

The effects of moisture content and gelatin binding agent on the mechanical and failure properties of an oxytetracycline formulation

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A study has been made of the effects of gelatin as a binding agent and of moisture content on the mechanical and failure properties of an oxytetracycline tablet formulation, using measurements of the shear strengths and tensile strengths. As the concentration of gelatin at any moisture level between 0 and 25% w/w is increased, the tensile strength of the formulation increases. Its cohesion and angle of internal friction also increase with gelatin concentration at moisture levels between 2 and 4% w/w. The results are discussed in the light of current theories concerning the bonding of particles by moisture and binding agents.

Oxytetracycline is usually presented as tablets of 250 mg of the active drug, plus appropriate excipients to enable the formulation to be wet granulated and then compressed at high speed.

The effects of moisture and binding agents in single powders and in simple mixtures of powders on the strengths of granules and/or of compacts prepared from them have been examined by Ahmad & Pilpel (1967), Harwood & Pilpel (1968), Davies & Gloor (1972), Hunter & Ganderton (1972) and Healey, Humphrey-Jones & Walters (1972) but few systematic studies of the effects of moisture and binding agents on the properties of actual tablet formulations have been reported. Virtually no data have been published from which it might be possible to establish correlations between the fundamental mechanical properties of the formulation and the properties of the finished tablets.

The fundamental mechanical properties of a fine powder in quantitative terms are expressed as measures of its shearing and tensile properties after consolidating it in a shear cell apparatus (Carr & Walker, 1968) or a tensile tester (Ashton, Farley & Valentin, 1964).

The results of the shear tests are plotted in the form of yield loci. From these, values of the cohesion, and angle of internal friction of the powder can be obtained which provide information about flow and failure properties (Ashton, Cheng & others, 1965; Williams & Birks, 1967).

We have measured the shearing and tensile properties of a typical oxytetracycline formulation, to see what effects are produced on the values of cohesion, angle of internal friction and tensile strength by changing the amounts of water and gelatin binding agent.

Measurements were made on the individual ingredients, then on the formulation without binding agent and on the formulation plus binding agent after wet granulation. The granules were dried and milled back to approximately the same particle size as the original mixtures. This was necessary to enable the shearing and tensile tests to

be performed (Eaves & Jones, 1971) and to ensure that complicating effects caused by differences of particle size (Cheng, 1968; Kočova & Pilpel, 1971-72; Eaves & Jones, 1972) were eliminated.

MATERIALS AND METHODS

Materials

The material examined was a formulated powder for oxytetracycline tablets consisting of an intimate mixture of % w/w oxytetracycline dihydrate 90.2, Avicel PH101 (Honeywell & Stein Ltd) 7.2, Alginic acid HED (Alginate Industries Ltd) 2.6 and gelatin Bloom No. 300 acid-treated-hide (Richard Hodgson Ltd).

Relevant physical properties of the ingredients and of the formulation are given in Table 1.

Table 1. *Physical properties of ingredients of the formulation.*

Material	Average particle diameter (μm) (by microscopy)	Effective particle density g cm^{-3} (by immersion in chloroform)	Moisture content % w/w (by wt loss at 50–70°)
Oxytetracycline dihydrate ..	6.0	1.454	2.1
Avicel	6.5	1.618	4.3
Alginic acid	4.6	1.674	6.1
Oxytetracycline formulation ..	4.8	1.461	4.0

Batches of the formulation (500 g) were mixed for 1½ min in a small planetary mixer with 250 ml of distilled water containing differing amounts of dissolved gelatin (prepared by soaking the gelatin for 30 min in cold water, warming this to 40° with stirring until dissolution occurred then cooling this to above the gelling temperature). The wet masses which contained between 0 and about 7.5% w/w of gelatin were granulated through a No. 12 mesh sieve and the granules dried for 48 h at 50°. They were then milled in a Bantam, Mikro-Pulverizer hammer mill to approximately the same particle size as the original ingredients and again dried for 24 h at 50°. The material decomposed at higher temperatures.

