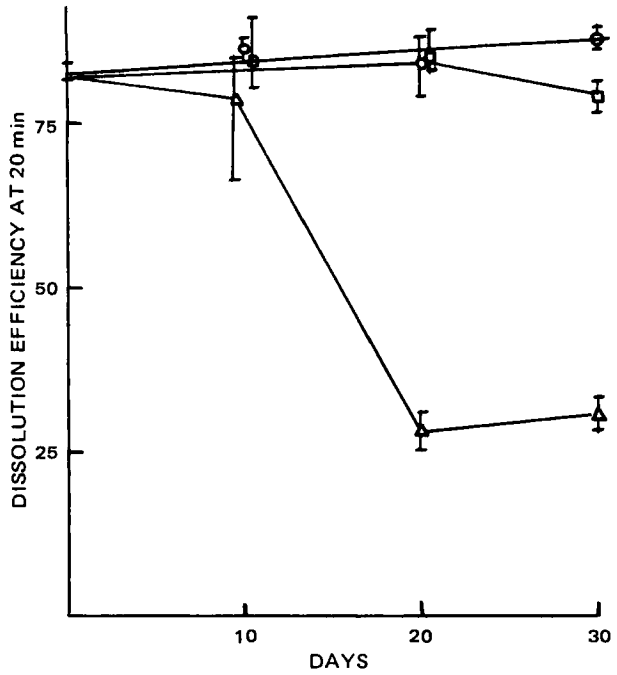

Figure 2—*Effect of storage time on the dissolution efficiency of I-A tablets. Key: ○, 23° and 75% R.H.; □, 45° and 75% R.H.; and △, 65° and 40% R.H.*

differed from that at the end of the storage stress period. Thus, those who rely upon hardness values as an indication of changes in dissolution may be following an unreliable practice.

Second, the reported data cast considerable doubt on the use of accelerated stability-type tests to predict changes at room temperature. Predictions of behavior at room temperature from data obtained at 45 and 65° would lead to unreliable results for the investigated systems.

It is interesting to speculate on the reasons for these results. The direct effect of water vapor on the disintegrant, as described by Khan and Rhodes (4), is probably involved. Also, in the case of povidone, it is reasonable to postulate a direct interaction between the dye and disintegrant. Fung *et al.* (5) made use of the stabilizing effect of the interaction between povidone and nitroglycerin for the formulation of that drug. More than one mechanism probably underlies the reported data, and further work in various tablet matrixes would be valuable to elucidate the principles operating in such systems.

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Disaggregation of Compressed Tablets

MICHAEL H. RUBINSTEIN ˣ and DOROTHY M. BODEY

Abstract □ Tablets of dibasic calcium phosphate containing varying proportions of intra- to extragranular maize starch were prepared at three compaction pressures. The surface area generated per tablet after 10 and 30 min of disintegration was measured with an automated counter by a new technique. The optimum starch combination that produced the maximum surface area in a tablet formulation was either 2.5% intra–12.5% extragranular or 15% intragranular starch alone. The distribution of starch did not affect the resultant strength of the tablets, and maximum generation of surface area was achieved by compacting the tablets at as low a pressure as practical.

Keyphrases □ Disaggregation—compressed tablets of dibasic calcium phosphate, with varying proportions of intra- to extragranular starch, effect of compaction pressure □ Dosage forms—compressed tablets, dibasic calcium phosphate with varying proportions of intra- to extragranular starch, disaggregation, effect of compaction pressure □ Tablets, compressed—dibasic calcium phosphate with varying proportions of intra- to extragranular starch, disaggregation, effect of compaction pressure □ Calcium phosphate, dibasic—compressed tablets with varying proportions of intra- to extragranular starch, disaggregation, effect of compaction pressure □ Starch, intra- and extragranular—varying proportions in dibasic calcium phosphate compressed tablets, disaggregation, effect of compaction pressure

Disintegration of a compressed tablet is the process by which a whole tablet breaks up into small pieces when in contact with fluid. If the process is considered to be a zero- or first-order reaction, the specific rate constant is inversely proportional to the disintegration time, as measured by the USP disintegration test. This official test is concerned solely with the breakdown of tablets to particles that pass the 10-mesh screen. No indication is given as to whether the undermesh material consists of coarse aggregates or fine particles, even though, as long ago as 1945, Kelly and Green (1) reported that it was clinically important that tablets disintegrated beyond the size of the original granules.

