Granule Consolidation during Compaction

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Abstract ☐ The deformation of small cylindrical aggregates of dibasic calcium phosphate was measured during compaction. An analogy between these aggregates and cylindrical granules was proposed. No change in the original shape of the aggregates occurred; the cylindrical shape was maintained even at high compaction pressures. Relaxation of the aggregates occurred at pressures higher than 420 MNm^{-2} (60.9 × 10^3 lb in.$^{-2}$) when removed from the compacts, but no relaxation took place at pressures below this value. In addition, the aggregates relaxed by an increase in thickness only; there was no corresponding change in diameter. Up to a pressure of 200 MNm^{-2} (29.0 × 10^3 lb in.$^{-2}$), an increase in aggregate diameter occurred, which was accompanied by a reduction in thickness. This change produced only a small reduction in volume, which was attributable to interparticulate slippage resulting in a closer packed arrangement. At a pressure of 200 MNm^{-2}, the aggregate diameter no longer increased because solid bridges were formed between the particles and the die wall, preventing further spreading. From 200 to 420 MNm^{-2}, failure of the material occurred by plastic deformation, which produced only a decrease in aggregate thickness. From 420 to 800 MNm^{-2} (116.0 × 10^3 lb in.$^{-2}$), a structure was formed that could support the applied load without further reduction of thickness, and this structure was shown to behave elastically.

Keyphrases ☐ Granules—consolidation during compaction, dibasic calcium phosphate aggregate deformation measured, effect of pressure, granule thickness ☐ Calcium phosphate, dibasic—deformation of aggregates measured during compaction, effect of pressure, granule thickness

The mechanism by which a mass of powder is compressed into a coherent tablet has been studied (1–4). By measuring the exposed punch length during static compression of heavy magnesium carbonate, Train (5) evaluated the relationship between the relative volume of the compact and the applied pressure. Using a modification of Train's method, Kristoffersson and Krogerus (6) measured the deformation of whole tablets containing polyethylene glycols; they recorded the changes in height at various compaction pressures.

Various theoretical attempts have been made to quantify the consolidation of powders as compression proceeds (7, 8). All of these treatments have involved measurements of the external dimensions of the finished tablet. Train (5), however, emphasized that evidence obtained from measurements of the external dimensions of compacts may not truly reflect the internal situation.

The present study was carried out to examine the deformation of granules during compaction and then the three-dimensional changes that occur with individual granules within the compacting mass.

EXPERIMENTAL

The powder used was dibasic calcium phosphate[1] because it is a common tablet excipient and produces hard tablets at low compaction pressures. The mean particle size was 48 μm with 100% by weight less than 90 μm (sieve analysis). The dibasic calcium phos-

phate powder was intimately mixed with 10% by weight of radiographic barium sulfate[1]. The barium sulfate was ground so that the powder was of an identical particle size. The powder mix was granulated in a coating pan with 4% mucilage of methylhydroxyethylcellulose[2] to produce spherical granules. The objectives of producing these round granules were to eliminate the shape factor that may influence the deformation process and to standardize, as far as possible, the surface roughness of the granules.

The resultant granules were carefully dried to maintain uniformity of composition, and the 387–500-μm fraction was selected for experimentation. The moisture content of this fraction was found by drying a sample to constant weight (0.5% w/w), and the uniformity of granule strength was checked by measuring the load applied at a constant rate to produce failure of individual granules. The apparatus used for testing granule strength was a modified version of a reported instrument (9). The belt-driven pulley of this apparatus was reversed so that the lower jaw was driven upward rather than downward. An individual granule was placed between the two jaws of the instrument. Movement of the lower jaw upward at a constant velocity of 6.6 × 10^{-5} m/sec applied a diametrical crushing load. The granule strength was read from the chart record as the maximum load applied before failure occurred. Thirty determinations were made.

