

# The prediction of the bulk densities of powder mixtures, and its relationship to the filling of hard gelatin capsules

J. M. NEWTON\* AND F. BADER\*\*

\* Pharmacy Department, Chelsea College, University of London, Manresa Road, London SW3 6LX, U.K. \*\* Pharmacy Department, University of Nottingham, Nottingham NG7 2RD, U.K.

From measurements of the properties of individual components, it has been found possible to predict the maximum tapped bulk density of two component mixtures of a range of particle size fractions of acetylsalicylic acid and lactose in varying proportions. This has been extended to the prediction of bulk density of such mixtures when filled into hard gelatin capsules by a system which results in the powders existing at the maximum tapped bulk density. Consequently the capsule fill weight can also be predicted for such systems. The method is less satisfactory for the prediction of the bulk density and capsule fill weight, when the capsules are filled by a process involving compression of the powder within the capsule shell.

The packing of particles is of fundamental importance in the filling of hard gelatin capsules. In plate filling methods, the capsule shell forms the volumetric measure of powder weight, while in the dosator nozzle and tamp filling machines, the bed from which the sample is taken, influences the capsule fill weight and its reproducibility. The prediction of powder bed packing from a knowledge of particle density, shape, rugosity size and size distribution and the method of bed formation is not usually possible, except for simple regular systems of particles with simple geometric shapes. The packing of practical systems involving powders of irregular particles, especially when mixtures of materials are involved, is usually complex. Verthalis & Pipel (1976) have shown that neither mixtures of paracetamol and lactose nor mixtures of oxytetracycline and lactose, produce blends the maximum tapped bulk density of which can be predicted from bulk density values of their individual components.

Westman & Hugill (1932) proposed a method by which the bulk density of two component systems of different particle size fractions, mixed together in different proportions, can be calculated from the individual values of bulk density, the particle size diameter, the mass of the two components, the total true volume and the apparent particle density of the single components. Staple (1975) illustrated that this approach could be used for mixtures of spherical glass beads of different particle size ranges. This approach has been adopted to study the bulk densities of mixtures of varying proportions and particle size of acetylsalicylic acid and lactose. The

blends were filled into hard gelatin capsules by methods which resulted in packing (a) to a maximum tapped bulk density and (b) to densities in excess of this value.

## Theory

Consider a system consisting of two component sets of particles, 1 and 2, with volume fractions represented by  $X_1$  and  $X_2$ . The measured volumes of solid per unit volume of each of the individual components are  $A_1$  and  $A_2$  respectively. When each component contributes its own volume,  $V_1$  and  $V_2$ , without interaction, to a mixture of the two components, the total volume per unit solid volume for mixtures,  $V_e$ , is given by (for nomenclature see p 626):

$$V_e = A_1X_1 + A_2X_2 \quad (1)$$

Such a system can occur when the two components are of approximately the same size and shape. Considering only size, then Equation 1 can apply when the two components have the same size and the size ratio  $r = 1$ . When, however, they are of considerably different dimensions, the situation could arise when one component occupies only the space between the other component, providing no contribution to the total volume of the system. Westman & Hugill (1932) have shown that in the case when  $r = \infty$ , the limiting values of  $V_1$  and  $V_2$  are given by:

$$V_1 = A_1X_1 \quad (2)$$

$$V_2 = X_1 + A_2X_2 \quad (3)$$

where particles of component 1 are the larger particles. Under these conditions, mixtures of the two components will, at a certain volume fraction,

\* Correspondence.

show a minimum volume  $V_{\min}$ , which can be obtained by equating  $V_1$  and  $V_2$  in equations 2 and 3, and solving for  $X_1$  and  $X_2$  at the point of intersection so that:

$$X_1 = \frac{A_2}{(A_1 + A_2 - 1)} \quad (4)$$

$$X_2 = \frac{(A_1 - 1)}{(A_1 + A_2 - 1)} \quad (5)$$

Staple (1975) proposed that the apparent volume per solid volume of mixtures,  $V_r$ , can be obtained from:

$$V_r = V_1 + f(V_e - V_1) \quad (6)$$

to the left of the minimum i.e. between the minimum and  $X_2 = 0$  and:

$$V_r = V_2 + f(V_e - V_2) \quad (7)$$

to the right of the minimum i.e. between the minimum and  $X_1 = 0$ .

