

Tensile strengths of paracetamol and Avicel powders and their mixtures

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Measurements were made of the tensile strengths of paracetamol and Avicel powders and of their mixtures. Two quantities were derived from the results; m , a universal constant whose value was 1.00 ± 0.23 and α , a constant of the material. The value of α for paracetamol was much larger than that for Avicel and increased slightly with increase in particle size. Adding 25% w/w of Avicel to paracetamol produced a significant decrease in α and this fact may account for its use as an excipient in the tableting of paracetamol.

Paracetamol has to be mixed with relatively large amounts (25–30% w/w) of excipients such as Avicel (Avicel Bulletin, FMC Corporation, 1975) if it is to be compressed on a commercial scale into firm tablets that do not cap or laminate (Carless & Leigh 1974; Leiberman & Lachman 1980). So far no one appears to have offered a satisfactory scientific explanation for this empirical observation. The present work has involved the measurement of the tensile strengths of various mixtures of paracetamol and Avicel and application of the results to recently derived equations (Cheng 1968; Chan et al 1983) in order to obtain values of m , a universal constant, and α . α is a constant for each material and is thought to be a measure of the 'strength' and 'range' of the forces that act between the particles and contribute to the compressibility of the material.

The purpose of the work has been to see whether there might be a connection between the α values of the mixtures and their known behaviour when subjected to compression to form them into tablets.

Theory

In his original theory for the tensile strength, T , of fine powders, Cheng (1968) allowed for the effects of particle size distribution, density, ρ_s and the operation of interparticle forces, and arrived at the following equation:

$$T = \frac{1}{2}abc \frac{\bar{s}}{\bar{V}} \frac{\rho}{\rho_s} H \left[t_0 - \frac{\bar{d}}{3} \left(\frac{\rho}{\rho_0} - 1 \right) \right] \quad (1)$$

where a is the number of particle pairs per unit area divided by the number of particle pairs per unit volume; b is the true area of contact per particle pair divided by the surface area per particle; c is the mean coordination number; H is the interparticle force per

unit area whose magnitude is dependent on the interparticle separation, t ; t_0 is the range of the attractive interparticle force; ρ is the bulk density and ρ_0 is its value when T equals zero; \bar{d} is the average particle diameter, \bar{s} is the average surface area and \bar{V} the average volume per particle.

To overcome the difficulty of deducing the values of ρ_0 and t_0 when $T = 0$ and the separation between the particles is large, Chan et al (1983) introduced the concepts of a reference state and a reduced tensile strength. They proposed the equation

$$T = kg \frac{\bar{d}\bar{s}}{4\bar{V}} \frac{\rho/\rho_s}{[1 - (\rho/\rho_s)]} H(t) \quad (2)$$

where k is a constant relating the coordination number to the packing density and g is a universal constant.

The surface separation between particles, t , can be related to the bed density. If it is assumed that no change in the type of packing of particles occurs as the density changes, then ρ is proportional to $1/L^3$ where

$$L = \frac{1}{2}(d_i + d_j) + t \quad (3)$$

where d_i and d_j are the particle diameters of the species.

For a small change in density, $(\delta\rho/\rho)^{\frac{1}{3}}$ is proportional to $-\delta L/L$ or $(\delta\rho/\rho)^{\frac{1}{3}}$ is proportional to $-\delta t/\bar{d}$. At any reference packing density

$$\left(\frac{\rho_r - \rho^{\dagger}}{\rho} \right)^{\frac{1}{3}} = \frac{t - tr}{\bar{d}} \quad (4)$$

$$\text{Thus} \quad t = tr + \lambda \quad (5)$$

$$\text{where} \quad \lambda = \bar{d} \left\{ \left(\frac{\rho_r}{\rho} \right)^{\frac{1}{3}} - 1 \right\} \quad (6)$$

The subscript r denotes the reference state and it is assumed that $tr \ll \bar{d}$. The 'reduced tensile strength',

* Correspondence.

R, which is a function of t is obtained from equation 2. thus:

$$R(t) = \frac{T}{\bar{d} \bar{s} \frac{\rho/\rho_s}{4\bar{V} [1 - (\rho/\rho_s)]}} \quad (7)$$

It follows that when R is plotted against ρ a similar R value for two size distributions would refer to the same but an unknown t value. By choosing a reference R value (R_r) such that data for the two distributions overlap, the value of ρ_r may be used to calculate λ in equation 6.

