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PHARMACEUTICAL TECHNOLOGY

Mechanism of Action of Starch as a Tablet Disintegrant VI: Location and Structure of Starch in Tablets

WERNER LOWENTHAL▲ and JOHN H. WOOD

Abstract □ By using a scanning electron microscope, the location and structure of starch grains in experimental and commercial aspirin tablets and aspirin–phenacetin–caffeine tablets were studied. By scrutinizing tablet faces and cross sections before and after the addition of water, it was observed that rupture of the surfaces occurred where starch agglomerates were found. It was postulated that water hydrates the hydroxy groups of the starch molecules, causing them to move apart. The slight swelling that occurs is due to the rapid hydration step and a slower sorption of addition water step. Channels or pores lined with starch were not evident. The conditions for rapid tablet disintegration are sufficient starch agglomerates, low pressure, and presence of water.

Keyphrases □ Starch as tablet disintegrant—location, structure in aspirin and aspirin–phenacetin–caffeine tablets, scanning electron microscope □ Aspirin, aspirin–phenacetin–caffeine tablets—location and structure of starch, scanning electron microscope □ Tablets, aspirin, aspirin–phenacetin–caffeine—location and structure of starch, scanning electron microscope □ Scanning electron microscopy—location, structure of starch in aspirin and aspirin–phenacetin–caffeine tablets □ Disintegrants—mechanism of action of starch in aspirin and aspirin–phenacetin–caffeine tablets, location and structure of starch agglomerates, conditions for rapid disintegration

Previous study has shown that corn and waxy maise starch grains plastically deform and that this deformation increases with increasing pressure. The addition of water has no apparent effect on this deformation (1, 2). Potato starch grains also have been shown to deform (3). It was also previously observed that when a small amount of moisture was added to corn and waxy maise starch tablets, a "blistering" effect and disruption of the moistened area occurred. Moisture did not cause the individual grains to regain their shape (1).

It is not practical to attempt to measure a change in volume due to the addition of moisture by the scanning electron microscope, because sample preparation for the scanning electron microscope involves the use of a vacuum which would remove the moisture and the sample is coated with a thin layer of a conductor of carbon and gold. When conductor layering was compared to an electrostatic method of sample preparation, similar results were obtained so that the scanning electron photomicrographs show a true picture of the surfaces (4).

The purpose of this investigation is to show the location of and the structure formed by the starch grains in experimental and commercial aspirin tablets and aspirin–phenacetin–caffeine tablets. The effect of moisture on these tablets is also shown.

EXPERIMENTAL

Tablets weighing 0.5 g. were compressed using 1.27-cm. (0.5-in.) diameter flat-face punches and die. Aspirin[1] was sieved to obtain 40–50- and 70–100-mesh crystal fractions. These fractions were mixed with starch[2] to give 2.5, 5, 7.5, 10, 12.5, and 15% (w/w) starch concentrations. The ingredients were mixed by tumbling. Tablets were made by compression at 10,000 psig. on a hydraulic laboratory press[3] with special holders for the punches and die. An aspirin–10% starch granulation[4], 12–50 mesh, was also used. Tablets from the commercial granulation were made by compression at 2500 psig. At higher pressures the tablets appeared to be impervious to water and did not disintegrate. For the photomicrographs only, the 40–50-mesh aspirin with 2.5 and 10%

[1] Catalog No. A-42, lot 752285, Fisher Scientific Co.
[2] STR-Rx, A. E. Staley Manufacturing Co.
[3] Model B, Fred S. Carver, Inc., Hydraulic Equipment.
[4] Lot QM-18, Monsanto Chemical Co.

Table I—Disintegration Times

Tablet	Disintegration Time, sec.	
	Average	Range
Aspirin 2.5%	530[a]	378-685
(40-50 mesh) 5	16[a]	9-40
10	6[a]	5-6
15	5[b]	4-6
Aspirin-starch granulation	173	45-490
Product B	10	8-13
Product S	11	9-12
Product N	13	10-14
Aspirin-phenacetin-caffeine	23	15-31

[a] Five tablets. [b] Three tablets.

starch was used. There was no apparent difference in disintegration times observed between the two particle-size ranges of aspirin, and very little difference was seen between the 5 and 15% concentration ranges of starch.