For some of the experiments, the milled material was moistened with controlled amounts of water—up to a maximum of 25% w/w—by spraying and simultaneously tumbling the powder in a small, cylindrical ball mill, to prevent granule formation. The amount of water added was determined from the loss in weight of the samples on subsequent drying.

Apparatus and procedure

Measurements of the tensile strengths and shear strengths of the samples were made using a tensile tester (constructed by Contest Instruments) of the same design as that used by Ashton & others (1964) and in an annular shear cell (constructed by Glaxo Laboratories) of the same design as that used by Carr & Walker (1968). (For details see Carr & Walker, 1968; Kočova & Pilpel, 1971–72.)

The experiments were made in a room fitted with a Drymatic 50 Dehumidifier which was adjusted to ensure that the moisture contents of the samples remained virtually constant during measurements.

RESULTS

The results of the particle size measurements on the original formulation and on the milled granules containing different amounts of gelatin are given in Fig. 1 in the form of cumulative number % undersize curves.

It is seen that the particle size distributions in all the samples investigated were similar to one another, thereby largely eliminating particle size as a variable in making comparisons between the shearing and tensile properties of the different samples.

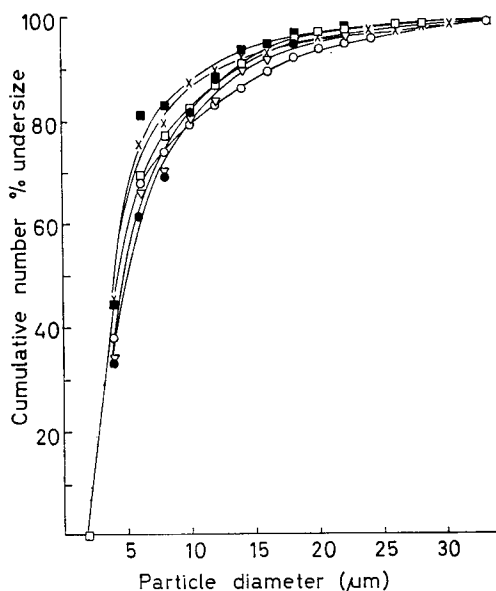


FIG. 1. Particle size distribution of milled O.T.C. granules (number basis). ● 0% Gelatin, mean diameter 4.8 μm. ▽ 2.5% Gelatin, mean diameter 5.1 μm. ■ 3.75% Gelatin, mean diameter 4.0 μm. ○ 5.0% Gelatin, mean diameter 4.6 μm. × 6.25% Gelatin, mean diameter 4.0 μm. □ 7.5% Gelatin, mean diameter 4.4 μm.

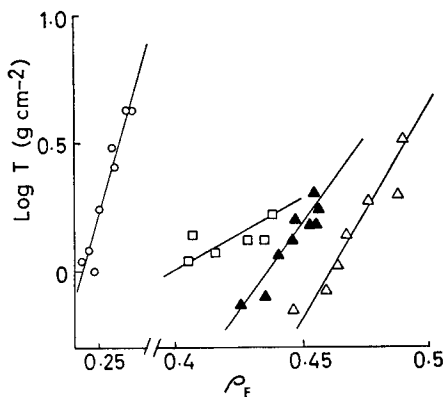


FIG. 2. Log tensile strength vs packing fraction. ○ Avicel powder. □ Alginate powder. △ Oxytetracycline powder. ▲ Oxytetracycline formulation.

The results of the tensile tests on the original formulation and on its individual ingredients are presented in the form of plots of log tensile strength versus packing fraction in Fig. 2. The observed scatter of the points is normal and several authors (Eaves & Jones, 1972; York & Pilpel, 1972a) have discussed the reasons for it.

Similar plots in Fig. 3 show how the addition of gelatin affects the tensile strength of the formulation (after milling the granules back to their original particle size) while maintaining the moisture level as constant as possible in the range of about 2–4% w/w. Representative graphs showing the effects of 5% w/w gelatin plus up to 22% w/w moisture on the tensile strengths of the milled granules are given in Fig. 4, the packing fractions being calculated on the dry basis (Eaves & Jones, 1971). Additional results are plotted in Figs 5 and 6.

