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Compression and tableting of pharmaceutical powders at elevated temperatures

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Summary

Measurements have been made of the tensile strength of some pharmaceutical powders and tablets over a range of temperatures from 20 to 200 °C. The tensile strengths increase with the packing fractions of the samples and with their temperature in relation to their melting points. The results are explained in terms of plastic deformation and/or melting of the asperitic points of contact between particles. Values are given for the activation energies of bonding. It is suggested that moderate heating might prove advantageous in the tableting of certain pharmaceutical powders.

Introduction

During the high-speed tableting of powders their overall temperature may rise more than 30 °C above ambient due to friction between moving particles and parts of the machines (Carstensen, 1980). Detailed examination of sectioned tablets reveals the presence of welded bonds. These could be formed either by plastic deformation or by actual melting followed by resolidification of the asperitic points of contact between particles where friction may momentarily generate localised temperatures as high as 100–200 °C.

A good deal of information is available on the effects of elevated temperatures on the mechanical properties of metal powders (Goetzel, 1950, 1952; Jones, 1960), ceramics (Lontz, 1964; Shapiro, 1983), plastics (Mascia, 1989), coal (Jayasinghe and Pilpel, 1970), etc. where the process of sintering is used to form them into pellets and compacts (Sordelet and Akinc, 1988). Some work has also been published on the effects of temperature on the mechanical properties of pharmaceutical powders (Jayasinghe et al., 1969/70; York and Pilpel 1972a,b, Britten and Pilpel, 1978; Esezobo and Pilpel, 1986). The subject is relevant in pharmacy when formulations contain low melting drugs and excipients whose melting points could be exceeded during a compression process.

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Superimposed on the ambient conditions, — normally between 10 and 35 °C — there are two separate effects of temperature that are involved during a high speed compression process: (a) the generation of frictional heat which may or may not lead to localised melting of components' surfaces; (b) a lowering of melting point which theoretically (Jeffreys, 1935; Skotnicky, 1953) occurs when high pressures are applied to particles in a powder.

Normally, pressure causes the melting point of a solid to increase by an amount predicted by the Clapeyron Clausius equation

$$\frac{d\theta_m}{dP} = \frac{\theta_m}{L}(V_L - V_S) \quad (1)$$

where θ_m is the melting point, P the applied pressure, $d\theta_m/dP$ the change in melting point with pressure, L the latent heat of melting (all in appropriate units, see Appendix 1) and V_S and V_L are the volumes in cm^3 of 1 g of the solid and 1 g of the corresponding liquid, respectively. For most solids (ice and type-metal alloys are exceptions) $V_L > V_S$ so $d\theta_m/dP$ is positive. However, it is now known that when pressure is applied to a powder it becomes concentrated at the asperitic points of contact between particles where, over areas of a few nm^2, it may rise to some thousands of atmospheres. Any liquefied material would be at a lower pressure in pore spaces so it is suggested that the term V_L in Eqn 1 can be neglected, leading to the prediction that at the asperitic points of contact the melting points should decrease with increasing pressure by about 0.1 °C per atm (see Appendix 1).

This decrease could contribute to the formation of welded bonds and should in principle be detectable by comparing the strengths of powder beds and tablets made under identical conditions but at different temperatures.

The present paper gives new experimental data under conditions in which variations in effects due to particle size, packing fraction, etc. were minimised, and considers a recently modified theory of tensile strength (Chan et al., 1983) to obtain more information on the combined role of temperature and pressure in determining the tensile strengths of compressed pharmaceutical powders. It is suggested that, as in powder metallurgy, there might be advantages in applying heat during the tableting of certain pharmaceutical powders, e.g. paracetamol, which normally requires the addition of ~ 30% w/w of an excipient such as microcrystalline cellulose (Bangudu, 1985).