The USP apparatus (5) with distilled water was used to determine disintegration times.

Three commercially made aspirin tablets (designated as Product B[6], Product S[6], and Product N[7]) and aspirin-phenacetin-caffeine[8] tablets were observed.

The scanning electron microscope and technique previously described were used (1). Both the "as is" face and the cross sections by breaking the tablets were examined. The effect of moisture was determined after a small drop of water was added to the surfaces.

RESULTS

In this study, aspirin mixed with varying concentrations of starch showed only a marked decrease in disintegration times when concentration of starch increased from 2.5 to 5%. This occurred with both 40-50- and 70-100-mesh aspirin. Tablets made with 5% or more starch all had similar disintegration times. As a result, only 40-50-mesh aspirin with 2.5 and 10% starch were examined
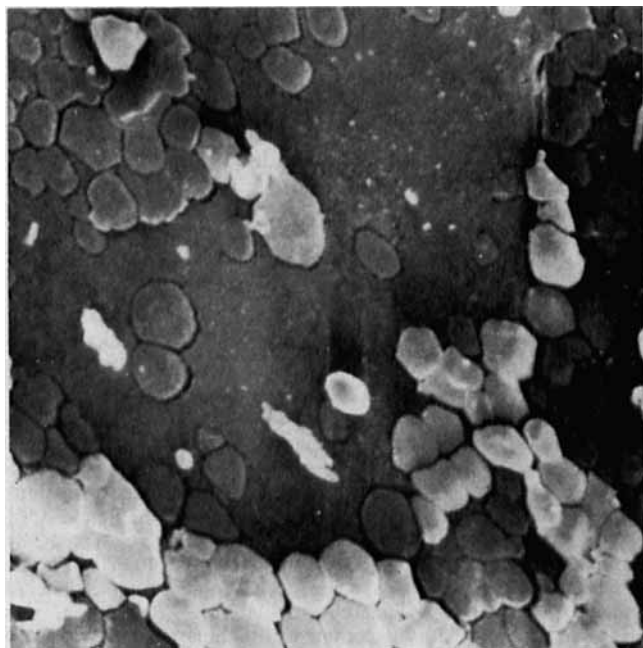

Figure 1—*Face view of aspirin plus 10% starch tablets, dry (about 600×).*
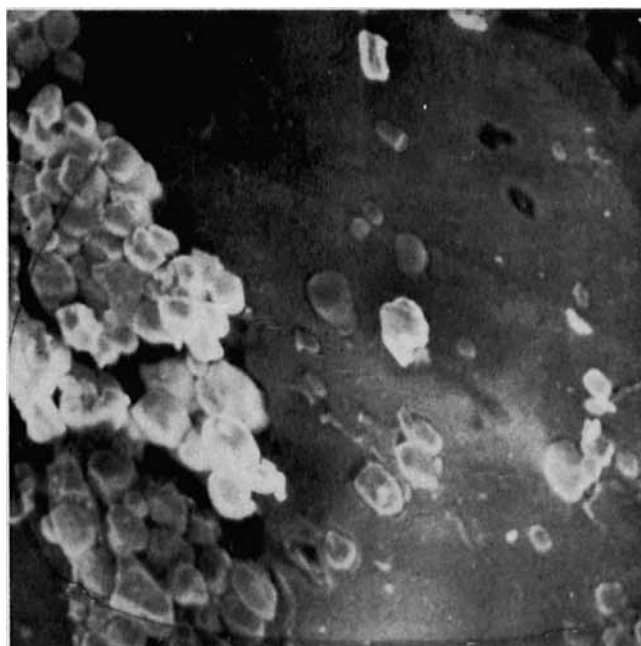
Figure 2—*Face view of aspirin plus 10% starch tablets, moistened (about 600×).*

microscopically. Table I gives the results of the disintegration times of the tablets used.

