Mechanism of Action of Starch as a Disintegrating Agent in Aspirin Tablets

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A study was made of the mechanisms by which starch may cause disintegration of tablets. Dried cornstarch was found to increase in volume by 78 per cent when suspended in water. In aspirin tablets where contact of starch grains is continuous in the interparticle spaces, disintegration is rapid and effective even when void spaces are eliminated. Where contact is not continuous, disintegration is slowed and appears to depend on the degree of contact between starch grains and aspirin particles and on the size of interparticle spaces. The primary mechanism appears to be a swelling action. Capillarity *per se* does not appear to have a disintegrating effect.

STARCH IS widely used as a disintegrating agent in tablets. It has been generally accepted that it acts as a disintegrating agent through a swelling action when exposed to water (1). Crisafi and Becker (2) have demonstrated that starch will absorb about 20% of its weight of water in 24 hr. when exposed to an atmosphere of 95% relative humidity at 27°. They make no mention of any volume changes involved in the process. Kerr (3), in his book on starch, states that in the natural state starch is insoluble in cold water but appears to absorb 25 to 30% and does not swell appreciably. Curlin (4) has suggested that the disintegrating effect is due to capillary action rather than swelling. The objective of this study was to investigate the mechanism by which starch functions as a tablet disintegrating agent.

EXPERIMENTAL

Swelling of Starch in Water.—Cornstarch (Argo brand) dried for 2 hr. at 110° was measured microscopically using a calibrated eye piece. Measurements were made along the longest dimension of the grain using high power (10× eyepiece and 45× objective). Slight adjustments of focus were made to get the sharpest image. Two-hundred grains were measured for each sample. Slides made of dry starch without a suspending medium gave an arithmetic mean diameter of 9.0 μ and a mean volume diameter of 10.8 μ. A light liquid petrolatum suspension gave values of 9.1 and 10.5 μ, respectively. When suspended in water at room temperature (23°), the arithmetic mean diameter increased within a few seconds to 11.2 μ, the mean volume diameter to 13.1 μ. The differences are statistically significant at the $P = 0.01$ level using the t test. Using the mean volume diameter and assuming a spherical shape, the increase in volume was calculated to be 78% of the original.

Mode of Disintegration of Tablets Containing Starch.—To eliminate variables other than the disintegrating agent, aspirin was chosen as the material for tableting. It was desired to note the effect of different sized spacings between the tablet particles on the mode and rate of disintegration and to eliminate as much as possible other spaces within the tablet. To this end, aspirin powder (U.S.P. grade, Merck) was recrystallized from acetone. The crystals were dried at 90° and screened into several sizes using a Fisher Ro-Tap sifter and standard screens (Tyler series). The crystal sizes were designated as $^{14}/_{20}$ (all crystals passing a No. 14 screen but not a No. 20), $^{20}/_{40}$, $^{40}/_{60}$, $^{60}/_{100}$, and below 100 (all crystals passing a No. 100 screen. The starch was dried at 110° for 2 hr. and stored in a tightly closed container until used. Tablets were compressed on a Colton model 3E single punch tablet press using concave 8.8-mm. punches. The material for each tablet (0.5 Gm.) was weighed out, placed manually in the die, and the machine turned slowly by hand to produce as much uniformity as possible in the tablets. The finished tablets were individually weighed and the thickness measured with a vernier caliper to insure uniformity in dimensions. Disintegration times were determined in a U.S.P.-type apparatus at 20 c.p.m. using distilled water at 23° and a No. 10 mesh screen on the bottom of the basket. Table I reports the results on aspirin tablets containing 10% by weight of starch. The results represent the averages obtained on 7 tablets at each crystal size.

The manner of disintegration changed between the $^{40}/_{60}$ and the $^{60}/_{100}$ tablets. The $^{14}/_{20}$, $^{20}/_{40}$, and $^{40}/_{60}$ tablets fell apart rapidly into a mass of crystals. The $^{60}/_{100}$ and below 100 tablets showed a progressive disintegration from all sides and a steadily shrinking core.

Samples of the tablets were examined microscopically to note the manner of distribution of starch. Transverse sections were made and scraped smooth with a razor blade. The sections were stained with iodine solution and examined after drying. The $^{14}/_{20}$ tablets showed a heavy concentration of starch grains in all the channels between the aspirin crystals. The $^{20}/_{40}$ and $^{40}/_{60}$ tablets showed a similar pattern but with decreasing amounts of starch in the channels. The $^{60}/_{100}$

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tablets displayed lines of starch granules around each crystal with many discontinuities where no starch was visible. In the below-100 tablets, starch grains were scattered in small groups among the aspirin crystals with few continuities in the channels.

