# Effect of Particle Size and Speed of Compaction on Density Changes in Tablets of Crystalline and Spray-Dried Lactose

J. T. FELL* and J. M. NEWTON

**Abstract** □ Tablets were prepared from three particle-size fractions of crystalline and spray-dried lactose by the application of known pressures at a slow speed (upper punch speed 1 mm./min.) and a high speed (upper punch speed 600 mm./min.). The relative volumes and densities of the tablets were determined after ejection from the die and, for the slow speed, under pressure. Changes in volume with load were dependent on the particle size, on the speed of compaction, and on whether the volume was determined at pressure or after release of pressure. Calculation of the mechanism of densification by two different methods showed that particle rearrangement was greatest for the smallest size fraction both at slow and high speeds. Calculation of the yield pressure and the pressure necessary to fill the interparticle void space also was made.

**Keyphrases** □ Tableting, lactose—effect of particle size and speed of compaction on density □ Compaction—effect of particle size and speed of compaction on lactose tablet density □ Density, lactose tablets—effect of particle size and speed of compaction □ Lactose, crystalline and spray dried—tablet density changes related to particle size and compaction speed

The changes in density of powder beds which take place during the application of an applied load are of fundamental importance in the process of tableting. In addition to the characterization of tablet dimensions, various authors discussed the changes in terms of the mechanisms involved in the densification process (1–4). In all cases, the authors admitted to oversimplification of the problem. Nevertheless, conclusions have been drawn as to the effect of material characteristics and particle size on the densification process.

In terms of the effect of particle size, there appears to be some confusion. From work with sodium chloride, sucrose, and quartz, Huffine and Bonilla (1) considered that slippage was predominant to a higher pressure range and that the pressing modulus (defined as the ratio of log applied pressure to relative volume of the compact, where relative volume = volume of the compact/true volume of solid in compact) was low for finer particles. In contrast, Heckel (2) reported that for metal powders, densification due to particle rearrangement was greater for larger size particles. Hersey and Rees (3) found that volume changes were independent of particle size when crystalline lactose and spray-dried lactose were compacted at pressure greater than 49 MN./m.$^2$. Their work with sodium chloride indicated densification effects related to particle size, but no calculation of the relative mechanisms was made.

The final stages of compaction are related to the material rather than the particle geometry. Heckel (2) related the yield strength of metal powders to the linear portion of the curve of $\ln 1/(1 - D)$ (where $D$ = apparent density) against pressure. Cooper and Eaton (4) supported this finding with studies of ceramic powders, the harder material requiring higher pressures to achieve densification.

**Table I**—Pressing Moduli for Particle-Size Fractions of Crystalline and Spray-Dried Lactose[a]

| | Particle Size, μm. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0–32 | | | 75–104 | | | 150–210 | | |
| | a | b | c | a | b | c | a | b | c |
| Spray dried | 2.70 | 2.94 | 4.51 | 3.22 | 3.83 | 3.07 | 3.66 | 3.93 | 3.31 |
| Crystalline | 2.81 | 3.01 | 2.82 | 3.11 | 3.76 | 3.07 | 3.88 | 3.88 | 3.31 |

[a] a = slow speed compaction, at pressure; b = slow speed compaction, after release of pressure; and c = fast compaction, after release of pressure.

In arriving at these conclusions, the methods of application of pressure have differed. In addition, the density of the compact has been assessed while under pressure (1, 4) and after the release of pressure (2, 3). The present study shows how these factors affect the assessment of the mechanisms of densification for different size fractions of lactose.

## EXPERIMENTAL

**Materials**—The crystalline lactose[1] was reagent grade α-lactose monohydrate complying with BP standards. The spray-dried lactose[2] complied with USP standards. Both types of lactose were found by polarimetric observation and estimation of moisture content to be entirely α-lactose monohydrate. Particle-size fractions of less than 32, 75–104, and 150–210 μm. were obtained by means of an air-jet sieve[3]. A sufficient quantity of each size fraction was dried at 90° for 24 hr. and stored over silica gel until required for use.

