Mechanism of Action of Starch as a Tablet Disintegrant IV: Effect of Medicaments and Disintegrants on Mean Pore Diameter and Porosity

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Abstract □ Two full factorial experiments were designed. The first one had three disintegrants (corn starch, cation-exchange resin, and waxy maise starch) at four different concentrations (0, 5, 10, and 15%), and three levels of compression pressure (1000, 3000, and 6000 psig.) with aspirin. The second experiment had four different medicaments (aspirin, MgO, Mg trisilicate, and salicylamide), three levels of pressure, and corn starch at the four concentration levels. Mean pore diameter, porosity, and disintegration time were the measured parameters. Mean pore diameters were measured in an air permeability apparatus and calculated from:

$$D_c = \frac{2}{7}\sqrt{\frac{\eta \cdot L \cdot Q}{\Delta P \cdot A \cdot t \cdot \epsilon}}$$

Dried corn starch with 2% moisture was compared to regular corn starch containing 11% moisture. The effect of colloidal silicon dioxide was also studied. Broad generalities as to the effect of the variables on the measured parameters could not be made because of the complexities and interactions of the variables; *i.e.*, disintegrant concentration effect on mean pore diameter varied with the medicament used, the pressure level, and even the specific disintegrant. Neither the effect on mean pore diameter nor porosity was found to be the mechanism of action of starch and other disintegrants in disintegrating tablets under the conditions of these experiments.

Keyphrases □ Starch—mechanism as tablet disintegrant □ Tablet disintegration—mean pore diameter, porosity, disintegration time parameters □ Disintegration, tablets—medicaments, disintegrant effects on mean pore diameter and porosity

Theories of the mechanism of action of starch as a tablet disintegrant were proposed with increasing frequency in the past 10 years. There is as yet no general agreement on what constitutes the mechanism of action. The knowledge of how starch acts as a disintegrant could lead to the development of more effective and reliable disintegrants.

Although starch grains swell to a significant degree, they do not swell until a temperature of about 65° is reached. At 37°, only a 5–10% increase in mean grain size of corn starch was observed (1, 2). Starch grains damaged by ball milling did increase in mean grain diameters by 40–80% (3). Manudhane *et al.* (4) showed that amylose, which does not swell in water, may be an effective tablet disintegrant.

Führer (5) found no swelling in potato starch grains. He claimed that the starch grains that were deformed under pressure did swell in water. Ingram and Lowenthal (3) could find no evidence of corn starch grain damage when pressures as high as 24,000 psig. were used and when a hard, abrasive material was added to the starch and the mixture was compressed.

The apparent ability of substances to absorb water is another proposed theory. It was suggested that water absorption was the mechanism by which colloidal silicon dioxide and rice starch, which swell very little, disintegrated tablets of calcium lactate and of a simple granulation. A capillary system in the tablets was also postulated (6). Jaminet *et al.* (7) claimed disintegration time was proportional to the amount of water absorbed by the disintegrant. Using sodium carboxymethylcellulose, sodium alginate, and potato starch, they found that the starch absorbed less water but was a good disintegrant. The adhesiveness and high viscosity of the gums may have hindered better tablet disintegration. Bánó *et al.* (8) showed that potato starch in a tablet absorbed a methylene blue solution more rapidly than did theophylline, corn starch, triticum starch, or theobromine. Since potato starch was a good disintegrant, it was theorized that water absorption is a primary factor in tablet disintegration. Potato starch also produced the largest porosity. As force increased from 400 to 800 kg., the porosity decreased from 7 to 3%. They felt that water decreases the adhesive energy between particles and thereby causes disintegration. Nogami *et al.* (9) found that even though microcrystalline cellulose had greater water uptake than potato starch, it was not a better disintegrant.

It has been proposed that the heat of wetting when water enters a tablet results in warming the entrapped air, with a subsequent increase in air volume which disintegrates the tablet (10).

Nogami *et al.* (11) postulated that immersional wetting may be the controlling factor in tablet disintegration. The wetting depends upon the material, moisture content, crystal structure, and compression conditions. They claimed that potato starch was hydrophilic with a high heat of wetting and that penetration of water into a packed bed of powder depends on the density, viscosity, and surface tension of the liquid; the contact angle of the liquid with the solid; and radii of the pores. In another study (12), it was stated that surfactants only decreased disintegration time if both surface tension and contact angle were decreased and if the contact angle was initially greater than 90°. This may help to explain the widely different results due to addition of surfactants on tablet disintegration.

Higuchi *et al.* (13) found that the logarithm of compression force is linearly related to tablet porosity, up to about 5000 lb. of force. Furthermore, tablet porosity is sensitive to the material used. Later, Higuchi *et al.* (14) reported that as porosity decreased, surface area in the tablet increased up to about 10% porosity. After this maximum, surface area decreased as porosity decreased. Matsumaru (15) determined the effect of pressure on pore radius and pore volume from the absorption isotherm of tablets. He reported that the peak of the pore radius distribution at 0.76 ton/cm.^{2} was 62.4 Å,

and the pore volume was 148 × 10^{-4} ml./g. Å; at 1.5 tons/cm.^{2}, 42.4 Å and 81 × 10^{-4} ml./g. Å; at 2.9 tons/cm.^{2}, 21 Å and 60.4 × 10^{-4} ml./g. Å; and at 4.2 tons/cm.^{2}, 21 Å and 35.9 × 10^{-4} ml./g. Å, respectively. At the last two pressures, the pore radius did not change. By using the Brunauer, Emmett, and Teller method, it was reported that aluminum silicate tablets contained bottleneck pores (16). As force increased, specific surface area, heat of absorption, and void space slowly decreased. The largest pore diameter in aluminum silicate tablets was found to be 124.8 Å (17). Wurster and Seitz (18) found that 0.10-cm. (0.04-in.) diameter pores drilled into benzoic acid compacts may be occluded by air preventing liquid from entering. Using a solution of 0.2% sodium lauryl sulfate resulted in the pores being filled with solution.