Experimental

Materials

The materials selected for investigation included both organic and inorganic powders with melting/softening points ranging from 70 °C to several hundred °C. Some were single pure chem-

TABLE 1

Physicochemical properties of materials

Material	Melting/ softening (°C)	Particle density ($g\ cm^{-3}$)	Particle diameter (μm)	Specific surface ($m^2\ g^{-1}$)	Moisture content (% w/w)
Stearic acid [a]	70	0.94	10	1.4	0.1
Lactose [b]	208	1.55	11	2.3	0.3
Chloroquine diphosphate [c]	194	1.41	8.4	2.9	0.1
Paracetamol formulation [d]	c.150	1.32	135	–	0.5
Griseofulvin formulation [e]	c.200	1.43	9.3	2.0	0.2
Sodium chloride [f]	804	2.15	12	1.7	0.3
Calcium carbonate [g]	d.825	2.68	5.9	2.6	0.1

[a] 99% pure BDH. [b] B.P. anhydrous Whey Products. [c] B.P. ICI Ltd. [d] Paracetamol 85%, Avicel PH 101 15% w/v. Winthrop Ltd. [e] Griseofulvin 90%, sucrose 5%, polyethylene glycol 4000 5% w/w. ICI. [f] B.P. Evans Medical. [g] Code SL Sturge Chemicals.

icals, others granulated formulations containing mixed components. All except the paracetamol were reduced to $< 33\ \mu m$ diameter by milling and sifting, then classified on a Microplex zig-zag classifier (Alpine Multiplex) to obtain the fraction below 20 μm diameter, dried by heating to appropriate temperatures under reduced pressure and stored over silica gel desiccant. The aim was to obtain comparable samples whose particle sizes and moisture contents were as closely as possible the same. To this extent the new data may supersede some of the earlier (and by inference possibly less accurate) results. Mean projected particle diameters were obtained by optical microscopy, particle densities with a Beckman air comparison pycnometer Model 930, and specific surface areas by gas adsorption with a Flowsorb 2300 sorptometer (Micrometrics). Melting/softening points of the mixtures were measured on a hot-stage microscope, moisture contents by heating to constant weight under vacuum. The properties of the powders are listed in Table 1.

Methods

Packed beds

Samples were compressed to packing fractions ρ_F (= bulk density/particle density) up to 0.55 in a split plate tensile tester (Jayasinghe et al., 1969/70; Britten and Pilpel, 1977) whose cell (9.5 cm i.d., 1.1 cm deep) had been plated inside with a nickel/tin alloy to prevent corrosion. It was enclosed in an insulating jacket in a room maintained at a relative humidity of 40% (Westair Drymatic) and its temperature was adjusted between ambient and about 200 °C by circulating silicone oil (DC 200/50 Hopkins and Williams) through the jacket and by passing preheated dry nitrogen gas around and through the porous base of the cell. Tensile strengths at six or more packing fractions were measured at selected temperatures and straight lines were fitted through the experimental points by regression to enable the strengths of all samples to be compared at an arbitrary fixed ρ_F of 0.41 without the need to extrapolate the graphs of log T vs ρ_F (Figs 1 and 2).

Tablets

300 mg samples of the powders were formed into tablets in triplicate in a 5 ton hydraulic press (Research Instruments Co.) using 10.3 mm diameter upper and lower punches and a die lubricated with magnesium stearate which were enclosed in a thermostatted jacket (Malamataris and Pilpel, 1981). Preheated silicone oil was circulated through the jacket and the whole unit was enclosed in a polythene cover through which preheated dry nitrogen gas was passed. Having filled the die with powder and maintained the required temperature for 10 min, the upper punch was lowered at the rate of 0.22 mm s^{-1} by applying pressure between 50 and 200 MN m^{-2} for a period of 1 min to produce tablets with packing fractions between 0.75 and 0.94. After storing for 24 h over silica gel to recover elastically, the tablets were subjected to diametral compression tests at selected temperatures (Malamataris and Pilpel, 1981) and their tensile strengths, T, were calculated from the expression