**Methods**—*Compaction by Physical Testing Instrument*—A physical testing instrument[4] was modified to take a conventional 12.7-mm. flat-faced punch and die system, as described previously (5). In all cases, 0.5-g. samples of the previously dried powder were compressed. The die was lubricated with a 5% suspension of magnesium stearate in carbon tetrachloride. Five tablets were prepared at each applied pressure at a compression rate of 1.0 mm./min. When the desired pressure was attained, the crosshead was reversed at the same speed as the compaction process. The loss of pressure due to die wall friction was found to be less than 1.5%. Corrections were applied for the distortion of the punches under pressure.

*Compaction by Instrumented Tablet Machine*—A single-punch tablet machine[5] was instrumented using foil strain gauges[6]. The outputs from the bridges constructed on the upper punch and lower punch holders were fed into a signal conditioning unit[7]; from here, the amplified signal was recorded on a UV recording galvanometer[8], using moving coil galvanometers[9]. The instrumentation was cali-

[1] British Drug Houses Ltd., Poole, Dorset, England.
[2] McKesson Robbins, London, E.C. 4, England.
[3] Alpine Air-Jet, Lavino (London) Ltd., London, E.C. 2, England.
[4] Floor model, Instron Ltd., High Wycombe, Bucks, England.
[5] Type E3, Manesty Ltd., Speke, Liverpool 24, England.
[6] Type HF 26, Showa Sokki, Kenkyusho, Japan.
[7] Type MR 701, Data Acquisition Ltd., Stockport, Cheshire, England.
[8] Type 2005, S.E. Laboratories (Engineering) Ltd., Feltham, Middlesex, England.
[9] Type B, 450, S.E. Laboratories (Engineering) Ltd., Feltham, Middlesex, England.

Table II—Values of $D_A$, $D_B$, and $D_0$ Obtained as Described by Heckel (2)[a]

| Density Determined | Particle-Size Fraction, μm. | Crystalline $D_0$ | Crystalline $D_A$ | Crystalline $D_B$ | Spray Dried $D_0$ | Spray Dried $D_A$ | Spray Dried $D_B$ |
|---|---|---|---|---|---|---|---|
| At pressure | 0–32 | 0.322 | 0.728 | 0.406 | 0.285 | 0.703 | 0.418 |
| | 75–104 | 0.587 | 0.760 | 0.173 | 0.538 | 0.748 | 0.210 |
| | 180–210 | 0.618 | 0.764 | 0.146 | 0.527 | 0.754 | 0.227 |
| Released after slow compaction | 0–32 | 0.322 | 0.728 | 0.406 | 0.285 | 0.696 | 0.411 |
| | 75–104 | 0.587 | 0.761 | 0.174 | 0.538 | 0.754 | 0.218 |
| | 180–210 | 0.618 | 0.769 | 0.151 | 0.527 | 0.754 | 0.227 |
| Released after fast compaction | 0–32 | 0.322 | 0.773 | 0.451 | 0.285 | 0.668 | 0.383 |
| | 75–104 | 0.587 | 0.731 | 0.144 | 0.538 | 0.728 | 0.190 |
| | 180–210 | 0.618 | 0.711 | 0.997 | 0.527 | 0.741 | 0.214 |

[a] $D_0$ = initial apparent relative density of powder; $D_A$ = densification due to die filling and particle rearrangement; and $D_B$ = densification due to particle rearrangement.

brated using the physical testing instrument to enable both upper and lower punch forces to be determined. A 12.7-mm. diameter flat-faced punch and die system was used, being cleaned and then lubricated with a suspension of magnesium stearate in carbon tetrachloride between the preparation of each tablet. The tablets were prepared at a machine speed of 40 tablets/min. (corresponding to an upper punch speed of 600 mm./min.), the die being filled with 0.5 g. of the required powder. Five tablets were prepared at each machine setting.

