the different formulations is shown in Table II and variation in void space is shown in Table III.

Damage varied from 8.0 to 15.1% for talc to 31.5 to 68.1% for sodium chloride. The ingredients did not produce correspondingly greater degrees of damage as hardness increased. Calamine, with a hardness of 5, produced a maximum starch grain damage of 27.5%; whereas calcium carbonate, with a hardness of 3, produced a maximum damage of 38.1%. The crystalline form or the brittleness of the ingredient may exert a greater influence on starch grain damage than hardness, as illustrated by the damage produced by sodium chloride. The void space percentages in the different formulations ranged from 0 to 2.3% for aspirin tablets to 24.0 to 38.2% for calcium carbonate tablets.

The results of the elastic recovery determinations for the different formulations after compression at 24,000 psig were: sodium chloride, 15.9%; sucrose, 19.5%; aspirin, 34.6%; calcium carbonate, 70.4%; calamine, 76.2%; and talc, 77.7%. There is no apparent correlation between the strain produced

[4] Void space in the sodium chloride and the sucrose tablets decreased with increasing pressure up to 6000 psig and then anomalously increased at 8000 psig. Outside of experimental error, no explanation could be found for this behavior and this increase is disregarded in forming generalizations on compressional effects. Fusion of some of the crystals at the higher pressures and subsequent recrystallization after removal of pressure might effect a void space increase, if expansion of the tablet occurs during recrystallization.

TABLE IV—EFFECT OF PRESSURE ON DISINTEGRATION TIME

Pressure, psig	Ingredient					
	Aspirin	Calcium Carbonate	Calamine	Talc	NaCl	Sucrose
2000	16.5[a]	25.6[a]	5.6[a]	>8[b]	9.4[a]	92.6[a]
4000	30.9	17.2	5.7	>8	15.7	351.2
6000	60.5	9.0	5.0	>8	18.2	440.4
8000	51.5	9.6	4.7	>8	19.4	427.6

[a] Time in sec. [b] Time in hr.

by elastic recovery and the extent of damage to the starch grains. Surprisingly, the results indicated an inverse relationship between strain and starch grain damage for all of the formulations except aspirin.

The relationship between compressional force and disintegration time varied with the ingredients. Disintegration times for the aspirin, sodium chloride, and sucrose tablets increased with increasing compressional force; whereas disintegration times for the calcium carbonate and the calamine tablets decreased with increasing compressional force. These relationships are shown by the data in Table IV. Since the disintegration times for the talc tablets compressed at all pressures were greater than 8 hr., no correlations for this formulation could be made.

As shown above, the relationships between disintegration time and void space or starch grain damage varied and no correlations could be made. The ingredients appear to be the main source of the variation.

Disintegration times for the aspirin, sodium chloride, and sucrose tablets increased with increasing starch grain damage and decreasing void space. Disintegration times for the calcium carbonate and the calamine tablets decreased with increasing starch grain damage and decreasing void space.

It had been previously demonstrated that the logarithm of disintegration time varies directly with compressional force (15). This study revealed a direct relationship between pressure and dissolution time for the tablet formulations containing sodium chloride and sucrose. It is questionable whether the small decreases in void spaces found justify the large increases in dissolution time. The extensive starch grain damage noted would indicate an increased swelling ability for the starch grains. This was not borne out with the two soluble tablet formulations. The increased damage and hence swelling ability of the starch grains may have actually exerted a detrimental effect on dissolution by formation of a paste which then would hinder penetration of SGF into the tablet.

The tablet formulations containing insoluble ingredients varied in the relationships between pressure and disintegration time. The greatest damage range observed in this group was in the calcium carbonate tablets. Starch grain damage in this formulation ranged from 16.5% to 38.1%. The disintegration times for calcium carbonate tablets decreased from 25.6 to 9.6 sec., indicating that the swelling may have exerted a favorable influence on disintegration. The large void space in this formulation, however, could overshadow any effect on disintegration produced by the increased swelling capability of the damaged starch grains. Also, the results from the ball milling experiment indicated that greater than 67% of the starch grains must be damaged before a significant increase in swelling is observed.

The range of disintegration times for calamine tablets was too small to allow any significant correlations to disintegration time.

The results of this investigation disclosed no correlation between starch grain damage and tablet disintegration. Outside of pressure, the inherent effect of the added ingredient was the only factor that appears to affect tablet disintegration. Starch grain damage, void space, and hardness of the ingredients are at best of secondary importance.