Analyzing the surfaces of aspirin plus 2.5% starch showed a few widely scattered chains of starch grains. These appeared to be only one layer thick. The starch appeared in scattered clusters and, because starch is poorly compressible, the grains stood out. The aspirin crystals were fused. The face of the tablets looked smooth except where the grains occurred. The starch was not fused to the aspirin. On moistening, aspirin crystals were recognizable, the surface was disrupted, and cracks arose. These cracks usually had starch grains in and around them. A few grains with dimples or depressions were observed, as was reported previously (1). The markings are due to the grains growing next to a protein (zein) membrane in the kernel, are due to enzyme action during storage, or are produced during refining.
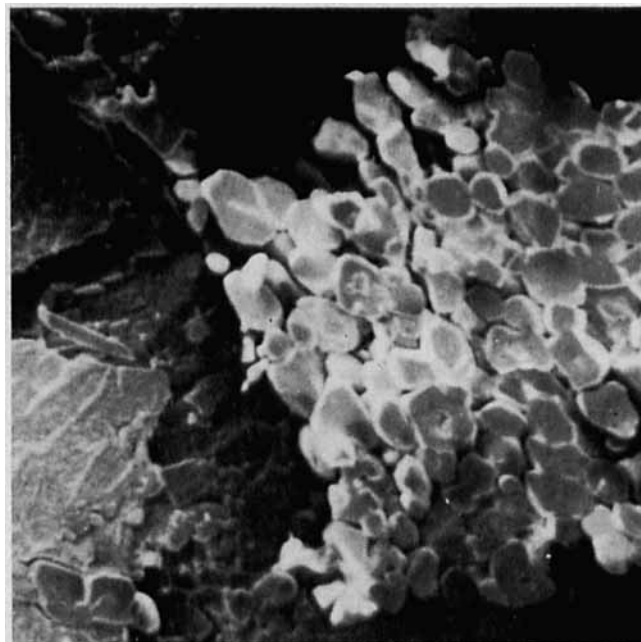

Figure 3—*Cross-sectional view of aspirin plus 10% starch tablets, dry (about 600×). Darkened, irregular shaped spots in starch grains are hilum canals.*
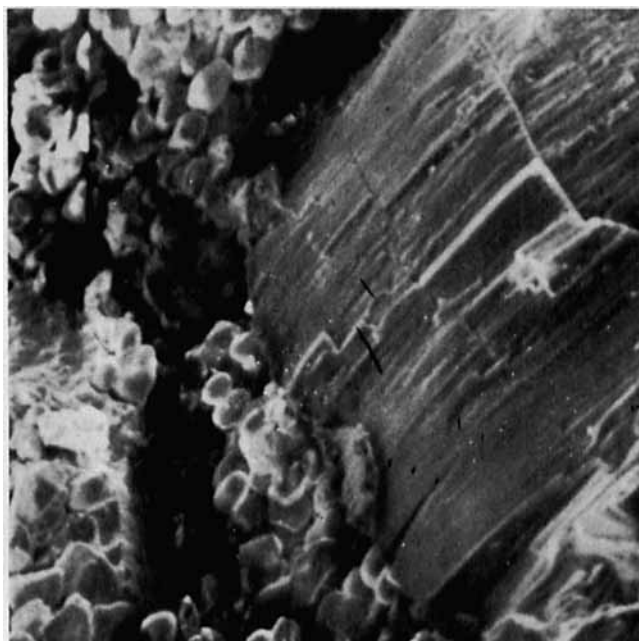
Figure 4—*Cross-sectional view of aspirin plus 10% starch tablets, moistened (about 600X). The large smooth surface is fused aspirin crystals.*