**Density Determinations**—*True Powder Density*—This was determined with an air pycnometer[10]. The value for all samples was 1.546 g./ml. Confirmation of the absence of entrapped air within the spray-dried particles was provided by the method of Verhoog (6).

*Apparent Density of Tablets*—The weight of tablets was determined to ±0.0001 g. after compaction. The volume of the ejected tablet was determined from its dimension, determined to ±0.005 mm. with a micrometer. The volume of tablets at pressure was determined from the area of the tablet die and the height, determined as the difference between the initial height of the Instron crosshead as compaction commences and the crosshead height at the given applied pressure. The apparent density of the compact is the mass divided by the tablet volume.

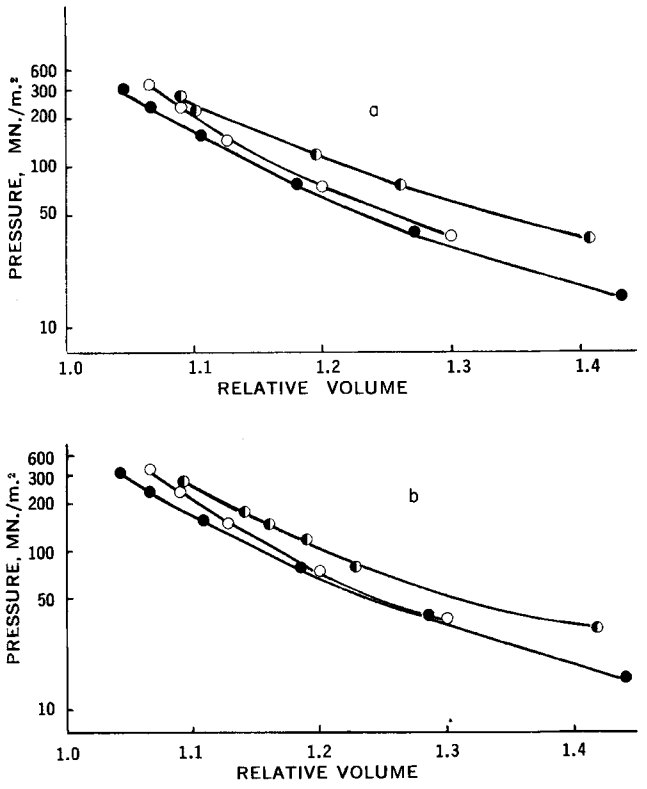


**Figure 1**—*Relative volumes of tablets compacted at known pressures, expressed by the method of Huffine and Bonilla (1). (a) = 75–104-μm. crystalline lactose. (b) = 75–104-μm. spray-dried lactose. Key: ●, relative volume determined at pressure, slow compaction; ○, relative volume determined after release of pressure, slow compaction; and ◐, relative volume determined after release of pressure, fast compaction.*

[10] Model 930, Beckman Instruments Ltd., Glenrothes, Fife, Scotland.

## RESULTS AND DISCUSSION

The increase in density of a powder bed as a pressure is applied forms the basis of the preparation of tablets. The mechanisms of density changes which are considered to occur were reported by many authors and recently listed by Hersey and Rees (3). There is, however, little quantitative evidence of the relative magnitude of the various postulated mechanisms and of the influence of various factors on these mechanisms. The overall changes are readily observable in the present powders when the results are expressed in the manner used by Huffine and Bonilla (1) (Fig. 1). The pressing modulus obtained from such plots is given in Table I.

Whichever compaction system is considered, the pressing modulus is usually lower for finer particles, indicating a greater change in volume for a given pressure increase for these finer powders. Tablets prepared at slow speed have a higher pressing modulus for ejected tablets than for tablets at presssure. At low loads, the relative volumes of tablets, both under load and ejected, are similar because there is little chance of elastic recovery; whereas at high loads, elastic recovery is significant, leading to a higher relative volume for ejected tablets and different pressing moduli. While the effects of particle size are reduced by compaction at a higher speed, it is surprising that Hersey and Rees (3) reported that they were absent. For the two larger size fractions, a higher relative volume (lower relative density) is obtained when the powders are compacted at a faster rate, supporting the findings of Bada and Nagufuji (7).