The coefficient,  $f$ , is an empirical factor which decreases with an increase in the diameter ratio  $r$  and has a peak value for concentrations corresponding to  $V_{\min}$ . Staple (1975) obtained values for  $f$  by mixing spherical glass beads, of known size fractions, in various proportions, and measuring the resultant maximum densities. After adjustment of the system to give the maximum densities, a series of  $f$  values for various  $r$  values could be calculated from measured values of  $V_r$  and the known values of  $V_1$  and  $V_2$ , plus calculated  $V_e$  values. Staple (1975) provided a calibration curve of values of  $f$  as a function of  $r$ , the value of  $f$  being that obtained experimentally at near maximum bulk density for the system. A modification was made by Staple (1975) to allow for the extent by which concentrations of the components differed from that at the minimum. For the present work, however, the unmodified values of  $f$ , interpolated from the graphical results given by Staple (1975), will be used to provide a first approximation of the technique.

Thus to calculate the theoretical value of  $V_r$  from equations 6 and 7 for a given mixture, the value of  $f$  for a given value of  $r$  is interpolated from the results of Staple (1975). The values of  $A_1$  and  $A_2$  can be determined, for the individual components, from their measured bulk densities  $B_1$  and  $B_2$ , and the apparent particle densities  $\rho_1$  and  $\rho_2$  as

$$A_1 = \frac{\rho_1}{B_1} \quad (8)$$

and

$$A_2 = \frac{\rho_2}{B_2} \quad (9)$$

The volume fraction of the two components  $X_1$  and  $X_2$  can be obtained from the masses of the two components  $W_1$  and  $W_2$ . The total true solid volume is given by:

$$V_t = \frac{W_1}{\rho_1} + \frac{W_2}{\rho_2} \quad (10)$$

Thus

$$X_1 = \frac{W_1}{\rho_1 V_t} \quad (11)$$

and

$$X_2 = \frac{W_2}{\rho_2 V_t} \quad (12)$$

Values of  $V_e$  and  $V_1$  or  $V_2$  from equations 6 and 7, as required, can be substituted in equations 2 or 3 to give  $V_r$  for the particular diameter and concentration ratio used to prepare the mixture. The theoretical bulk density for a mixture is given by:

$$B_{12} = \frac{\rho_{12}}{V_r} \quad (13)$$

where

$$\rho_{12} = \rho_1 X_1 + \rho_2 X_2 \quad (14)$$

## MATERIALS AND METHODS

### Materials

The six acetylsalicylic acid and four lactose particle size fractions were those used previously (Newton & Bader 1980). Blends of these samples were prepared to combine each size fraction of acetylsalicylic acid with each size fraction of lactose to give, 20, 40, 60 and 80% w/w of acetylsalicylic acid in lactose. This provides a  $6 \times 4 \times 4$  factorial design.

### Methods

The apparent particle densities of the various particle size fractions of acetylsalicylic acid and lactose were determined with a Beckman Air Comparison Pycnometer (Model 930). The apparent particle densities of selected mixtures established the assumption made in equation 14. The maximum bulk densities of the systems were determined by application of the British Standard method, tapping the cylinder until no further reduction in volume occurred. Ten capsules were filled by tapping a Perspex block containing the capsule bodies in drilled holes at the same rate and displacement as that for maximum bulk density determinations. A layer of powder contained by a retaining lip provided a constant source of powder. Tapping was continued until no further increase in capsule fill weight was observed. The excess powder was removed, the cap