Using an air permeability apparatus, Nogami *et al.* (12) obtained pore diameters with magnesium oxide tablets made with 5% potato starch as disintegrant and 3% starch paste as binder. They found pore diameters decreased with increasing pressure; an increase from 0.5 to 2.0 tons/cm.^{2} resulted in a decrease from 0.197 to 0.069 μ. They obtained an increase in pore diameters with an increasing concentration of potato starch. At 0.5 ton/cm.^{2}, aspirin tablets without starch had pore diameters of 0.36–0.47 μ; with 10% potato starch, the diameters went up to 1.14, 1.43, and 1.23 μ. In magnesium oxide tablets without disintegrant, diameters were 0.07 and 0.09 μ; with 10% potato starch, they were 0.30 and 0.32 μ. There were no linear correlations between compression force and pore diameter or pore diameter and disintegration time.

Later, Nogami *et al.* (19) measured pore diameters, porosity, and dissolution and disintegration times. The variables were aspirin particle size, pressure, starch concentration, and potato and corn starches. Porosity decreased with increasing pressure. With large aspirin particles (d_{vs} = 0.953 mm.) and 1 ton pressure, pore diameter increased (from 0.05 to 0.38 μ) with corn starch concentration (from 0 to 20%). Pore diameter also increased with particle size of aspirin. With small aspirin particles (d_{vs} = 0.0119 mm.), pore diameter did not increase with starch concentration. Tablets made from small- or medium-sized aspirin particles and starch "dissolved" rather than disintegrated. The difference, if any, between corn and potato starches was not made clear, although the investigators claimed that potato starch was better under certain conditions. It appeared as if not all of the data from the 87 experiments were given or analyzed. The authors postulated a critical amount of starch, depending on the drug and starch particle sizes or relative surface areas. This was related to the interfacial characteristics of the capillary walls. When sufficient starch is added, the pores consist of starch or starch and some aspirin. An inadequate amount of starch results in pores consisting mainly of aspirin. Aspirin was reported to have a contact angle greater than 90° and starch as having one less than 90°, so that starch is more easily wetted. For medium- and large-sized aspirin particles, 5–10% starch is required for disintegration. That there is critical starch concentration for drug particle size for minimum disintegration times agrees with the observations of other investigators (20–22).

Nogami *et al.* (9) reported, in a study of aspirin using microcrystalline cellulose or potato starch as disintegrants, that even though the former produced equal or larger pore diameters in some cases, the starch was a better disintegrant. The writers felt that the cellulose allowed water only to travel into the pores, whereas the potato starch also absorbed water. The cellulose could also act as a binder. Interestingly, the writers claimed that the cellulose had a contact angle smaller than potato starch.

Reich and Gstirner (22) also studied tablet pore radius and pore volume. They verified that pore volume and radius decreased as pressure increased. As tablet height increased, both volume and radius increased, but both parameters decreased as moisture content of starch increased. At 950 lb./cm.^{2} force, they reported radii in the 1–2-μ range. Borzunov and Shevchenko (23) reported that potato starch increased the porosity of both bromisovalum and terpin hydrate tablets. They also postulated a microcapillary system due to the addition of the starch.

That pores or capillaries exist in tablets is undeniable. When the drug particles or granules are mixed with starch as the last step before compression, one would expect to find the disintegrant around the granules and even appearing to adhere to the granules. Hence, when the mixture is compressed, the starch appears to form "pores" around the granules. The pores appear to be connected because the starch surrounding the particles now comes together as the mixture is compressed. The evidence of Patel and Hopponen (24) and the rationalization of Reich and Gstirner (22) that the pores are lined with starch grains requires verification. Why are not the pores lined with lubricant?

Whether the major mechanism of starch in tablet disintegration is by starch grain deformation, heating or wetting, or rate of fluid penetration into the tablet, it seems logical that the disintegrating fluid (*i.e.*, water or gastric juice) must get into the tablet. Pharmaceutical tablets are known to be porous to a varying degree, depending on the material, method of granulating, and compression force used. It is necessary to extend the work of Nogami *et al.* (19) to determine the existence of statistical correlations between such variables as types of active ingredients, chemically different disintegrants, disintegrant concentrations, and compression forces, using mean pore diameter, porosity, and disintegration times as the measurable parameters. Interactions among single factors should be determined for more subtle relationships and to see if there are any optimum conditions for tablet disintegration. Finally, if it is true that aspirin–starch tablets compressed to maximum density still have good disintegration times (24), then one can ask if pores in tablets are necessary for disintegration.

EXPERIMENTAL

Tablet Compression—The proper quantities of drug and disintegrant were mixed on a roller mill for 15–30 min. to obtain a uniform mixture. A roller mill was used so there would be a minimum of change in the particle-size distribution. Amounts (0.5 g.) for the tablets, weighed to the nearest 0.1 mg., were placed in a

