J. Pharm. Pharmac., 1976, **28**, 415–419 *Received November 6, 1975*

Anomalies in some properties of powder mixtures

S. VARTHALIS** AND N. PILPEL*

Department of Pharmacy, Chelsea College, University of London, Manresa Road, SW3 6LX, U.K.

Mixtures of lactose and paracetamol and of lactose and oxytetracycline exhibit anomalous properties. The mean particle sizes, tensile strengths and flow properties of the mixtures are not proportionally intermediate between those of the constituents. The results are ascribed to changes that occur in the packing arrangements of the particles. These changes could have practical consequences in monitoring the progress of a mixing operation by measuring apparent particle size and in controlling the properties of granules, capsules and tablets prepared from the mixtures.

Several workers (Heywood, 1961; Pecht, 1961; Kočova & Pilpel, 1974) have noted that when powders are mixed in different proportions, the properties of the mixtures, such as gas permeability (used for determining the volume-surface mean diameter of the particles) tensile strength, packing fraction, flow, may not be proportionally intermediate between those of the constituents. This is thought to arise from changes that occur in the packing arrangement of the particles.

Packing of powders depends on the density, shape, rugosity, size and size distribution of the particles (Furnas, 1961; Sempere, 1969) and on the amplitude and frequency of any vibration that may have been applied to them (Shatalova, Gorbunov & Likhtman, 1967). Neumann (1953) for example, using simple tapping experiments, was able to demonstrate qualitative correlations between some of the above variables and the rates at which consolidation or packing occurred in a variety of powders.

Monosize, regular particles tend to pack in regular ways (Cadle, 1965). But the packing of real powders, which consist of irregular particles of various sizes usually occurs in a variable and complex manner (Heywood, 1961).

The well-known Kozeny-Carman equation (Carman, 1937)

$$u = \frac{E^3}{(1-E)^2} \quad \frac{\Delta p}{B\eta l S_w^2 \rho^2} \qquad .. \quad .. \quad (1)$$

where u = the average approach velocity of the fluid; E = the porosity of powder bed; η = the viscosity of the fluid; Δp = pressure difference across the bed; l = length of powder bed; B = a constant (=5); ρ = density of powder; S_w = surface area per unit weight of the powder, is based on the Poiseuille equation (Allen, 1975) and is used to calculate the permeability of a powder bed and hence to evaluate the mean particle diameter in the range 5–50 μm. The terms B and $E^3/(1-E)^2$ partly but not completely (Carman, 1947; Lea & Nurse, 1947; Kaye, 1967) allow for the effects that the packing arrangement of the particles have on the porosity and tortuosity of the bed and hence on the values that are obtained for mean particle diameter.

The tensile strength, T(N m^{-2}), of the powder is also dependent, *inter alia*, on the packing arrangement of its particles and it is now well established (Farley & Valentin, 1967–8; Esezobo & Pilpel, 1974) that for many powders the relationship

$$\log T = a + b P_f \qquad .. \quad .. \quad (2)$$

applies, where a and b are constant for each material and $P_f = 1-E$, is the packing fraction.

In the present work measurements have been made of the mean particle diameter (using gas permeability), of the tensile strengths and of the packing characteristics when tapped, of mixtures of lactose and paracetamol and of lactose and oxytetracycline. The purpose has been to demonstrate the occurrence of anomalies in the properties of the mixtures, presumably due to changes in the packing arrangements of the particles, and to discuss some of their potential consequences in pharmaceutical practice.

MATERIALS AND METHODS

The materials used were, paracetamol B.P., microcrystalline powder from Bush, oxytetracycline dihydrate B.P., microcrystalline powder from ICI, lactose B.P. fine powder from Whey Products.

Free moisture (as distinct from water of hydration) was removed by heating for 2 h at 60° (the oxytetracycline darkened at higher temp.). Some of the relevant physical properties of the materials are given in Table 1.

Mixtures of lactose and paracetamol and of lactose and oxytetracycline with the compositions

*Correspondence

**Present address: Abbot Laboratories Ltd, Queensborough, Kent. This work was carried out in part fulfilment of the requirements of the M.Sc. in Pharmaceutical Technology at Chelsea College.

Table 1. *Properties of materials.*

Material	Mean Part. diam. d_{vs}(μm)*	Range of diam. (μm)	Wt. loss (2h at 60°) dry basis (%)	Apparent true density† (kg m^{-3})	Effective Stoke's density‡ (kg m^{-3})
Paracet. (P)	20·3	5–40	1	$1{\cdot}290\times10^3$	$1{\cdot}292\times10^3$
OTC	15·8	1–40	2	$1{\cdot}454\times10^3$	$1{\cdot}454\times10^3$
Lactose (L)	22·7	5–50	0·5	$1{\cdot}550\times10^3$	$1{\cdot}561\times10^3$

* Determined by Fisher sub-sieve sizer.
† Determined by liquid displacement method.
‡ See Burt, Fewtrell, & Wharton, 1973.