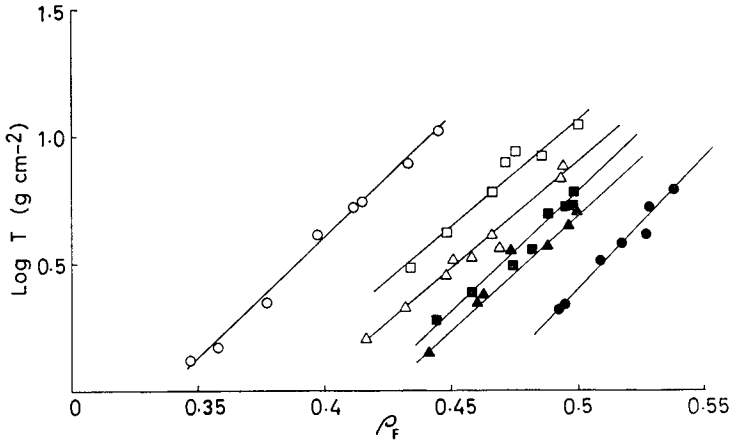


FIG. 3. Effect of gelatin content on log tensile strength vs packing fraction of milled granules at approximately constant moisture content. ● 0% gelatin, 2.0% moisture. ▲ 2.5% Gelatin, 2.3% moisture. ■ 3.75% Gelatin, 4.0% moisture. △ 5.0% Gelatin, 3.8% moisture. □ 6.25% Gelatin, 3.3% moisture. ○ 7.5% Gelatin, 4.3% moisture.

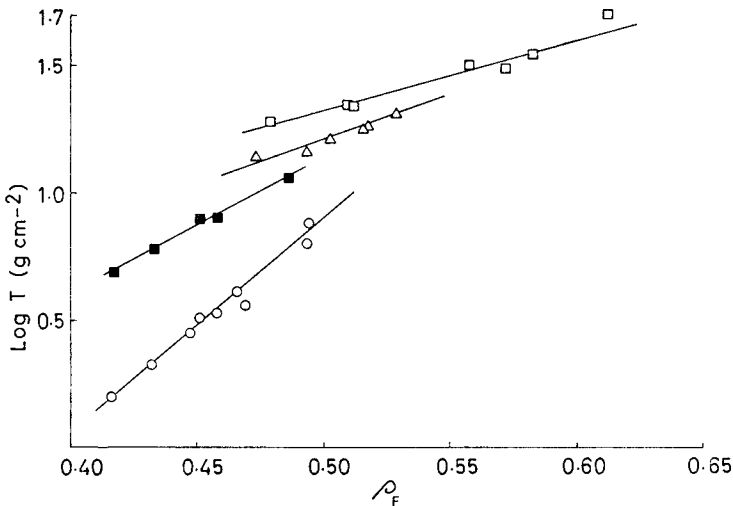


FIG. 4. Effect of moisture on log tensile strength vs packing fraction of milled granules containing 5% gelatin. Moisture % w/w. ○ 3.8, ■ 8.2, △ 15.1, □ 22.3.