BACKGROUND

The official disintegration tests assume that two tablets with the same disintegration times disintegrate in the same manner to produce fragments that, for all intents and purposes, have similar size distri-

Table I—Tablet Formulation Composition

	Dry Weight Percentage in Formulation						
	I	II	III	IV	V	VI	VII
Dibasic calcium phosphate	83	83	83	83	83	83	83
Maize starch:							
Intragranular	0	2.5	5.0	7.5	10.0	12.5	15.0
Extragranular	15	12.5	10.0	7.5	5.0	2.0	0
Starch mucilage	2	2	2	2	2	2	2

butions and surface areas. The equivalency of particle distribution and surface area is important, since these parameters directly determine the dissolution rate as defined by the Noyes–Whitney (2) equation. However, two formulated tablets can have the same disintegration times but different generated surface areas.

Figure 1 shows the disintegration of two tablet formulations, A and B, both having identical disintegration times. With Formulation A, large fragments break into two to produce smaller fragments; these fragments, in turn, break down into finer fragments until, at the disintegration time, the largest aggregates just pass through the 10-mesh sieve. With this type of breakdown, there is a relatively large number of large fragments.

With Formulation B, however, the fragments erode away so that their size gradually diminishes. The time taken for the largest particles to erode and pass through the screen is the disintegration time. This type of disintegration yields a lot of fine material with few large fragments. The fragments from Formulation A have a relatively small surface area while those from B have a relatively large surface area, even though both formulations have the same disintegration times.

A better method, therefore, of characterizing the disintegration process is to measure directly the surface area generated with respect to time. The first attempt to do this was described by Nogami *et al.* (3), who modified a thermal analysis method used by Suito and Hirai (4). Several applications of the thermal analysis method have been described subsequently (5–7). Sanders (8) and Sandell (9), recognizing that the extent of disaggregation was important, used a crude wet-sieving method to measure the particle size produced by tablets after disintegration. This technique was refined by Shotton and Leonard (10), who used a wet-sieving process to measure coarse fragments and an automated counter[1] to measure very fine particles. These tests, however, were crude and were not sensitive enough to measure the change of particle size at different time intervals.

The purpose of the present investigation was to evaluate a disintegration test based upon measurements of generated surface area at fixed disaggregation times. The method utilized an automated counter[1] and was used to compare tablets of calcium orthophosphate containing varying proportions of intra- to extragranular maize starch.

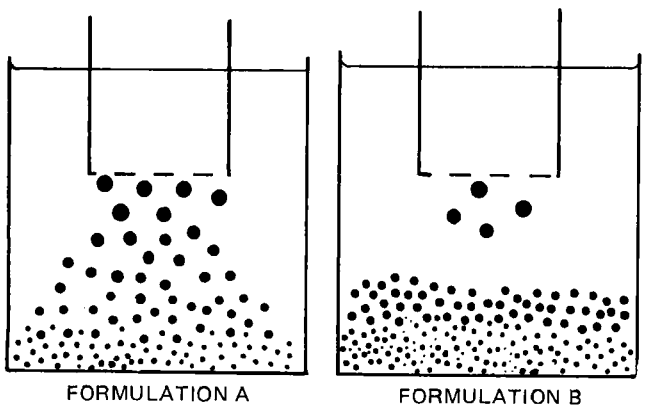

Figure 1—*Comparison of the mechanism of disintegration of two formulated tablets, A (small surface area of tablet fragments) and B (large surface area of tablet fragments).*

[1] Coulter.