The magnitude of the interparticle forces is dependent on the distance apart of the particles, i.e. H is a function of t.

The relationship between H(t) and t can be written as analogous to the Lennard-Jones type of intermolecular potential (Hirschfelder et al 1954).

$$H(t) \text{ is proportional to } \frac{1}{t^m} \quad (8)$$

where m is a positive index.

Hakala (1967) showed that any two-body intermolecular potential function could be put into a dimensionless form involving only one energy parameter ϵ_0 , and only one length parameter t_0 (defined as the 'range' of the interparticle forces) in addition to any dimensionless intermolecular parameters that describe the simplest form of this 'potential function'. Cheng (1968) used this result to derive a law of corresponding states (a universal relationship between dimensionless variables) for the behaviour of single powder systems, and produced the relationship

$$\frac{t_0^3}{\epsilon_0} H(t) = \phi \frac{t}{t_0} \quad (9)$$

where ϵ_0 is a measure of the 'strength' of the interparticle force and t_0 is a measure of the 'range' of this force and ϕ denotes a functional relationship. Modifying equation 9 to introduce the concept of an arbitrary t_r value we have

$$H(t) = \frac{\epsilon_0}{t_0^3} \left(\frac{t_0}{t} \right)^m \quad (10)$$

with t_0 being a representative value of t and m a universal constant. From equation 2

$$H(t) = \frac{R}{\text{kg}} \quad (11)$$

and combining equations 10 and 11

$$R = \frac{\alpha}{t^m} \quad (12)$$

where

$$\alpha = \frac{\text{kg } \epsilon_0}{t_0^{3-m}} \quad (13)$$

Equation 7 becomes

$$T = \frac{\bar{d} \bar{s} \frac{\rho/\rho_s}{4\bar{V} [1 - (\rho/\rho_s)]} \alpha}{t^m} \quad (14)$$

α denoting a parameter characteristic of each material.

In a binary mixture of powders A and B (e.g. paracetamol and Avicel), three different pairings of the two species of particle are possible (A-A, B-B and A-B or B-A) giving rise to three types of interparticle forces. The tensile strength of the mixture depends on the number fractions of particles and the particle size of each species in the mixture and the relevant equation (Chan et al 1983) is

$$T = \frac{\text{kg} \bar{d}_{\text{mix}} \rho/\rho_{s \text{ mix}}}{4\bar{V}_{\text{mix}} [1 - (\rho/\rho_{s \text{ mix}})]} \times [U_A^2 \bar{s}_{AA} H_{AA} + 2U_A U_B \bar{s}_{AB} H_{AB} + U_B^2 \bar{s}_{BB} H_{BB}] \quad (15)$$

where U_A and U_B are the number fractions of species A and B respectively, H_{AA} , H_{BB} and H_{AB} are the forces between particles of type A-A, B-B and A-B respectively per unit area and the subscript mix denotes a mixture. Thus, when $U_A = 1.0$ (and $U_B = 0$), equations 2 and 15 become identical describing a single component powder.

The corresponding reduced tensile strength equation is

$$R_{(t)} = \frac{T}{\bar{d}_{\text{mix}} \bar{s}_{\text{mix}} \frac{\rho/\rho_{s \text{ mix}}}{4\bar{V}_{\text{mix}} (1 - \rho/\rho_{s \text{ mix}})}} \quad (16)$$

where R is a function of t.

By applying the law of corresponding states,

$$R = \frac{\alpha_{\text{mix}}}{t^m} \quad (17)$$

where

$$\alpha_{\text{mix}} = \frac{1}{\bar{s}_{\text{mix}}}$$

$$\times (U_A^2 \bar{s}_{AA} \alpha_{AA} + 2U_A U_B \bar{s}_{AB} \alpha_{AB} + U_B^2 \bar{s}_{BB} \alpha_{BB}) \quad (18)$$

and α_{mix} is a parameter characteristic of a binary mixture and α_{AA} , α_{BB} and α_{AB} are the parameters characteristic of the interacting particles of type A-A, B-B and A-B respectively, \bar{s}_{AA} , \bar{s}_{BB} and \bar{s}_{AB} are the corresponding mean effective surface areas per particle.