Table 2. *Particle interaction coefficients (P.I.C.) (at E indicated = 0·45).*

Composition of mixtures of L & P	P.I.C.	Composition of mixtures of L & OTC	P.I.C.
P 75%	1.022	OTC 75%	0.990
P 50%	1.053	OTC 50%	0.962
P 25%	1.083	OTC 25%	0.971

shown in Table 2 were prepared by mixing the ingredients in a rotating bottle for 0·5 h using diagonal baffles to facilitate mixing. The degree of mixing was subsequently checked by analysis and was found to be $>0{\cdot}95$.

Apparatus and procedure

Surface-volume mean diameters, d_{vs}, were determined with a Fisher Sub-sieve sizer at porosities between 0·40 and 0·45. The mass of material to be used in each determination was obtained from its apparent true density as measured by liquid displacement.

The relevant equations for calculating the particle diameters are:

$$d_{vs} = \frac{clV}{(Al-V)^{3/2}}\sqrt{\frac{F}{P-F}} \quad .. \quad .. \quad (3)$$

and

$$E = \frac{Al-V}{Al} \quad .. \quad .. \quad (4)$$

(Edmundson & Tootill, 1963) where A = cross-sectional area of the powder bed; c = instrument constant; l = length of the powder bed; V = volume excluding the pores occupied by the particles in the sample tube; F = pressure drop across the flowmeter resistance; P = pressure of air entering the powder bed.

When the mass of the sample is numerically equal to its particle density ρ, V = 1 cm^3 and d_{vs} can then be read off directly from the instrument chart.

Tensile strengths of compressed beds of the ingredients and of the various mixtures were measured at different packing fractions in a tensile tester of the same type as that used by Ashton, Cheng & others (1965). Full experimental details of the technique have been published elsewhere (Cheng, Farley & Valentin, 1968).

The packing fractions (P_f) were also measured after subjecting them to various numbers of taps in a cylinder container, the taps being applied at the rate of 38 per minute (British Standard 1460). In both cases the values of P_f were obtained from the apparent true densities of the samples measured by liquid displacement. All the measurements were carried out in a room fitted with a Drymatic Dehumidifier at a relative humidity of 50% and the free moisture content of the samples was checked periodically to ensure that no change had occurred.

RESULTS

The measured values of d_{vs} for the mixtures of lactose and paracetamol and of lactose and oxytetracycline are plotted in Fig. 1. The dotted lines show the values that would have been expected if the mixing had been ideal, and no change had occurred in the packing arrangement of the particles. [Points on these dotted lines were in fact obtained by measuring d_{vs} on layered beds containing the relevant amounts of the two components before they had been mixed together].

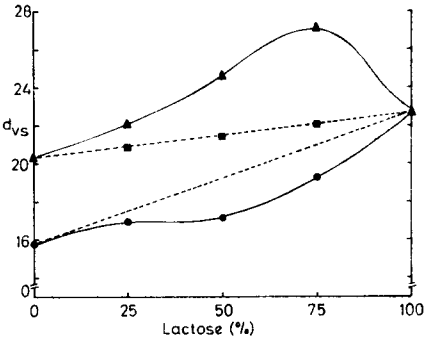

FIG. 1. Mean particle diameter, d_{vs}(μm), versus composition. ▲ observed values for paracetamol mixtures; ■ observed values for paracetamol and lactose unmixed samples; ● observed values for oxytetracycline mixture; – – – predicted values.

Fig. 2 shows plots of log tensile strength against composition of the mixtures at a particular packing fraction of 0·55. Once again the dotted lines show what would have been expected if there had been no change in the packing. It may be mentioned that for all the systems investigated straight lines were

obtained when log T was plotted against P_f. This is as expected (Farley & Valentin, 1967–8; Cheng & others, 1968).

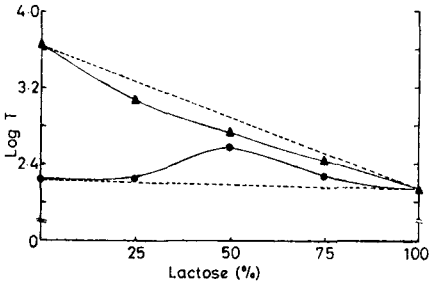

FIG. 2. Log tensile strength (log T), versus composition at packing fraction 0·45. ▲ observed values for paracetamol mixtures; ● observed values for oxytetracycline mixtures; - - - predicted values.