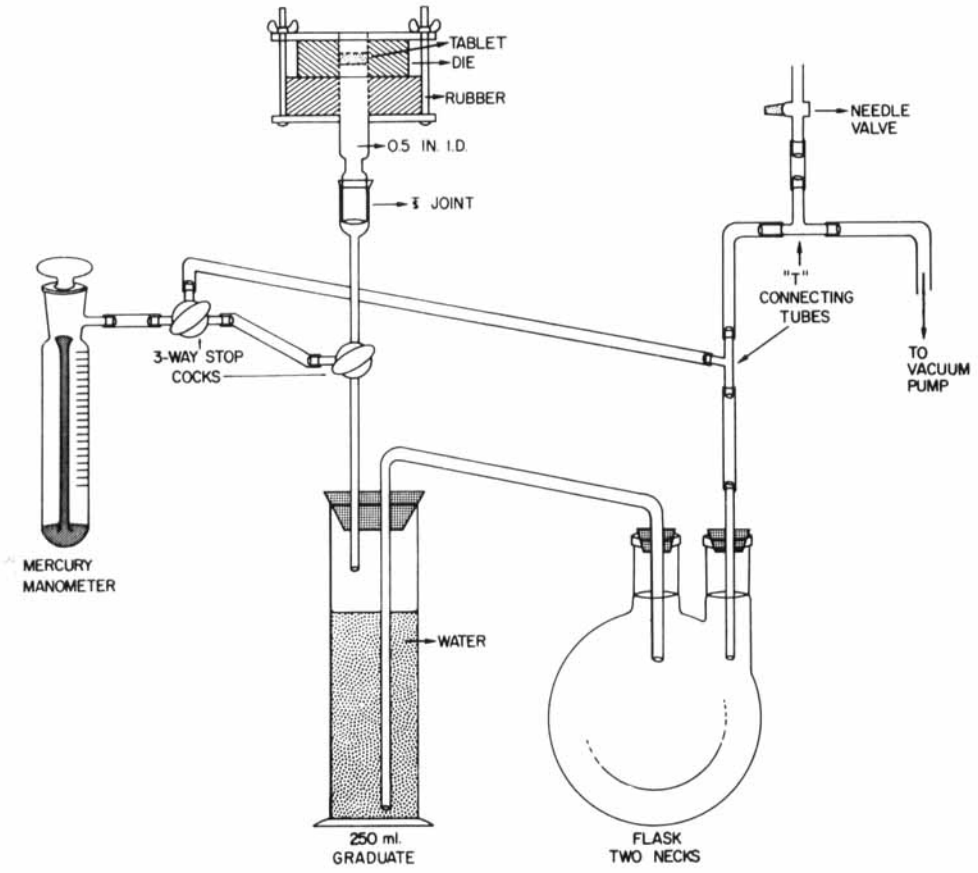

Figure 1—*Tablet air permeability apparatus.*

tablet die held in a special holder on the Carver laboratory press[1] and compressed with 1.27-cm. (0.5-in.) diameter, flat-face punches to 1000, 3000, or 6000 psig. This corresponds to 5093, 15,279, and 30,558 lb. when the ram pressure is converted to the pressure on the 1.27-cm. (0.5-in.) diameter punches. The tablet was left in the die for the pore diameter and porosity measurements. The tablets for the disintegration studies were compressed similarly but removed from the die. The die was not lubricated.

Predominant Disintegration Times—The USP tablet disintegration apparatus (25) was used, with distilled water as the disintegrating fluid, to determine tablet disintegration times.

Porosity Measurement—Freshly boiled, cooled water was used in the graduated cylinder in Fig. 1. The stoppers were sealed into place, and the threeway stopcocks were opened. The tablet in its die was sealed onto the rubber stopper in the tablet die holder. The equilibrium vacuum of 10 cm. Hg used in this study was obtained after about 10 min. with a vacuum pump[2]. Prior work showed that 10 cm. Hg pressure below the tablet gave reasonable rates of air flow through the tablets so that accurate readings of water displacement and of time could be obtained. When the vacuum below the tablet became constant and the rate of water displacement uniform, its level in the graduate was noted and the timer[3] was started. When the pressure below the tablet changed 0.1 cm., as seen on the manometer (Fig. 1), the water level was again noted and the timer stopped. The amount of water displaced in the cylinder, in the given time interval, was equal to the amount of air drawn through the tablet. Two sets of readings were taken on each tablet. The barometric pressure and room temperature were also recorded at this time.

Air was used as the fluid in these measurements to prevent any effect due to dissolution of the ingredients and to minimize any change in packing within the tablets that may occur if even a nonpolar solvent is used.

[1] Model B, Fred S. Carver, Inc.
[2] Duo Seal Vacuum Pump, model 1405, The Welch Scientific Co.
[3] Precision Scientific Co., Catalog No. 69239.

Porosity–Porosity was determined by compressing the powder mixture to 24,000 psig. (122,231 lb.) to eliminate all void spaces. Tablet thicknesses and diameter measurements were made by a 25-mm. micrometer[4].

Particle Size—The mean particle sizes of the four different drugs were determined microscopically with a calibrated eyepiece. The mean particle size was calculated from 100 particles measured at random orientation. In this manner, all particle dimensions were eventually measured.

Materials—Corn starch USP[5] (11% moisture), waxy maise starch[6], a potassium salt of a carboxylic cation-exchange resin[7] dried at 60° to 6.1% moisture, and colloidal silicon dioxide[8] were used as disintegrants. The waxy maise starch was used because it has been recommended as a tablet disintegrant and consists entirely of amylopectin. The cation-exchange resin was previously reported as a disintegrant that may swell when hydrated (26). The colloidal silicon dioxide was included in this study to see if the high bulk volume of this material would affect tablet pore diameter. It had been reported to increase tablet porosity (27). The percent disintegrant added was based on the weight of the drug.

Aspirin USP[9] comminuted through an 80-mesh screen, magnesium oxide USP[10] (heavy), magnesium trisilicate USP[11], and salicylamide powder NF[12] were used as examples of drugs. Aspirin was used because of its wide commercial use and because several previous studies employed this drug so that it serves as a standard for comparison with other studies. Magnesium oxide (MgO) was also used in previous tableting investigations (12). Magnesium trisilicate and salicylamide served as additional examples of insoluble inorganic and organic drugs of pharmaceutical importance.

[4] Catalog No. 436 MRL, L. S. Starrett Co.
[5] STR-R, A. E. Staley Manufacturing Co.
[6] Amioca, National Starch and Chemical Corp.
[7] Amberlite IRP-88, lot 0430, Rohm & Haas Co., formerly XE-88.
[8] Cab-O-Sil M-5, Cabot Corp.
[9] Merck & Co., Inc., lot 60706.
[10] J. T. Baker Chemical Co.
[11] Mallinckrodt Chemical Works, Control SAS1.
[12] S. B. Penick & Co., lot 15-NEO-209.

Table I—Analysis of Variance of Pore Diameters in Tablets Containing Various Disintegrants

Source	*df*	*SS*	*MS*	*F*
Disintegrants (*D*)	2	2.0688	1.0344	3.42[a]
D_1 *versus* D_2	1	1.5000	1.5000	4.96[b]
D_1 *versus* D_3	1	0.001665	0.001665	0.0055[a]
Pressure (*P*)	2	804.0538	402.0269	1328.57[c]
P_1 *versus* P_3	1	734.8252	734.8252	2428.37[c]
P_1 and P_3 *versus* P_2	1	69.2271	69.2271	228.77[c]
Disintegrant concentration (*C*)	3	56.4452	18.8150	62.18[c]
C_2 *versus* C_3	1	0.3472	0.3472	1.15[a]
C_2 and C_3 *versus* C_1	1	11.1157	11.1157	36.73[c]
C_2 and C_3 *versus* C_4	1	27.1646	27.1646	89.77[c]
$D \times C$	6	19.2288	3.2048	10.59[c]
$P \times C$	6	12.7905	2.1317	7.04[c]
Error[d]	16	4.8421	0.3026	—

[a] Not significant. [b] Significant at $p = 0.05$. [c] Significant at $p = 0.001$. [d] Term is sum of the three-factor interaction and $D \times P$ interaction which was not statistically significant.

