

Effect of temperature changes on the densification and compression of griseofulvin and sucrose powders

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A study has been made of the effect of varying the temperature between +60° and -25 °C on the densification and low pressure compression of griseofulvin, sucrose and mixtures of the two powders. Densification and compression of the materials were facilitated as they were cooled in the range of homologous temperatures (ratio of the experimental temperature in °K to melting point of the material in °K) from 0.7 to 0.5. This was attributed to a reduction in the cohesive forces operating between the particles. Values are given for the activation energies of densification and compression derived by plotting the logarithms of these properties versus the reciprocal of the absolute temperature. For both materials and their mixtures the activation energies were in the range of about 1 to 10 kJ mol⁻¹ showing that physical rather than chemical forces were operating between the particles.

Densification or packing of powders can be measured simply by the increase in their density which occurs when a compression or compaction force, or alternatively energy in the form of tapping or vibration (MacLeod 1980) is applied to them. Schwarzkopf (1947) defined compressibility as the extent to which the density of the powder was increased by a given pressure. He defined the compactibility as the minimum pressure needed to produce a given "strength" in a compact formed in the cold, without sintering.

Considerable work has been done on the densification of powders at room temperature (Heckel 1961; Carr 1965; Neumann 1967; Carless & Leigh 1974; Peleg & Mannheim 1973; Chowhan & Chow 1980; MacLeod 1980) but comparatively little has been recorded at temperatures below ambient (Malamataris & Pilpel 1980).

Heckel (1961) and others (Cooper & Eaton 1962) identified several stages during the compaction of powders in dies: first rearrangement and slipping of particles past each other to produce close packing; next, the filling of small voids by plastic deformation or fragmentation of particles; and finally, at high pressures, the formation of welded bonds between the points of contact on neighbouring surfaces. Stages 1 and 2 occur during densification and compression at relatively low pressures. Stage 3 occurs during compaction at high applied pressures and the effects are increased by raising the temperature as in the process of sintering (Goetzl 1950; Evans & Train 1963).

It has been shown that changes in temperature over certain ranges cause considerable changes in the cohesion (Jayasinghe et al 1969/70; York & Pilpel 1972) hardness (Pilpel & Britten 1979) and flowability (Pilpel & Britten 1979; Onyekweli & Pilpel 1980) of many powders. These include pharmaceutical formulations containing low melting excipients such as waxes, fatty acids, sugars, esters etc. Very little has yet been reported on the corresponding changes that might be expected to occur in the densification and compression of these powders.

The present paper provides data on the effects of temperature on the packing densities of sucrose, griseofulvin and mixtures of the two when subjected (a) to tapping and (b) to compression at pressures up to about 10 000 Nm⁻² for griseofulvin and about 3000 to 4000 Nm⁻² for sucrose and the mixtures of sucrose and griseofulvin.

MATERIALS AND METHODS

Materials

Griseofulvin was in the form of fine white acicular crystals from ICI Pharmaceuticals Division. Sucrose was white sugar from the British Sugar Corporation. They were separately milled in a Moulineux mill and the sub 50 µm sieve fraction was collected using an Alpine Airjet Sieve. These sub 50 µm fractions were classified on a Microplex Zig-Zag Classifier to give fractions of each powder in the range between 5 and 15 µm. Mixtures containing 97% w/w griseofulvin, 3% w/w sucrose, M₁; 87% w/w griseofulvin, 13% w/w sucrose, M₂; and 60% w/w griseofulvin, 40% w/w sucrose, M₃ were prepared in a Kenwood mixer by adding the required quantity of sucrose in aqueous

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solution to the griseofulvin, drying the masses, then milling and classifying as above. Mixtures containing more than 40% w/w sucrose could not be prepared by this method because of the formation of slurries which exhibited physical and chemical changes during subsequent drying. All samples were dried at 60 °C before use. Their particle size distributions were checked by optical microscopy; and the particle densities were measured by the specific gravity bottle method, employing light petroleum (b.p. 100–120 °C) as the immersion liquid. Relevant physico-chemical properties are listed in Table 1.

Measurements

These were carried out in a room fitted with a Drymatic dehumidifier which controlled the relative humidity at about 50%.

Densification by tapping

Tap densities were measured in a standard tap density apparatus (Scientific Developments, Romford) (Neumann 1967) modified to operate over a range of temperatures by having the glass cylinders enclosed in a thermostat jacket.