Examination of the surfaces of aspirin with 10% starch showed large agglomerations of starch grains. These masses seem to have created cracks and what could be interpreted as stresses in the tablet. The aspirin was fused to itself but not to the starch. A few short, dispersed chains were noted. Disruption of the surfaces occurred in the moistened area, with the rest of the area still smooth. The grains appeared prominent, and the subsurface also may have been loosened because of movement of the starch grains. Figure 1 shows clumps of flattened grains on the surface, and Fig. 2 shows how the grains seem to have become raised above the surface after moistening. The darker spots could have been places where the grains popped out. Figure 3 is part of a cross section illustrating clumping, two short chains, aspirin fusion, and hilum channels. Figure 4 gives a view of a crack with the characteristic clusters of starch grains.
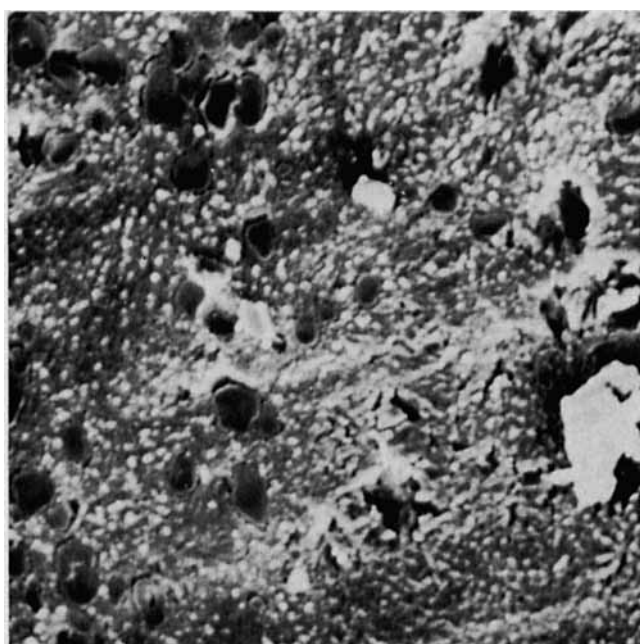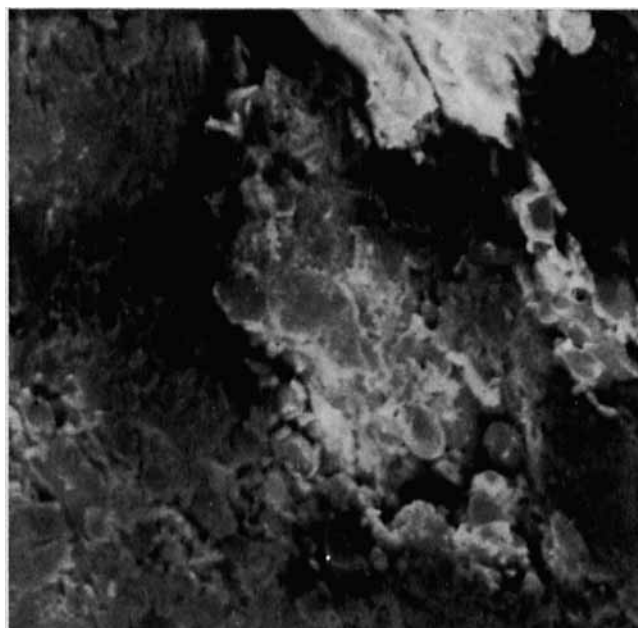

Figure 6—*Face view of tablet made from the commercial aspirin granulation, moistened (about 600X).*

In the tablets made with the commercial aspirin granulation, the starch grains appeared to be scattered and isolated with only a few agglomerates. When viewing the surface, the grains often seemed hidden under a thin layer of aspirin. The faces of the tablets appeared rough and grainy. Both the faces and cross sections appeared similar (Fig. 5). When water was added, there was only a minimal surface disruption and a minimal increase in roughness; starch grains became more visible. In cross sections, grains with hilum canals were seen. Figures 6 and 7 illustrate these surfaces after they were moistened; cracks appeared and the agglomerates became more pronounced.

