Mechanism of Action of Starch as a Tablet Disintegrant I

Factors that Affect the Swelling of Starch Grains at 37°

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A study was initiated to determine if starch grains swell at 37° and what environmental conditions may influence swelling. To determine the extent of swelling which starch undergoes in various media, individual grain dimensions were measured microscopically. Full factorial experiments were conducted, and analyses of variance were calculated to determine whether significant differences in the mean grain sizes could be demonstrated when environmental conditions were changed. Potato, corn, and amioca starches and moisture content showed significant swelling in distilled water and simulated gastric fluid U.S.P. This was postulated as due to initial size difference of the grains being maintained during the experiment. Variation in pH had very little effect on swelling; however, evidence was obtained to show that the less acid medium produced more swelling than the media of lower pH. Salts did affect swelling, and results indicated that salts of polyvalent cations produced more swelling than the salts of monovalent cations. Analysis of the effect of time on swelling indicated that any swelling of the starch grains is apparently instantaneous.

It is desirable that a tablet, when used, disintegrate as rapidly as possible. Ideally, the process of tableting should not alter the therapeutic action of a drug or the time in which this action is produced. The same effect should be produced in essentially the same time when a tablet is swallowed as when the drug is taken in powder form.

The rate at which a physiological effect is produced from a drug taken orally is dependent upon the rate of absorption from the gastrointestinal tract. Before a drug in tablet form may be absorbed, it must first be released from the tablet by disintegration of the tablet. The usefulness of a tablet, therefore, arises almost wholly from its ability to disintegrate upon contact with liquid.

Compressed tablets are ordinarily manufactured containing substances to accelerate or aid their disintegration. Cornstarch has long been the standard disintegrant for compressed tablets. The mechanism by which starch functions as a tablet disintegrant has been assumed to be that the starch grains swell when in contact with moisture, causing the tablet to break open.

Knowledge of the exact mechanism of action of starch as a tablet disintegrant would be useful in the development of more efficient disintegrating agents.

DISCUSSION

Review of Pertinent Literature.—Little work has been reported on the exact mechanism of action of starch as a disintegrating agent. After an extensive literature search, all references which had been located state that starch acts as a disintegrant by swelling, but no data or proof are presented or referred to indicate that starch swells sufficiently *in vivo* or *in vitro* to cause disintegration (1, 2).

Curlin (3) tested the disintegration of aspirin tablets in cold water and found by microscopic examination that the starch grains were not swollen after disintegration.

Billups and Cooper (4) reviewed the proposed theories explaining the mechanism of action of tablet disintegration. They indicate that the most widely held view is that disintegration is caused by absorption of water by the disintegrating agent and development of pressure within the tablet by swelling or expansion of the disintegrating agent. In their study on the correlation of water absorption with tablet disintegration time, they concluded that while water absorption is a common qualitative characteristic of many disintegrating agents, it is not a quantitative measure of their effectiveness. Disintegrating agents with the highest rates of water absorption did not produce the fastest disintegration times. Some evidence supported the view that disintegrating agents with the highest rates of water absorption produced the longest disintegration times. Their results also showed that the amount of water absorbed by cornstarch, dried to a constant weight, after exposure to 98% relative humidity, was only 0.5% w/w in 50 min.

Crossland and Favor (5) employing a viscous water-binding dispersion medium (sodium alginate and high viscosity type carboxymethylcellulose), showed by means of viscosity measurements the stages of swelling. In the starch–alginate–water system, the first indications of swelling are observed at about 55°.

Leach, McCowen, and Schoch (6) evaluated swelling of various starches over a range of pasting temperatures (about 50–95°) and found that the swelling pattern was greatly influenced by the species of starch. Cornstarch showed a limited two-stage swelling, whereas potato starch underwent very

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rapid and unrestricted swelling at about 55°. The swelling of the grains was determined from the weighing of starch after submersion in water and correcting the value for solubles.

Hellman, Boesch, and Melvin (7) compared swelling of starch grains to water absorbed from atmospheres of different moisture content by following the dimensional changes of individual starch grains microscopically at a temperature of 25.10° over a period of 8–24 hr. At 100% relative humidity cornstarch showed a 9.1% increase in diameter over the diameter of vacuum dried starch. The corresponding increases for other starches examined under similar conditions were 12.7% for potato starch, 28.4% for tapioca starch, and 22.7% for waxy cornstarch.