CALCULATIONS

Porosity—Tablet porosities were calculated from the following equation:

$$\text{porosity} = 1 - \frac{\text{apparent density}}{\text{true density}} \qquad \text{(Eq. 1)}$$

The true density of the powder mixture was determined by compressing to eliminate all void spaces. Since the weight of each tablet was kept constant, as was the radius, only the tablet height varied; therefore, the ratio of densities in Eq. 1 becomes a ratio of heights. Thus,

$$\text{porosity} = 1 - \frac{\text{height of tablet at true density}}{\text{height of tablet under study}} \qquad \text{(Eq. 2)}$$

Pore Diameters—Mean tablet pore diameters were calculated from an equation derived from specific surface areas, developed from Darcy's law by Kozeny and Carman (12, 28–31):

$$S_w = \frac{14}{\rho}\frac{\Delta P \cdot A \cdot t}{\eta \cdot L \cdot Q}\frac{\epsilon^2}{(1-\epsilon)^2} \qquad \text{(Eq. 3)}$$

where S_w is the specific surface area in the tablet, ρ is the density of the powder, A is the cross sectional area of the tablet surface, Q is the volume of air that permeated through the tablet in time t, ΔP is the pressure difference across the thickness (L) of the tablet, η is the viscosity of air at the temperature of the experiment, and ϵ is the porosity.

Pore diameter, D_c, is found from:

$$D_c = \frac{4}{S_w}\frac{\epsilon}{1-\epsilon} \qquad \text{(Eq. 4)}$$

Combining Eqs. 3 and 4 gives:

$$D_c = \frac{2}{7}\sqrt{\frac{\eta \cdot L \cdot Q}{\Delta P \cdot A \cdot t \cdot \epsilon}} \qquad \text{(Eq. 5)}$$

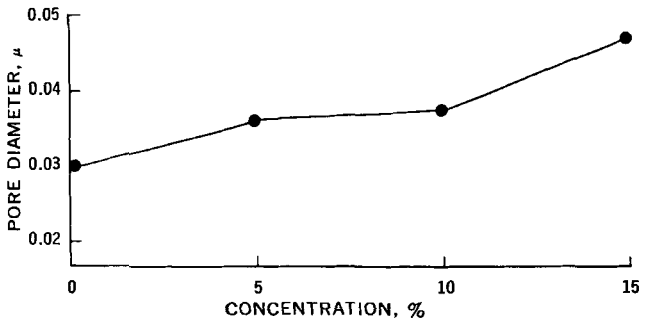

Figure 2—*Effect of disintegrant concentration on mean pore diameter in aspirin tablets.*

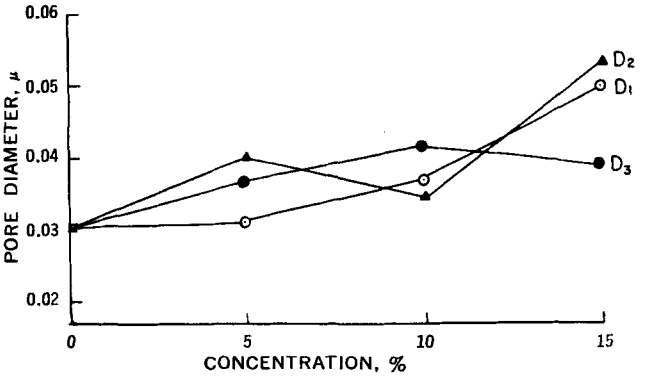

Figure 3—*Effect of distintegrant concentration on mean pore diameter in aspirin tablets. Key:* D_1, *corn starch;* D_2, *cation-exchange resin; and* D_3, *waxy maise starch.*

RESULTS AND CONCLUSIONS

Using aspirin, the first experiment was designed to determine the effect of compression force at three levels (P_1 = 1000 psig., P_2 = 3000 psig., and P_3 = 6000 psig.), disintegrant concentration at four levels (C_1 = 0%, C_2 = 5%, C_3 = 10%, and C_4 = 15%), and three different disintegrants (D_1 = corn starch, D_2 = cation-exchange resin, and D_3 = waxy maise starch) on mean pore diameter and porosity. This gave a 3 × 4 × 3 full factorial design experiment. The analysis of variance is given in Table I.

The analysis of variance showed that there was no significant difference in the mean pore diameters between the two starches. The cation-exchange resin produced larger mean pore diameters than either of the two starches.

Mean pore diameters decreased from 0.070 to 0.028 to 0.015 μ as compression pressure increased from 1000 to 3000 to 6000 psig., respectively. The decrease was of the same order of magnitude for each individual disintegrant. The relationship of diameters to compression pressure was not logarithmic.

Mean pore diameters increased with increasing concentration of the disintegrants (Fig. 2). There was no significant difference in mean pore diameters at 5 and 10% concentrations, but these diameters were significantly different from those at both 0 and 15%. The $D \times C$ interaction disclosed that the increase in mean pore diameters with increasing concentration occurred only with corn starch. The resin produced a decrease at 10%, while the waxy maise starch had a slight decrease at the 15% level (Fig. 3). The significance of the $C \times P$ interaction is shown in Fig. 4. At 1000 psig., there was an increase in mean pore diameters with concentration. At 3000 psig., there was a decrease in diameters at 10% concentration; at 6000 psig., the 5 and 10% levels had the same mean pore diameters. Moreover, the rate of diameter increase dropped as the pressure

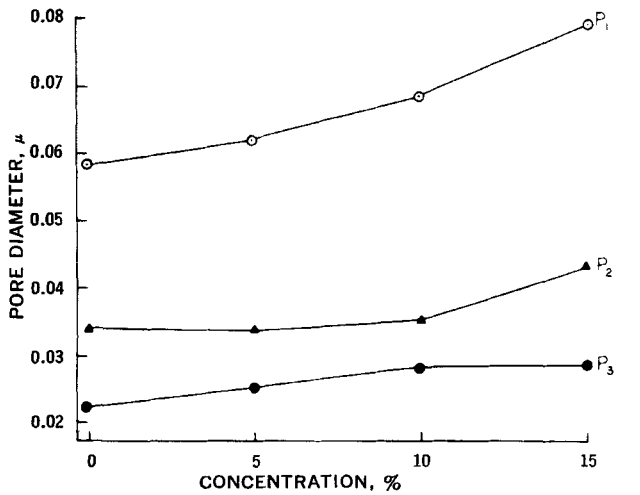

Figure 4—*Effect of disintegrant concentration on mean pore diameter in aspirin tablets. Key:* P_1, *1000 psig.;* P_2, *3000 psig.; and* P_3, *6000 psig.*