Analysis of the surfaces of commercial aspirin tablets (Product B) showed that there were agglomerates of starch grains. There was no evidence of channels or pores lined with starch. Aspirin was mostly fused, but aspirin crystals and granules were often visible.
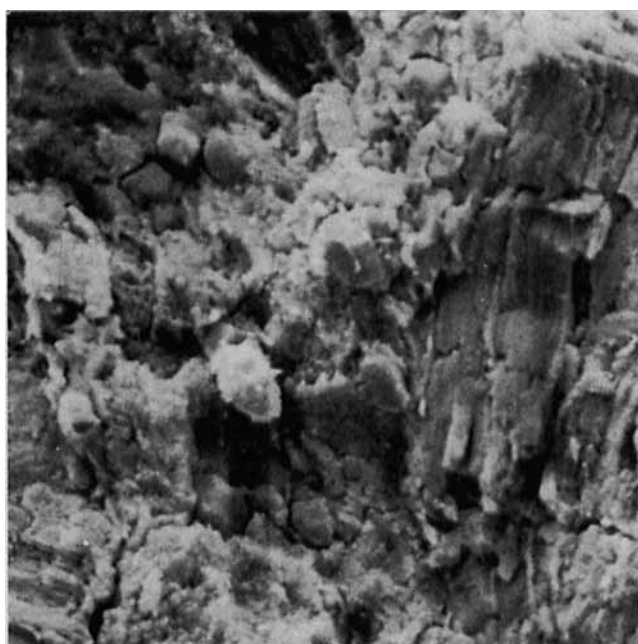

Figure 5—*Cross-sectional view of tablet made from the commercial aspirin granulation, dry (about 600X).*

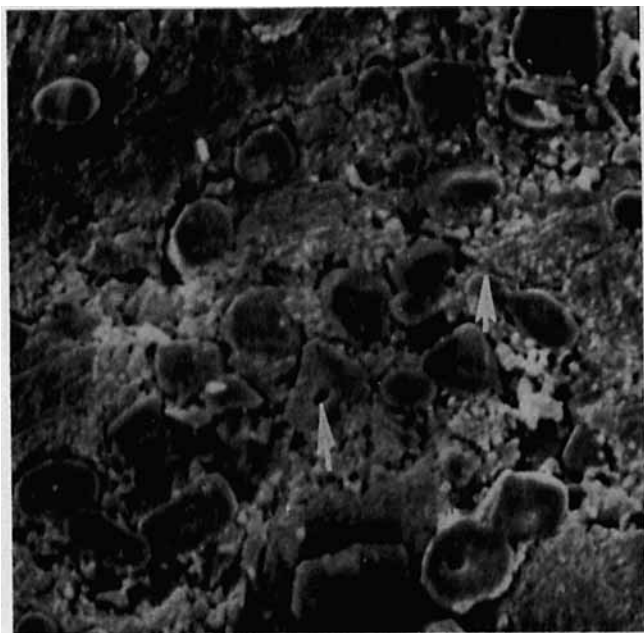**Figure 7**—*Cross-sectional view of tablet made from the commercial aspirin granulation, moistened (about 600X).*

Figure 8—Cross-sectional view of Product B, dry (about 720X). Hilum canals are readily apparent. The arrows point to hilum canals and cracks.

Figure 10—Face view of Product B, moistened (about 720X).

There was very little difference between the face and cross sections of the tablet. Figures 8 and 9 show clumping of starch, cracks in the surfaces, some loose aspirin crystals, and the rough surface. Examination of embossed letters showed less fusion of the aspirin. When moistened, the water soaked in very rapidly and did not spread on the surface. The moistened surfaces became raised and flaky in appearance. Figure 10 shows the disruption of the face of the tablets when moisture was added, and cracks, aspirin crystals, and starch are plainly visible. Figures 11 and 12 give evidence of disruption and clumps of starch grains but only an occasional chain, one grain thick. Hilum canals are again observed in the cross section.