Variation in the effect of different salt solutions on initial gelatinization of starches was shown by Sandstedt, Kempf, and Abbott (8). They showed that salt solutions change not only the temperature of initial gelatinization but also the initial temperature of each stage of gelatinization, length of transition period between stages, and rate or amount of gelatinization in each stage of the entire course of gelatinization. These changes were not correlated with each other. Their data indicated that each change in the course of gelatinization was due to a different property of the salt.

Abbott *et al.* (9) determined *in vitro* disintegration time of several commercial tablets in simulated gastric juice and human gastric juice and showed that disintegration is prolonged in human gastric juice. There is some correlation between prolongation of disintegration and gastric mucoid content. A high mucoid content in gastric juice may increase the rate of disintegration more than 16 times. *In vitro* disintegration is prolonged in simulated gastric juice if the tablets are first exposed to mucoidal material from human gastric juice.

EXPERIMENTAL

This study was planned to determine if starch grains swell at 37° and what environmental conditions may influence the swelling of starch grains at 37°. The following variables were studied: (*a*) time, (*b*) pH, (*c*) effect of ions and ionic concentration, (*d*) starch species, and (*e*) simulated gastric fluid U.S.P. (SGF). Evanson and DeKay (10), in a study of tablet disintegration, reported inconsistent results when distilled water was compared with artificial gastric juice with respect to time. For this reason distilled water was included as a submersion medium in this study to allow comparisons with other submersion media.

Procedure.—To determine the extent of swelling, if any, which starch undergoes in various media, microscopic examination was used and individual grain dimensions were measured. For the measurements of corn and amioca starches, an oil immersion 97× objective and 5× ocular micrometer were used. For the measurements of potato starch, a 43× objective and a 5× ocular micrometer were used, and measurements were mathematically converted to 485 magnification. Owing to the spherical and ellipsoidal shapes of the grains, the apparent grain length changed with position of focus. To achieve uniformity, each grain was measured at that depth of focus producing maximum diameter. The starch samples were slurried in the appropriate media at 37° and maintained at that temperature until a sample was removed at the appropriate time, placed on a slide, and covered with a cover slip. One hundred or 200-grain measurements were made from each slide. A mechanical stage was used and as the field of view was moved horizontally, each starch grain crossing the micrometer scale was measured. Each scale division on the micrometer represents 1.80 μ when using the 485 magnification.

Commercial grades of corn, potato, and amioca (waxy corn) starches were chosen for the initial investigation. To determine the effect of moisture content on swelling, both low and high moisture content forms of each starch were examined. For the high moisture content, the commercially available starches[1] were used. For the low moisture content, each starch was dried at 93° until a constant moisture content was obtained as determined on a moisture balance.[2] Moisture contents obtained were as follows: cornstarch, 2.25% w/w; potato starch, 2.25% w/w; and amioca starch, 2.88% w/w. In addition to these dried starches, a commercial redried cornstarch[3] (P-825) containing 1.5% maximum moisture was examined.

RESULTS AND DISCUSSION

In examining the factors influencing the swelling of starch grains, full factorial experiments were designed, and analyses of variance were calculated to determine whether significant differences in the grain sizes could be demonstrated when environmental conditions were changed. Preliminary experiments showed that the method of measurement was reproducible.

Distilled water and SGF were compared as submersion media by varying the type of starch, moisture content, and time in two 2 × 3 × 3 factorial designs. The mean grain sizes are shown in Table I for the distilled water and in Table II for SGF. In each experiment the only single effect producing a significant difference in grain size was the type of starch. In each case, the type of starch was significant at the 0.5% level and was shown by Duncan's multiple range tests (11) to be due to the potato starch. No significant difference was shown between corn and amioca starches.

The mean grain size of potato starch is approximately 29 μ while that of cornstarch is approximately 10.5 μ and that of amioca is approximately 9.5 μ. The large difference in mean grain sizes between the potato and the cornstarches would result in a larger error mean square term in the analyses of variance. This is due to the fact that the variances are proportional to the mean grain sizes. Because of this, the analyses of variance were recalculated omitting the potato starch data. This was done to obtain a more sensitive comparison between corn and amioca starches, whose mean grain sizes were more nearly the same. Moisture content and time became significant at the 2.5%

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[1] Cornstarch and potato starch marketed by S. B. Penick and Co. as Melojel (MJ) and amioca starch marketed by National Starch and Chemical Corp.