Table II—Analysis of Variance of Porosities of Aspirin Tablets Containing Various Disintegrants

Source	*df*	*SS*[a]	*MS*	*F*
Disintegrants (*D*)	2	5.6504	2.8252	3.51[b]
D_1 *versus* D_3	1	0.7820	0.7820	0.971[b]
D_1 and D_3 *versus* D_2	1	5.5722	5.5722	6.92[c]
Concentration (*C*)	3	48.8714	16.2904	20.23[d]
C_1 *versus* C_2	1	0.1250	0.1250	0.155[b]
C_1 and C_2 *versus* C_3	1	25.8476	25.8476	32.09[d]
C_1 and C_2 *versus* C_4	1	7.9349	7.9349	9.95[e]
Pressure	2	617.1066	308.5533	383.11[d]
P_1 *versus* P_3	1	592.1251	592.1251	735.19[d]
P_1 and P_3 *versus* P_2	1	24.9806	24.9806	31.02[d]
$D \times C$	6	27.4533	4.5755	5.68[e]
$C \times P$	6	16.2144	2.7024	3.36[e]
Error[f]	16	12.8868	0.8054	—

[a] The sum of squares (*SS*) of the individual effects may not add up to the *SS* of the total effect because the comparisons are not quite orthogonal but were the comparisons of interest according to the data. [b] Not significant. [c] Significant at $p = 0.05$. [d] Significant at $p = 0.001$. [e] Significant at $p = 0.01$. [f] Term is the sum of the three-factor interaction and $D \times P$ interacting which was not statistically significant.

increased. Although overall there was a decrease in mean pore diameters as pressure increased and an increase in diameters as disintegrant concentration increased (Fig. 2), these effects actually varied with the specific disintegrant and the compression pressure used to form the tablets. The broad generalities based on averaging data over different variables may at times be misleading.

The same experimental design was used to determine the effect of the variables on tablet porosities. The analysis of variance is shown in Table II.

Overall there was no significant difference between the disintegrants, although a comparison of the two starches with the resin showed that the starches produced significantly higher tablet porosities in aspirin tablets than the resin. The resin produced larger mean pore diameters in aspirin tablets.

Porosity decreased with increasing compression force. The porosities at 1000, 3000, and 6000 psig. were 0.127, 0.0600, and 0.0280, respectively. The relationship was not logarithmic. The $C \times P$ interaction indicated that the decrease of porosity at each concentration level was at about the same rate for each pressure, but the porosities *per se* at the 10 and 15% levels were significantly different from 0 and 5% levels. The porosity also decreased with increasing pressure at the same rate with all three disintegrants.

The disintegrant concentration effect on tablet porosity was variable (Fig. 5). This is the reason for the statistical significance of the $D \times C$ interaction.

The next experiment was devised to determine the effect on mean pore diameter and porosity of the four different medicaments (M_1 = aspirin, M_2 = MgO, M_3 = Mg trisilicate, and M_4 = salicylamide), four concentrations of corn starch, and three different

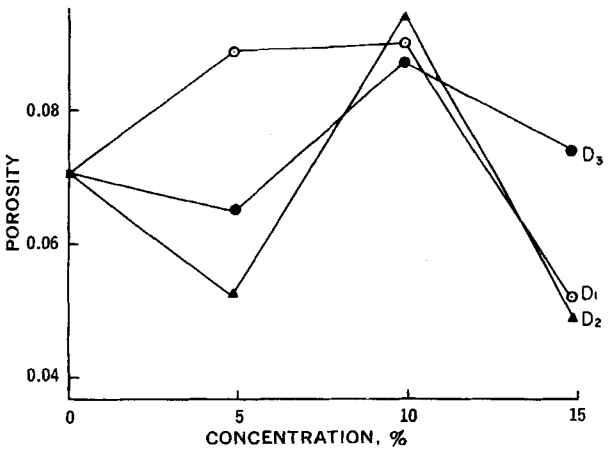

Figure 5—*Effect of disintegrant concentration on porosity in aspirin tablets. Key:* D_1, *corn starch;* D_2, *cation-exchange resin; and* D_3, *waxy maise starch.*

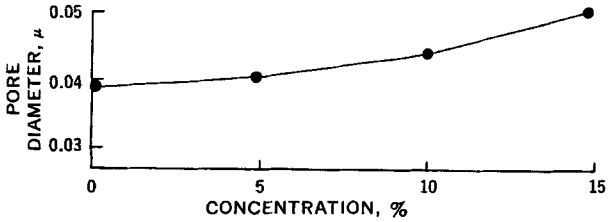

Figure 6—*Effect of corn starch concentration on mean pore diameter in four medicaments.*

compression forces. This resulted in a $4 \times 4 \times 3$ full factorial design experiment.

The analysis of variance in Table III showed that the medicaments gave significantly different pore diameters. Salicylamide had a mean pore diameter of 0.076 μ, aspirin 0.037 μ, MgO 0.030 μ, and Mg trisilicate 0.030 μ. Mean pore diameters decreased as compression increased. Thus, at 1000, 3000, and 6000 psig., mean pore diameters were 0.067, 0.037, and 0.027 μ, respectively. Mean pore diameters increased with increasing corn starch concentration (Fig. 6).

The significance of the $M \times P$ interaction supports the fact that each medicament behaved differently with respect to mean pore diameters and pressure (Fig. 7). Salicylamide and aspirin, which had the largest mean pore diameters, also had the largest decrease with increasing pressure. The two magnesium compounds showed the least effect. The greatest change in diameters occurred between 1000 and 3000 psig., probably due to the greater compressibility of the powders. Although the overall effect of starch concentration is shown in Fig. 6, a statistically significant $M \times C$ interaction implies the concentration effect is not simple. This is demonstrated in Fig. 8 where only aspirin (M_1) showed an increase in mean pore diameter with increasing corn starch concentration. The other three medicaments had a variable effect; *i.e.*, there was a slight increase in mean pore diameter with three out of four medicaments at the 5% level and three of the four medicaments showed an increase in diameters at 15%, but the drugs differed. The significance of the $P \times C$ interaction is similar to the one previously shown in Fig. 4.

The second experimental design was also used to determine the effects of the variables on tablet porosity.