Examination of a second commercial aspirin tablet (Product N) demonstrated a rough surface, with aspirin crystals and starch grains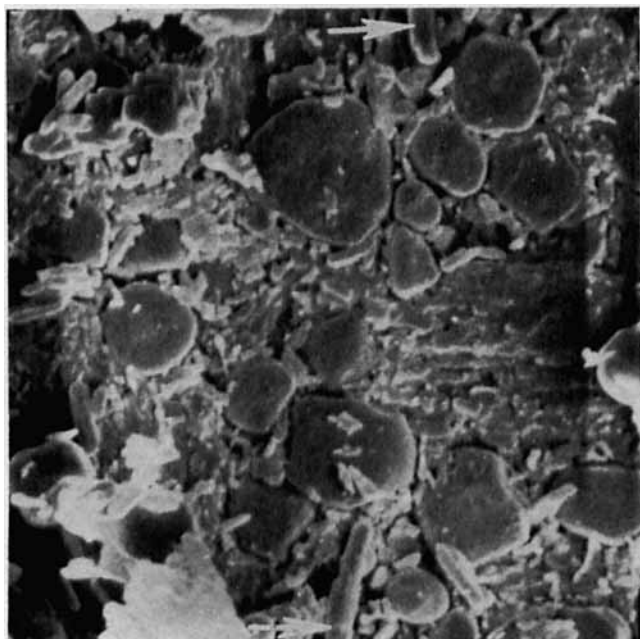 readily visible (Fig. 13). The agglomerates did not seem as plentiful as was observed in Product B. Figure 14 shows a cross section of the tablet with hilum canals discernible, and Fig. 15 verifies surface disruption when moisture was added. The aspirin crystals and starch grains are readily apparent. Figure 16 shows the edge of the moistened area. The degree of breakup of the brighter two-thirds compared to the relative smoothness of the darker one-third is evident. The water readily soaked into the tablet surfaces, leaving no sharp boundary visible.

The third brand of aspirin tablets (Product S) studied again showed relatively rough surfaces, with aspirin crystals and starch grains discernible (Fig. 17). Figure 18 illustrates fused aspirin and a large clump of starch grains. When the surfaces were moistened, the aspirin crystals and starch grains were more conspicuous. Compare Figs. 17 and 19. The area moistened was only just visible to the naked eye. Fine cracks appeared where there was a local concentration of starch grains. The layer of plate-like crystals seen

Figure 9—Face view of Product B, dry (about 720X). The arrows point to loose aspirin crystals.

Figure 11—Cross-sectional view of Product B, moistened (about 720X).
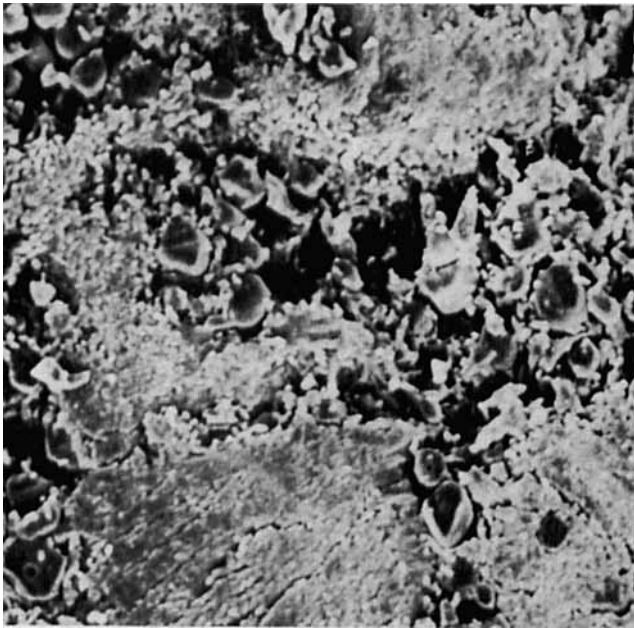
Figure 12—*Cross-sectional view of Product B, moistened (about 450×).*

Figure 14—*Cross-sectional view of Product N, dry (about 720×). The arrow points to the hilum canals.*

in Fig. 20, a view of the moistened cross section showing disorganization of the area, was not observed in other tablets.

Finally, aspirin–phenacetin–caffeine tablets were examined. The surfaces were smooth, with only occasional starch grains and crystals evident. Water did not readily penetrate the surfaces and no discernible disruption, occurred. The faces exhibited more discontinuity than the cross sections where only occasional starch grains were observed. No new additional structures not previously mentioned were seen in these tablets.