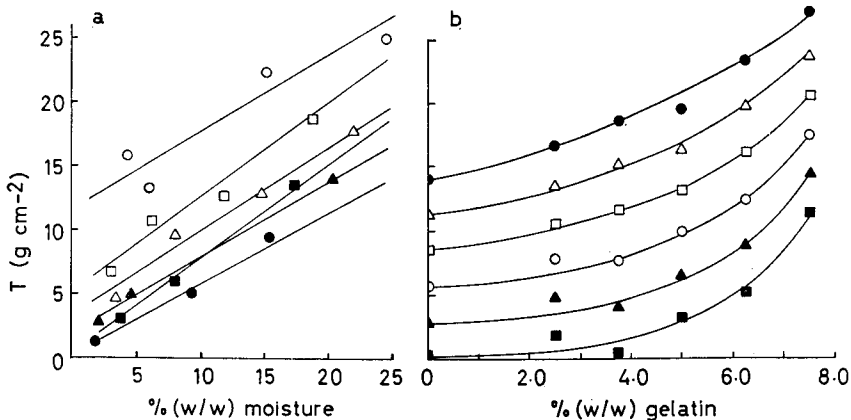


FIG. 5. Effect of moisture and gelatin concentration on tensile strengths of milled granules at $\rho_F = 0.47$. (a) Gelatin %: ● 0, ▲ 2.5, ■ 3.75, △ 5.0, □ 6.25, ○ 7.5. (b) Moisture %: ■ 0, ▲ 5, ○ 10, □ 15, △ 20, ● 25. Bottom curve obtained by extrapolation of results from Fig. 5a to zero moisture content.

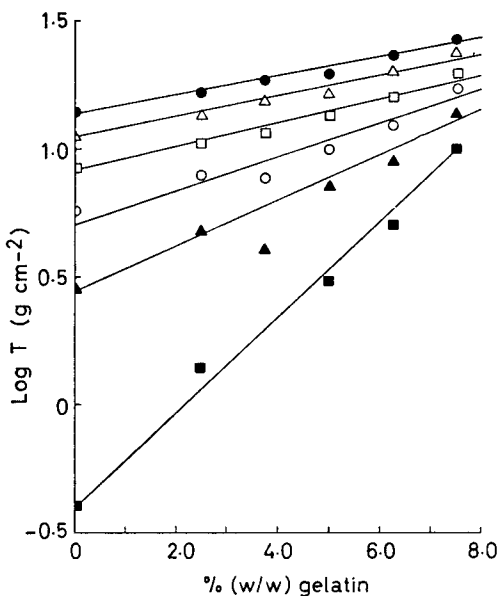


FIG. 6. Combined effects of moisture and gelatin concentration on tensile strengths of milled granules at $\rho_F = 0.47$. Slope: ■ 1.65, ▲ 0.60, ○ 0.42, □ 0.30, △ 0.27, ● 0.25. Bottom curve obtained as in Fig. 5.

Typical yield loci showing the results of shear tests on one of the samples are plotted in Fig. 7. Here the shear stress at failure τ_F is plotted against the applied normal stress σ_N at each value of the packing fraction achieved during the initial consolidation of the sample. Extrapolating the loci to $\sigma_N = 0$ and noting the intercepts on the ordinate, gives the cohesion, C , of the sample at the packing fraction concerned, while the intercept on the negative side of the abscissa is the tensile strength, T , whose value is obtained in the tensile tests (see above).

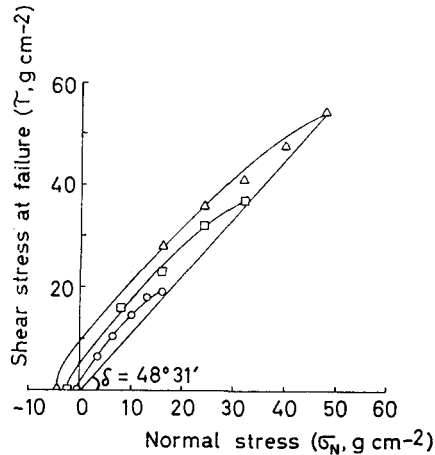


FIG. 7. Yield loci of milled granules containing 2.5% gelatin and 2.3% moisture. ρF : ○ 0.408; □ 0.466; △ 0.492.

In the event, the values of the cohesion were obtained by making use of the Warren Spring equation (Ashton & others, 1965) in its logarithmic form:

$$\text{i.e. } \text{Log } \tau = \log \frac{C}{T} \frac{1}{n} + \frac{1}{n} \log (\sigma_N + T) \quad \dots \quad (1)$$

where $(\sigma_N + T) \equiv \sigma_N$ is termed the compound normal stress, plotting $\log \tau$ versus $\log (\sigma_N + T)$ to give straight lines whose intercepts on the ordinate yielded values of $C/T^{1/n}$ and hence of C .