The analysis of variance presented in Table IV disclosed that the porosities of aspirin and salicylamide tablets were similar, even though the mean pore diameters were different. The two magnesium compounds had significantly higher porosities than aspirin or salicylamide. In this experiment, the concentration of corn starch had no effect on porosity. The $M \times C$ interaction disclosed the reasons for this situation. All four medicaments behaved differently, as shown in Fig. 9.

Porosities decreased as compression pressure increased, but the rate of change was not as large as in the previous experiment. The

Table III—Analysis of Variance of Pore Diameters of Tablets Containing Various Medicaments

Source	*df*	*SS*	*MS*	*F*
Medicaments (*M*)	3	715.5500	238.5166	320.76[a]
M_1 *versus* M_2	1	10.6666	10.6666	14.35[b]
M_1 and M_2 *versus* M_3	1	4.4005	4.4005	5.92[c]
M_1 and M_2 and M_3 *versus* M_4	1	700.4839	700.4839	942.02[a]
Pressure (*P*)	2	567.5419	283.7709	381.62[a]
P_1 *versus* P_3	1	523.2593	523.2593	703.68[a]
P_1 and P_3 *versus* P_2	1	44.2814	44.2814	59.55[a]
Starch concentration (*C*)	3	35.4701	11.8233	15.90[a]
C_1 *versus* C_2	1	0.2816	0.2816	0.38[d]
C_1 and C_2 *versus* C_3	1	5.6674	5.6674	7.62[c]
C_1 and C_2 and C_3 *versus* C_4	1	29.5211	29.5211	39.70[a]
$M \times P$	6	272.3713	45.3952	61.05[a]
$M \times C$	9	37.3322	4.1480	5.58[b]
$P \times C$	6	14.1540	2.3590	3.17[c]
Error[e]	18	13.3842	0.7435	—

[a] Significant at $p = 0.001$. [b] Significant at $p = 0.01$. [c] Significant at $p = 0.05$. [d] Not significant. [e] Term is the three-factor interaction.

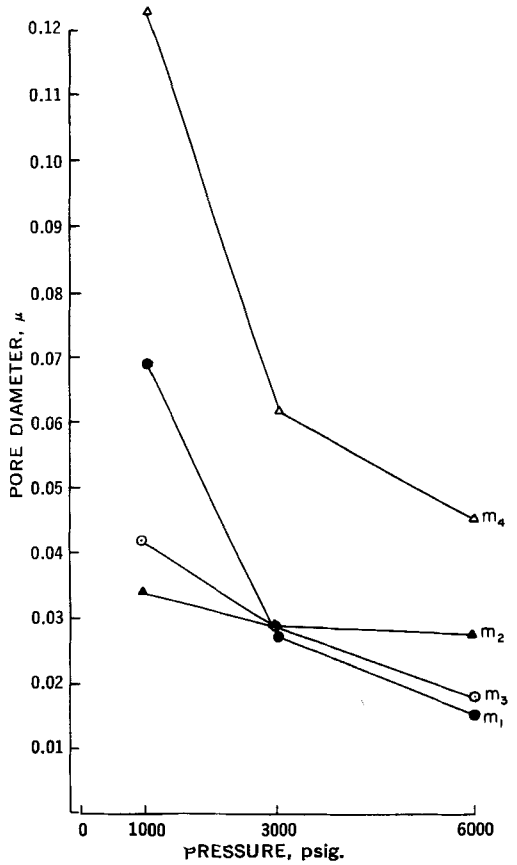

Figure 7—*Effect of pressure on mean pore diameter. Key:* M_1, *aspirin;* M_2, *MgO;* M_3, *Mg trisilicate; and* M_4, *salicylamide.*

porosities at 1000, 3000, and 6000 psig. were 0.261, 0.175, and 0.123, respectively. The average porosities were also generally higher than previously described, possibly due to the very high porosities of the two magnesium compounds. The importance of the $M \times P$ interaction is illustrated in Fig. 10, where the difference in porosities of the four medicaments becomes evident. The general shape of the curves is similar, indicating a parallel rate of porosity decrease with pressure.

Only qualitative correlations of tablet disintegration times with mean pore diameter or porosities could be made because tablets

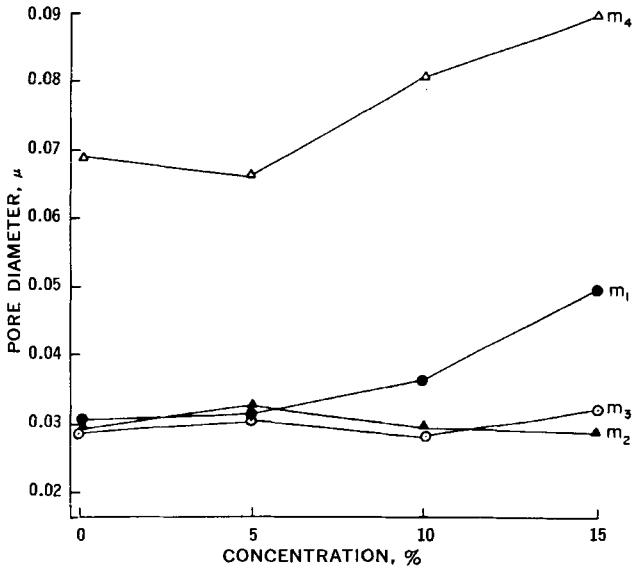

Figure 8—*Effect of corn starch concentration on mean pore diameter. Key:* M_1, *aspirin;* M_2, *MgO;* M_3, *Mg trisilicate; and* M_4, *salicylamide.*

Table IV—Analysis of Variance of Porosities of Tablets Containing Various Medicaments

Source	*df*	*SS*	*MS*	*F*
Medicaments (*M*)	3	7026.7104	2342.2368	993.78[a]
M_1 *versus* M_4	1	5.2266	5.2266	2.22[b]
M_1 and M_4 *versus* M_2	1	2663.2764	2663.2764	1129.99[a]
M_1 and M_4 *versus* M_3	1	6311.2354	6311.2354	2677.77[a]
Concentration (*C*)	3	8.0228	2.6742	1.13[b]
Pressure (*P*)	2	1567.0254	783.5127	332.43[a]
P_1 *versus* P_3	1	1538.1792	1538.1792	652.63[a]
P_1 and P_3 *versus* P_2	1	28.8422	28.8422	12.24[a]
$M \times C$	9	226.1976	25.1330	10.66[a]
$M \times P$	6	135.0128	22.5021	9.55[a]
Error[c]	24	56.5653	2.3569	—

[a] Significant at $p = 0.001$. [b] Not significant. [c] Term is sum of the three-factor interactions and $C \times P$ interaction which was not statistically significant.

did not disintegrate within 1 hr. in many instances (Tables V and VI).