EXPERIMENTAL

Materials—The dibasic calcium phosphate was reagent grade, and the maize starch and magnesium stearate used were of BP quality. The moisture content of the maize starch, dibasic calcium phosphate, and magnesium stearate was 0.5, 0.5, and 3% (w/w), respectively. The dibasic calcium phosphate was milled so that the mean particle size was 48 μm with 100% by weight less than 90 μm (automated counter).

Methods—*Granulation*—Granules were prepared by wet massing and screening. Formulations were produced according to the data in Table I. Each formulation (I–VII) contained the same amount of maize starch [15% (w/w)], but it was distributed in varying proportions as intra- or extragranular starch. In all batches, a consistent amount of binder, 10% (w/w) starch mucilage, was used [equivalent to 2% (w/w) dry binder in the final tablet]. If an intragranular disintegrant was required in the formulation, it was dry mixed with the dibasic calcium phosphate before the addition of the granulating agent.

The wet granules were passed through a 44-mesh screen and dried in a hot air oven at 55° for 2 hr. The 44–60-mesh sieve fraction was collected, extragranular starch was added (if required), and the granules were dried in a hot oven at 55° for 12 hr. In all cases, the granules contained less than 0.5% of moisture.

Compression—The tablets were prepared individually between 9.5-mm diameter flat-faced punches. Each formulation was compressed at three compaction pressures: 58.5, 87.6, and 116.4 MNm^{-2}. The die wall was dusted lightly with magnesium stearate as a lubricant, and the lower and upper faces of the punches were cleaned after the production of each tablet. Individual tablets were blown free of fine powder before storage in sealed jars.

Hardness Testing—Tablet hardness[2] was determined using each formulation. Each stroke was timed to take 1 sec in an effort to apply a uniform force at a uniform rate. Ten determinations were carried out for each formulation and at each compaction pressure.

Disintegration Testing—The BP disintegration test was carried out on each group of tablets. In addition, the test was performed at room temperature (20°) and in the electrolyte (discussed later) at 20°.

Disaggregation Apparatus—The apparatus (Fig. 2) consisted of a USP dissolution test basket[3] submerged 3 cm below the surface of 200 ml of electrolyte contained in a 250-ml measuring cylinder (internal diameter of 3.5 cm and height of 31.5 cm). The basket containing the tablet was rotated at a constant speed of 100 rpm (±1%). The narrow diameter of the measuring cylinder produced a lot of turbulence in the area around and within the basket but little turbulence 3 cm below the basket base. This arrangement ensured that there was adequate agitation while the tablet disintegrated in the basket. However, once the tablet fragments passed through the mesh, they were not subjected to any further mixing action.

Disintegration measurements with the apparatus were carried out by timing how long it took individual tablets to pass completely through the basket mesh.

Counter and Surface Area Determinations—An automated counter[4] with a 560-μm diameter orifice sampling tube was used. Sampling times were kept constant at 4 sec, and this time was consistently equivalent to a sample volume of 4.40 ml. When using a 560-μm tube and calibrating at the high end, particles in the 321–25-μm range could be measured.

Preliminary experimentation showed that the most suitable electrolyte for this work was a filtered mixture of 60% (v/v) glycerin BP and 40% (v/v) modified Eagle's solution[5]. This mixture possessed a reasonable rate of flow through the 560-μm orifice tube, had the right electrical resistivity, and was viscous enough to prevent quick settlement of any large tablet fragments. In addition, the viscosity of the mixture (measured with a U-tube viscometer) was close to that of gastric juice. The electrolyte was filtered through a 0.22-μm membrane.

A tablet was placed in the basket of the disaggregation apparatus

[2] Strong-Cobb tester, Strong Cobb Arner Inc.
[3] See USP XIX, p. 651.
[4] Coulter, model B, with model M volume converter.
[5] Isoton, Coulter Electronics Ltd.

