Effect of Compaction on Particle Size

K. A. KHAN * and C. T. RHODES ˣ

Abstract □ Compressed tablets were prepared on a hydraulic press at several different compaction pressures by a standardized technique, using aspirin, dicalcium phosphate dihydrate, calcium phosphato-carbonate, alumina, and microcrystalline cellulose. All tablets except microcrystalline cellulose contained a cation-exchange resin as disintegrant. The particle-size spectra of the disintegrating compacts were evaluated using a particle-size counter or an air jet sieve. It is shown that compacts made from different materials but of the same initial particle-size spectra disintegrate to give particles of a considerably different size. Determination of the change in particle size produced by the compaction process provides useful insight into the nature of the compaction process.

Keyphrases □ Compaction pressure—effect on particle-size spectrum of disintegrating compacts, aspirin, dicalcium phosphate dihydrate, calcium phosphato-carbonate, alumina, microcrystalline cellulose □ Particle size, disintegrating compacts—determination, relationship between particle size and nature of compaction process □ Pressure, compaction—effect on particle-size spectrum of disintegrating compacts □ Compressed tablets—evaluation of particle-size spectra □ Tablets, compressed—evaluation of particle-size spectra

The relevance of particle-size control to pharmaceuticals has been recognized for many years. Most studies have been concerned with the influence of particle size on tableting characteristics (1) or on dissolution rate (2). Several studies reported the effect of compressional force on the specific surface area of tablets (3, 4) and showed that, as pressure increases, specific surface area initially increases and then decreases.

Studies of the effect of compaction on the particle size of a pharmaceutical system may be expected to provide data relevant to deciding whether the particles within the compact exist as crystal units or aggregates or have undergone extensive fragmentation. Examination of the literature reveals the comparative paucity of such work. Cid and Jaminet (5) showed that the maximum dissolution rate of the aspirin formulations they investigated was obtained from the system giving the smallest particle-size distribution when the tablet disintegrated. Smith *et al.* (6) proposed that an increase in compressional force enhances the dissolution by causing fragmentation within the compact.

Since the effect of compaction pressure on aggregation or fragmentation within a compact is related to the fundamental molecular properties of the material being compressed, it seemed likely that a study of particle-size distributions within disintegrating compacts would help elucidate both compressional properties and the effect of compressional force on dissolution behavior. Therefore, it was considered that if powders of known particle-size spectra were compressed and then allowed to disintegrate, evidence of fragmentation or interparticulate bonding might be obtained. Of course, experimental problems involved in the determination of the particle size of disintegrating compacts meant that the data obtained might represent relative rather than absolute values, even with carefully standardized techniques.

Five materials were selected for this study: alumina was chosen as a brittle material that forms unstable compacts; aspirin was chosen as a granular, directly compressible drug; and microcrystalline cellulose, dicalcium phosphate dihydrate, and calcium phosphato-carbonate complex were chosen as direct compression diluents.

EXPERIMENTAL

Materials—Aspirin[1] BP, dicalcium phosphate dihydrate[2], and calcium phosphato-carbonate complex[3] were all screened to obtain a −35 + 60 B.S.S.[4] mesh particle-size fraction (mean particle-size fraction 335 μm); fines were removed by use of an air jet sieve[5]. Because the coarse fraction of alumina[6] was not compressible, it was necessary to use a finer sieve fraction (−100 + 200 B.S.S., mean particle size 113 μm). Microcrystalline cellulose[7] was used as supplied by the manufacturer. Magnesium stearate[8] was also used in the formulations.

For the dicalcium phosphate dihydrate, calcium phosphato-carbonate complex, and alumina, 3% of the cation-exchange resin[9] was used as disintegrant. For aspirin formulations, 5% of the resin was needed.

Methods—Compacts, 13 mm in diameter, were prepared by means of a hydraulic press; the powder samples were subjected to known pressures for 30 sec. To effect disintegration of the compacts without agitation, which might cause particulate fracture, the compacts contained a particularly effective disintegrant. In the case of the compacts prepared from the insoluble materials (dicalcium phosphate dihydrate and calcium phosphato-carbonate complex), distilled water was used as the disintegration vehicle; for the other systems, appropriate saturated solutions were used.