Figures 7 and 8 show that MgO exhibited the least decrease in mean pore diameter with pressure and corn starch concentration, and Fig. 9 shows that MgO tablet porosity increased steadily above 5% corn starch concentration. Table VI indicates that at 5% and greater disintegrant concentration, MgO tablets disintegrated in 5–10 sec. at all pressures. This would seem to indicate that the small change in mean pore diameter is reflected in a constant disintegration time above 5% starch concentration, but it does not explain the porosity effect. The decrease in mean pore diameter and a decrease in porosity (Figs. 7 and 10) with pressure for Mg trisilicate tablets corresponded to an increase in disintegration times (Table VI). The concentration of starch had no effect on mean pore diameter and a variable effect on porosity in Mg trisilicate tablets, which could not be correlated to disintegration times.

The decrease of mean pore diameters with pressure (Fig. 7) corresponded to an increase in disintegration times with pressure at 10 and 15% corn starch concentrations in aspirin and salicylamide. Mean pore diameters in aspirin and salicylamide tablets (Fig. 8) increased above 5% starch concentration and this correlates with the disintegration data in Table VI. While there was some correlation between mean pore diameters and disintegration times, the

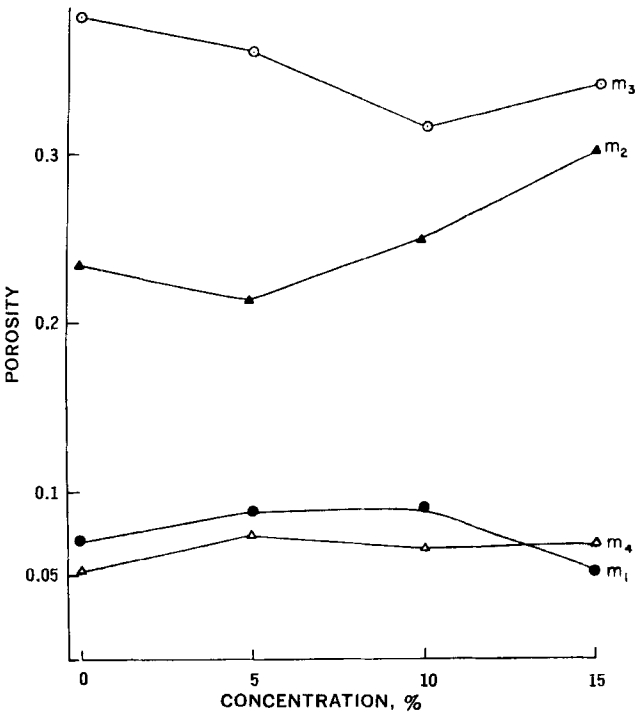

Figure 9—*Effect of corn starch concentration on porosity. Key:* M_1, *aspirin;* M_2, *MgO;* M_3, *Mg trisilicate; and* M_4, *salicylamide.*

Table V—Predominate Disintegration Times of Aspirin Tablets[a]

Disintegrant	Concentration, %	Pressure, psig. 1000	3000	6000
Corn starch	0	>3600	>3600	>3600
	5	>3600	>3600	>3600
	10	550	970	>3600
	15	38	49	25
Cation-exchange resin	0	>3600	>3600	>3600
	5	25[b]	25[b]	25[b]
	10	25[b]	25[b]	25[b]
	15	15	12	25[b]
Waxy maise starch	0	>3600	>3600	>3600
	5	>3600	>3600	>3600
	10	39	50[b]	50[b]
	15	50[b]	50[b]	50[b]

[a] Seconds. [b] Chips remained in basket for long time.

porosity of aspirin tablets and salicylamide tablets in Fig. 9 could not be correlated to disintegration times.

The resin at 5% and greater concentrations and at all pressures caused tablets to break apart into small chips within 25 sec., yet this is not reflected in its effect on mean pore diameters or porosity (Figs. 3 and 5).

The medicaments in Fig. 8 that had the least change in mean pore diameters also exhibited minimal changes in disintegration times, while those with the largest change in mean pore diameters with starch concentration had the greatest change in disintegration times.

The degree of change in mean pore diameters at the three pressure levels illustrated in Fig. 4 was reflected in the corresponding degree of change in disintegration times at the various pressures.

The two magnesium salts had the largest porosities (Fig. 9) and the best disintegration times, but the changes in porosity with starch concentration were not correlated to disintegration times. Tablets of the two organic compounds had the lowest porosities and the poorest disintegration times (Table VI).

Porosity decreased and, in general, disintegration times decreased with increasing pressure. Taking the data in Fig. 6, one could qualitatively say that the increase in mean pore diameters with increasing starch concentration correlates with the data in Table VI. Yet to conclude that disintegration times decrease as porosity decreases or starch concentration increases is an oversimplification (Fig. 10). MgO tablets also showed a decrease in porosity with increasing pressure; but above 5% starch concentration, pressure had no apparent effect on disintegration times.

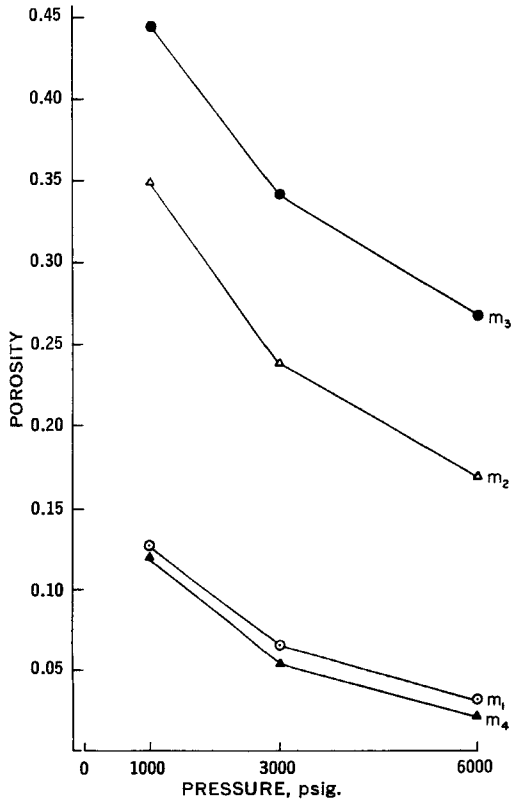

Figure 10—*Effect of pressure on porosity. Key:* M_1, *aspirin;* M_2, *MgO;* M_3, *Mg trisilicate; and* M_4, *salicylamide.*