$$T = \frac{2P}{D\pi t} \tag{2}$$

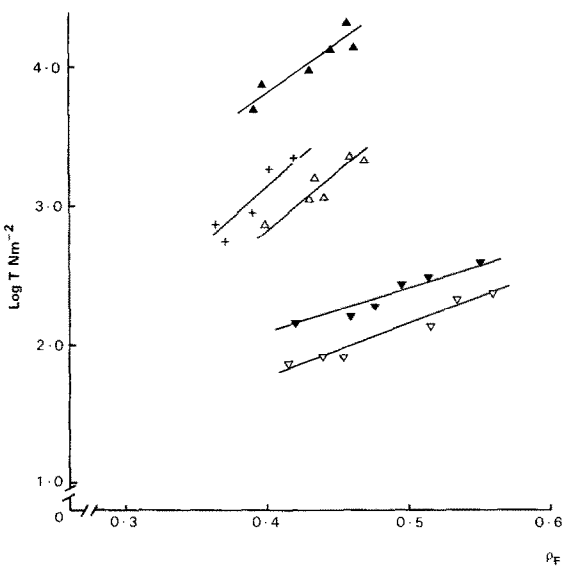

Fig. 1. Log tensile strength (N m^{-2}) vs packing fraction. Chloroquine diphosphate: (▽) 23 °C; (▼) 155 °C. Griseofulvin formulation: (△) 20 °C; (▲) 107 °C. Sodium chloride: (+) 20–166 °C.

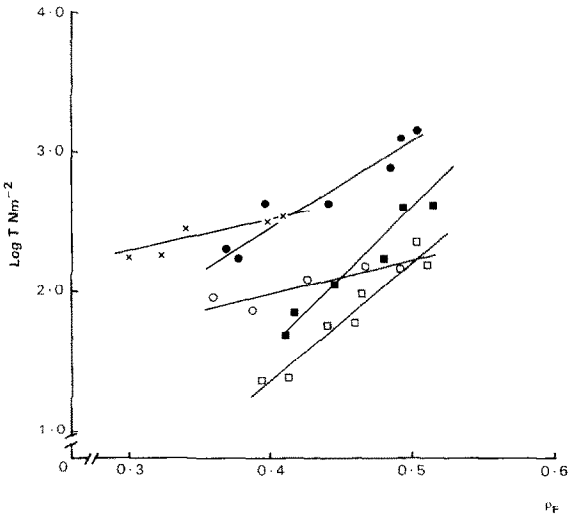

Fig. 2. Log tensile strength (N m^{-2}) vs packing fraction. Stearic acid: (□) 23° C; (■) 53° C. Lactose: (○) 23° C; (●) 160° C. Calcium carbonate: (×) 20–189° C.

where P is the breaking load, D the diameter and t the thickness of the tablet.

Results

By interpolation of the graphs of log T vs ρ_F at different temperatures, which are shown typically for the low packing fractions in Figs 1 and 2 and for the high packing fractions in Figs 3 and 4, the values of the tensile strengths of all the materials were obtained at the two arbitrarily selected ρ_F values of 0.41 (appropriate for compressed beds)

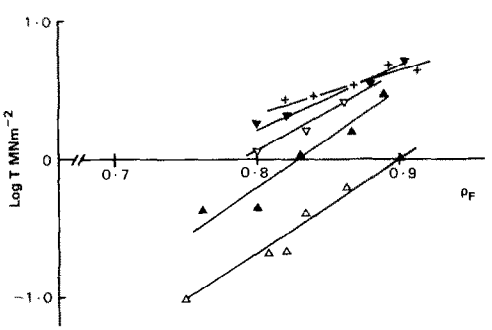

Fig. 3. Log tensile strength (MN m^{-2}) vs packing fraction. Chloroquine diphosphate: (▽) 23° C; (▼) 65° C. Griseofulvin formulation: (△) 21° C; (▲) 172° C. Sodium chloride: (+) 20–173° C.