Particle-size determinations of the disintegrated compacts were made using either a particle-size counter[10] or air jet sieve[5]. The particle-size counter, with a 400-μm orifice tube, was used where the maximum particle size was less than 160 μm. The counter was used as described previously (8), with 1% (w/v) sodium chloride as the electrolyte. For most of the particle-size determinations, the air jet sieve was used. The tablets were allowed to disintegrate and then were filtered and dried before sieve analysis. A standard procedure was adopted by which the material was sieved for 3 min on each British Standard sieve. From the amount remaining on each sieve, percentage undersize values were calculated. At least four compacts were used for each experiment; the means of the differ-

[1] Monsanto, London, England.
[2] Albright and Wilson, Oldbury, England.
[3] Calfos, London, England.
[4] British Standard sieve.
[5] Alpine.
[6] Thermo Syndicate, London, England.
[7] Avicel PH102, Honeywell and Stein, London, England.
[8] B.D.H., Poole, England.
[9] Amberlite IRP 88, Lenning, London, England.
[10] Coulter.

Table I—Effect of Applied Pressure on the Mean Particle Size of Disintegrated Compacts

Applied Pressure, MNm^{-2}	Mean Particle Size (Micrometers) of Compacts after Disintegration Containing			
	Alumina[a]	Aspirin[b]	Dicalcium Phosphate Dihydrate[b]	Calcium Phosphato-carbonate Complex[b]
74	—	277	68	208
149	82	282	100	194
298	80	272	120	183
447	66	266	149	177
597	—	263	150	180

[a] Alumina, initial mean particle size 112.5 μm. [b] Aspirin, dicalcium phosphate dihydrate, and calcium phosphato-carbonate complex, initial mean particle size 335 μm.

ent values, all of which were in good agreement with one another (±4%), were calculated.

The effect of compaction pressure on the particle-size distribution of microcrystalline cellulose, as determined by use of the particle-size counter, is shown in Fig. 1. Similar data for aspirin, dicalcium phosphate dihydrate, calcium phosphato-carbonate complex, and alumina obtained by use of the air jet sieve are shown in Figs. 2–4. The effect of compaction pressure on the mean particle size of the disintegrated compacts is shown in Table I.

RESULTS AND DISCUSSION

It can be seen in Fig. 1 that an increase in compaction pressure[11] from 74 to 298 MNm^{-2} caused some fragmentation of the microcrystalline cellulose. However, the particle-size distributions of compacts prepared at 446 and 597 MNm^{-2} were very similar to that determined at 298 MNm^{-2}. Because this material is known to undergo considerable interparticulate bonding by plastic flow (9), the results shown in Fig. 1 may initially appear to be somewhat strange. Reier and Shangraw (10), however, proposed that the most important factor contributing to the compaction of microcrystalline cellulose is hydrogen bonding. These investigators stated that crystals are compacted close enough so that hydrogen bonding between them can occur. The results presented in Fig. 1 support Reier and Shangraw's (10) hypothesis that, as may be expected, penetration of water would interrupt hydrogen bonding and break the compact into its original constituents. Thus, the curves (Fig. 1) only show fragmentation, which is caused by the effect of compression.

Figure 2 shows the effect of pressure on the particle-size distribution of compacts prepared from alumina (Fig. 2A) and aspirin (Fig. 2B). The compacts prepared from alumina were soft and very unstable. Compacts of this material apparently were formed merely by fragmentation, which increases slightly with an increase in pressure; mean particle size of the disintegrated compacts undergoes gradual reduction as the applied pressure increases. There did not appear to be any agglomeration or recombination of particles as a result of pressure. These results are similar to those obtained by Varma *et al.* (11), who studied the effect of pressure on the particle-size distribution of compacts prepared from some brittle materials.

Figure 2B shows the effect of pressure on the particle-size distribution of compacts prepared from granular aspirin. It seems that increasing pressure caused some fragmentation of aspirin crystals; the effect, however, was extremely small. The mean particle size was reduced from 277 μm when compacted at 74 MNm^{-2} to a slightly lower value of 263 μm when compacted at 597.1 MNm^{-2}. There was also very little effect on the pattern of particle-size distribution. During the initial compression, as rearrangement of these crystals takes place, the edges and corners of some crystals possibly may be knocked off, thus causing a slight decrease in particle size. After this stage, it seems that a strongly bonded system has been formed and further increases in pressure, as evident from

[11] In this paper, Standard International units of newtons per square meter are used for compaction pressures, 1 newton = kg^{-2}.