DISCUSSION

The scanning electron photomicrographs reveal that the surface of the starch grains is smooth. The hilum normally seen in light microscopy appears to be an internal phenomenon since it is not visible in the scanning electron photomicrographs (6). Cross sectioning of tablets also results in the cross sectioning of starch grains,

so hilum channels are clearly visible, indicating a hollow starch grain. These channels appear normal, indicating no damage due to heat or other processing treatments[9], but drying may increase the number of the canals (7, 8). Not all grain cross sections showed this channel, since the channel may not cover the whole length of the grain. Since birefringence is present, the canals apparently do not affect molecular orientation (7).

There was no indication of starch-lined pores, but occasional chains of starch grains were observed. These were only one grain thick and of finite length (from six to eight grains). The macroscopic and microscopic observations of Patel and Hopponen (9) and Commons et al. (10) that the starch formed chains and that starch lined pores could not be confirmed after study of a large
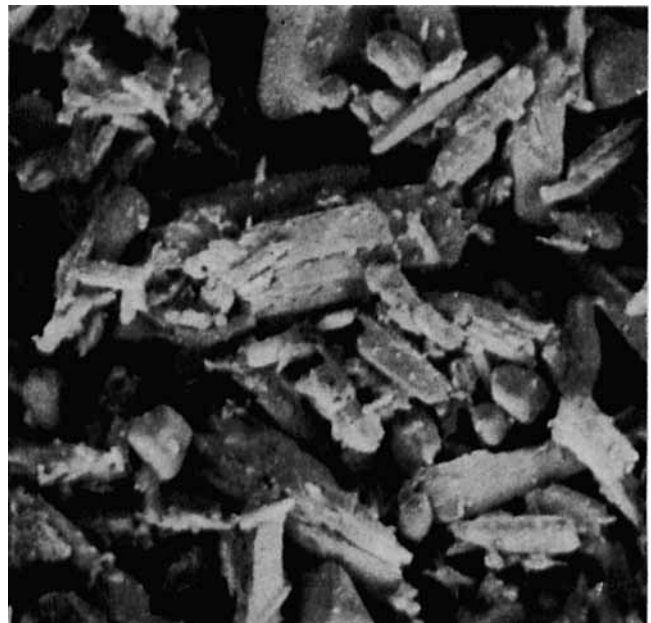

Figure 13—*Face view of Product N, dry (about 720×).*

Figure 15—*Face view of Product N, moistened (about 720×).*
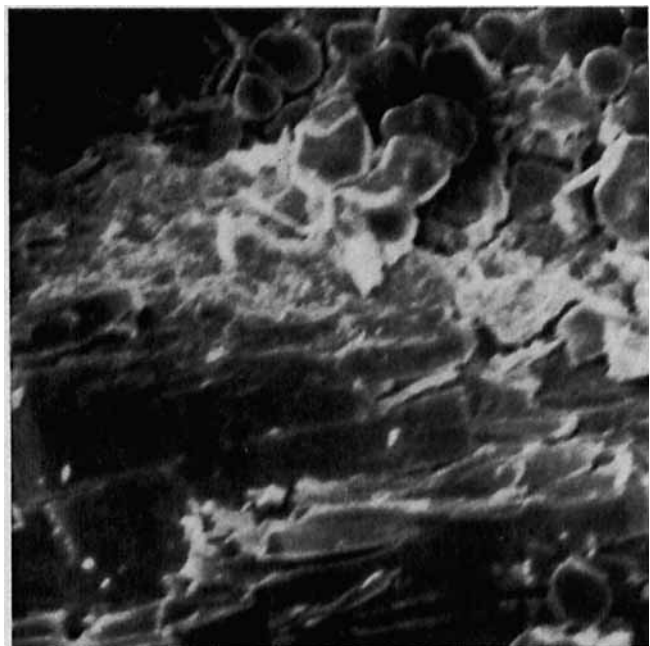
Figure 16—*Face view of Product N at edge of moistened area (about 720X).*

Figure 18—*Cross-sectional view of Product S, dry (about 720X). Large, smooth area appears to be aspirin crystals.*

number of tablet cross sections. The occasional isolated chains observed (Figs. 3 and 12) would not have a significant effect on tablet disintegration. Starch-lined pores or starch surrounding individual granules or crystals were absent. If they did occur, there would have been evidence of starch chains at least two grains thick on a cross section. These were never seen.