Substituting equations 17 and 18 into equation 15, T can now be written as

$$T = \frac{\bar{d}_{\text{mix}} \bar{s}_{\text{mix}} (\rho/\rho_{\text{s mix}}) \alpha_{\text{mix}}}{4\bar{V}_{\text{mix}} [1 - (\rho/\rho_{\text{s mix}})] t^m} \quad (19)$$

It can now be seen that equation 19 reduces to equation 14 when U_A or $U_B = 1.0$, i.e. when the powder contains only one species of particle.

MATERIALS AND METHODS

The two materials used in the present investigation were paracetamol powder (Cambrian Chemicals UK) designated P and Avicel, microcrystalline cellulose pH 101 (Honeywill and Stein Ltd, UK) designated A.

They were separately milled in a laboratory hammer mill (Micropul Ltd) and classified into different size fractions using a Microplex zig-zag classifier. The projected mean diameters were measured under a microscope and the required particle size parameters calculated (Cheng 1968). The particle densities were determined with a Beckmann air-comparison pycnometer Model 930. The designation of representative fractions is given in Table 1.

Samples P_1 and A_2 were mixed together in a rotating cylinder mixer for 30 min to produce mixtures M_1 – M_8 whose compositions were respectively 95, 90, 85, 70, 50, 25 and 10% weight of paracetamol.

The mixtures were assayed spectrophotometrically for paracetamol at 249 nm and their degree of mixing (Rose 1959) was found to be >0.93 . The mixtures were dried for 12 h at 60°C in an oven and their moisture contents were $<1\%$ w/w as determined on a Townson and Mercer vacuum moisture

tester. They were stored in airtight glass jars at 20°C and 40% relative humidity. It was confirmed that under these conditions uptake of moisture was insignificant.

Tensile strengths

These were measured with a tensile tester whose design and operation have been described elsewhere (Ashton et al 1964). The tests were performed at 20°C in a humidity controlled room at 40% RH $\pm 5\%$ provided by a Westair Drymatic dehumidifier.

RESULTS

Table 1 gives representative values of the particle size parameters \bar{d} , \bar{s} , \bar{V} of the materials and of the mixtures calculated from their size distributions (Cheng 1968).

Table 2 gives the tensile strengths and reduced tensile strengths of representative materials and of the mixtures at different packing densities.

Fig. 1 shows the plots of R versus ρ for some of the materials and mixtures. The reference R value (R_r) depends on the lie of the experimental data. An R_r value of 8000 Nm^{-2} was chosen for samples P_1 and P_2 and M_1 – M_6 , and of 4000 Nm^{-2} for all the Avicel fractions and P_3 and M_7 and M_8 . These R_r values were used to determine the corresponding ρ_r values from the plots in Fig. 1 and the results were used to calculate the appropriate λ values using equation 6. All the results are given in Table 2.

By employing equations 7 and 12 and by assuming that $t_r \ll \bar{d}$ and that the law of corresponding states holds, $\log R$ may be plotted against $\log t$ using

Table 1. Compositions and particle size parameters.

Code	Paracetamol	U_A	U_B	ρ_s g cm^{-3}	\bar{d} or \bar{d}_{mix} (μm)	\bar{s} or \bar{s}_{mix} (μm) ²	\bar{V} or \bar{V}_{mix} (μm) ³
P_1	100	1.000	0.000	1.29	7.7	46.0	382.8
P_2	100	1.000	0.000	1.29	16.8	220.3	4186.8
P_3	100	1.000	0.000	1.29	24.2	458.8	8967.0
A_1	0	0.000	1.000	1.52	6.3	30.9	211.9
A_2	0	0.000	1.000	1.52	16.8	220.2	3270.0
A_3	0	0.000	1.000	1.52	27.7	604.4	13565.0
M_1	95	0.995	0.005	1.30	7.7	46.7	397.8
M_2	90	0.989	0.011	1.31	7.8	47.3	414.4
M_3	85	0.983	0.017	1.32	7.8	48.0	432.6
M_4	80	0.976	0.024	1.33	7.9	48.8	452.8
M_5	70	0.959	0.041	1.35	8.0	50.7	500.7
M_6	50	0.910	0.090	1.40	8.5	56.5	643.8
M_7	25	0.770	0.230	1.46	9.8	74.7	1045.8
M_8	10	0.528	0.472	1.49	12.0	112.2	1745.8

Table 2. Representative tensile strength and reduced tensile strength data, and the derived values of λ , m and α .