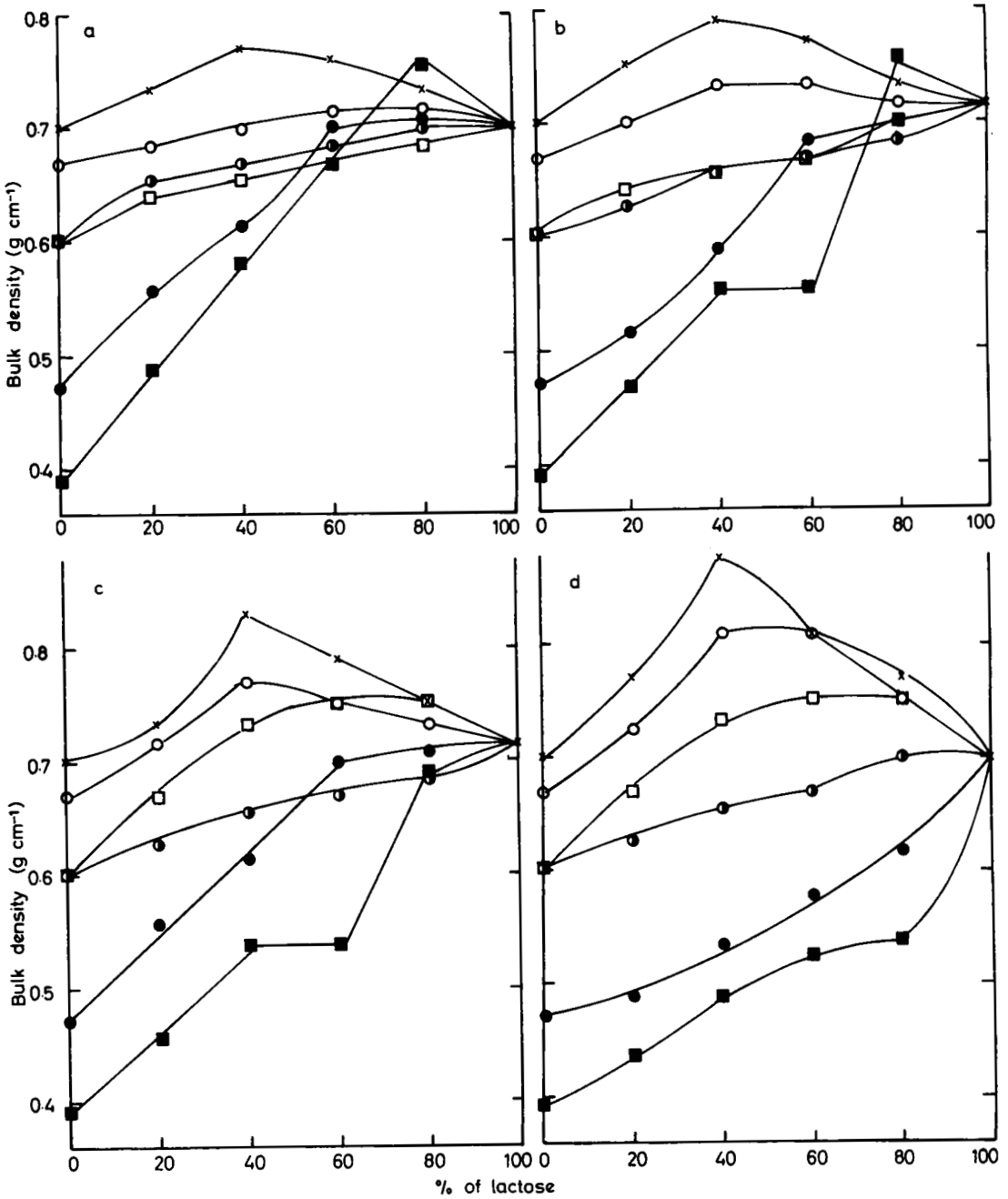


Fig. 1. Tapped bulk density of mixtures of various particle size fractions of acetylsalicylic acid and lactose. Mean particle diameter of lactose (a) 217 μm. (b) 150 μm. (c) 94 μm. (d) 65 μm. Mean particle diameter of acetylsalicylic acid X 430 μm. O 330 μm. ● 250 μm. □ 170 μm. ● 117 μm. ■ 64 μm.