A known weight of freshly sieved sample (BS 1460:1948) was introduced into the cylinder while holding it at approximately 70° to the horizontal and flushing it with dry nitrogen gas. The cylinder was sealed with clear plastic film, the sample levelled by gentle rotation, then transferred either to a hot air oven or to a bin of solid carbon dioxide. After about 10 min, the cylinder was placed on the tapping apparatus and its temperature adjusted (± 5 °C) to the required value by passing pre-heated or pre-cooled dry nitrogen gas through the insulating

jacket. The bulk volume was recorded after every 5 taps until it became constant (after about 100 taps) and the packing density was calculated as the mean of 4 replicates which differed by not more than ± 2 standard deviations (BS 1460:1948).

Compression tests

The apparatus consisted of a split-cell tensile tester of the Warren spring type (Ashton et al 1964) modified (Britten & Pilpel 1977) to permit compression measurements to be carried out at both low and elevated temperatures. The cell was 9.5 cm internal diameter, 1.1 cm deep and had a removable stainless steel mesh, pore size 10 μm at the bottom through which pre-cooled or pre-heated dry nitrogen gas could be introduced. The cell was surrounded by copper tubing which carried pre-cooled or pre-heated ethylene glycol and it was enclosed in an insulating jacket.

Known weights of sample were spread evenly into the cell and maintained at the required temperature for 10 min by means of the circulating nitrogen and ethylene glycol. Then the bed was compressed by placing a known weight on the load platform and operating the plunger. The resulting packing density ($\rho_F = \text{bulk density/particle density}$) was calculated as the mean of four replicates from the known weight and the measured thickness of the bed.

RESULTS

Fig. 1 shows the packing density vs the applied pressure for the different samples at temperatures between -10° and 60 °C (omitting some of the results for the mixtures to avoid confusion). [When the packing densities were plotted against $\log P$,

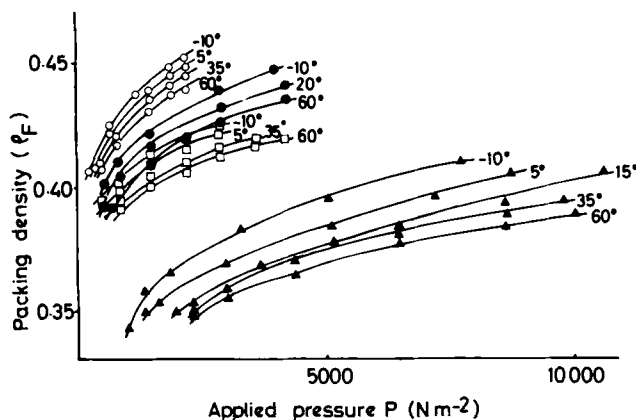


FIG. 1. Packing density (ρ_F) at different temperatures vs applied pressure ($P \text{ N m}^{-2}$). \blacktriangle = Griseofulvin. \circ = Sucrose. \square = Mixture M_1 . \bullet = Mixture M_2 .

straight lines were obtained with correlation coefficients > 0.95 over the ranges of packing densities employed]. It is seen from Fig. 1 that the pressure required to achieve any particular packing density decreased as the sample was cooled from 60° to -10°C .

Fig. 2 shows how the packing density achieved by tapping was affected by varying the temperature between -25° and 50°C (here, to avoid confusion,

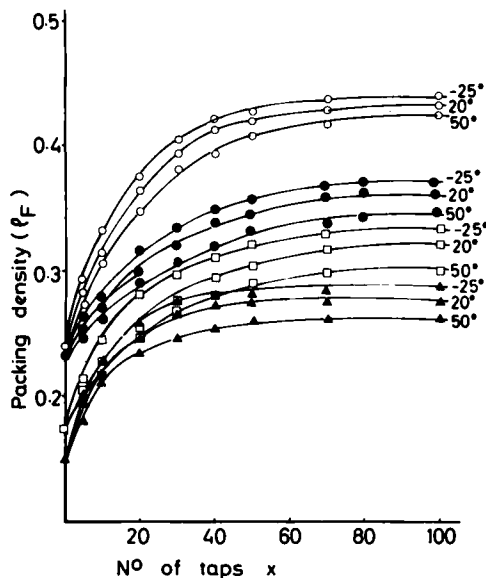


FIG. 2. Packing density (ρ_F) at different temperatures vs number of taps (x) ▲ = Griseofulvin. ○ = Sucrose. □ = Mixture M_1 . ● = Mixture M_2 .

the results for mixture M_3 were omitted). The curves became asymptotic after about 100 taps and it is seen that in every case the highest packing density was achieved at the lowest temperature.