The granules were then mixed with 1% (w/w) dried magnesium stearate, and consolidation was performed at 15 MNm^{-2} (2.175 × 10^3 lb in.$^{-2}$) between 3.20-mm diameter, new flat-faced punches. The die was filled by hand; a collection of small cylindrical aggregates were produced which were identical in weight, thickness, and diameter. The 15 MNm^{-2} was just enough pressure to aggregate the spherical granules, and the granule structure could be readily observed by eye.

The diameter and thickness of each cylindrical aggregate were individually measured with a traveling microscope to 0.01 mm, and the aggregate volume was calculated from these data. Each measured aggregate was numbered for subsequent identification and each was considered to be one "granule," which could be subsequently compacted at much higher pressures. It can be argued that there might be significant differences in particle to particle bond strength and void space between materials making up these aggregates and true granules. However, for the purposes of this work, the analogy between the two was close enough for the aggregates to be assumed to be cylindrical granules.

Sucrose was granulated similarly to the dibasic calcium phosphate except that 7.5% (w/v) povidone[3] in industrial methylated spirits was used as the granulating agent. The sucrose[1] was milled so that this material possessed the same particle size as the dibasic calcium phosphate. A 1-g quantity of the dried sucrose granules was introduced into a specially hardened die[4], 2.54 cm in diameter. After leveling, three aggregates were positioned diametrically upon the surface of the sucrose granules: one in the center and one each 5 mm from the die wall. A further 1-g quantity of sucrose granules was poured into the die, and the mass was compacted at 30 MNm^{-2} (43.5 × 10^3 lb in.$^{-2}$) on a stationary precision press[5]. This arrangement ensured, as far as possible, that the dibasic calcium phosphate aggregates were compressed to the same compaction pressure within the larger diameter compacts.

Fifteen additional compacts were produced at increasing pressures up to 800 MNm^{-2}. At each compaction pressure, three compacts were produced. Then X-rays, in two directions at right angles, were taken of the large compacts. From the radiographs, diameter and thickness measurements of the dibasic calcium phosphate aggregates were again determined with the traveling microscope and the volumes were calculated. The aggregates were recov-
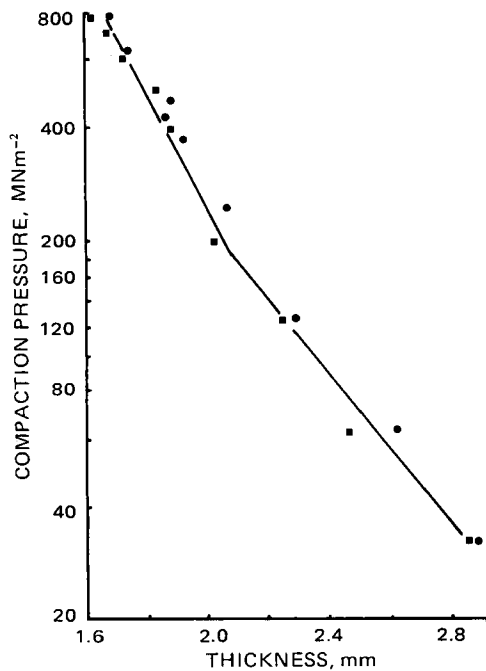
Figure 1—*Variation of compact thickness with compaction pressure. Key: ●, sucrose; and ■, dibasic calcium phosphate (90% w/w) and barium sulfate (10% w/w).*

ered from the large compacts by dissolving out the sucrose with water. An inspection confirmed that no damage was done to the aggregates by this process.

The recovered, intact, identifiable dibasic calcium phosphate aggregates were again measured with the traveling microscope, and the volumes were calculated. Confirmation of the volume values was carried out by water-displacement measurements in a specific gravity bottle. Finally, the crushing strength of the recovered aggregates was determined in the granule strength apparatus by measuring the load applied at a constant rate of 6.6×10^{-5} m/sec to produce failure.

To confirm that the compaction characteristics of sucrose and dibasic calcium phosphate and barium sulfate were similar, thickness measurements were recorded for 2-g compacts composed of only sucrose and of only dibasic calcium phosphate and barium sulfate.