Rather than consider actual changes in volume with pressure, information on the mechanism of densification can be obtained by

Table III—Values of Coefficients $a_1$ and $a_2$ Determined as Described by Cooper and Eaton (4)[a]

| Particle-Size Fraction, μm. | Crystalline Lactose $a_1$ | Crystalline Lactose $a_1 + a_2$ | Spray-Dried Lactose $a_1$ | Spray-Dried Lactose $a_1 + a_2$ |
|---|---|---|---|---|
| 0–32 | 0.66 | 1.00 | 0.60 | 1.00 |
| 75–104 | 0.62 | 1.00 | 0.72 | 1.00 |
| 180–210 | 0.59 | 1.00 | 0.61 | 1.00 |

[a] $a_1$ = fraction of theoretical compaction that would be achieved at infinite pressure for the filling of voids of the same dimensions as the particle; and $a_1 + a_2$ = total fraction of theoretical compaction that can be achieved by filling voids of the same and smaller dimensions than the particles.

**Table IV**—Yield Pressure and Pressure Necessary to Fill Voids within Compacts for Three Particle-Size Fractions of Crystalline and Spray-Dried Lactose

| Compaction Conditions and Density Determination | Particle-Size Fraction, μm. | Crystalline Lactose | | | Spray-Dried Lactose | | |
|---|---|---|---|---|---|---|---|
| | | Yield Pressure $Py$, MN./m.² | Pressure to Fill Voids, MN./m.² | | Yield Pressure $Py$, MN./m.² | Pressure to Fill Voids, MN./m.² | |
| | | | $k_1$ | $k_2$ | | $k_1$ | $k_2$ |
| Slow compaction at pressure | 0–32 | 164 | 2.7 | 42.4 | 162 | 2.4 | 32.7 |
| | 75–104 | 171 | 3.6 | 38.0 | 163 | 2.7 | 36.4 |
| | 150–210 | 139 | 2.7 | 28.6 | 127 | 2.6 | 23.6 |
| Slow compaction, released | 0–32 | 220 | 2.7 | 67.2 | 209 | 2.4 | 50.1 |
| | 75–104 | 222 | 3.6 | 71.0 | 355 | 2.7 | 75.8 |
| | 150–210 | 212 | 2.7 | 69.2 | 186 | 2.6 | 63.5 |
| Fast compaction, released | 0–32 | 179 | — | — | 135 | — | — |
| | 75–104 | 235 | — | — | 240 | — | — |
| | 150–210 | 204 | — | — | 179 | — | — |

expressing the results in the manner described by Heckel (2). The results do not obey the relationship:

$$\ln \frac{1}{(1 - D)} = KP + A \qquad \text{(Eq. 1)}$$

where $D$ = relative density = apparent density of tablet/true density of powder, $A$ and $K$ are constants, and $P$ = applied pressure. However, there is usually sufficient linear portion to allow extrapolation to calculate the density functions described by Heckel (2) (Fig. 2). The results given in Table II show clearly that for tablets compressed at slow speeds, the total densification due to filling of the die and particle rearrangement, $D_A$, increases as the size of the particle increases. This supports the findings of Heckel (2); but when the effect of die filling is taken into consideration, the present results are opposite to those of Heckel (2). That is, the present results show that densification due to particle rearrangement, $D_B$, decreases with a decrease in particle size. The reason for this difference stems from the values of $D_0$, the value for relative apparent density of the powder. The values given by Heckel (2) increase with a decrease in particle size. This is somewhat surprising, because it is generally considered (8) that bulk density decreases with a decrease in particle size.