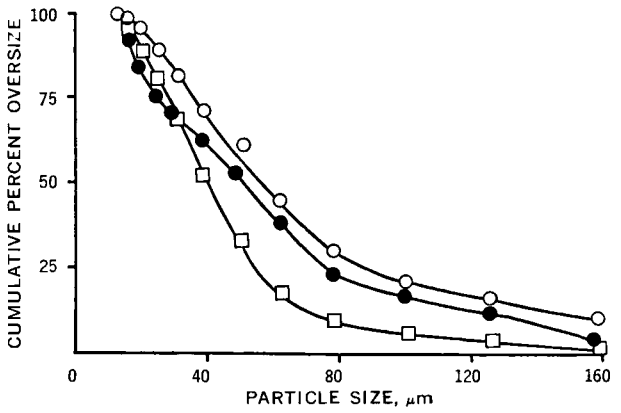

Figure 1—*Effect of pressure on the particle-size distribution of disintegrating microcrystalline cellulose compacts. Key: ○, before compaction; ●, compacted at 74 MNm^{-2}; and □, compacted at 298 MNm^{-2}.*

Fig. 2B and Table I, have very little effect on the particle-size distribution. These results are supported by the findings of Ganderton (12), who also found that aspirin crystals underwent deformation but retained their integrity at all practical pressures.

Figure 3 shows the effect of pressure on the particle-size distribution of compacts prepared from dicalcium phosphate dihydrate. The particle size of this material was reduced after compaction at 74 MNm^{-2} (mean size 68 μm), increased again when compacted at 149.3 MNm^{-2} (mean size 100 μm), and continued to increase with increasing pressure in the pressure range used in this study (Table I and Fig. 3). These results are very similar to those obtained in studies of the effect of pressure on the surface area of compacts (3, 4) in which the surface area of the compacts initially increased due to fragmentation and then decreased due to particle bonding.

Although the mean particle size of dicalcium phosphate dihydrate compacts clearly indicates the effect of pressure on the com-

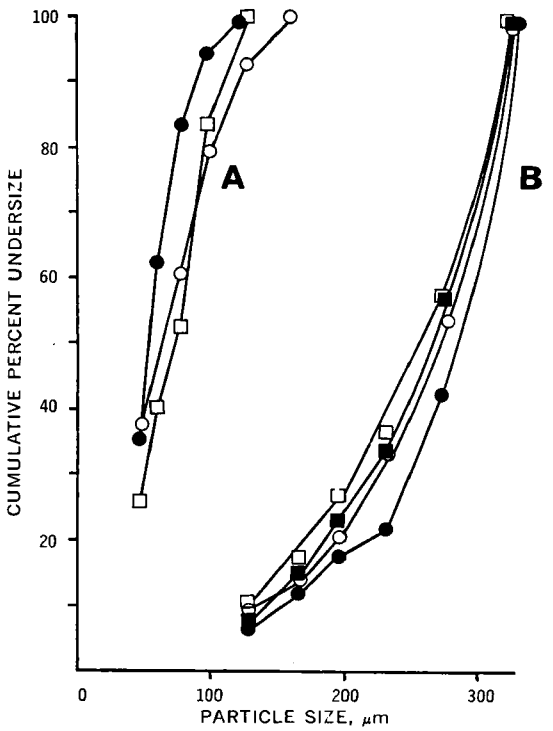

Figure 2—*Effect of pressure on the particle-size distribution of disintegrating compacts made from alumina (A) or aspirin (B). Key (A, alumina, original mean particle size 113 μm): ○, 149 MNm^{-2}; □, 298 MNm^{-2}; and ●, 446 MNm^{-2}. Key (B, aspirin, original mean particle size 336 μm): ●, 149 MNm^{-2}; ○, 298 MNm^{-2}; ■, 447 MNm^{-2}; and □, 597 MNm^{-2}.*

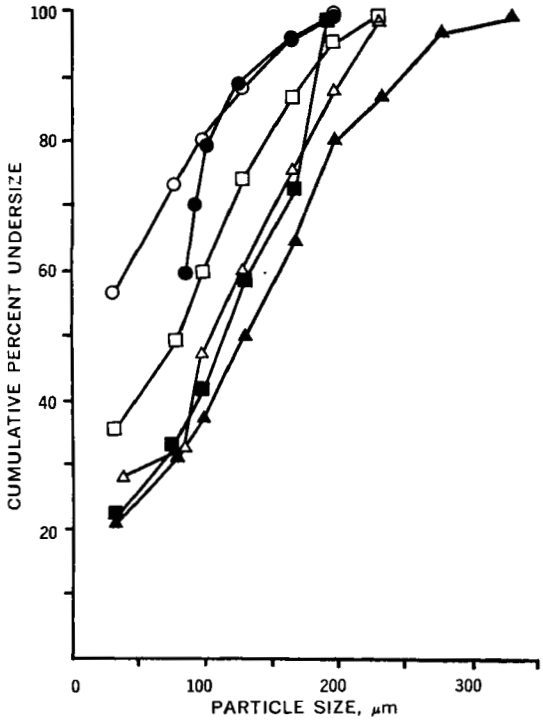

Figure 3—*Effect of pressure on the particle-size distribution of disintegrating dicalcium phosphate dihydrate compacts (original mean particle size 335 μm). Key: ○, 74 MNm⁻²; ●, 149 MNm⁻²; □, 224 MNm⁻²; △, 298 MNm⁻²; ■, 372 MNm⁻²; and ▲, 447 MNm⁻².*