RESULTS AND DISCUSSION

Figure 1 shows the results obtained when compact thickness was plotted against compaction pressure for the sucrose and dibasic calcium phosphate granulations. In all figures, each point represents the mean values of nine determinations; the range of the measured values for the various properties was not more than 10% of the plotted means. Identical graphs were obtained in Fig. 1, indicating that both materials consolidated in a similar manner to produce compacts of identical dimensions.

Table I shows the volumes of the aggregates calculated from dimensional measurements after removal from the large compacts and the corresponding values obtained by water-displacement measurements. There was a negligible difference between the values, indicating that no change in the cylindrical shape of the aggregates had occurred over the whole pressure range studied. This finding was also confirmed by a close inspection of the radiographs. Apparently, the initial shape of the aggregates is maintained inside the compacts and granule shape may be an important factor in the compaction process.

Figure 2 shows the amount the volume of the dibasic calcium phosphate aggregates was reduced at increasing compaction pressures. Inside the compacts up to about 200 MNm^{-2}, the volume of the aggregates was not greatly reduced (about 0.8×10^{-3} ml). From 200 to 420 MNm^{-2}, there was a much greater reduction in volume, ranging from 0.8×10^{-3} ml at 200 MNm^{-2} to a maximum value of 4.6×10^{-3} ml at 420 MNm^{-2}. Over this compaction range, a linear relationship existed between aggregate volume reduction

Table I—Volumes of the Aggregates Removed from the Compacts Calculated from Dimensional and Water-Displacement Measurements

Compaction Pressure, MNm^{-2}	Volume Calculated from Water-Displacement Measurements, ml	Volume Calculated from Dimensional Measurements, ml
32	0.0079	0.0081
32	0.0084	0.0082
32	0.0076	0.0082
360	0.0102	0.0104
360	0.0096	0.0111
360	0.0094	0.0101
540	0.0092	0.0104
540	0.0098	0.0092
540	0.0105	0.0096
660	0.0114	0.0103
660	0.0103	0.0101
660	0.0098	0.0112

and compaction pressure. Beyond 420 MNm^{-2}, no further volume reduction occurred and a constant value of 4.6×10^{-3} ml over the pressure range of 420–800 MNm^{-2} was recorded.

The graphs obtained when the aggregates were removed from the large compacts were the same up to about 380 MNm^{-2} (55.1 $\times$ 10^3 lb in.$^{-2}$), indicating no relaxation of the aggregates. After 380 MNm^{-2}, the aggregates relaxed and increased in volume by a constant amount, 0.9×10^{-3} ml. Therefore, capping probably would be more liable to occur at compaction pressures higher than 380 MNm^{-2} and there probably would be no tendency to cap below 380 MNm^{-2}. This transition point, at which elasticity is first exhibited, could provide a useful index for measuring the capping tendencies of different granular systems.

The relationship between aggregate thickness and compaction pressure is shown in Fig. 3. Again, similar graphs were obtained inside the compacts and removed from the compacts up to 420 MNm^{-2}. At pressures higher than 420 MNm^{-2}, an increase in thickness was observed when the aggregates were removed from the compacts. This increase in thickness accounted for the relaxa-
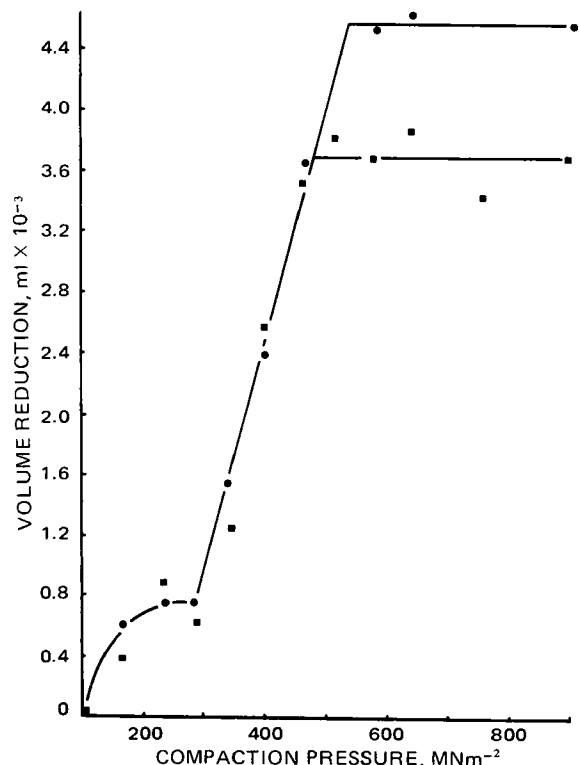

