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The effect of temperature on the tensile strength and disintegration of paracetamol and oxytetracycline tablets

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The tensile strengths and disintegration times of paracetamol and oxytetracycline tablets at room temperature are higher when they have been prepared at high temperatures, e.g. 85°, than at room temperature or below, e.g. −20°. The activation energies of the two materials, 3 and 1 k cal mol^{-1} (13 and 4 $kJmol^{-1}$) respectively, were derived from plots of log tensile strength and log disintegration time versus the reciprocal of the absolute temperature. The results have been explained in terms of sintering theory and the formation of welded bonds between particles.

The effects of temperature on the mechanical properties of some pharmaceutical powders were reported by Jayasinghe, Pilpel & Harwood (1969) and York & Pilpel (1972a,b). They showed that the tensile strength and cohesion at a fixed packing fraction and the angle of internal friction of the powders increased as the temperature at which they were measured was raised.

Quite large temperature changes occur during the tableting of pharmaceutical powders and/or granules due to the generation of frictional heat at the points of contact between particles (Nelson, Busse & Higuchi, 1955; Hanus & King, 1968; Travers & Merriman, 1970). Moreover, it has been suggested (Rankell & Higuchi, 1968) that because of the very high pressures at these points of contact, the melting points of the material may be lowered by amounts which can be calculated from thermodynamic considerations (Skotnicky, 1953). Both mechanisms could contribute to the formation of welded bonds between particles and thus influence the properties of compressed powders or tablets such as their hardness, tensile strength and rates of disintegration and dissolution. It is to be expected that the number of welded bonds formed, and hence the tensile strength, will depend on the temperature at which compression occurs.

In the present work, some formulated powders have been examined at different temperatures and they have been compressed into tablets at a range of temperatures from −20° to +120°. (This appears to be the first report of pharmaceutical materials being tableted at temperatures below zero). The tablets were then stored at room temperature and measurements were made of their tensile strengths and disintegration times to see how these properties depended on temperatures during preparation.

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MATERIALS AND METHODS

Materials

The materials were formulated powders for oxytetracycline and paracetamol tablets. The oxytetracycline formulation consisted of an intimate mixture of % w/w oxytetracycline dihydrate (ICI Pharmaceutical Division) 90·2, avicel PH101 (Honeywell & Stein Ltd.) 7·2, alginic acid HED (Aliginate Industries Ltd.) 2·6 and gelatin Bloom No. 300 acid-treated hide (Richard Hodgson Ltd.). The paracetamol formulation consisted of % w/w paracetamol powder (Cambrian Chemicals Ltd.) 90, maize starch B.P. (Evans Medical Ltd.) 10, and polyvinylpyrrolidone, PVP K30 (Fine Dyestuff & Chemical). Relevant physicochemical properties of the drugs are given in Table 1.

Granulation

250 g of each drug with its excipients was dry mixed for 15 min in a laboratory ball mill and sieved through a No. 20 mesh sieve.

125 ml of freshly prepared 5% w/w aqueous gelatin or PVP binder solutions were added to the formulations in a small planetary mixer and massing continued for 90 s. The wet masses were granulated through a No. 12 mesh sieve and the granules dried for 12 h at 50° for oxytetracycline and for 12 h at 60° for paracetamol, screened through a No. 16

Table 1. *Physicochemical properties of the drugs.*

Property	Oxytet.	Paracetamol
Molecular weight	496·5	151·2
Melting point (°C)	181–182 d	169–172
Particle dens. (kg m^{-3}) $\times 10^3$	1·46	1·29
Av. particle size (μm)	6·0	4·8
Moisture cont.of formulations (% w/w)	2·1	1·0
Gran. size (μm) Cumul. wt % oversize 80	360	380
60	540	680
50	640	900
40	750	1250

sieve and stored in glass jars. The moisture contents of the granules were determined from their loss in weight on drying to constant weight and their size distributions were determined by sieve analysis (BS4101 method) (see Table 1).

Preparation of tablets at different temperatures

1% w/w magnesium stearate (BDH) or 1% w/w stearic acid (BDH) were mixed with the formulated oxytetracycline and paracetamol granules respectively in a ball mill for 5 min to act as lubricants.

Oxytetracycline granules in 600 mg batches and paracetamol granules in 550 mg batches were placed in sealed glass containers (within plastic bags containing silica gel) and were heated or cooled under dry conditions either in an oven or in solid carbon dioxide, until they had reached the required temperature.

The granules were quickly emptied into a 1·25 cm diameter die with a shallow concave punch that had been kept at the same temperature within a plastic bag. The temperature was measured and the granules were then compressed for 1 min into tablets of the required packing fraction using a laboratory hand-press. They were ejected and stored in sealed pill-vials at ambient temperature for 24 h to allow for hardening and elastic recovery.