Sample	ρ (g cm^{-3})	ρ/ρ_s	$T \times 10^{-3}$ (Nm^{-2})	$R \times 10^{-3}$ (Nm^{-2})	$R_r \times 10^{-3}$ (Nm^{-2})	ρ_r (g cm^{-3})	λ (μm)	t_r (μm)	m	α or $\alpha_{\text{mix}} \times 10^{-3}$ [$\text{Nm}^{-2}(\mu\text{m})^m$]
P ₁	0.28	0.22	0.46	7.07	8	0.29	0.05	0.90	1.23	7.1
	0.31	0.24	0.88	11.83			-0.22			
	0.30	0.23	0.66	9.58			-0.07			
	0.33	0.26	1.34	16.67			-0.36			
	0.34	0.26	1.39	17.11			-0.38			
	0.35	0.27	1.55	18.11			-0.47			
	0.28	0.22	0.45	7.04			0.08			
P ₃	0.38	0.30	0.46	3.51	4	0.41	0.53	2.4	0.79	8.3
	0.46	0.36	0.96	5.62			-0.92			
	0.43	0.33	0.76	4.96			-0.35			
	0.45	0.35	1.03	6.15			-0.84			
	0.41	0.31	0.57	3.99			0.05			
	0.44	0.34	0.84	5.29			-0.55			
A ₁	0.29	0.19	0.06	1.20	4	0.34	0.37	0.25	0.93	1.0
	0.34	0.23	0.23	3.40			0.01			
	0.35	0.23	0.33	4.80			-0.06			
	0.33	0.21	0.20	3.25			0.11			
	0.35	0.23	0.28	4.11			-0.02			
	0.36	0.24	0.36	5.06			-0.10			
	0.30	0.20	0.12	2.12			0.28			
A ₃	0.42	0.28	0.26	2.15	4	0.44	0.44	0.15	0.81	1.3
	0.41	0.27	0.18	1.56			0.65			
	0.44	0.29	0.44	3.53			0.07			
	0.41	0.27	0.14	1.18			0.71			
	0.43	0.28	0.37	3.01			0.23			
	0.44	0.29	0.45	3.62			0.16			
M ₁	0.30	0.23	0.28	4.20	8	0.33	0.23	1.00	0.86	7.7
	0.38	0.29	1.11	11.94			-0.39			
	0.33	0.26	0.73	9.38			-0.07			
	0.37	0.28	1.07	12.13			-0.30			
	0.31	0.24	0.55	7.80			0.15			
	0.32	0.25	0.34	7.80			0.00			
	0.39	0.30	1.01	10.50			-0.43			
	0.34	0.26	0.65	8.13			-0.10			
	0.31	0.24	0.60	8.54			0.14			
	M ₆	0.34	0.25	0.28			4.61			
0.39		0.28	0.83	11.47	-0.20					
0.36		0.26	0.51	7.85	0.03					
0.35		0.25	0.38	6.11	0.13					
0.37		0.27	0.64	9.40	-0.11					
M ₈	0.37	0.25	0.12	1.94	4	0.40	0.38	0.35	0.96	1.5
	0.41	0.28	0.37	5.05			-0.06			
	0.40	0.27	0.23	3.32			0.08			
	0.37	0.25	0.14	2.15			0.37			
	0.39	0.26	0.18	2.71			0.19			
	0.41	0.27	0.28	3.92			0.00			

different values of t_r by a trial and error method until a straight line is obtained. (This procedure allows for variation in the value chosen for R_r .) (Chan et al 1983) The slope gives m and the intercept on the ordinate α . This is shown in Fig. 2. Fig. 3 shows how the values of α vary as the % w/w of Avicel in the mixtures is increased.

DISCUSSION

Table 2 and Fig. 1 show that as the packing densities of all the samples are increased, their values of T and R both increase. This is due to the enhancement in the van der Waals', electrostatic, frictional mechanical interlocking and other forces (Krupp 1967;