The end points of the loci, plotted on axes of τ vs $(\sigma_N + T)$ fell on straight lines through origins of the axes and their slopes gave the angles of internal friction Δ of the samples (Williams & Birks, 1967). Typical values are listed in Table 2 and Fig. 8 is a representative graph to show the effect of the gelatin concentration on the angle of internal friction and cohesion of some samples containing between about 2 and 4% w/w of water.

Table 2. Values of cohesion, tensile strength and change of angle of internal friction at different concentrations of gelatin and moisture levels of between 2.04–4.35% w/w.

Concentration of gelatin in OTC formulation (% w/w)	Moisture content (% w/w dry basis)	Cohesion at a packing fraction of 0.47 (g cm^{-2})	Tensile strength at a packing fraction of 0.47 (g cm^{-2})	Angle of internal friction (Δ)	Change of angle of internal friction (Δ)
0.00	2.04	3.8	1.32	43°23'	0°0'
2.50	2.28	6.1	2.75	45°51'	+2°28'
3.75	3.98	7.6	3.09	46°15'	+2°52'
5.00	3.80	9.8	4.47	47°08'	+3°45'
6.25	3.29	12.2	6.46	—	—
7.50	4.35	19.2	15.85	49°48'	+6°25'

DISCUSSION

Fig. 2 shows that the tensile strength of oxytetracycline is different from that of Avicel or Alginic acid after allowance has been made for the small, but unavoidable differences in their particle size distributions and moisture contents. Addition of about 7% w/w Avicel and about 3% of alginic acid produces a noticeable increase in the tensile strength of the drug at any particular packing fraction. The addition reduces the coefficient of reassertion of oxytetracycline and thus prevents spontaneous fracture of compacts prepared from it. This might be due, in part, to mechanical interlocking of the additive particles, caused by their fibrous nature and irregular shapes.

The effects of moisture on the tensile strengths of powders are now well known. Except at the very lowest concentrations, there is usually an increase in tensile strength with increase in moisture content (Eaves & Jones, 1972; Cheng, 1970), due to changes in the strengths and ranges of the forces that act between particles.

This is confirmed by the results in Figs 4 and 5(a) and (b) though it is seen that the increase in T with moisture content, also depends on the amount of gelatin binding agent that is present.

Fig. 6 shows that at any particular moisture level, increasing the amount of gelatin in the milled granules causes an increase in their tensile strength. The relationship is seen to be of the form:

$$\log T = kB + A_1 \quad \dots \quad \dots \quad \dots \quad \dots \quad (2)$$

where k and A_1 are constants, which depend on the moisture level and B is the concentration of the binding agent. The intercept A_1 increases with moisture concentration, the slope k decreases with moisture content.

A similar relation, namely:

$$T = k'B \quad \dots \quad \dots \quad \dots \quad \dots \quad \dots \quad (3)$$

has been reported (Harwood & Pilpel, 1968) for the effects produced on the strengths of dry griseofulvin granules by adding polyvinylpyrrolidone as the binding agent.

Turning next to the results of the shearing tests, Fig. 8 shows that the cohesion and angle of internal friction of milled granules both increase with increase in the concentration of gelatin binding agent. As noted previously, the samples unavoidably contained slightly different amounts of moisture (between 2-4% w/w) but this fact does not alter the general conclusion that there is a considerable increase in the mechanical strength and a decrease in the flowability of the formulation as the concentration of binding agent in it is raised.

A good deal of work has now been done on the effect of moisture on the tensile strength of powder compacts. Rumpf (1962) and Newitt & Conway-Jones (1958) distinguished between the pendular, funicular and capillary states as water increasingly fills the void spaces between neighbouring particles. Pietsch & Rumpf (1967) obtained the following expression for the tensile strength:

$$T = \frac{9}{16} \cdot \frac{\rho f}{1 - \rho f} \cdot \frac{\gamma}{R} \cdot F \quad \dots \quad \dots \quad \dots \quad \dots \quad (4)$$

where γ is the surface tension of the water, R is the radius of the particles and F is the dimensionless adhesion force between particles and is a complicated function of the