placed on the capsule body and the mean weight of the contents of ten capsules determined, allowing for the weight of the shell. Such a filling system simulates capsule filling by plate systems such as the Tevopharm and possibly the Coulton 8. To simulate capsule filling in which a degree of compression is applied e.g. Höfliger & Kärger, the capsules were filled as described above, then a Perspex block from which protruded pegs, of the same diameter as the internal diameter of the capsule body, was placed on the powder within the capsules. A 10 kg was applied to the block to compress the powder. The weight and block were removed and more powder placed into the capsule shells. The process was repeated until no further powder could be filled into the capsule. The capsules were removed from the block and the mean weight of their contents determined.

#### RESULTS AND DISCUSSION

The maximum tapped bulk densities of the various blends of the different particle size fractions of acetylsalicylic acid and lactose, are shown as a function of the proportion of lactose, in Fig. 1a-d. In no case is the bulk density of a mixture the sum of the individual bulk densities of the relative proportions of the two components. The deviation from the additive bulk densities varies with the particle and proportion size of both acetylsalicylic acid and lactose. There is usually a maximum bulk density (i.e. a minimum volume per unit volume of solid) indicating a degree filling of the voids between larger particles. The position and the value of the maximum varies with particle size of both components. As could be anticipated, the maximum density is achieved by mixing the smallest particle size fraction with the largest particle size fraction (64  $\mu\text{m}$  lactose with 430  $\mu\text{m}$  size acetylsalicylic acid). The existence of a maximum value for the bulk density suggests that the theoretical approach might provide a prediction of the bulk density of the mixed systems.

Values were therefore obtained for each blend as described in the theoretical section and plotted as a function of observed values in Fig. 2. Least squares linear regression related calculated and experimental values for the tapped bulk densities ( $B_{12}$  and  $B_e$ ) by the expression

$$B_{12} = 1.001 B_e + 0.008$$

with correlation coefficient of 0.985. The highly significant correlation coefficient, the slope of approximately unity and the small value of the intercept indicate that the approach provides an excellent prediction of the observed bulk density

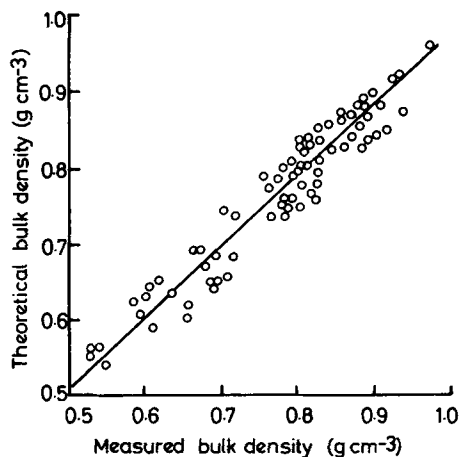


FIG. 2. Relationship between theoretical and measured maximum tapped bulk densities of mixtures of different proportions and particle size fractions of acetylsalicylic acid and lactose.

values. Thus it is possible to predict the maximum tapped bulk density of the mixtures from the individual values of bulk density, the particle diameter, and the apparent particle density of the two components together with the mass of the two components.