[2] Cenco Moisture Balance, Central Scientific Co., catalog No. 26680-1.

[3] Marketed as Purity 825 by National Starch and Chemical Corp.

TABLE I.—EFFECT OF MOISTURE CONTENT AND TIME ON MEAN GRAIN SIZES OF VARIOUS STARCHES SUBMERSED IN DISTILLED WATER

		Mean Grain Sizes in Scale Divisions[a] — Time, min.		
Type	Moisture	0	5	30
Corn	High (MJ)	6.133	6.129	5.823
	Low (P-825)	5.676	5.919	5.652
Potato	High	16.354	14.863	11.948
	Low	16.243	12.935	14.679
Amioca	High	5.482	6.157	6.221
	Low	5.063	5.672	6.245

[a] One scale division = 1.8 μ.

TABLE II.—EFFECT OF MOISTURE CONTENT AND TIME ON MEAN GRAIN SIZES OF VARIOUS STARCHES SUBMERSED IN SGF

		Mean Grain Sizes in Scale Divisions[a] — Time, min.		
Type	Moisture	0	5	30
Corn	High (MJ)	6.133	6.408	6.221
	Low (P-825)	5.676	5.805	5.955
Potato	High	16.354	13.482	12.935
	Low	16.243	20.042	17.065
Amioca	High	5.482	6.388	6.467
	Low	5.063	6.320	6.225

[a] One scale division = 1.8 μ.

TABLE III.—EFFECT OF TIME OF SUBMERSION ON MEAN GRAIN SIZES OF VARIOUS LOW MOISTURE CONTENT STARCHES IN SGF

	Mean Grain Sizes in Scale Divisions[a] — Time, min.					
Type	0	5	30	60	120	180
Corn (dried)	5.020	5.475	5.050	5.185	5.620	5.620
Corn (P-825)	5.676	5.805	5.955	6.600	5.645	5.510
Potato (dried)	16.243	20.042	17.065	18.376	13.821	15.198

[a] One scale division = 1.8 μ.

level in the distilled water experiment and at the 10 and 5% levels, respectively, for the SGF experiment. Duncan's multiple range tests showed in each case that the difference in grain size was between unsubmerged starch (zero time) and starch which had been submerged. No significant difference in grain diameter was observed in the starches which had been submerged between 5 and 30 min. Preliminary experiments had shown that submersion time was not significant but no comparisons were made to unsubmerged starch.

Starch moisture content effect was probably significant because the initial size differences between the high and low moisture content of the starches were maintained throughout the experiment.

To investigate further the effect of moisture content and submersion time on swelling, a 3 × 6 factorial experiment was designed using three low moisture content starches and SGF as the submersion medium. The starches were slurried and the diameters measured at various time intervals up to 3 hr. The data are given in Table III. The analysis of variance showed that the only significant difference observed was in the type of starch. This was again shown by Duncan's multiple range test to be due to the potato starch; the two forms of cornstarch were not significantly different.

The analysis of variance was recalculated, omitting the potato starch, and a significant difference was shown between the two cornstarches at the 10% level. This difference is again most likely due to the initial differences in the grain sizes which was maintained up to 120 min.

A 3 × 6 factorial experiment was designed to determine the effect of pH and time of submersion on swelling. Commercially dried cornstarch[3] was used for this experiment. The mean grain sizes are presented in Table IV. The analysis of variance showed that pH was significant at the 10% level, and a breakdown of this effect showed that at a pH of 5.3 the swelling that occurred was significantly greater than that at pH 1.3 or 3.3. The significance of the swelling at pH 5.3 could be due to onset of starch hydrolysis. Starch will hydrolyze at an alkaline pH. Unsubmerged starch (zero time) was included in this experiment to allow better comparisons between pH and time, but no significant difference was demonstrated between the measurements at the various time intervals.