Tensile strengths of formulated powders at ambient and elevated temperatures

These were measured in a tensile tester which was essentially of the same design as that of Ashton, Farley & Valentin (1964), but modified for use at elevated temperatures (Jayasinghe & others, 1969; York & Pilpel 1972a,b) by having the split cell, 9·5 cm in diameter and 1·0 cm in depth enclosed in a heating chamber. (Further modifications enable the apparatus also to be used at temperatures below ambient, Britten & Pilpel, 1977).

Tensile strengths of tablets. The tensile strengths of the tablets were measured at room temperature (23°) in triplicate by diametral compression employing the same equipment and equations for the calculation as previously (York & Pilpel, 1973; Esezobo & Pilpel, 1976; Kurup & Pilpel, 1977).

Disintegration of tablets. Disintegration times were measured individually on five tablets from each batch in distilled water at 37 ± 0·5° using the B.P. method and a Manesty disintegration tester and an average was calculated.

RESULTS

Although not shown here the graphs of the logarithm of tensile strength *vs* packing fraction for the paracetamol and oxytetracycline powder formulations at two different temperatures were rectilinear. The tensile strength of the former increases with temperature at all packing fractions but that of the latter increases only slightly at packing fractions above about 0·48. Corresponding tensile strength results for the tablets are shown in Fig. 1a,b and are summarized in Table 2.

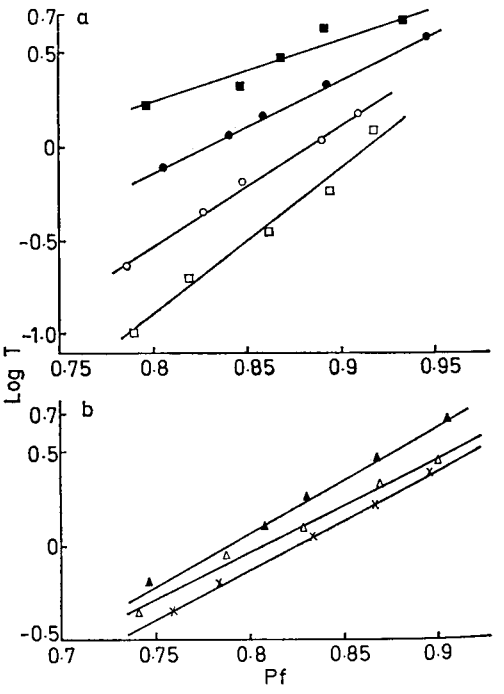

FIG. 1. Effect of temperature on log tensile strength (log T) *vs* packing fraction (Pf) for a—paracetamol tablets. Temp. □ −19·5, ○ 23, ● 85, ■ 120. b—oxytetracycline tablets. Temp. × −19·5, △ 23, ▲ 85.

Table 2. *Log tensile strengths (MN m^{-2}; A) and log disintegration times (min; B) of tablets made at different temperatures, packing fraction* = 0·85.

Tablets	Temperature °C	°K	1/K × 10^3	A	B
Paracetamol	−19·5	253·5	3·95	−0·50	−0·10
	23	296	3·38	−0·22	−0·10
	85	358	2·79	0·10	0·45
	120	393	2·55	0·40	—
Oxytetracycline	−19·5	253·5	3·95	0·13	0·91
	23	296	3·38	0·21	1·03
	85	358	2·79	0·34	1·18

The results of the disintegration tests on these tablets prepared at different temperatures are plotted in Fig. 2. It is seen that for both drugs, the disintegration time increases with the temperature employed during preparation, the effect being most noticeable at packing fractions above 0·8.

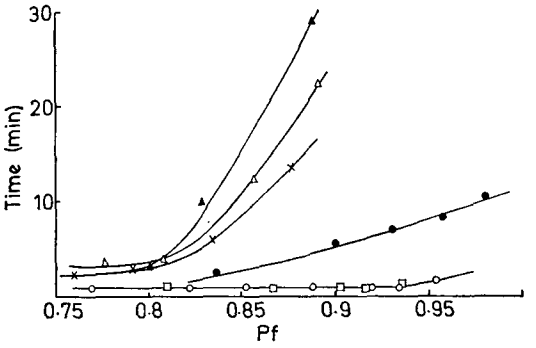

FIG. 2. Effect of temperature on disintegration times (min) *vs* packing fraction (Pf) for paracetamol and oxytetracycline tablets. Paracetamol tablets, temperature □ −19·5, ○ 23, ● 85. Oxytetracycline tablets, temperature × −19·5, △ 23, ▲ 85.

Fig. 3 shows plots of log tensile strength and log disintegration time *vs* the reciprocal of the absolute temperature during preparation of the tablets.