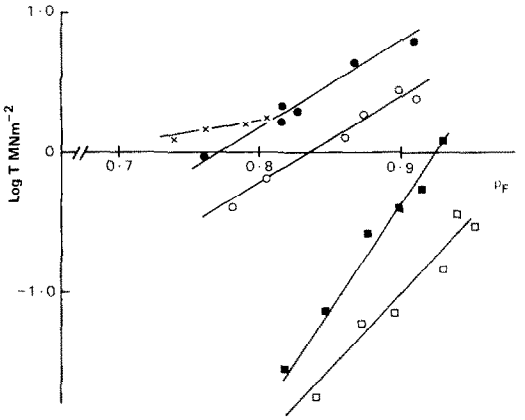

Fig. 4. Log tensile strength (MN m^{-2}) vs packing fraction. Stearic acid: (□) 23° C; (■) 51° C. Lactose: (○) 22° C; (●) 148° C. Calcium carbonate: (×) 23–191° C.

and 0.84 (appropriate for tablets). (The high values of T for the griseofulvin formulation could be due to the binding action of the polyethylene glycol.) Reproducibility of results between replicates was ±8%; error bars have been omitted to avoid confusion on the graphs.

In order to show how log T at the selected ρ_F varied with temperature while at the same time

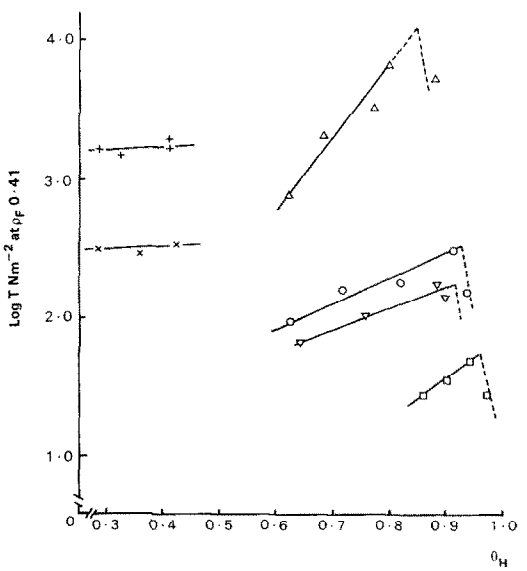

Fig. 5. Log tensile strength (N m^{-2}) at ρ_F 0.41 vs homologous temperature. (□) Stearic acid; (○) lactose; (▽) chloroquine diphosphate; (△) griseofulvin formulation; (+) sodium chloride; (×) calcium carbonate.

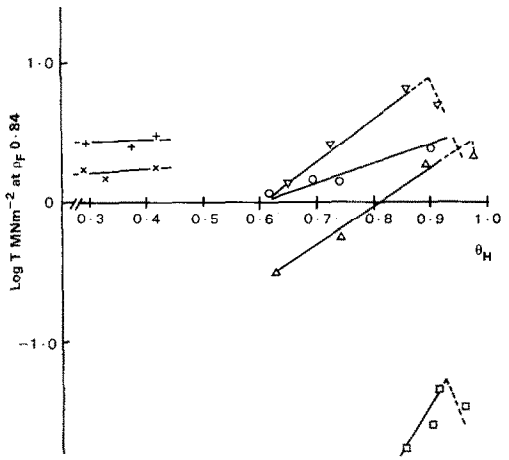

Fig. 6. Log tensile strength (MN m^{-2}) at ρ_F 0.84 vs homologous temperature. Symbols as in Fig. 5.

allowing for the different melting/softening points of the materials concerned, the values of log T were plotted vs the homologous temperature θ_H [= temperature of testing (K)/normal melting point (K)]. Plots of log T at the two packing fractions vs θ_H are shown in Figs 5 and 6. It is seen for all materials: (a) that at each temperature the tensile strength at ρ_F 0.84 was much greater than at ρ_F 0.41, which is in agreement with the well established relationship (Cheng, 1968)

$$T = A + A'\rho_F^B \tag{3}$$

where A, A' and B (> 1) are constants for each material; (b) that the tensile strengths increased with homologous temperature; (c) that the graphs in Figs 5 and 6, though restricted by the range of temperatures (20 °–200 °C) over which measurements could be made, tended to maxima at homologous temperatures ~ 0.9, i.e. significantly below the normal melting point of the material concerned, and then decreased.