Since the disintegration times of the tablets containing 10% starch were so short, a series was prepared with only 5% starch. Two additional crystal size designations were made, $^{100}/_{250}$ and below 250. The tablets were prepared in the same manner as previously. The screen on the disintegrating apparatus was replaced with a No. 6 screen to facilitate passage of the larger size crystals. The results, reported in Table II, represent the average disintegration times for five tablets.

The $^{14}/_{20}$ and $^{20}/_{40}$ tablets separated rapidly into large particles. The $^{40}/_{60}$ and $^{60}/_{100}$ tablets slowly broke up into large fragments which then disintegrated into crystals. The $^{100}/_{250}$ tablets separated in slices from the faces to the center, the slices then separating into granules. The below-250 tablets were not affected for some time, then separated into slices from the faces toward the center. The slices slowly separated into granules. Microscopic examination of the tablets revealed that the starch channels were continuous only in the $^{14}/_{20}$ and $^{20}/_{40}$ tablets.

TABLE I.—DISINTEGRATION TIMES OF ASPIRIN TABLETS CONTAINING 10% STARCH

Crystal Size	Time, sec.
$^{14}/_{20}$	60[a]
$^{20}/_{40}$	24[a]
$^{40}/_{60}$	12
$^{60}/_{100}$	18[b]
Below 100	35[b]

[a] The tablets fell into large particles in less than 10 sec. However, the particles passed the screen very slowly; thus, the recorded times are not a true measure of the time for the tablet to lose its shape and identity. [b] The tablets disintegrated toward the center from all sides retaining their shape during disintegration. The time indicated essentially marks the time of disintegration of the last of the tablet core.

TABLE II.—DISINTEGRATION TIMES FOR ASPIRIN TABLETS CONTAINING 5% STARCH

Crystal Size	Time, sec.
$^{14}/_{20}$	17
$^{20}/_{40}$	17
$^{40}/_{60}$	55
$^{60}/_{100}$	50
$^{100}/_{250}$	120
Below 250	>900

Penetration of Water into Tablets.—The change of the mode of disintegration of tablets containing 10% starch from the $^{40}/_{60}$ to the $^{60}/_{100}$ tablets and the appearance of discontinuities in the pattern of starch distribution in the $^{60}/_{100}$ tablets suggests a relationship between the two. Conceivably, the change in disintegration could be due to a change in the facility or the degree of penetration of water into the tablet. Samples of each crystal size group of the tablets were tested to determine to what extent water would penetrate into the tablet in a given time period. A series of flat-faced tablets with 10% starch were prepared for this purpose. The thickness of each tablet was measured with a vernier caliper. A 0.05-ml. drop of iodine solution, containing 50% alcohol to retard swelling of the starch, was placed in the center of a small watch glass coated with liquid paraffin to prevent spreading of the drop. The tablet was placed in contact with the drop and penetration allowed to proceed for 10 sec. The tablet was removed, blotted dry, and allowed to dry at room temperature. It was then carefully shaved with a razor blade to remove the colored portion, and the thickness of the remainder measured. The tablets showed the following per cent of penetration: $^{14}/_{20}$, 49%; $^{20}/_{40}$, 38%; $^{40}/_{60}$, 38%; $^{60}/_{100}$, 22%; and below 100, 9%.

Effect of Capillarity Alone.—To determine the effect of capillarity without expansion as a disintegrating effect, tablets of aspirin and dextrose were prepared and tested for disintegration time. Dextrose was chosen because it is a highly water-soluble material with a strong attraction for water. It has a chemical structure closely related to that of starch. It should be able to draw water into the spaces between the hydrophilic aspirin crystals without any concomitant swelling. Powdered dextrose (U.S.P. anhydrous, Mallinckrodt) was passed through a No. 80 screen and added in 10% concentration to $^{40}/_{60}$ aspirin crystals. Compression into 0.5-Gm. tablets was done with 8.8-mm. flat-faced punches. The material for each tablet was individually weighed and 5 series of tablets of increasing hardness were prepared by lowering the position of the upper punch for each succeeding series. When subjected to a disintegration test they showed the following disintegration times (average of four tablets): 140, 130, 191, 210, and 253 sec. The mode of disintegration in this case appeared to be a loss of cohesiveness of the tablet as the dextrose dissolved. The tablets gradually eroded away as fragments separated from the outer sides. The fragments for the most part were of the size of the aspirin crystals used. It appeared that the crystals simply fell away as the dextrose layer dissolved. There were no indications that disintegrating forces were acting in the interior of the tablet. A drop of