Further support for the present findings is obtained by treating the results as described by Cooper and Eaton (4). (Only those tablets produced at slow compaction could, in fact, be treated by this procedure due to difficulties in obtaining tablets in the high porosity region on the tablet machine.) Tablet densities at low pressure are the same at pressure and when released; hence, values of $a_1$ are the same for both systems. This analysis is based on dividing the compaction process into two stages: (*a*) filling of holes of the same dimension of the particles by rearrangement, and (*b*) filling of holes of smaller dimensions than the particles by fragmentation and plastic flow. The relative magnitude of the dimensionless coefficients, $a_1$ and $a_2$, in the equation:

$$V^* = a_1 e^{-(k_1/P)} + a_2 e^{-(k_2/P)} \qquad \text{(Eq. 2)}$$

where $V^*$ = fractional volume compaction[11], $k_1$ and $k_2$ are coefficients with units of pressure, and $P$ = applied pressure, indicates the fraction of theoretical compaction that would be achieved at infinite pressure by each particular process. The results in Table III show that particle rearrangement $a_1$ would form a higher fraction of theoretical compaction for smaller particles than larger particles of crystalline lactose. The results are not conclusive for spray-dried lactose. Thus, the indications again support the concept that particle rearrangement is a more important feature of the compaction of small particles. The value of 1.0 obtained for $a_1$ and $a_2$ in all cases indicates that, theoretically, it should be possible to compact all the samples to zero porosity.

A further insight into the mechanism of compaction is provided by consideration of the constants $K$ of Eq. 1 and $k_1$ and $k_2$ of Eq. 2. The former constant was related by Heckel (2) to the yield strength of the material and further related by Hersey and Rees (3) to the yield pressure, $Py$, by the equation:

$$K = \frac{1}{Py} \qquad \text{(Eq. 3)}$$

The values of $Py$ for the different size fractions of different types of lactose are given in Table IV. Certain general trends are present. The values for yield pressure obtained when tablet density is measured at pressure are generally lower than those where tablet density is determined after ejection from the die. The density value at pressure also contains an elastic component which can give a false low value to the yield pressure. The 75–104-μm. size fraction has the highest yield pressure, irrespective of the method of application of load and measurement of density. The yield pressures for the samples of spray-dried lactose are generally lower than those for crystalline lactose. The lower value of yield pressure tends to favor plastic deformation during compaction. The values reported here are all lower than the average value of 401.7 MN./m.² reported by Hersey and Rees (3).

The values for $k_1$ and $k_2$ in Eq. 2 are related to the force necessary for the two stages of compaction reported by Cooper and Eaton (4). The values in Table IV confirm the findings of these workers in that the values for $k_1$, the pressure necessary to fill the interparticle void space of the same dimensions of the particle, are lower than the values for $k_2$, the pressure necessary to fill the interparticle void space of smaller dimensions than the particles. The values of $k_1$ and $k_2$ again support the findings for yield pressure that spray-dried lactose requires less pressure to fill voids than crystalline lactose. Due to elastic recovery, the values of $k_1$ and $k_2$ deter-

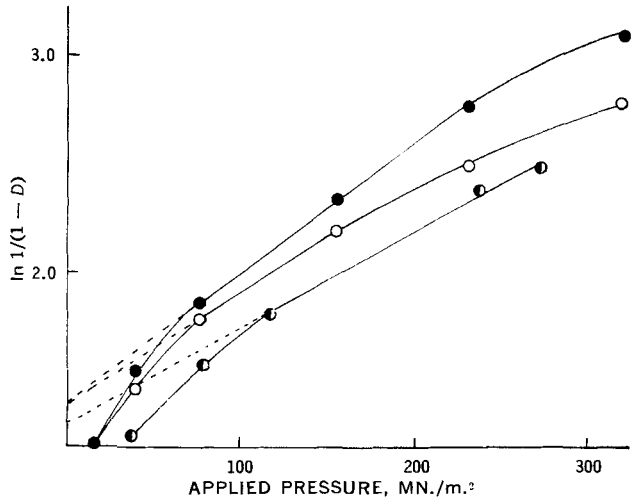


**Figure 2**—*Changes in tablet relative densities with applied pressure, expressed by the method of Heckel (2), for crystallized lactose of 75–104 μm. Key: ●, relative density determined at pressure, slow compaction; ○, relative density determined after release, slow compaction; and ◐, relative density determined after release, fast compaction.*