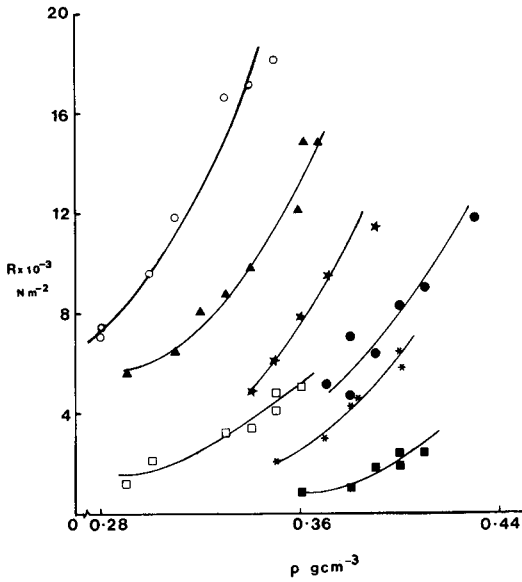


Fig. 1. Plot of R versus P for representative samples. Key: \circ — \circ P₁, \bullet — \bullet P₂, \square — \square A₁, \blacksquare — \blacksquare A₂, \blacktriangle — \blacktriangle M₅, \star — \star M₆, \ast — \ast M₇.

Cheng 1968) that operate between the particles as they are brought into closer contact.

Fig. 2 shows a series of straight lines almost parallel to each other. Their slopes give the values of m and their intercepts at log t = 0, i.e. t = 1 μm give α or α_{mix}. The values are given in Table 2: m ranged from 0.77 to 1.23; but considering the assumptions made in the derivation of the theory (Chan et al

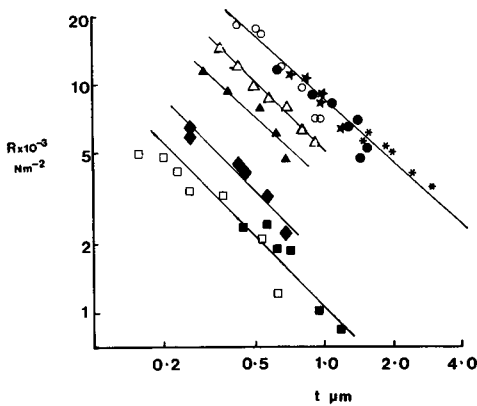


Fig. 2. Plot of log R versus log t for representative samples. Key: \circ — \circ P₁, \bullet — \bullet P₂, \ast — \ast P₃, \square — \square A₁, \blacksquare — \blacksquare A₂, \star — \star M₂, \triangle — \triangle M₅, \blacktriangle — \blacktriangle M₆, \blacklozenge — \blacklozenge M₇.

1983) it can be reasonably concluded that m is a universal constant, as implied by equation 10 with a (average) value of 1.00 ± 0.23.

Fig. 2 shows that all the points for the different size fractions of paracetamol and Avicel can be accommodated approximately on two different straight lines. [The correlation coefficients were >0.95 and the scatter can be ascribed to the experimental technique (Sutton 1976), to the assumptions in the theory employed (Cheng 1968; Chan et al 1983) and also possibly to variations in particle shape between the different samples (Pilpel & Walton 1974). In the theory the particles are assumed to be spherical; in fact optical microscopy revealed them to be acicular.]

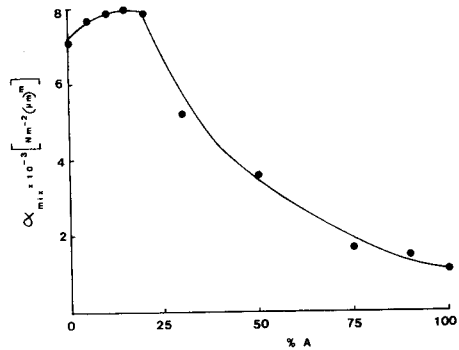


Fig. 3. Plot of α_{mix} versus % w/w of Avicel in the mixture.

The α value for paracetamol was very much greater than that for Avicel (Table 2) and increased slightly with increase in particle size. Although the term compressibility is interpreted in different ways by different authors, α appears to be a measure of the compressibility of a material. Paracetamol with a high value of α is very difficult to compress and compacts formed from it immediately cap and laminate (Leigh et al 1967). Avicel with a low value of α is soft and readily compressible (Esezobo & Pilpel 1977) and it is therefore used as an excipient for tableting paracetamol and other pharmaceutical drugs. At least 25% of Avicel has to be mixed with paracetamol before the α value of the mixture is substantially reduced below that of the pure drug (Fig. 3). This provides an explanation for the observation that in production it is necessary to incorporate 25 to 30% w/w of Avicel in paracetamol in order to compress it into satisfactory tablets which do not cap or laminate.

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