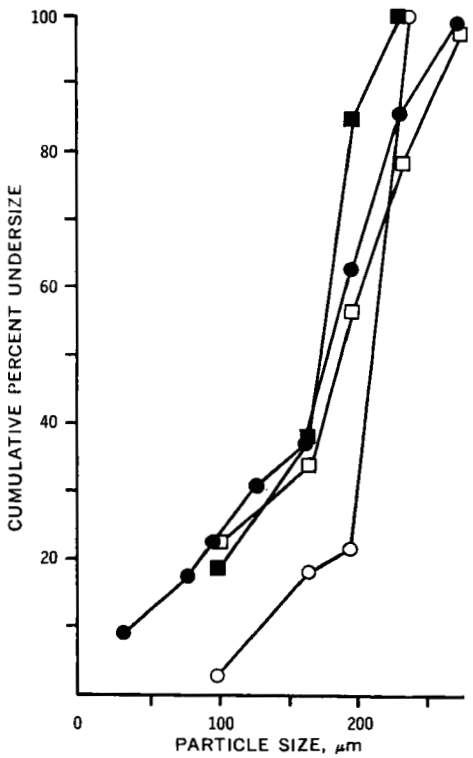

Figure 4—*Effect of pressure on the particle-size distribution of disintegrating calcium phosphato-carbonate compacts (original mean particle size 335 μm). Key: ○, 149 MNm⁻²; □, 298 MNm⁻²; ●, 447 MNm⁻²; and ■, 672 MNm⁻².*

pression of this material (Table I), the particle-size distribution curves are more informative (Fig. 3). These curves show the great amount of fragmentation that occurred during compression, with the curve changing from a very narrow size range to a much wider distribution. At low pressure, grinding is the predominant process, but as the compression increases, although grinding still continues, recombination also takes place and the distribution curve covers a greater size range and becomes flatter. These curves show that fragmentation occurs initially during compression; but as the compression is increased, bonding also takes place. Thus, the mean particle diameter and specific surface area will depend on the balance of these two processes which, in turn, depend upon the applied pressure.

Figure 4 shows the effect of pressure on the particle-size distribution of compacts prepared from calcium phosphato-carbonate complex. The effect of pressure on the particle-size distribution of this substance apparently is very similar to that of aspirin; once a strongly bonded system has been formed, a further increase in pressure causes very little fragmentation. The behavior of this material on compression differs from that of dicalcium phosphate dihydrate in that the former undergoes less fragmentation on compression and, after initial fragmentation, a further increase in pressure does not cause any apparent bonding and recombination of particles, as shown by the compression of dicalcium phosphate dihydrate (Figs. 3 and 4 and Table I).

Previously, it was shown that calcium phosphato-carbonate complex has somewhat superior compression properties to that shown by dicalcium phosphate dihydrate (7). Calcium phosphato-carbonate complex produces harder tablets at lower pressure; its compressibility also appears to be higher than that of dicalcium phosphate dihydrate. The results presented in Fig. 4 indicate that, although the increase in pressure causes some fragmentation, the curve changes from one of a narrow range to that of a much wider distribution. Mean particle size decreases only slightly with increasing pressure (Table I). From these results and those reported previously (7), it appears possible that calcium phosphato-carbonate complex is a useful direct compression diluent which forms a strongly bonded system at a low compaction pressure.

In conclusion, it seems that compacts of different materials made from the same initial particle size and compressed at the same pressures show different size distributions, which appear to be indicative of their compaction behavior. The techniques of estimating particle-size distribution of disintegrated compacts can be a useful guide to the compression properties of a formulation.

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Water-Sorption Properties of Tablet Disintegrants

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Abstract □ The water-sorption properties of four tablet disintegrants, starch, sodium carboxymethylcellulose, sodium starch glycolate, and a cation-exchange resin, were examined in the form of powders and in compressed tablets prepared from calcium phosphate dibasic dihydrate. Dissolution properties of the tablets compare well to the water-sorption properties. The effect of storage in the presence of water vapor upon tablets containing the various disintegrants was evaluated in terms of tablet hardness and disintegration time. Differences in the effects produced in the various tablet formulations can be related to the differing mechanisms whereby the disintegrants effect tablet rupture. Photomicrographic data support the conclusions drawn from the water-sorption, disintegration, and dissolution studies. Sodium starch glycolate and the cation-exchange resin merit careful consideration by formulators using calcium phosphate dibasic dihydrate or similar direct compression matrixes.