Effect of Compressional Force on Aspirin Tablet Properties—In order to obtain more information on the effect of compressional force, aspirin tablets prepared over a pressure range of 1000 to 24,000 psig were examined for relationships existing among disintegration time, void space, and damage to the starch grains.

The inverse relationship between compressional force and void space observed in the previous study is again obvious over the wider pressure range. Figure 2 shows that void space decreased rapidly with increases in pressure up to 3000 psig. Above 3000 psig the void space decreased slowly up to 7000 psig, at which point zero percent void space was attained.

No relationship between compressional force and degree of starch grain damage was observed over the pressure range studied. Damage varied from 9.4 to 19.2%, but did not consistently increase as the pressure increased.

The increase in disintegration time with increasing

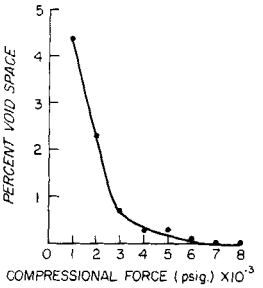

Fig. 2—Influence of compressional force on percent void space in aspirin tablets.

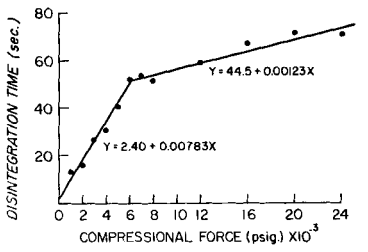

Fig. 3—Influence of compressional force on disintegration time of aspirin tablets.

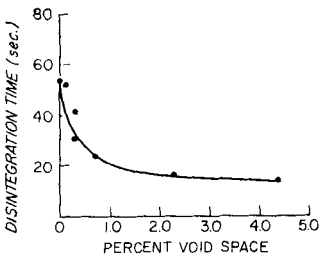

Fig. 4—Relationship between disintegration time and percent void space in aspirin tablets.

compressional force for the aspirin tablets is shown in Fig. 3. Disintegration times increased linearly with compressional forces between 1000 and 6000 psig. Tablets produced with greater than 6000 psig pressure also had disintegration times that were linearly dependent on compressional force; however, the disintegration rate was slower.

Disintegration times increased slowly with decreasing void space until 0.7% void space (3000 psig) was attained. Below 0.7% void space disintegration times increased rapidly until zero percent void space was reached at 6000–7000 psig. After zero percent void space was reached, disintegration times continued to increase with pressure. It appears, at least with aspirin, that the disintegration time is little affected until a certain value at about 0.7% void space is attained, and that further application of pressure affects disintegration greatly. Figure 4 illustrates the relationship between void space and disintegration time in aspirin tablets.

Since there was no correlation between compressional force and degree of damage to the starch grains, the percent damage could not be related to disintegration. Damaged starch grains do not appear to play a significant role in disintegration of aspirin tablets. The tablet that had the shortest disintegration time produced a starch grain damage of only 11.9%.

Since compaction pressure produced by impact due to the rapid action of a tableting machine might effect greater damage than that produced in the slower, hand-operated Carver press, aspirin tablets prepared on a Colton model 321 tablet press[5] were examined for evidence of starch grain damage. Observation of 200 grains showed only 2.6% damage. Disintegration time for these tablets was 15.4 sec. This again indicates that starch grain damage apparently has no significant effect on disintegration.

SUMMARY AND CONCLUSIONS

A procedure for estimation of starch grain damage is described. Swelling of damaged starch grains in SGF at 37° was demonstrated by experiments with cornstarch damaged by ball milling.

Damage to the grains, resulting from compression of pure cornstarch at pressures up to 24,000 psig was shown to be not significant.

The effect of compressional force and hardness of the tablet ingredients on starch grain damage was examined together with the relationships among compressional force, elastic recovery, void space, and disintegration time for the formulations.

In each formulation the starch grain damage increased as the compressional force was increased. The ingredient apparently had no effect on the direct proportionality of this relationship, but only on the degree to which it occurs. There was no correlation between degree of starch grain damage and hardness of the ingredient. The crystalline form of the ingredient may exert a greater influence on starch damage than hardness of the ingredient. This was illustrated by the sodium chloride and sucrose formulations, which produced the greatest degree of starch damage. There was no correlation between starch damage and stress produced by elastic recovery. Contrary to what might be expected, there was an inverse relation between the amount of stress and the degree of starch grain damage for all of the formulations except aspirin.