Starch is poorly compressible and does not appear to adhere to itself or to other materials in the tablet, and it does not fuse. The starch was not uniformly distributed in the tablets and often appeared as agglomerates in the tablets examined. These result in weak points within the tablet and in fine cracks around the agglomerates.

Isolated and embedded grains cannot cause disruption of the tablet that would result in disintegration. When moisture is added, the surface is generally disrupted. The degree of breakup of the surface depends on the number and size of the starch grain agglomerates (total starch concentration in the tablet) and the pressure

used. The greater the number and size of agglomerates, the greater is the disruption. There could be a critical concentration, as suggested by Commons et al. (10). The greater the pressure used to form the tablet, the greater is the fusion of the tablet ingredients (except starch) and the greater is the force needed to disrupt the tablet.

Drying starch grains may cause the surface layer of molecules to become more tightly bonded intermolecularly (7). It was postulated (12) that microcrystalline cellulose in tablets is a special form of cellulose fibril in which the individual crystallites are held together mainly by hydrogen bonding. Water causes these bonds to break, producing tablet disintegration. When moisture is added, the degree of association of the starch molecules is reduced because the hydrogen bonds between the hydroxy groups are broken. The hydrated molecules could reduce surface attraction and even cause the grains to repel each other. Thus, the moisture releases stress built up in the starch grains due to their relatively low moisture

Figure 17—*Face view of Product S, dry (about 720X).*

Figure 19—*Face view of Product S, moistened (about 720X).*

Figure 20—*Cross-sectional view of Product S, moistened (about 720×).*

content and distortion caused by pressure. Fuhrer (3) mentioned that pressure distorts potato starch grains and theorized that energy-rich grains are formed, so that no additional energy is needed for swelling. Close scrutiny of the grains before and after water was added seemed to indicate that the grains are less angular, supporting the theory that there is a degree of restoration to the original grain shape due to hydration of the starch molecules. The hydration and resulting effects occur rapidly (*i.e.*, a fraction of a second). The hydration of the hydroxy groups and sorption of water could account for the slight swelling (5–10%) of the starch (9, 11). This amount of swelling could result in about a 70% increase in volume,

and the swelling would take a few seconds. These two combined effects of the attachment of water molecules and the increase in volume of the grains cause sufficient force to break up the tablet. Channels or pores lined with starch grains were not manifest in any of the surfaces examined. Therefore, the thesis that starch grains act as as a "wicking agent" and draw water into the tablet should be layed aside. The conditions for rapid disintegration are sufficient starch agglomerates, low pressure, and presence of water.

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Dissolution Rate Studies III: Effect of Type and Intensity of Agitation on Dissolution Rate

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Abstract ☐ The effect of flow rates on dissolution rates using a continuous flow, column-type apparatus was determined. The flow method of agitation is compared to three other types used with the static beaker procedure. The advantages of the column-type apparatus in attaining low intensities of agitation without sacrificing accuracy or homogeneity are discussed.

Keyphrases ☐ Dissolution rates—effect of flow agitation, compared to compendial methods, column-type equipment ☐ Agitation, column flow type—effect on dissolution rates, compared to compendial methods

The importance of low agitation intensities in detecting real differences in dissolution rates and in obtaining good *in vitro–in vivo* correlations in dissolution rate experiments has been established (1, 2). In addition, the importance of the accurate control of the

degree of agitation has been pointed out (2). However, the use of low agitation intensities and the accurate control of variables associated with agitation are severely limited with the static beaker method but not with the continuous flow, column-type procedure (3,