Figure 2—*Reduction of aggregate volume with compaction pressure. Key: ●, inside compacts; and ■, removed from compacts.*
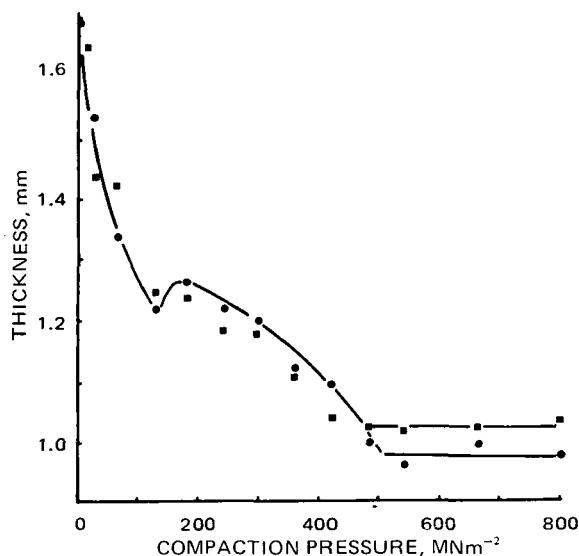
Figure 3—*Change in aggregate thickness with compaction pressure. Key:* ●, *inside compacts; and* ■, *removed from compacts.*

tion of the aggregates at high compaction pressures and demonstrated that the structure was then behaving elastically.

The change in aggregate diameter with compaction pressure inside the compacts and removed from the compacts is shown in Fig. 4. Both graphs are identical, indicating that no change in diameter occurred when the aggregates were removed from the compacts over the whole pressure range. Therefore, it can be concluded that relaxation of the aggregates occurred only in a direction perpendicular to the compact faces; that is, the aggregates relaxed in thickness only at pressures higher than 420 MNn^{-2} and no elasticity was exhibited at lower pressures.

By combining Figs. 2–4, a picture can be built of what happens during compaction. Up to 200 MNm^{-2}, there is an increase in aggregate diameter accompanied by a corresponding reduction in thickness. The result is that there is only a relatively small reduction in aggregate volume. This phase may be attributable to interparticulate slippage, which leads to a closer packed arrangement. The increase in diameter is the result of granules being squeezed outward by the descending upper punch. At about 200 MNm^{-2}, the aggregate diameter no longer increases because solid bridges
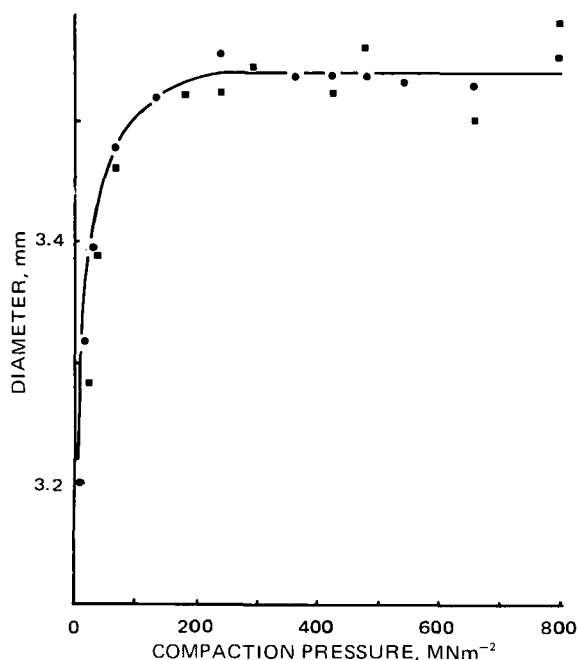