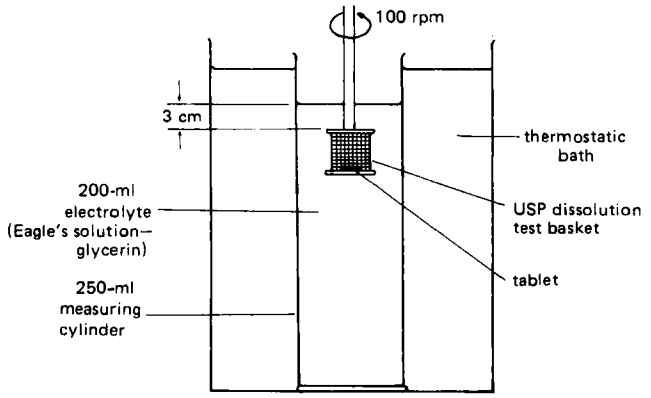

Figure 2—*Disaggregation test apparatus.*

and allowed to revolve for 10 min. The basket assembly was then removed from the electrolyte, and the contents of the measuring cylinder were immediately transferred to a 250-ml beaker containing a magnetic stirrer. The suspension was carefully poured down the inside of the beaker to avoid the production of air bubbles. The beaker contents were allowed to mix for 15 sec, and then a 12-point automated analysis was performed. With a 4-sec count, a complete analysis could be accomplished in about 1 min. All counts were within the recommended 5% coincidence level. From each tablet batch, five replicate determinations were performed.

The whole procedure was repeated with fresh tablets from each batch at a disaggregation time of 30 min. However, the 5% coincidence level was exceeded with these counts, and a 1:5 electrolyte dilution had to be performed before a count could be taken.

In addition to the size analysis, the data from the counter directly produced values for the volume occupied by the tablet fragments within each specific size interval. By using these data and assuming that the fragments were solid spheres, the total surface area of the tablet fragments in 200 ml of suspension could be calculated.

The volume converter produced values of ΔnV_i, the total volume (in arbitrary units) occupied by the tablet fragments within the size interval i. Conversion to real units was accomplished by calibration with spheres of known size, number, and volume. The calibration factor was 2.1×10^{-6} ml; thus, $2.1 \times 10^{-6}\ \Delta nV_i$ cm^3 represents the total volume in cubic centimeters occupied by the tablet fragments in the size interval i. If $\overline{di}$ is the mean particle diameter (in micrometers) within size interval i, then the total surface area (S) of fragments within this size interval is:

$$S = \frac{2.1 \times 10^{-6}\ \Delta nV_i 6}{\overline{di}\ 10^{-4}}\ \text{cm}^2 \qquad \text{(Eq. 1}a\text{)}$$

$$S = \frac{12.6 \times 10^{-2}\ \Delta nV_i}{\overline{di}}\ \text{cm}^2 \qquad \text{(Eq. 1}b\text{)}$$

The total surface area, S_T, in 200 ml of suspension is then:

$$S_T = \frac{12.6 \times 10^{-2}\ V_1 f}{V_2} \sum_{i=12}^{i=1} \frac{\Delta nV_i}{\overline{di}}\ \text{cm}^2 \qquad \text{(Eq. 2)}$$

where V_1 = total volume of suspension (200 ml), V_2 = sample volume passing through orifice tube (4.40 ml), and f = dilution factor.

Values for S_T were plotted for each formulation at each of the two disaggregation times.

RESULTS AND DISCUSSION

Figure 3 shows the graphs obtained when the BP disintegration time was plotted for each tablet formulation. Similarly shaped graphs were obtained when using electrolyte as the disintegration medium and when disintegration was carried out in the disaggregation apparatus. As expected, an increase in compaction pressure increased the disintegration time. Increasing the ratio of extragranular starch above 5% (w/w) produced a decrease in disintegration time, although the reduction was not very great.