Keyphrases □ Water sorption of tablet disintegrants (starch, sodium carboxymethylcellulose, sodium starch glycolate, cation-exchange resin)—disintegration and dissolution, powders and calcium phosphate dibasic dihydrate tablets □ Tablet disintegrants (starch, sodium carboxymethylcellulose, sodium starch glycolate, cation-exchange resin)—water sorption of powders and calcium phosphate dibasic dihydrate tablets, disintegration, dissolution

Previously, the disintegration and dissolution properties of tablets containing sodium starch glycolate and a cation-exchange resin were reported (1, 2). The results of these evaluations clearly showed that both the cation-exchange resin and sodium starch glycolate are extremely efficient disintegrants in a variety of tablet systems. The objective of the present study was to examine the water-sorption properties of these disintegrants in an attempt to evaluate the basic factors controlling their disintegrant action. Starch and sodium carboxymethylcellulose were included for comparative purposes.

EXPERIMENTAL

Materials—The following were used: calcium phosphate dibasic dihydrate[1] (unmilled), corn starch[2] BP, sodium salicylate[2], amaranth[2] BPC, a cation-exchange resin[3], sodium starch glycolate[4], sodium carboxymethylcellulose[5], and magnesium stearate[6].

Dried Disintegrant Powders—The dried disintegrants were exposed to 100% relative humidity at 37°. Two replicate readings of water uptake, always in good agreement, were obtained at various times over 25 hr. Figure 1 shows the water sorption by the disintegrant as a function of time.

Table I—Effect of Humidity on Disintegration Properties of Calcium Phosphate Dibasic Dihydrate Tablets, Containing Several Disintegrants, Stored at 100% Relative Humidity at 37° [Punch Size 1.1 cm ($^7/_{16}$ in.) Flat]

Disintegrants, 10% (w/v)	Disintegration Time, min					
	Initial	2 hr	4 hr	8 hr	22 hr	30 hr
Starch	15[a]	15[a]	15[a]	15[a]	15[a]	15[a]
Sodium carboxymethylcellulose	43	50	50	55	55	60
Sodium starch glycolate	0.6	2.8	7.0	13.0	15	15
Cation-exchange resin	0.83	2.0	7.0	8.0	60	60

[a] Particles remaining.

Tablet Containing 10% Disintegrant—Calcium phosphate dibasic dihydrate was chosen as the excipient because of its very low equilibrium moisture content (2.5%). Furthermore, tablets made from the material were easier to handle after having absorbed moisture than were other tablets, such as those prepared from lactose.

The tablets containing 10% disintegrant were made using 1.1-cm ($^7/_{16}$-in.) flat punches on a single-punch tablet press[7]. All tablets were made under the same conditions of pressure and die fill settings. Fifty tablets of each formulation were used for the water-sorption study. Five lots of 10 tablets of each formulation (one lot for each time interval of 5, 10, 15, 20, and 25 hr) were weighed and labeled individually; their thickness and diameter measurements were taken, using a micrometer, before and after exposure to 100% relative humidity.

Figure 2 shows the water uptake by these tablets as a function of time. The results of expansion and thickness changes accompanying water sorption are presented in Figs. 3 and 4. (Changes in density reflect overall structural changes, whereas individual measurement of thickness and diameter changes allows observation of whether expansion occurs preferentially in, or at right angles to, the plane of compression.) These tablets were also tested for disintegration time[8] using the BP method and for hardness[9]. The effect of storage on disintegration time and hardness of tablets prepared from calcium phosphate dibasic dihydrate is shown in Tables I and II.

To express the relative affinities for water of these disintegrants, the term "absorption efficiency" was used; it is calculated in a similar way as dissolution efficiency (3). Figures 5 and 6 show the absorption efficiencies of pure disintegrants and of the disintegrants

[1] Albright and Wilson, Oldbury, England.
[2] J. M. Loveridge, Southampton, England.
[3] Amberlite IRP88, Lenning, London, England.
[4] Primojel, Slater, Winsford, England.
[5] Courlose P20, British Celanese, Coventry, England.
[6] British Drug Houses, Poole, England.
[7] Manesty F3.
[8] Manesty disintegration tester.
[9] Erweka hardness tester.