TABLE III.—VOID SPACES IN FLAT-FACED TABLETS OF ASPIRIN CONTAINING 5% STARCH

Crystal Size	Wt., Gm.	Vol., ml.	Void Space, ml.	Void Space, %
$^{14}/_{20}$	0.2999	0.2250	0.0110	4.89
$^{20}/_{40}$	0.2997	0.2242	0.0104	4.64
$^{40}/_{60}$	0.2993	0.2244	0.0109	4.85
$^{60}/_{100}$	0.2966	0.2208	0.0102	4.62
$^{100}/_{250}$	0.2942	0.2193	0.0095	4.34
Below 250	0.2950	0.2211	0.0106	4.77

dilute aqueous gentian violet solution placed on the surface of these tablets penetrated approximately 50% of all tablets in 4 min., except the softest in the series which was completely penetrated in less than 2 min.

The effect of capillarity was further checked by the use of aluminum hydroxide tablets. Aluminum hydroxide powder (dried gel, Reheis) was made into granules by slugging. Preparation of slugs in the usual manner was not possible because jamming of the machine occurred. Individual slugs were prepared by manually placing the aluminum hydroxide in the die and turning the machine by hand. Before preparing each slug, the punches and the die were lightly lubricated with magnesium stearate applied with a camel hair brush. The slugs were crushed and screened into granules of three sizes, $^{14}/_{20}$, $^{20}/_{60}$, and below 60. When compressed into tablets with 10% starch and tested, they disintegrated in times of 8, 18, and 20 sec., respectively. Microscopic examination of the tablets stained with iodine solution showed the distribution of starch to be continuous around the aluminum hydroxide particles. When placed in 95% ethanol, where penetration of solvent can still occur but no swelling of starch results, the tablets did not disintegrate. The penetration of the tablets by ethanol was checked by the same procedure as used to determine the penetration of aspirin tablets by an iodine solution. A measured drop of an ethanolic solution of iodine was used. In 10 sec. it penetrated the tablets to an average depth of 50% of the total thickness. This would seem to indicate that swelling is a necessary condition for disintegration but does not entirely eliminate the possibility of capillarity as a disintegrating force. The surface tension of ethanol is only about one-third that of water. In its simplest terms, the pressure produced by capillarity can be equated to $2\ \gamma/r$, where γ is the surface tension of the liquid, and r is the radius of the capillary. The difference in surface tensions of ethanol and water could very well be sufficient to prevent any capillary effect from being noted. The search for a liquid with a surface tension near that of water, capable of wetting starch, and not able to dissolve aspirin too readily nor too rapidly, suggested glycerin. It has a surface tension of 63 dynes/cm. compared to a value of 73 for water (5). It did not cause disintegration of $^{20}/_{40}$-aspirin tablets containing 10% starch even after 12 hr. of contact. The penetration of glycerin into the interior of the tablets was checked to insure that it did occur. A drop of glycerin (the volume was not measured because the viscosity makes such measurement almost meaningless) containing 0.6% iodine was placed on the surface of flat-faced $^{20}/_{40}$ tablets. It penetrated to an average depth of 30% in 2 min. These results again suggest that capillarity does not constitute a disintegrating force in this situation.

Relation of Void Space to Disintegration Time.—Since the volume of starch increased in water, the authors felt it would be of interest to investigate the relationship of the volume increase and the void-space volume of the tablets. In order to measure the volume, 8.8-mm. flat-faced punches were used to prepare the tablets. The dimensions of the tablets were measured with a vernier caliper. The densities of the aspirin crystals and of the starch were determined by the pycnometer method (6) using petroleum ether as the liquid. At 20° the density of aspirin was found to be 1.396 Gm./ml., that of starch 1.513 Gm./ml. Void spaces were determined as the difference between the volume calculated from the dimensions of the tablet and the volume of the tablet solids calculated from their densities.[1]

Table IV.—Influence of Compression Force on Void Space and Disintegration Time of Aspirin Tablets Containing 10% Starch

Pressure, lb./sq. in.	Void Space, %	Time, sec.
2000	7.0	7
4000	4.5	6
6000	2.3	8
8000	2.7	7
10000	2.0	8
12000	1.6	10
14000	0.1	10
16000	<0.1	10

Table V.—Influence of Compression Force on Void Space and Disintegration Time of Aspirin Tablets Containing 5% Starch

Pressure, lb./sq. in.	Void Space, %	Void Space as % of Starch Vol.	Time, sec.
2000	3.36	75	50
4000	3.20	71	60
5000	2.95	66	30
7000	1.95	43	53
10000	1.78	39	63
13000	0.97	21	64
15000	0.46	10	60

Tablets prepared from equal weights of different sizes of crystals and compressed to an equal volume should exhibit the same amount of void space, although the size of individual pores may differ substantially. A good uniformity of void volume was found in such a series prepared with 5% starch. The results are reported in Table III representing the averages of four tablets in each group.