The data from these graphs were found statistically to fit a first-order polynomial ($p = 0.05$) relating disintegration time with starch content and compaction pressure. If D_e is the disintegration time in electrolyte (minutes), P is the compaction pressure (MNm^{-2}), and s equals (percent extragranular starch–percent intragranular starch), then by using the method of least squares to fit the response surface,

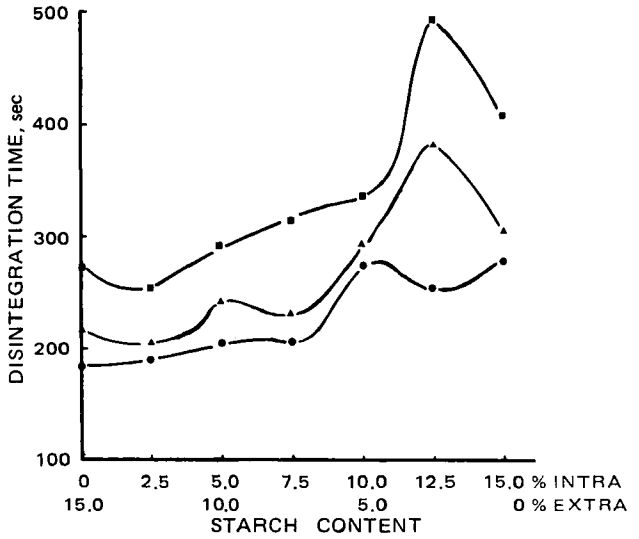

Figure 3—*Effect of starch distribution on tablet disintegration time. Key: ●, 58.5 MNm^{-2}; ▲, 87.6 MNm^{-2}; and ■, 116.4 MNm^{-2}.*

it was found that:

$$D_e = 1.85 - 0.08s + 0.032P \qquad \text{(Eq. 3)}$$

A minimum value for D_e occurs when s is high and P is low, *i.e.*, with tablets produced at as low a compaction pressure as possible and with a formulation containing 15% extra-0% intragranular starch. All other things being equal, this set of formulation and production conditions would be applied to produce the best disintegrating tablets as far as the BP disintegration test is concerned.

Figure 4 depicts tablet hardness values for the various formulations at the three compaction pressures. Again, as expected, increasing the compaction pressure increased the hardness. Variation in the proportion of extragranular starch did not appear to produce a significant variation in hardness, and this finding was confirmed by calculating the respective correlation coefficients (r). At 58.5 MNm^{-2}, r was −0.388; at 87.6 MNm^{-2}, r equaled 0.029; at 116.4 MNm^{-2}, r was 0.474 ($p = 0.05$, $\phi = 5$). Again, these data were found statistically to fit a first-order polynomial ($p = 0.05$):

$$H = 0.005s - 1.76 + 0.07P \qquad \text{(Eq. 4)}$$

where H = hardness in Strong-Cobb units.

From Eq. 4, it can be seen that the siting of the starch does not greatly affect the hardness of the resultant tablets. The compaction pressure appears to be the dominant factor.

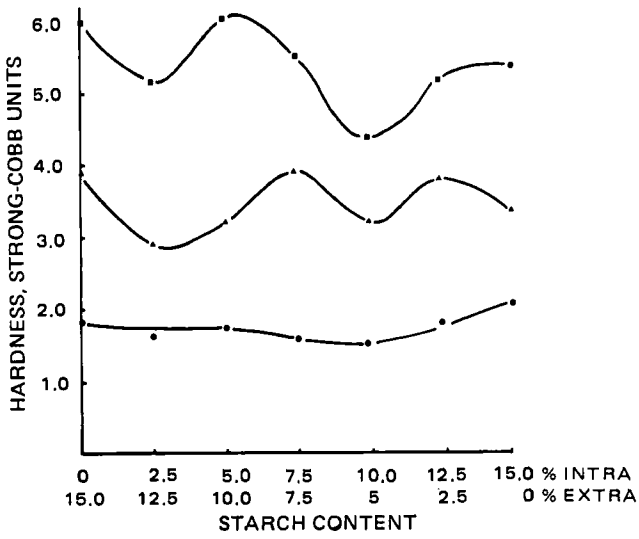

Figure 4—*Variation of tablet hardness with starch distribution. Key: ●, 58.5 MNm^{-2}; ▲, 87.6 MNm^{-2}; and ■, 116.4 MNm^{-2}.*