Figure 4—*Change in aggregate diameter with compaction pressure. Key:* ●, *inside compacts; and* ■, *removed from compacts.*
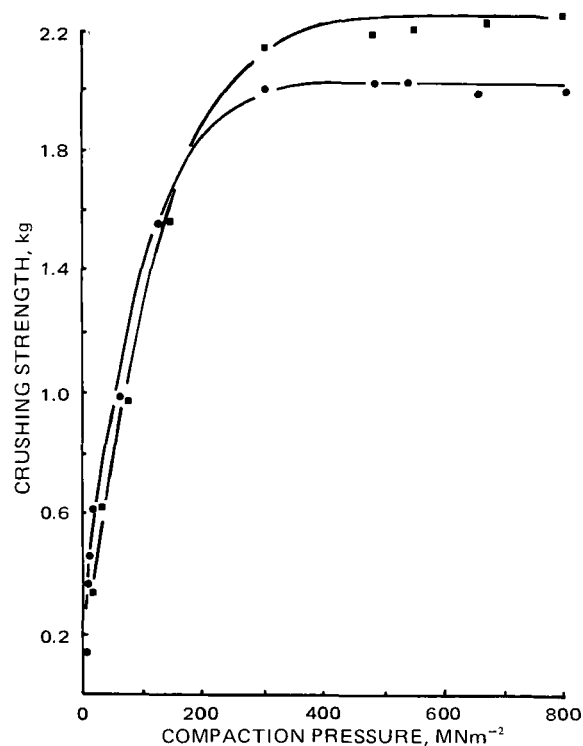

Figure 5—*Variation of aggregate crushing strength with compaction pressure. Key:* ●, *aggregates removed from compacts; and* ■, *aggregates compressed directly.*

are formed between the particles making up the granules and the die walls, preventing any further squeezing out of the granules. From 200 to 420 MNm^{-2}, failure of the granular material occurs by plastic deformation and a consolidation occurs by a reduction in aggregate thickness only. Finally, from 420 to 800 MNm^{-2}, a structure is formed that can support the applied load without further consolidation. This structure behaves elastically, since the aggregates increase in size when removed from the compacts.

This theory is supported by Fig. 5. This figure shows the crushing strength of dibasic calcium phosphate aggregates after removal from the compacts and of similar aggregates, compressed at varying pressures, that had not been inside the sucrose compacts. Similar shaped curves were obtained in each case. The aggregates that had been inside the compacts were weaker at pressures above 200 MNm^{-2} than were similar aggregates that had been directly compressed. The water used to dissolve the sucrose probably had modified the crushing strength characteristics of the aggregates. However, it can still be seen from both graphs that a constant value of crushing strength existed when the final elastic structure had been formed at pressures above 420 MNm^{-2} while increasingly weaker structures were found at pressures below 240 MNm^{-2} (34.8×10^3 lb in.$^{-2}$).

It was not possible to extend the scope of the present work to spherical aggregates due to the difficulty in producing aggregates of a perfectly round shape. Spherical aggregates might behave in a different manner than cylindrical aggregates because the compressional forces would probably be distributed differently. However, small short cylinders are likely to be the usual shape produced by a wet massing and screening granulation process. Thus, the results should be applicable to granules produced in this way.

CONCLUSIONS

The results indicate that cylindrical granules of dibasic calcium phosphate do not change their shape when compacted. Deformation occurs by a change in granule thickness and diameter at low compaction pressures and by only a reduction in thickness at intermediate pressures. High pressures produce no further consolidation. Only after being compacted at high pressures do granules exhibit relaxation when the applied pressure is removed. No granule relaxation occurs at low or intermediate pressures.