These findings are qualitatively in agreement with earlier results that have been obtained on some of these materials. Quantitative differences can be ascribed to improvements in the experimental technique, to variation between the particle sizes and shape distributions of the earlier specimens and to the fact that their tensile strengths relate to different packing fractions from the present ones.

Discussion

The marked dependence of T on ρ_F can be explained on the basis of Cheng's theory (Cheng, 1968) in which each particle is pictured in contact with neighbouring particles only at the points where their surface asperities touch, and the coordination number depends on the density of the bed. With small ~ 10 μm diameter particles, as in the present case little breakage appears to occur when they are compressed to ρ_F values up to 0.5 (Nikolakakis and Pilpel, 1988). Breakage does occur at higher packing fractions but the theory allows for this. In its most recent formulation (Chan et al., 1983) it predicts that the tensile strength of a powder

$$T = \frac{\bar{d}\bar{s}}{4\bar{v}} \frac{\rho_F}{1-\rho_F} \frac{\alpha}{\tau^\beta} \tag{4}$$

For a mixed powder the expression is

$$T_{mix} = \frac{\bar{d}_{mix}\bar{s}_{mix}}{4\bar{v}_{mix}} \frac{\rho_{F_{mix}}}{1-\rho_{F_{mix}}} \frac{\alpha_{mix}}{\tau_{mix}^\beta} \tag{4a}$$

$\bar{d}$, $\bar{s}$, and $\bar{v}$ are, respectively, the mean particle diameter, surface area and volume, τ is the mean separation between particles, β is a universal constant whose value obtained experimentally (Chan et al., 1983; Bangudu, 1985) is between 0.8 and 1.2 and α is a quantity characteristic of each material. Its value, which ranges between about 0.5 and 10 kN m^{-2} $(\mu m)^\beta$ at 20 °C, depends on the number of particle pairs per unit area in the plane of tensile break divided by the number of particle pairs per unit volume; on the true area of contact per particle pair divided by the surface area per particle; on the mean coordination number of the bed; on the interparticle force per unit area whose magnitude is inversely proportional to the average interparticle separation; on the range of the interparticle forces and on the packing fraction of the bed at which its tensile strength becomes zero. The

relationship between α and these quantities at 20 °C has been published (Chan et al., 1983; Bangudu, 1985).

The present finding that T increased markedly with ρ_F is consistent with Eqns 4 and 4a since $\rho_F/(1-\rho_F)$ and α both increase and τ decreases as the packing fraction of the bed is increased. During the processes of consolidation and tableting the pressure being applied to a powder becomes localised at the true points of contact between the particles where it could exceed 1000 atm. The combined action of this pressure and the temperature arising from friction and the applied external heating would be expected to cause the asperities to deform plastically leading to an increase in the true area of contact between particles and hence to the observed increases in the tensile strengths of the bed or tablet. But when the temperature approaches $0.9\theta_H$ some of the localised regions of contact may weaken and this could explain why the tensile strengths in Figs 5 and 6 begin to decrease at temperatures below the materials' normal melting points ($\theta_H = 1$).

An alternative explanation is that there may be actual melting of asperities in accordance with the prediction (Jeffreys, 1935; Skotnicky, 1953), the amount depending both on the localised pressure and on the temperature due to the frictional and ambient heating.

It is difficult unequivocally to distinguish between plastic deformation and asperitic melting. Even on specially prepared clean metallic surfaces the findings are open to alternative explanations (Gane et al., 1974); but new techniques are being developed (Frenken, 1990) which may help to resolve the matter. Electron micrographs of sectioned tablets made from some of the present powders proved to be inconclusive. They are not included but see for comparison Fig. 5 (Sordelet and Akinc, 1988) and Fig. 1 (Nystrom and Karehill 1986).