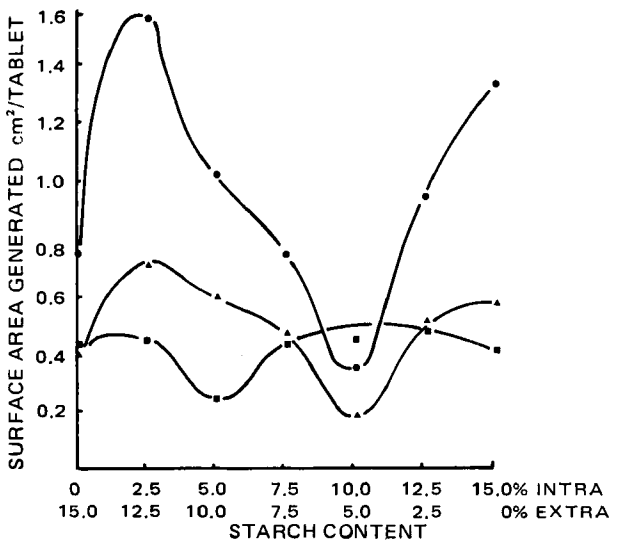

Figure 5—*Effect of starch distribution on the surface area generated per tablet after 10 min of disintegration. Key: ●, 58.5 MNm^{-2}; ▲, 87.6 MNm^{-2}; and ■, 116.4 MNm^{-2}.*

Correlation coefficients for the hardness and disintegration measurements at similar compaction pressures showed that there was no correlation between tablet hardness and disintegration time at all compaction pressures [disintegration in water: r = 0.191 (58.5 MNm^{-2}), −0.311 (87.6 MNm^{-2}), and −0.648 (116.4 MNm^{-2}); disintegration in electrolyte: r = 0.303 (58.5 MNm^{-2}), 0.213 (87.6 MNm^{-2}), and −0.334 (116.4 MNm^{-2})].

The particle-size distributions of the suspensions recovered from the disaggregation test were log normally distributed and, in all cases, were bimodal or occasionally trimodal. Increasing the time of disaggregation did not greatly affect the particle-size distributions, and no meaningful conclusions could be elucidated from comparisons of the median particle diameters obtained from each group of tablets. At 58.5 MNm^{-2}, the number of small particles increased as the proportion of extragranular starch increased from 0%. However, this

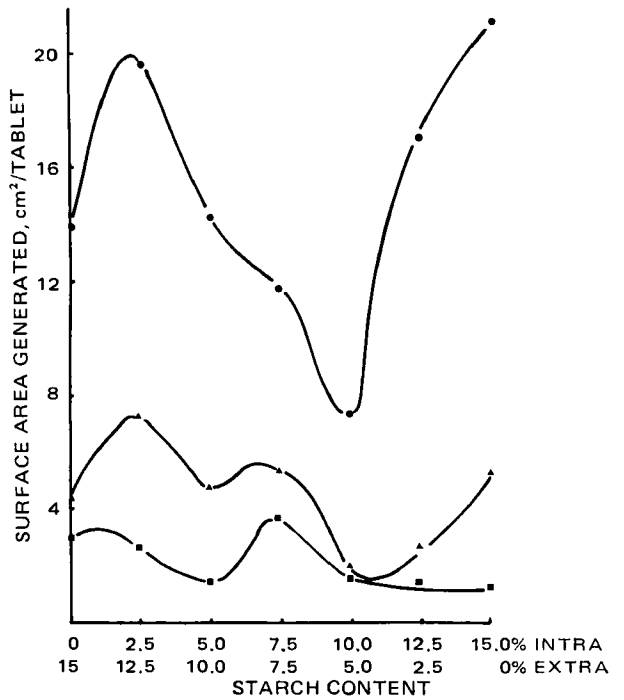

Figure 6—*Effect of starch distribution on the surface area generated per tablet after 30 min of disintegration. Key: ●, 58.5 MNm^{-2}; ▲, 87.6 MNm^{-2}; and ■, 116.4 MNm^{-2}.*