Fig. 3 shows how the packing fractions P_f or porosities $E = (1-P_f)$ of the paracetamol mixtures varied with the number of taps applied. The curves became asymptotic after about 100–150 taps. Similar behaviour was exhibited by the oxytetracycline systems. It was found that for all the systems there was a relationship between the porosity E and the

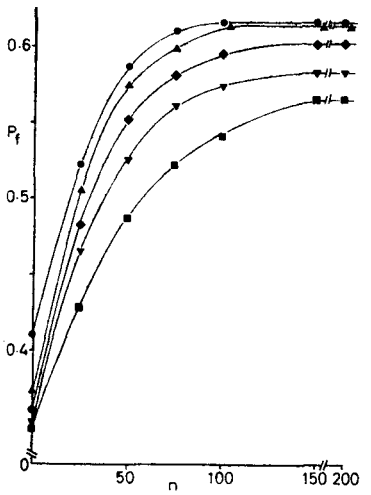

FIG.. 3. Packing fraction, P_f, versus tap numbers, n, for different oxytetracycline and lactose mixtures. ■ OTC 100%; ▼ OTC 75%; ◆ OTC 50%; ▲ OTC 25%; ● lactose.

number of taps n. Plotting $E^2n/(1-E)$, ($\equiv K$), against n gave a series of straight lines whose intercepts on the ordinate were defined as K_0. Then plotting $(K-K_0)$ against n gave the lines shown in Fig. 4a and 4b. This showed that the relationship between E and n was of the form:

$$\frac{E^2}{1-E} = G + \frac{K_0}{n} \qquad \ldots \quad \ldots \quad (5)$$

where G is constant for each system.

The slopes of the lines in Figs. 4a and b were defined as $\tan\theta$ and when θ, (termed the angle of internal flow for reasons which will become apparent later) was plotted against the compositions of the mixtures, Fig. 5 was obtained. This exhibited the type of deviation from ideal behaviour as shown in Figs 1 and 2.

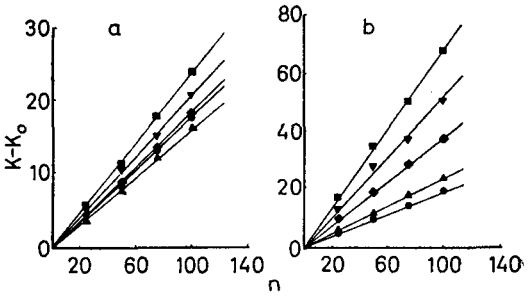

FIG. 4. $(K-K_0)$ versus tap numbers, n, (a) for oxytetracycline mixtures, ■ OTC 100%; ▼ OTC 75%; ◆ OTC 50%; ▲ OTC 25%; ● lactose, (b) for paracetamol mixtures, ■ P 100%; ▼ P 75%; ◆ P 50%; ▲ P 25%.

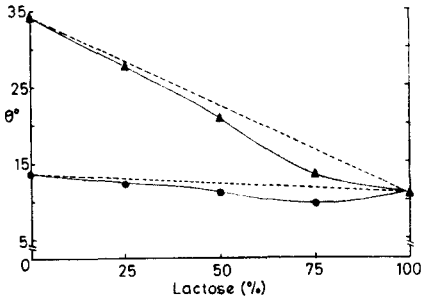

FIG. 5. Angle of internal flow, θ, versus composition. ▲ observed values for paracetamol mixtures; ● observed values for oxytetracycline mixtures; - - - predicted values.

DISCUSSION

The deviations are believed to arise as a result of changes in the packing arrangements of the particles and are presumably due to the differences in the shapes and size distributions of particles of different species in the mixtures.

As the composition of a mixture is altered so changes will occur in the range and magnitude of the interaction forces that operate between the particles (Cheng & others, 1968; Kočova & Pilpel, 1973). These include ionic valency, lattice and van der Waals' forces, frictional forces between surface asperities, and capillary forces due to the presence

of liquid or adsorbed films of moisture even in so-called dry powders (Krupp, 1967).

The interaction force between two lactose particles is different from that between two oxytetracycline particles and different again from that between an oxytetracycline and a lactose particle. Thus as the composition is altered both the geometry and the 'strength' of the packing may change and this could account for the anomalies observed, particularly in the values of the tensile strength and tan θ.

Ado, Nakajima & Tanaka (1968) suggested that in the particular case of particle size, d_{vs}, the anomalies might also be caused by a change in the effective particle density of one, or both of the components in the mixture. The value of particle density obtained by the liquid immersion method will depend on the extent to which the liquid is able to penetrate the material's internal pore structure. But when gas permeability is employed (as in the Fisher apparatus) the effective particle density changes because air is better able to penetrate the internal pores than the liquid. In a mixture some of the pores of one component might become blocked by very fine particles of the second. This would alter the effective particle density of the first component and also the packing structure and hence the value of the term B in the Kozeny Carman equation. The effective particle densities and the values of B and of constant c of equation (3) will depend on the composition of the mixture and changes will cause changes in the values of d_{vs} obtained by the use of equation 3.