[11] $V^* = (V_0 - V)/(V_0 - V_\infty)$, where $V_0$ = volume of powder at zero pressure, $V$ = volume of tablet at pressure $P$, and $V_\infty$ = volume of tablet when all of the holes are filled, *i.e.*, the true volume of the solid present in the tablet.

mined from results with ejected tablets indicate that higher pressures are needed to fill the interparticulate void space than are in fact necessary. The effect of particle size is less clearly defined in the values of $k_1$ and $k_2$ but, again, there is the indication that the 75–104-$\mu$m. size fraction is the most resistant to deformation.

These results deal only with samples of lactose. When taken in conjunction with the previous work (1, 2, 4), the conclusion possibly could have application to other materials.

## CONCLUSIONS

1. For tablet volumes determined at pressure, the smaller the original particle size, the greater is the relative volume at all applied pressures.

2. For tablet volumes determined after ejection from the die, the difference in relative volume between the two larger particle-size fractions is considerably reduced. The relative volumes for tablets prepared at slow compaction are lower than those of the two larger particle-size fractions, but the opposite is true for tablets prepared at the higher rate of compaction.

3. Calculation of the densification due to particle rearrangement by the method of Heckel (2) shows that the smallest size fraction undergoes the greatest rearrangement both at slow and high speed compaction. Particle rearrangement is generally greater for the spray-dried lactose.

4. Calculation of the densification due to particle rearrangement by the method of Cooper and Eaton (4) confirms this finding for crystalline lactose. The results for spray-dried lactose are, however, inconclusive.

5. The yield pressure calculated from the slope of the densification–pressure curves of Heckel (2) indicates that the middle size fraction has the highest value for both compaction systems and methods of measuring tablet density. The yield pressures are higher for tablets ejected from the die.

6. The yield pressure for spray-dried lactose is generally lower than for crystalline lactose.

7. The pressures necessary to fill the voids of smaller sizes than the particles, *i.e.*, those required to cause particle fracture and plastic flow, are always higher than the pressures necessary to fill the voids of the same dimensions as the particles, *i.e.*, to effect particle rearrangement.

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# Batch Production of Pharmaceutical Granulations in a Fluidized Bed I: Effects of Process Variables on Physical Properties of Final Granulation


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**Abstract** □ The investigation concerns the effects of process variables associated with the fluidized bed granulation technique on the physical properties of the final granulation. The process variables investigated include binder solution addition rate, air pressure to the binary nozzle, inlet air temperature during the granulation cycle, and binary nozzle position with respect to the fluidized solids. When the rate at which the aqueous binder solution added to the fluidized bed of powders was increased, the ability of the solution to wet and penetrate the solids was enhanced, resulting in: (*a*) a larger average granule size, (*b*) a less friable granulation, (*c*) a more fluid granulation, and (*d*) a decreased granulation bulkiness. Similar results, also traceable to enhanced binder solution efficiency, occurred with a decrease either in the binary nozzle air pressure or in the inlet air temperature during the granulation cycle. The position of the binary nozzle with respect to the fluidized powders had significant effects upon the average granule size and granule friability. The effects upon the granulation flow properties and bulkiness, however, were slight.



**Keyphrases** □ Granulation, fluidized bed—effects of process variables on granule and tablet physical properties □ Fluidized bed granulation—effects of process variables on granule and tablet physical properties


Although fluidization theory and techniques have been known for many years and have been discussed extensively in the literature (1–5), pharmaceutical applications in this area are relatively recent. Uses have been limited to the drying (6–9) and coating (10–16) of solids; there has been little investigation in the area of granulation.

Granulation in a fluidized bed for tableting purposes was first introduced by Wurster (11). He determined material loss from the column and the drug and moisture content of the final granulation. Theory, design, and operation of equipment for the continuous production of tablet granulations in a fluidized bed were presented by Scott *et al.* (17) and Rankell *et al.* (18).