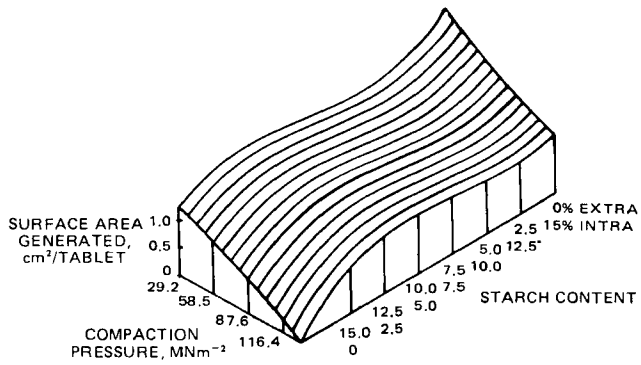

Figure 7—*Computer-produced three-dimensional contour model. The contour system shows how variation in starch content and compaction pressure affects the generated surface area per tablet after 10 min of disintegration.*

pattern was not exhibited at higher pressures.

One very prominent feature that was observed was the large number of particles between 63.7 and 80.3 μm for all formulations containing 2.5% extra–12.5% intragranular starch. A satisfactory explanation for this phenomenon has not been found. These results do not bear out the findings of Shotton and Leonard (10), who found that the use of intragranular starch resulted in the recovery of much finer particles than did the use of extragranular starch. However, Shotton and Leonard did not report the compaction pressure at which comparisons were made, and it seems from the present investigation that compacting pressure plays a large part in determining the extent of disaggregation. Shotton and Leonard assumed that the size values obtained from sieving and by automated counter measurement were directly compatible. This assumption has been shown not to be the case (11) and could give rise to misleading results. In addition, these workers took no account of the possibility that disintegration probably took place by dissolution of the water-soluble binder povidone (included in their tablets) as well as by the breakdown resulting from starch disintegration.

For the various formulations, the surface area generated per tablet after 10 and 30 min are shown in Figs. 5 and 6, respectively. Each point on these graphs was calculated from the individual measurements of some 35,000 fragments; therefore, a very high degree of precision could be expected.

Roughly 12 times the surface area is generated after 30 min than after 10 min. After 30 min, decreasing the compaction pressure increased the generated surface area of the tablet fragments. However, after 10 min there appeared to be an interaction between compaction pressure and starch content.

The surface area data were found statistically to fit a third-order polynomial (p = 0.05), confirming that an interaction did exist. After 10 min:

$$S_T = 1.2000 + 0.0156s - 0.0107P + 0.0030s^2 + 0.004sP - 0.002s^3 \quad \text{(Eq. 5)}$$

and after 30 min:

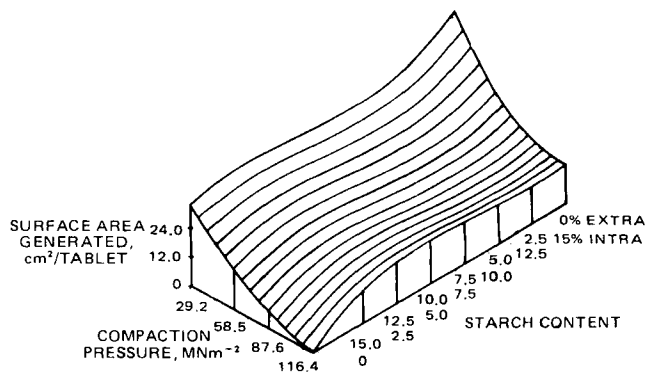

Figure 8—*Effect of compaction pressure and starch distribution on the surface area generated per tablet after 30 min of disintegration.*

$$S_T = 52.048 - 0.324s - 0.955P - 0.232s^2 + 0.016sP - 0.053s^2 - 0.003s^2P \quad \text{(Eq. 6)}$$