However, there is some experimental evidence

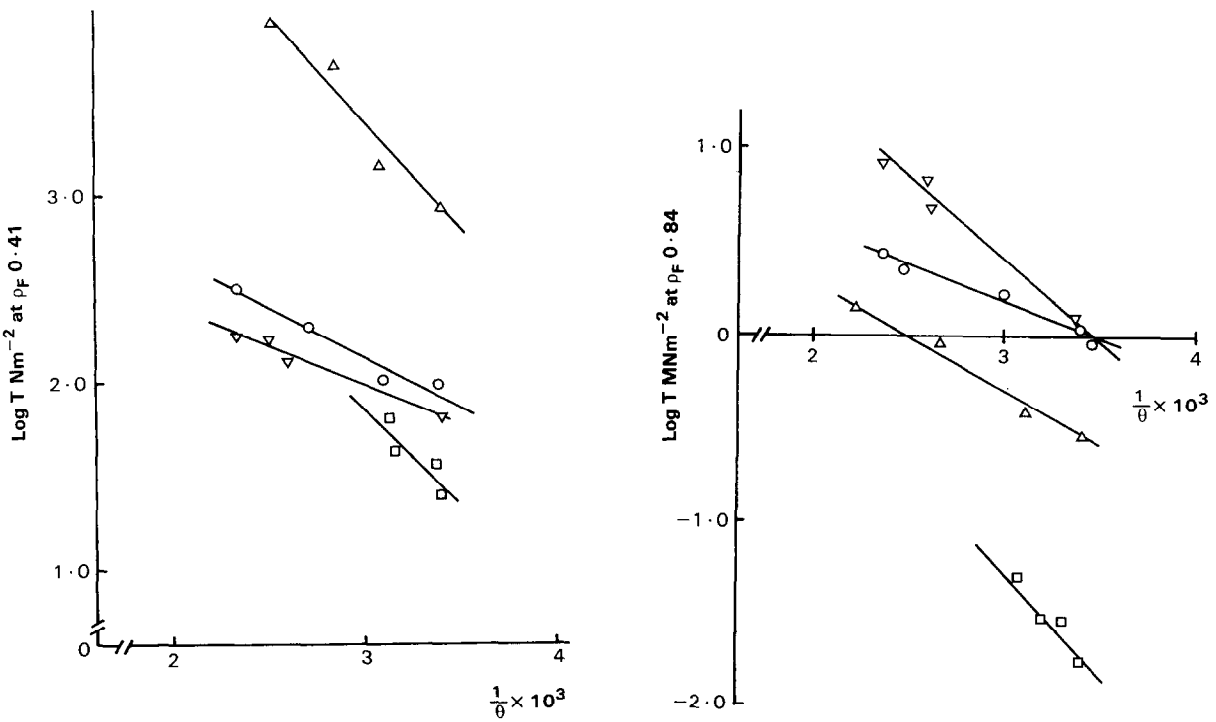

Fig. 7. (a) Log tensile strength (Nm^{-2}) at ρ_F 0.41 vs reciprocal temperature (K). Symbols as in Fig. 5. (b) Log tensile strength (MN m^{-2}) at ρ_F 0.84 vs reciprocal temperature K. Symbols as in Fig. 5.

to support the hypothesis of asperitic melting. For example, measurements of electrical conductivity (York and Pilpel, 1972b) suggest the presence of a liquid phase at temperatures below the normal melting point. Also, when the particles of the powders are coated with between one and five molecular layers of various liquids and semi-solids, the tensile strengths of their tablets are found to decrease in a similar manner to that exhibited at $\theta_H \sim 0.9$ in Figs 5 and 6 (Pilpel et al., 1991).

It has already been observed that the compression of powders is accompanied by an overall rise in temperature of between 5 and 30 °C measured by the use of thermistors and thermochromic indicators (Carstensen, 1980). To devise experiments to measure temperatures on individual apserities would be much more difficult. In principle, it is conceivable that one might be able to calculate both the overall and the localised temperatures from the total work expended during compression using force-displacement graphs (Marshall, 1977; Carstensen, 1980) with allowance for heat losses and die wall friction and from detailed knowledge of experimental variables such as the interparticle geometry (Chan et al., 1983), diameter, packing fraction, weight and specific heat of the sample, speed of compression, etc. (Lammens et al., 1980) but this would be even more difficult.