DISCUSSION

The results in Fig. 1a,b are similar to those reported for other single and multicomponent pharmaceutical powders (Jayasinghe & others, 1969; York & Pilpel, 1972a,b). The higher disintegration times of the tablets prepared at high temperatures—Fig. 2—are consistent with the supposition that at any particular packing fraction, their particles are more strongly bonded together resulting in higher tensile strengths. During compression of the granules, the applied pressure is probably acting only over a very small area of true contact, possibly as little as 1/1000 of the

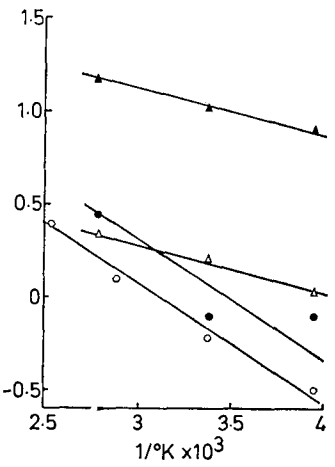

FIG. 3. Log tensile strength and log disintegration time *vs* reciprocal of absolute temperature (K) for paracetamol and oxytetracycline tablets at Pf = 0·85. Tensile strength △ oxytetracycline tablets, ○ paracetamol tablets. Disintegration times ▲ oxytetracycline tablets, E_o = 1·1 kcal mol^{-1} (4 kJ mol^{-1}), ● paracetamol tablets, E_o = 3·0 kcal mol^{-1} (13 kJ mol^{-1}). Ordinate—Log tensile strength (MNm^{-2}) and log disintegration time (min).

apparent area of contact between the particles; thus very high pressures develop at these localized points of contact.

In addition to the frictional heat generated during compression (Hanus & King, 1968; Rankell & Higuchi, 1968; Travers & Merriman, 1970), Skotnicky's (1953) equation predicts that the melting point of the material will be lowered by the applied pressure irrespective of any change in volume that may occur on melting. The equation is

$$\frac{d\theta}{dP} = -\frac{V\theta}{\Delta H} \quad .. \quad .. \quad .. \quad (1)$$

where $d\theta/dP$ = the change in melting point with pressure; ΔH = the latent heat of fusion (cal^{-1} g); V = the volume g^{-1} solid (cm^3 g^{-1}); and θ = the melting point of solid (°K), and it has been confirmed by a number of workers (Jayasinghe & others, 1969; York & Pilpel, 1972a,b) including Skotnicky.

On releasing the pressure, the material (including the gelatin or polyvinylpyrrolidone binding agents) which has melted under the combined action of frictional heat and the lowering of melting point, will resolidify to form welded bonds between the particles and this would account for the observed strength and hardness of the tablets. (Pietsch, 1967;

Rankell & Higuchi, 1968). Clearly, the amount of melting produced and the number of solid bonds formed subsequently will increase as the temperature at which the tablets are prepared is increased. This is confirmed in Figs 1(a,b) and 2.

Another way of interpreting the present results could be in terms of the mechanisms of atomic transport and/or diffusion of material across particle boundaries as occurs during the process of sintering.

It has been shown (Bowden & Tabor, 1953, 1964; Kuczynski, 1950; Polke, 1969) that many physical and mechanical properties of materials vary with temperature according to the Arrhenius equation

$$\text{Property} = ke^{-Eo/R\emptyset} \quad .. \quad .. \quad (2)$$

where k and R are constants, E_0 is the activation energy and ø is the absolute temperature.

It was thought of interest to see whether this equation also applied to the tensile strength and disintegration results of the tablets prepared at the different temperatures.

Fig. 3 shows plots of the tensile strength and disintegration time *vs* the reciprocal of the absolute temperature for the two types of tablets over the temperature range −19·5 to 120° at a particular packing fraction of 0·85. It is seen that reasonably straight lines were obtained. Taking the value of R as 2 cal mol^{-1} (8·3 J mol^{-1}), the activation energy of the oxytetracycline works out at about 1 kcal mol^{-1} (4 kJ mol^{-1}) and that of the paracetamol at approximately 3 kcal mol^{-1} (13 kJ mol^{-1}). These values are somewhat lower, though of a comparable order of magnitude to those for hydrogen bonds (i.e. about 3–8 kcal mol^{-1}; 13–33 kJ mol^{-1}).

At higher packing fractions a similar pattern of behaviour was obtained as would be expected from the results shown in Fig. 2, but at lower packing fractions the effects of temperature on both the tensile strengths and disintegration times of the tablets were hardly noticeable. This is presumably because the pressures then being applied during tableting were too low to produce appreciable melting of the asperities so that fewer welded bonds were being formed between the particles.

The very low tensile strengths and disintegration times obtained for the tablets made at the low temperature of −19·5°, which is reflected in their fragile and dusty appearance, indicates that the main forces holding the particles together are probably van der Waals' and mechanical forces due to interlocking of irregularities on the surfaces of particles. Little if any asperity melting or sintering has occurred at this temperature. This is in agreement with the findings of York & Pilpel (1972a,b) who showed that these mechanisms only begin to operate when the ratio of the temperature during measurement to the melting point of the material concerned is greater than 0·6.

It may be concluded that except for the possibility of retarding the decomposition of thermally unstable drugs and perhaps increasing the flowability of cohesive granulations, (Britten & Pilpel, 1977) little benefit is likely to result from carrying out tableting operations at temperatures below ambient.

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