Since the void volumes are substantially the same, the size of the openings between particles must get smaller as the crystal sizes get smaller and the number of crystals per tablet increases. This would lead either to the presence of interparticle spaces too small to permit ready entry of water or to discontinuities between starch grains in the spaces. Either circumstance would explain the longer disintegration time and the change in mode of disintegration for tablets of small crystal size.

The average volume of starch in the tablets was 0.00984 ml. which on swelling by the 78% indicated in water suspension would increase by 0.00768 ml. The increase is less than the void volume but, since disintegration requires only that the aspirin

[1] The void space calculated in this manner may not accurately represent the spaces between crystals since crushing of crystals during compression may lead to formation of new spaces in which no starch will be found. However, it will represent a good first approximation of the space into which water can penetrate.

particles be forced apart from each other, the effect could be exerted by starch grains properly located between aspirin particles even though empty spaces remained in the tablet structure. This suggests that an optimum ratio of starch volume to void space may exist at which disintegration would be most effective. In an attempt to find such a ratio, a series of tablets was prepared using 10% starch and $^{40}/_{60}$ aspirin crystals. Flat-faced tablets were prepared using a Carver hydraulic laboratory press to supply the compression force. The material for each tablet was individually weighed, placed in the die, and compressed. The pressures recorded were the dial readings of the press. The tablets were weighed and measured to determine void spaces and their disintegration times then determined. The averages obtained on six tablets at each pressure are reported in Table IV.

The disintegration times were too close together to detect any real minimum due to starch–void ratios. It was surprising to find that even at the highest pressures used, when void spaces were substantially eliminated, a rapid disintegration was still effected. This would indicate that as long as the starch grains were in continuous contact with each other their affinity for water would draw it into the tablet without regard to pore size. The three hardest tablets in the series (those with times of 10 sec.) showed a change in the mode of disintegration. They disintegrated from the outer sides toward the center.

If an optimum ratio of starch volume to void space did exist, it should be most readily detected when the channels were not completely filled with starch grains. To check this point, a series of flat-faced tablets was prepared from $^{40}/_{60}$-aspirin crystals with 5% starch. The results on six tablets at each pressure are recorded in Table V.

The decrease in disintegration time at 5000 lb. of pressure would seem to indicate the most favorable combination of conditions for this particular series. In each case the calculated increase in starch volume is larger than the total void space.

DISCUSSION

The increase in volume of starch in water strongly suggests that this is the principal mechanism for its action as a disintegrating agent. The disintegration of starch-containing tablets of aluminum hydroxide in water but not in ethanol and of aspirin tablets in water but not in glycerin adds support to this view. Where contact of starch grains in the interparticle spaces is continuous, disintegration is most rapid and is only slightly affected by changes in the amount of interparticle void space. In this situation, even when void space is substantially eliminated, starch is capable of drawing water into the interior of the tablet and producing rapid disintegration. When contact of starch grains in the interparticle channels is not continuous, the situation changes. The time for disintegration increases and the mode of disintegration changes. The appearance of a minimum disintegration time produced in aspirin tablets containing 5% starch in discontinuous contact might be attributed to two factors under the experimental conditions used. Berry and Ridout (7) have suggested that decreases in disintegration time would be produced by increasing contact between tablet particles and starch grains. This appears to be the case until a minimum time is reached. At this point, the second factor, a limit to the pore size which will allow entry of water into the tablet, begins to operate. A smaller pore size which could be occluded by air would hinder entry of water as was demonstrated by Wurster and Seitz (8). This would be particularly true in the case of a hydrophobic substance such as aspirin. In this situation, disintegration of the tablet would be slowed but could continue, either as the pores are enlarged by expanding starch grains near the surface of the tablet, or as diffusing water vapor progressively reaches and swells starch grains deeper in the interior of the tablet. Capillarity *per se* does not appear to have a disintegrating effect, although it may be a factor in aiding the entry of water into the tablet when the pore size is favorable.

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