Table VI—Predominate Tablet Disintegration Times[a]

Medicament	Starch Concentration, %	Pressure, psig. 1000	3000	6000
Aspirin	0	>3600	>3600	>3600
	5	>3600	>3600	>3600
	10	550	970	>3600
	15	38	49	25
MgO	0	>3600	>3600	>3600
	5	9	5	5
	10	5	9	9
	15	7	8	10
Mg trisilicate	0	228	>3600	>3600
	5	12	728	>3600
	10	16	23	90
	15	11	8	24
Salicylamide	0	>3600	>3600	>3600
	5	1300	>3600	>3600
	10	356	65	211
	15	30	100	87

[a] Seconds.

The suggestion of Nogami *et al.* (19) that there may be a critical amount of disintegrant could not be verified for different medicaments and particle sizes in this study. The MgO used had a particle size of 23 ± 8 μ, which was similar to that of aspirin (28 ± 19 μ), but the MgO tablets disintegrated more rapidly (Table VI) at the same starch concentrations. Mg trisilicate, with a particle size less than 2 μ, had faster disintegration times than either aspirin or salicylamide (particle size 61 ± 28 μ) at the same starch concentrations.

The mean pore diameters and porosities of aspirin tablets made with colloidal silicon dioxide are shown in Table VII. Concentration greater than 5% colloidal silicon dioxide could not be used because the increase in bulk density gave difficulty in filling the material into the die cavity. The 0.5% concentration resulted in larger mean pore diameter than the 5% level. The increase due to the addition of 5% colloidal silicon dioxide was the same order of magnitude as, for example, 15% corn starch. The porosities decreased as pressure increased and the 5% concentration had higher porosities than the 0.5% level. The order of magnitude corresponded to the porosities with 5–10% concentration of the other disintegrants. Since the aspirin tablets with colloidal silicon dioxide did not disintegrate, the mean pore diameter and the porosity were not determining factors in this instance.

Table VII—Aspirin–Colloidal Silicon Dioxide Tablets

Pressure, psig.	Concentration, %	Pore Diameter, μ	Porosity
1000	0.5	0.120	0.120
	5.0	0.088	0.158
3000	0.5	0.054	0.530
	5.0	0.040	0.084
6000	0.5	0.047	0.0305
	5.0	0.034	0.0473

Table VIII—Porosity of Magnesium Oxide Tablets Made with Regular and Dried Corn Starches

Pressure	Dried Starch	Regular Starch
1000	0.294	0.350
3000	0.207	0.240
6000	0.142	0.169

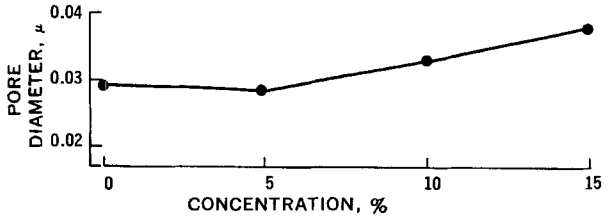

Figure 11—*Effect of dried corn starch concentration on mean pore diameter of MgO tablets.*

The effect on mean pore diameters, porosity, and disintegration times of corn starch dried to 2% moisture in MgO tablets was investigated. The mean pore diameters for MgO tablets with dried starch were similar to that of MgO tablets plus the "wet" starch, except at the 15% concentration. This occurred at all three compression forces, as can be seen by comparing curve M_2 in Fig. 8 with Fig. 11. The decrease in mean pore diameters due to increasing pressure was similar to the regular starch.

The porosities of MgO tablets containing dried starch were similar to those due to the addition of regular starch at all concentrations, except 15%, when the dried starch had a porosity of 0.205 and the "wet" starch had a porosity of 0.307. Table VIII shows that the effect of pressure on the porosities of MgO tablets containing the two starches was different in that the dried starch addition resulted in lower porosities.

There was no significant difference in disintegration times of MgO tablets made with the dried or "wet" starches except at the 5% concentration. The MgO dried starch tablets did not disintegrate within 10 min., whereas the MgO "wet" starch tablets disintegrated in 5–9 sec.

SUMMARY

Two full factorial experiments were designed. The first one had three disintegrants at four different concentrations and three levels of compression pressure with aspirin. The second experiment had four different medicaments, three levels of pressure, and corn starch at four concentration levels. Mean pore diameter, porosity, and disintegration time were the measured parameters. Under the conditions of these experiments, the following conclusions could be made.

1. The apparent decrease in mean pore diameter with increasing pressure and the apparent increase in mean pore diameter with increasing disintegrant concentration that were observed in both experiments actually varied with the particular disintegrant, pressure, medicament, and disintegrant concentration. For example, of the three disintegrants, only corn starch with aspirin gave a constant increase in mean pore diameter with increasing concentration. Only at 1000 psig. did the mean pore diameter consistently increase with the disintegrant concentration. The rate of mean pore diameter increase due to increasing corn starch concentration dropped as pressure increased.

2. The cation-exchange resin produced larger mean pore diameters and lower porosities than the two starches but could not be correlated with disintegration times.

3. Apparent porosity decreased with increasing pressure.

4. Starch concentration had a different effect on porosity for all four medicaments.

5. Porosities decreased with increasing pressure for all four medicaments at about the same rate.

6. Medicaments that had the least change in mean pore diameters exhibited minimal changes in disintegration time; the converse was also true.

7. Broad generalities as to the effect of pressure, disintegrant, disintegrant concentration, and medicament on mean pore diameter, porosity, and disintegration time of tablets cannot be made because of the complexity of the interactions of the variables.

8. Because apparent mean pore diameter and porosity decreased with increasing pressure under the conditions of these experiments, which only correlates with increasing disintegration time in specific instances, it cannot be concluded that the mechanism of starch as a tablet disintegrant is by its effect on mean pore diameter or porosity. Large mean pore diameter or porosity did not always give rapid disintegration time, nor did small mean pore diameter or porosity imply poor disintegration.

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