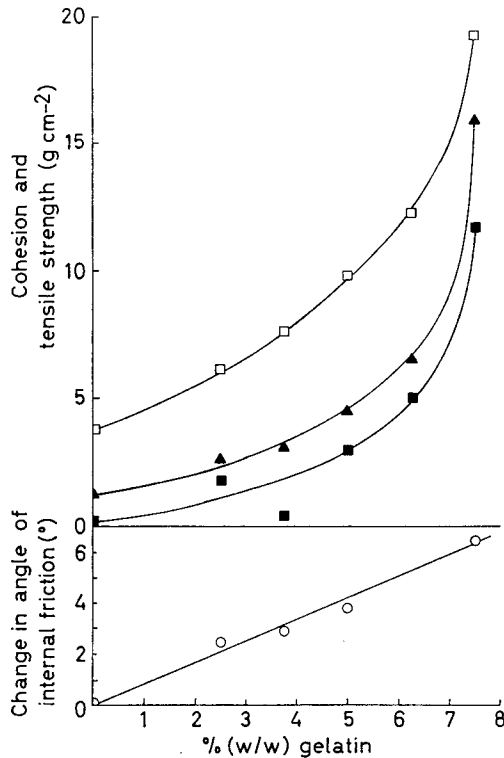


FIG. 8. Effect of moisture and gelatin concentration on cohesion, tensile strength, and angle of internal friction of milled granules $\rho_F = 0.47$. \circ Angle of internal friction. \square Cohesion, \blacktriangle Tensile strength. All at moisture between 2 and 4.3%. \blacksquare Tensile strength at 0% moisture. Bottom curve obtained as in Fig. 5.

half-centre angle of the particle, the solid/liquid contact angle and the interparticle separation.

The value is considerably greater than that predicted for the dry material by using the equation proposed by Ashton & others (1965),

$$T = A(\rho)^m \quad \dots \quad (5)$$

(where A and m are constants and ρ is the bulk density of the bed) on the assumption that the particles are equi-sized spheres, whose surfaces, however, are capable of some degree of plastic deformation. This is because the surface tension and capillary forces are stronger and act over longer distances than the electrochemical and van der Waals forces, which act only at a limited number of points where the particles are in actual contact.

When the water is replaced by a suitable binder solution, the tensile strength of the subsequently dried compact can exceed that of the moist mass by a factor of 10 or more. This has been explicitly demonstrated in the present work and by other workers using both pharmaceutical systems e.g. griseofulvin and polyvinylpyrrolidone (Harwood & Pilpel, 1968) and others—coal + polyisobutylene (Jayasinghe & Pilpel, 1969)—iron ore and fertilizers with concentrated salt solutions as the binding agents (Burak, 1966). However, it has not been possible to develop expressions for the ten-

sile strengths of systems which contain binding agents in the same way as for the systems which contain water.

Even with water, the agreement between the predicted and measured tensile strengths is generally poor. Cheng's (1970) modification of the theoretical equations to allow for the effects of particle size distribution and the presence of surface asperities is restricted to the case of the water being in the pendular state. The modifications involve several unproven assumptions and Cheng himself admits that they are not well supported by the results of experiments.

It seems highly unlikely that further modifications could be made to allow also for the presence of a binding agent which on drying, would form solid bonds between the particles (Rumpf, 1962). This is because fracture in the mass could then occur either through component particles, or through the solid bonds between the particles or at the binder/particle interfaces, whichever were the weakest. It has in fact been shown (Pietsch, 1967) that where solid bonds are formed by evaporation of moisture, the tensile strength is considerably affected by the rate of drying and the drying temperature, part of the effect probably being due to welding of asperities on the particles at temperatures appreciably below their conventional melting points (York & Pilpel, 1972a,b).

The results that have been obtained are therefore specific to the systems investigated, to the grade of gelatin binder, and to the conditions of granulation, milling and drying that have been employed before measuring the tensile strengths of the milled granules.