This finding is of considerable value if the capsule can, in fact, be filled to give a maximum tapped bulk density. From the weights of the contents of the capsules and the measured volume of the capsule body (obtained by filling and weighing a number of capsule bodies with liquid paraffin of known density), the bulk density of the capsule contents of the various blends was derived. These were plotted as a function of the bulk density of the blends derived

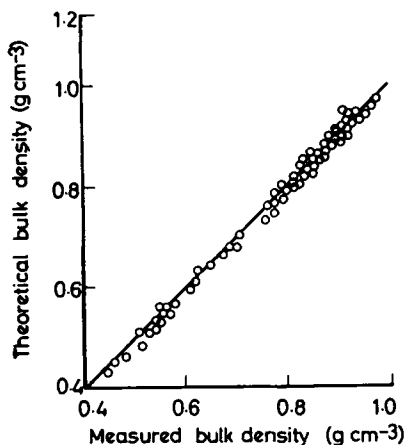


FIG. 3. Relationship between theoretical and measured bulk densities of mixtures of different proportions and particle size fractions of acetylsalicylic acid and lactose, filled into capsules by tapping.

from the approach, see Fig. 3. The relationship between the calculated and experimental values for the bulk density ( $B_{12}$  and  $B_{ec}$ ), calculated by least squares linear regression was  $B_{12} = 1.008 B_{ec} + 0.006$  with a correlation coefficient of 0.990. This again illustrates the excellent agreement

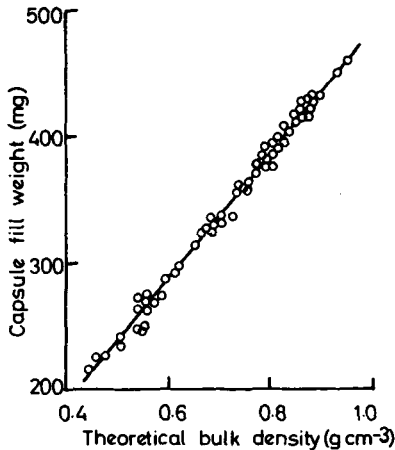


FIG. 4. Relationship between theoretical bulk density and capsule fill weight of mixtures of different proportions and particle size fractions of acetylsalicylic acid and lactose, filled into capsules by tapping.

between the theoretical and the experimental values of bulk density. It also indicates that, for capsules filled under conditions providing a maximum tapped bulk density, the value determined by a standard maximum tapped bulk density will provide an accurate estimate of the bulk density within the capsule.

The ability to calculate the bulk density which can

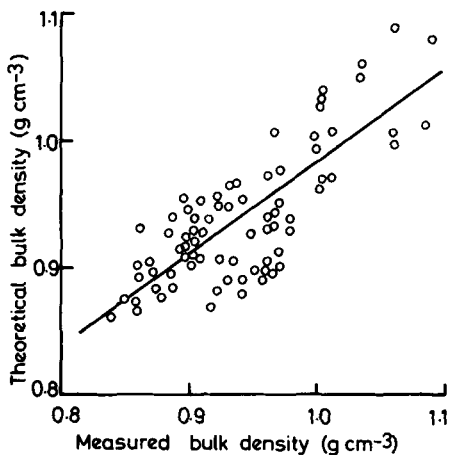


FIG. 5. Relationship between theoretical and measured bulk densities of mixtures of different proportions and particle size fractions of acetylsalicylic acid and lactose, filled into capsules by compression.

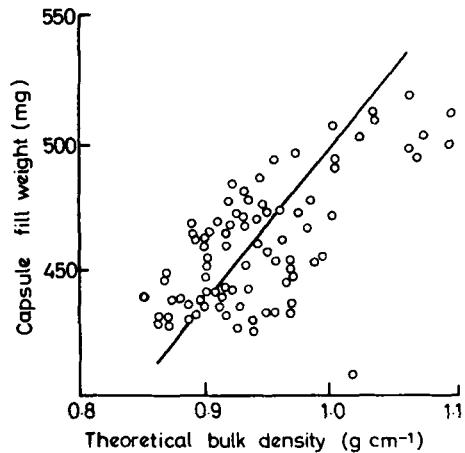


FIG. 6. Relationship between theoretical bulk density and capsule fill weight of mixtures of different proportions and particle size fractions of acetylsalicylic acid and lactose, filled into capsules by compression.