There was no evident relationship demonstrated between disintegration time and starch grain damage. Dissolution times for sucrose and sodium chloride tablets increased as the degree of starch grain damage increased. Disintegration times for the calcium carbonate tablets decreased with increasing starch damage, but the large void space in this formulation could overshadow any effect of swelling due to damage. Outside of compressional force, the inherent effect of the tablet ingredient was the only factor that appeared to affect disintegration, although starch grain swelling cannot be eliminated as a possible mechanism.

Most compressed tablets are composed of more than one ingredient and require several steps in manufacture. Ingredients commonly used in tablets represent a wide range of chemical and physical properties. Thus, it is possible that disintegration is influenced by a wide variety of factors which are specific for only a given tablet formulation and it is difficult to determine the mechanism of action of starch as a tablet disintegrant. The long-accepted swelling mechanism of action of starch as a tablet disintegrant could not be demonstrated in this study. The results of the investigation revealed no measurable correlations between starch grain damage and disintegration or between starch grain swelling and compressional force.

The proposals of Patel and Hopponen (16) and Nogami *et al.* (17) on the effect of capillaries, starch wettability, and liquid penetration into tablets become more substantial.

[5] Arthur Colton Co., Cedar Rapids, Iowa.

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Keyphrases

Cornstarch grains
Tablet disintegration–starch grain damage
Crystalline substance–starch grain damage
Compression force–starch grain damage
Starch swelling–tablet disintegration

Metabolic Fate of Orally Administered 2,3,5-Triiodobenzoic Acid in Lactating Animals

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The whole body retention, excretion, distribution, thyroid uptake, and metabolism of 2(^{131}I),3,5-triiodobenzoic acid (TI*BA) were studied in goats and a cow. A single oral dose of TIBA exhibited a two-component whole body radioactivity retention curve and was excreted primarily in the urine. TIBA plus nine metabolites, four of which were identified, were found in the urine. The major metabolite was 2,5-diiodobenzoic acid (2,5-DIBA). Trace amounts of 2,3-diiodobenzoic acid (2,3-DIBA), orthoiodobenzoic acid (OIBA), and iodide ion were found. TIBA was metabolized by deiodination. Iodide ion was concentrated in the thyroid and excreted by way of milk and urine.

In soybeans, 2,3,5-triiodobenzoic acid (TIBA) affects plant morphology and flowering response (1, 2). When properly used, soybean production is increased through a better utilization of photosynthate, lodging is decreased, and a more compact plant results (3). Spitznagle (4) has reported a residue in soybeans treated with TIBA. Soybean products are used for animal and human food consumption and the question arises as to the environmental health safety of TIBA. The metabolic fate of TIBA in lactating animals is important to a thorough understanding of the potential hazards.

Ice *et al.* (5) reviewed TIBA and using TIBA labeled with ^{131}I in the two position, orally administered to rats, observed two whole body retention components—one with a biological half-life of 11.8–17.9 hr. and the second of 395–403 hr. Of the administered dose, 70–78% was excreted in the urine, while 3–4% was excreted in the feces over 4 days. Three metabolites plus TIBA and iodide ion were located in the urine. Whole body retention of radioactivity was evident. Distribution studies in rats indicated a marked thyroid uptake of radioactivity.

Ebert and Ware (3) and Barker *et al.* (6) using carboxyl labeled TIBA-^{14}C orally administered to rats, found TIBA and/or its metabolites in all organs analyzed. Seventy-five percent of radioactivity was excreted *via* the urine and 29% *via* the feces. Chromatographic studies indicated two to six metabolites plus TIBA in the urine.

Gutenmann *et al.* (7) found no TIBA in the milk or feces of the dairy cow during a period of 4 days. In urine, 13.5% of the dose excreted was TIBA. A second compound in the urine was identified as 2,5-DIBA and accounted for 53.5% of the TIBA fed.

EXPERIMENTAL

Instrumental Methods—Whole body radioactivity was measured in goats using large volume liquid scintillation counting techniques. The basic mechanisms and characteristics of the 2 π liquid scintillation detector have been previously reported (8). The detector has since been modified by the addition of an upper detecting tank, which allows 4 π geometry. Dosages were adjusted to provide negligible coincidence loss.

A 3-in. diameter standard NaI(Tl) crystal, centrally located in a steel vault, was used for counting liter samples of excreta and tissue. A 3-in. diameter NaI(Tl) well crystal was used to determine the radioactivity in 3-ml. samples of tissue, to count eluent fractions from chromatography columns, to

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