It has been found that the addition of the excipients, avicel and alginic acid powders, enhances the tensile strength of the active ingredient (i.e. oxytetracycline powder). The results might prove useful in predicting quantitatively the mechanical properties of a tablet from a knowledge of the properties of the single components.

It has been shown that the increase in the gelatin concentration causes a corresponding increase in the tensile strength (T), cohesion (C) and the angle of internal friction (Δ) of the oxytetracycline formulation.

Within the moisture levels investigated, it has been found that the increase in the magnitude of the tensile strength and cohesive force of the milled granules is a function of the quantity of gelatin present in the formulation. This finding illustrates the importance of moisture in formulated granules.

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REFERENCES

- AHMAD, M. & PILPEL, N. (1967). *Manuf. Chem. and Aerosol News* (Jan.), 37-38.
- ASHTON, M. D., FARLEY, R. & VALENTIN, F. H. H. (1964). *J. scient. Instrum.*, **41**, 763-765.
- ASHTON, M. D., CHENG, D. C-H., FARLEY, R. & VALENTIN, F. H. H. (1965). *Rheol. Acta*, **4**, 206-217.
- BURAK, N. (1966). *Chem. Ind.*, 844-850.
- CARR, J. F. & WALKER, D. M. (1968). *Powder Technol.*, **1**(6), 369-373.
- CHENG, D. C-H. (1968). *Chem. Eng. Sci.*, **23**, 1405-1420.
- CHENG, D. C-H. (1970). *J. Adhesion*, **2**, 82-92.
- DAVIES, W. L. & GLOOR, W. T., Jr. (1972). *J. pharm. Sci.*, **61**, 618-622.
- EAVES, T. & JONES, T. M. (1971). *Rheol. Acta*, **10**, 127-134.
- EAVES, T. & JONES, T. M. (1972). *J. pharm. Sci.*, **61**, 256-261.
- HARWOOD, C. F. & PILPEL, N. (1968). *Ibid.*, **57**, 478-481.
- HEALEY, J. N. C., HUMPHREYS-JONES, J. F. & WALTERS, V. (1972). *J. Pharm. Pharmac.*, **24**, *Suppl.*, 121P-122P.

- HUNTER, B. M. & GANDERTON, D. (1972). *Ibid.*, **24**, *Suppl.*, 17P-24P.
- JAYASINGHE, S. S. & PILPEL, N. (1969). *J. Inst. Fuel*, June, 231-234.
- KOČOVA, S. & PILPEL, N. (1971-72). *Powder Technol.*, **5**, 329-343.
- NEWITT, D. M. & CONWAY-JONES, J. M. (1958). *Trans. Instn. Chem. Engrs.*, **36**, 422-442.
- PIETSCH, W. (1967). *Aufbereitungs-Technik.*, **8**, 297-307.
- PIETSCH, W. & RUMPF, H. (1967). *Chemie-Ingenieur-Technik*, **39**, 885-893.
- RUMPF, H. (1962). *Intern. Symp. on Agglomeration*, pp. 379-418. Editor: Knepper, W. A., New York and London: Interscience.
- WILLIAMS, J. C. & BIRKS, A. H. (1967). *Powder Technol.*, **1**, 199-206.
- YORK, P. & PILPEL, N. (1972a). *J. Pharm. Pharmac.*, **24**, *Suppl.*, 47P-56P.
- YORK, P. & PILPEL, N. (1972b). *Mat. Sci. Eng.*, **9**, 281-291.

List of symbols used:

A = a constant. A_i = a constant depending on moisture level. B = concentration of binding agent. C = cohesion, (g cm^{-2}). k = a constant depending on moisture level. k^1 = a constant. m = a constant. n = shear index, the exponent of the powder's yield locus equation. T = tensile strength, g cm^{-2} . Δ = angle of internal friction. ρ = bulk density, gm cm^{-3} . ρ_t = packing fraction. σ_N = applied normal stress (g cm^{-2}). $\sigma_N \equiv (\sigma_N + T)$ = compound normal stress (g cm^{-2}). τ = shear stress at failure (g cm^{-2}).