be obtained within the capsule suggests that it should be possible to predict the weight of powder which can be filled into a capsule. When the capsule fill weight  $C$  is plotted as a function of the theoretical bulk densities  $B_{12}$  of the mixtures, there is a highly significant linear relationship, see Fig. 4. The least squares linear regression equation was obtained as:

$$C = 0.493 B_{12} + 0.005$$

with a correlation coefficient of 0.990. The slope of the line approximates to the measured capsule volume of  $0.489 \text{ cm}^3$ , which should be the case for volumetric filling.

Thus for capsule filling as a simple volumetric filling, fill weights, or alternatively capsule volumes can be predicted for two component systems. When the filling system is changed to one in which the particles are forced to take up alternative configurations, e.g. the application of a compressive stress, then the situation could change. This was found to be the case for capsules filled by the application of a compression stress after the initial filling to a maximum bulk density. The relationship between the bulk density within the capsule and the composition was far more complex than for the maximum bulk density determinations illustrated in Fig. 1. Similarly, the relationship between the calculated value of the bulk density  $B_{12}$  and the bulk density with the capsule filled by compression  $B_{ec}$ , while still showing a significant correlation,  $r = 0.763$ , provides a greater scatter of results, see Fig. 5, and relationship with a slope which is less than unity and which has an intercept, namely:

$$B_{12} = 0.62 B_{ec} + 0.203$$

Extending this to applying the calculation of bulk density to the filling of capsules  $C_c$ , again shows a greater scatter of results, although there is still a significant correlation,  $r = 0.751$ , and a slope which is less than the capsule volume, see Fig. 6:

$$C_c = 0.29 B_{12} + 0.188$$

Less reliance could be placed on use of these predicated values of bulk density and it appears that the approach requires modification before it can be extended to situations in which capsules are filled by methods which provide packing conditions other than those of the maximum tapped bulk density.

#### REFERENCES

- Newton, J. M., Bader, F. (1980) *J. Pharm. Pharmacol.* 32: 167-171
- Staple, W. J. (1975) *Soil Sci. Soc. Am. Proc.* 39: 404-408
- Verthais, S., Pilpel, N. (1976) *J. Pharm. Pharmacol.* 28: 415-419
- Westman, A. E. R., Hugill, H. R. (1932) *J. Am. Ceram. Soc.* 13: 767-779

#### Nomenclature

- $A_1$  Measured volume of solid/unit volume of particle components 1 and 2
- $A_2$  Measured volume of solid/unit volume of particle components 1 and 2
- $B_1$  Measured bulk density of particle components 1 and 2
- $B_2$  Measured bulk density of particle components 1 and 2
- $B_{12}$  Theoretical bulk density of a mixture of particle components 1 and 2
- $B_e$  Experimental tapped bulk density of a mixture of particle components 1 and 2
- $B_{cc}$  Experimental bulk density of a mixture of particle components 1 and 2 determined by compression within a capsule
- $C$  Capsule fill weight, capsules filled by tapping
- $C_c$  Capsule fill weight, capsules filled by compression
- $f$  Empirical factor
- $r$  Size ratio of particle components 1 and 2
- $V_1$  Volume contribution of particle components 1 and 2
- $V_2$  Volume contribution of particle components 1 and 2
- $V_{min}$  Minimum volume of a two component system
- $V_r$  Apparent volume/solid volume of a two component system
- $V_t$  Total true solid volume of a two component system
- $X_1$  Volume fraction of particle components 1 and 2
- $X_2$  Volume fraction of particle components 1 and 2
- $W_1$  Mass of particle components 1 and 2
- $W_2$  Mass of particle components 1 and 2
- $\rho_1$  Apparent particle density of particle components 1 and 2
- $\rho_2$  Apparent particle density of particle components 1 and 2
- $\rho_{12}$  Apparent particle density of mixed particle component system