In fact, the effect can be neutralized by employing a mass $\neq\rho$ in the sample tube of the Fisher apparatus. When $V' \neq 1$ cm^3 the equation 3 and equation 4 become

$$d'_{vs} = \frac{clV'}{(Al-V')^{3/2}}\sqrt{\frac{F}{P-F}} \quad .. \quad .. \quad (6)$$

and

$$E' = \frac{Al-V'}{Al} \quad .. \quad .. \quad .. \quad (7)$$

The quantity $1/V'$, is termed the Particle Interaction Coefficient (P.I.C.) and its value is obtained from the ratio of d_{vs} expected to d'_{vs} as measured via the equation:

$$\frac{d_{vs}}{d'_{vs}} = \left(\frac{E}{1-(1-E)V'}\right)^{3/2} \cdot V' \quad .. \quad .. \quad (8)$$

derived by combining equations 3, 4, 6 and 7 (equation 8 is solved by a trial and error method). [Since for a fixed mass of material, density is inversely proportional to volume, it follows that the P.I.C. is also the ratio of the effective to expected particle density of the mixture].

Values of P.I.C. calculated from Fig. 1 for selected mixtures of lactose and paracetamol and of lactose and oxytetracycline are given in Table 2. It is seen that, for paracetamol mixtures, the P.I.C. > 1 and for oxytetracycline mixtures < 1. Detailed analysis of all the experimental results revealed that there was a connection between the tensile strengths, T, of the mixtures, tan θ and n, the numbers of taps applied during the tapping experiments which was independent of packing fraction. This was:

$$\frac{(a + b - \log T)^2}{b\,(\log T - a)} = \tan\theta + \frac{K_0}{n} \quad .. \quad (9)$$

where b and a were respectively the slopes and the intercepts on the ordinate of the straight lines obtained when log T was plotted against P_f.

The paracetamol with a value of $\theta = 34{\cdot}2°$ appeared to be a more cohesive powder than the oxytetracycline, $\theta = 13{\cdot}6°$, or lactose, $\theta = 10{\cdot}9°$.

Since the 'cohesiveness' of a powder is a measure of the difficulty with which the particles can flow past each other when tapped or compressed, θ appears to be related to the materials' angle of internal friction (Kočova & Pilpel, 1973) and can be termed the angle of internal flow. But further work will be required to quantify any relationship that may exist between the two angles.

Pharmaceutical applications

Mixing. Due to the rearrangement of the particles in a two component system, the value that is obtained for d_{vs} alters as mixing proceeds until an equilibrium value is attained. This is shown in Fig. 6 for one of the present mixtures of lactose and paracetamol. The progress of a mixing operation could therefore be monitored by successive measurements of d_{vs} until its value reaches a value corresponding to a particular degree of mixing (determined by analysis).

By establishing the connection between d_{vs} and degree of mixing in each system, it should be possible readily to maintain the uniformity of composition in batches. This possibility was first suggested by Kaye (1967).

Granules, tablets and capsules. The packing arrangement of the particles in granules (prepared either by wet or dry methods, Pilpel, 1969) affects their density, porosity, flow properties, hardness, and crushing strength and these properties in turn will affect the properties of tablets and capsules that are prepared from them.

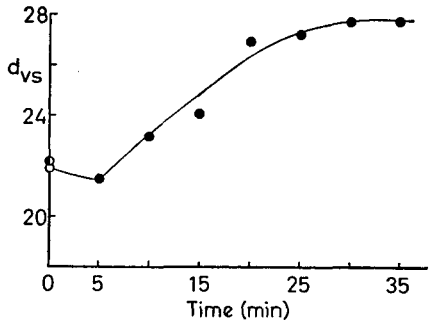

FIG. 6. Mean particle diameter, $d_{vs}(\mu m)$ versus time of mixing for P 25% mixture. ● observed values; ◑ observed value (unmixed sample); ○ predicted value.

Ganderton & Hunter (1971) showed that the amount of densification achieved during tableting depended on the porosity of the starting granules. Harwood & Pilpel (1969) related the flow properties of granules to their bulk densities. More recently Newton & Rowley (1970) studied the connection between granule porosity and the rates at which dissolution and drug release occurred from hard gelatin capsules.

Esezobo & Pilpel (1976) made similar investigations of the rates of disintegration and dissolution of oxytetracycline tablets.

In all these applications changes in the effective particle sizes of mixtures (with corresponding changes in their solubility and permeability to gases and liquids) and changes in their tensile strength, and flow characteristics, brought about by rearrangement in their packing structure, will be expected to affect the mechanical properties of the finished products and the rates of drug release.

The occurrence of anomalies in the properties of powder mixtures, demonstrated in the present work, is thus likely to have consequences in several areas of pharmaceutical practice.

Acknowledgements

The authors thank ICI Pharmaceuticals Division for the gift of chemicals.

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