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Effect of Cycloamyloses on Apparent Dissociation Constants of Carboxylic Acids and Phenols: Equilibrium Analytical Selectivity Induced by Complex Formation

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Abstract □ Apparent dissociation constants of organic acids were determined by potentiometric titration in the presence of cyclohexaamylose or cycloheptaamylose. The quantity $\Delta pKa' = pKa'$ (cycloamylose) − pKa (water) was positive or zero for all carboxylic acids studied and negative or zero for all phenols. The term $\Delta pKa'$ can be related to the cycloamylose concentration, K_{11a}, and K_{11b}, where K_{11a} and K_{11b} are 1:1 stability constants for complexes of the acid and the anion, respectively. From the dependence of $\Delta pKa'$ on cycloamylose concentration, estimates of K_{11a} and K_{11b} can be obtained. If $\Delta pKa' \neq 0$, then $K_{11a} \neq K_{11b}$; for carboxylic acids, $K_{11a} \geq K_{11b}$; for phenols, $K_{11b} \geq K_{11a}$. Because of variable pKa' shifts, it is possible to carry out differentiating titrations of some acid mixtures in cycloamylose solutions, whereas the same acids cannot be differentiated in water. If an acid is weakened by cycloamylose, its conjugate base is strengthened, and some carboxylate salts can be readily titrated in the presence of a cycloamylose.

Keyphrases □ Cycloamyloses—effect on apparent dissociation constants of carboxylic acids and phenols, stability constants for complex formation □ Dissociation constants, apparent—carboxylic acids and phenols, effect of cycloamyloses, complex formation □ Carboxylic acids—apparent dissociation constants, effect of cycloamyloses □ Phenols—apparent dissociation constants, effect of cycloamyloses

Cycloamyloses (also called cyclodextrins or Schardinger dextrins) are cyclic oligomers containing six or more D-glucose units linked 1 → 4; they are produced by the action of Bacillus macerans amylase on starch. The six-unit and seven-unit substances are called cyclohexaamylose (α-cyclodextrin) and cycloheptaamylose (β-cyclodextrin), respectively. These molecules are doughnut shaped, and their possession of a cavity of fixed size and shape has led to considerable interest in their chemical properties. The production, purification, and chemistry of the cycloamyloses have been reviewed (1, 2). The catalytic properties of cycloamyloses, which have been widely studied as enzyme models, also have been discussed (3).

Any molecule smaller than the cavity of a cycloamylose molecule can enter the cavity and there undergo noncovalent interaction with the atoms lining and rimming the cavity. The resulting association product is called an inclusion compound or complex. The cycloamylose is thus a "host" for the smaller "guest" molecule. A 1:1 stoichiometry is typical, although other ratios have been observed and interpreted as the result of another guest molecule lying across the cavity opening. The dimensions of the cavity are such that many mono- and disubstituted benzene derivatives can fit into the cyclohexaamylose cavity, but polysubstituted benzenes may be excluded.

By forming an inclusion complex with a guest molecule, a cycloamylose is capable of altering some physical and chemical properties of the guest substance; it is by such changes that the complex formation is recognized and studied. Among the solution properties that can be modified are solubility, chemical reactivity, vapor pressure, and the electronic absorption spectrum. This capability for changing the chemical and physical behavior of solutes through complex formation may have analytical potential, and the present study examines the effects of cyclodextrins on the apparent dissociation constants of organic acids in aqueous solution.

It has been well established that many organic acids interact with the cycloamyloses (4–10), although little is known about the effects of complexing on acid dissociation equilibria. The potentiometric titration curve of monophenylphosphoric acid in the presence of cycloamylose reveals changes in pKa values, and even in the stoichiometric consumption of base, that require specific intermolecular interactions for their interpretation (2, 11). The pKa of