By computer simulation, the three-dimensional contour systems were produced from these equations. The mathematical models are shown in Figs. 7 and 8, respectively. As was found from disintegration time measurements, decreasing the compaction pressure increased the generated surface area of the tablet fragment with all formulations. However, with this test, the highest values of surface area occurred with formulations containing 2.5% intra–12.5% extragranular starch and 15% intragranular starch. On the basis of this test, these formulations should be selected, not the one containing 15% extragranular starch, as found from BP disintegration test determinations. This test also shows that there are large differences in surface area values for starch combinations less than 10% intra–5% extragranular, a fact not shown by simple disintegration time measurements. In addition, the common practice of incorporating 5% extragranular starch into a formulation actually produced the lowest values of surface area, again a fact not shown by simple disintegration time measurements.

This new type of disaggregation test appears to be particularly sensitive. It is capable of monitoring small formulation differences with a high degree of precision and of producing an index that is more directly relatable to tablet dissolution. The official disintegration test, however, may produce misleading results, because the insensitivity of the test can mask real and significant differences between tablets. The new disaggregation test reported here thus appears to provide a more sensitive tool for evaluating the disintegrating properties of tablets.

CONCLUSIONS

The authors consider that the official disintegration test is only sufficiently sensitive to detect gross differences between tablets. An alternative and more sensitive technique is proposed; it utilizes an automated counter and measures the surface area generated per tablet during disintegration. This new disaggregation method was used to show that the optimum starch combination in a tablet formulation is either 2.5% intra–12.5% extragranular or 15% intragranular starch alone. Furthermore, the distribution of starch will not affect the resultant hardness of the tablets and, to achieve maximum generation of surface area, tablets should be compacted at as low a pressure as possible.

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Dissolution Characteristics and Oral Absorption of Digitoxin and Digoxin Coprecipitates

RANJIT K. REDDY, SAID A. KHALIL [*], and M. WAFIK GOUDA [x]

Abstract □ A marked increase in the dissolution rates of digitoxin and digoxin was attained by dispersing the drugs in two inert solid carriers, poloxamer 188 and deoxycholic acid. The 1 and 10% (w/w) drug–carrier solid dispersions were prepared by the solvent method. The former dissolved significantly faster than the latter. The oral administration of 10% (w/w) digitoxin–carrier coprecipitates to mice significantly increased toxicity. This observed increase is attributed to an increase in the rate and, possibly, the extent of oral absorption of the drug. Although a 10% coprecipitate of digoxin in both carriers showed an increase in the dissolution rate, no increase in oral toxicity was observed. X-ray diffraction patterns indicated that both digitoxin and deoxycholic acid undergo crystalline modifications due to treatment by the solvent, but the exact nature of the drug–carrier solid dispersions was not revealed.

Keyphrases □ Digitoxin—coprecipitates with inert solid carriers, dissolution and oral absorption, mice □ Digoxin—coprecipitates with inert solid carriers, dissolution and oral absorption, mice □ Dissolution—digitoxin and digoxin, coprecipitates with inert solid carriers, mice □ Absorption, oral—digitoxin and digoxin, coprecipitates with inert solid carriers, mice □ Coprecipitates—digitoxin and digoxin with inert solid carriers, dissolution and oral absorption, mice □ Dosage forms—digitoxin and digoxin coprecipitates with inert solid carriers, dissolution and oral absorption, mice

It is well documented that the bioavailability of digoxin from commercial tablet dosage forms is not uniform (1–7). Furthermore, the absorption efficiency from tablets is considerably less than from an oral solution (6, 8). Solid dosage forms of digitoxin are also suspected of exhibiting bioavailability differences (9).

Mortar grinding increased the dissolution rate of three digoxin samples studied (10). Tablets and capsules of digoxin made after crushing material that passed the BP requirements gave higher area under the concentration–time curves than did formulations made of the same material before crushing (11). It was concluded