Nevertheless, it was found that the overall effect of the temperature produced by friction and by the ambient conditions on the tensile strengths of the present materials resulted in approximately rectilinear graphs up to $\theta_H \sim 0.9$ – bearing in mind the nature of the materials and the type of data being discussed – when log T was plotted against the reciprocal of the absolute temperature (in K). The graphs are shown in Fig. 7a and b.

Conclusion

The conclusion is that irrespective of whether the mechanism is plastic deformation or melting followed by resolidification of asperities (and the question remains unresolved (Carstensen, 1980)) the tensile strengths of pharmaceutical tablets appear to vary in the same way with the ambient temperature as those of sintered metals, etc. and obey a form of the Arrhenius equation

$$T = ke^{-E_0/R\theta} \tag{5}$$

where $R = 8.3$ J mol^{-1}, E_0 is the activation energy of bonding, k is a constant for each material at each packing fraction and θ is the temperature in K). Values of E_0 obtained from the slopes ($= -E_0/2.303R$) of the graphs in Fig. 7a and b are listed in Table 2. They are of the order of magnitude expected for bonds formed by physical processes at surfaces rather than by chemical reaction. (The differences between the two columns in the case of the drugs indicates a change in energy of bonding as the packing fraction is altered.)

TABLE 2

Activation energies

Material	E_0 (kJ mol^{-1})	
	ρ_F 0.41	ρ_F 0.84
Stearic acid	22.8	19.1
Lactose (anhydrous)	8.2	7.6
Chloroquine phosphate	7.8	16.4
Griseofulvin formulation	25.1	11.4

The implication of the present results is that the increases that occur in the tensile strengths of pharmaceutical powders when they are heated during compression might be usefully applied to the process of tableting.

To test the idea some additional experiments were performed using batches of paracetamol (B.P. Cambrian Chemicals) 85% w/w and Microcrystalline cellulose (Avicel PH 101) 15% w/w granules prepared by wet granulation in the size range 120–150 μm. After drying they were formed into 300 ± 10 mg, 1.03 cm diameter, flat-faced tablets in a single-punch Manesty machine operated at 70 strokes min^{-1}. It was observed that when the granules were preheated to 70 °C before feeding into the machine there was approx. 50% reduction in the incidence of lamination and breakage.

This finding suggests that moderate heating might prove beneficial also in other cases. If so it should not be difficult to adapt a conventional

single-punch machine to operate at temperatures up to about 100 °C.

Appendix 1

Consider the effect of an additional pressure of 1 atm on the melting point of stearic acid powder. Normal m.p. 70 °C = 343 K, latent heat $L = 55.5$ kJ mol^{-1}, M.W. 284, $V_S = 1/0.941$ cm^3 g^{-1} = $1.062 \times 10^{-6} \times 284 = 3.02 \times 10^{-4}$ m^3 mol^{-1}. Assuming

$$\frac{d\theta_m}{dP} = -\frac{\theta_m V_S}{L}$$

$$\frac{d\theta_m}{\theta_m} = -\frac{V_S\, dP}{L} = -\frac{3.02 \times 10^{-4}}{55.5 \times 10^3}\, dP$$

$$= -5.44 \times 10^{-9}\, dP$$

Integrating

$$\ln\theta_m = -5.44 \times 10^{-9} P + C$$

To evalute C, at $P = 1$ atm $= 10^5$ Pa, $\theta_m = 343$ K, therefore

$$\ln 343 = -5.44 \times 10^{-9} \times 10^5 + C$$

and therefore

$$C = 5.838$$

The general equation is

$$\ln \theta_m = -5.44 \times 10^{-9} P + 5.838$$

When the additional pressure is 1 atm $P = 10^5$ Pa, therefore

$$\ln \theta_m = -5.44 \times 10^{-4} + 5.838 = 5.8375$$

and therefore

$$\theta_m = 342.9\ K = 69.9\,°C$$

Therefore, the melting point of the powder should decrease by 0.1 °C per atm where asperities are in contact.

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