To investigate the effect of salts on swelling of untreated starch grains, a 2 × 2 × 3 × 4 factorial experiment was designed. Unsubmerged starch

TABLE IV.—EFFECT OF pH OF SUBMERSION MEDIUM ON MEAN GRAIN SIZES OF LOW MOISTURE CONTENT CORNSTARCH

	Mean Grain Sizes in Scale Divisions[a] — pH		
Time, min.	1.3	3.3	5.3
0	5.676	5.676	5.676
5	5.675	5.285	6.070
30	5.995	5.750	5.930
60	5.455	5.610	6.020
120	5.225	5.585	6.490
180	5.925	6.215	6.195

[a] One scale division = 1.8 μ.

TABLE V.—EFFECT OF SALT AND ITS CONCENTRATION IN SUBMERSION MEDIUM ON MEAN GRAIN SIZES OF CORN AND AMIOCA STARCHES

Mean Grain Sizes in Scale Divisions[a]					
			Time, min.		
Type	Medium	Concn., %	0	5	30
Corn	Na_2SO_4	0.2	5.275	5.708	5.398
		0.9	5.275	5.851	5.652
	$MgCl_2$	0.2	5.275	6.439	5.835
		0.9	5.275	5.597	5.716
	$AlCl_3$	0.2	5.275	5.891	5.851
		0.9	5.275	5.338	5.796
	NaCl	0.2	5.275	5.664	5.323
		0.9	5.275	5.442	5.466
Amioca	Na_2SO_4	0.2	5.482	5.911	5.728
		0.9	5.482	5.633	6.177
	$MgCl_2$	0.2	5.482	6.511	6.348
		0.9	5.482	6.436	6.750
	$AlCl_3$	0.2	5.482	6.940	6.626
		0.9	5.482	6.034	6.773
	NaCl	0.2	5.482	6.078	6.269
		0.9	5.482	6.054	5.652

[a] One scale division = 1.8 μ.

was included as zero time in the experiment to allow comparisons between salt effect and time. Table V shows the variables investigated and the mean grain sizes. The analysis of variance showed that the single effects of type of starch, time submersed, and submersion medium, each produced a significant difference at the 0.5% level. Concentration of the salt in the submersion medium was not significant. Three-factor interactions were not significant. All statistical two-factor interactions involving time produced a significant difference in grain diameters at the 10% level or less. Duncan's multiple range tests showed in each case that the mean grain sizes of the unsubmerged starch (zero time) were significantly different from those of the submerged starch. Duncan's multiple range tests performed on the time-submersion medium interaction and on the single effect of submersion medium showed a significant difference at the 10% level between the salts with polyvalent cations ($MgCl_2$ and $AlCl_3$) and the salts with monovalent cations (Na_2SO_4 and NaCl), $MgCl_2$ and $AlCl_3$ producing greater diameter changes.

SUMMARY AND CONCLUSIONS

The literature pertaining to swelling of starch grains was reviewed, and a procedure for determining swelling of starch grains in various environmental conditions is described.

Corn and amioca starches and the moisture content of these starches showed a significant difference in grain sizes when submersed in distilled water or simulated gastric fluid U.S.P. This was postulated as due to the initial size differences of the starches. It was observed that initially high moisture content starches had larger mean grain sizes than low moisture content starches and that this difference was maintained throughout the time of the experiments. The initial differences in mean grain sizes of the corn and amioca starches was also maintained throughout the experiments.

The two cornstarches submersed 5 to 30 min. in simulated gastric fluid U.S.P. had greater increase in grain sizes over those submersed in distilled water.

Changes in pH had little effect on swelling. However, evidence was obtained to show that starch grains may swell more at a pH of 5.3 than in lower pH media.

Salts affected the swelling of starch grains, with polyvalent cationic salts ($MgCl_2$ and $AlCl_3$) producing more swelling than monovalent cationic salts (NaCl and Na_2SO_4). Ionic concentration did not show any effect on swelling.

There was no significant difference in swelling of starch grains demonstrated between the various time intervals. However, when unsubmerged starches were included in the analyses of variance, significant size differences were shown between the unsubmerged starches and the starches slurried for 5 min. and longer. No significant additional increase in mean grain size was found after 5-min. submersion, indicating any swelling that occurs is apparently instantaneous.

The swelling of the starch grains observed was in the order of 5 to 10% increase in mean grain size. At present, this does not seem to be a large enough change to cause tablets to rupture. Further work is in progress to determine other factors that may influence the swelling of starch grains, and to determine whether the observed increases in mean grain diameter are sufficient to rupture tablets.

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