Analysis of these results showed that they could be fitted to the general equation:

$$\rho_F = \rho_{F100} - (\rho_{F100} - \rho_{F0})e^{-Qx} \quad (1)$$

where ρ_F = Packing density achieved; ρ_{F100} = asymptotic value of packing density after 100 taps; ρ_{F0} = initial packing density (when $x \rightarrow 0$); x = number of taps; e = base of natural logarithms (i.e. 2.718); Q = material constant, with an accuracy better than $\pm 5\%$. The values of Q decreased with temperature and they are shown in Fig. 3 plotted against the homologous temperature (defined as the ratio of the experimental temperature in K to the melting point of the material in K).*

DISCUSSION

The increasing ease with which the powders could be packed and compressed as they were cooled (Figs 1 and 2) can be ascribed to them becoming intrinsically less cohesive (Onyekweli & Pilpel 1980), the order of the effect being griseofulvin $> M_3 \approx M_1 > M_2 >$ sucrose. The difference between the results is due to the particles of griseofulvin having a more irregular shape and being intrinsically more cohesive than sucrose. The cohesion values for the mixtures were intermediate between those of the two constituents.

Because of its higher cohesiveness it required a much higher pressure to compress griseofulvin than sucrose to a particular packing density. This is illustrated in Fig. 4 from which it is seen that to achieve a packing density of 0.41 at an homologous temperature of 0.55, a pressure of about 7500 Nm^{-2} was required for griseofulvin in contrast to 200 Nm^{-2} for sucrose.

As regards the effect of temperature on the compression and densification of the powders, it is seen in Fig. 4 that the pressure required to achieve the packing density of 0.41 in all the samples decreased as the homologous temperature was reduced from 0.7 to about 0.5. This was presumably because at the lower temperatures there was less tendency for the surfaces of particles to deform

* The melting points of the mixtures were taken as midway in the range over which they softened when heated in a capillary tube—see Table 1.

Table 1. Physicochemical properties of materials.

Material	Melting/Softening Point °C	Melting/Softening Point K	Particle Density $\times 10^{-3} \text{ kg m}^{-3}$	Moisture Content* %/w/w	Particle Diameter Range μm
Griseofulvin	209	482	1.430	<1	5-15
Sucrose	180	453	1.640	<1	5-15
Mixture M_1	190-200	463-473	1.436	<1	5-15
Mixture M_2	190-200	463-473	1.454	<1	5-15
Mixture M_3	188-198	461-471	1.507	<1	5-15

* Measured with a vacuum moisture meter (Townson and Mercer).

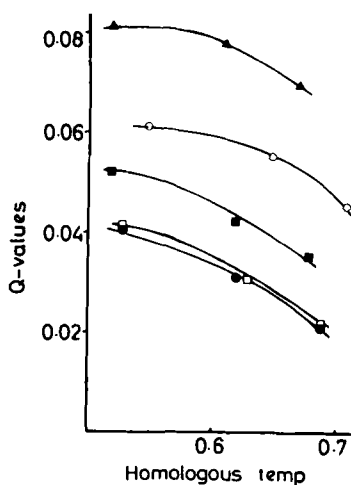


FIG. 3. Values of Q versus homologous temperature. ▲ = Griseofulvin. ○ = Sucrose. ■ = Mixture M_1 . ● = Mixture M_2 . □ = Mixture M_3 .

plastically under pressure or to melt (Jayasinghe et al 1969/70) to form welded bonds. The particles could move fairly easily past each other to form a close packed bed.

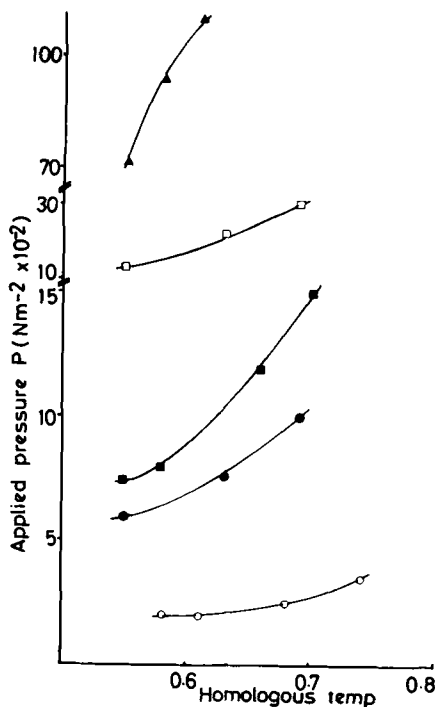


FIG. 4. Applied pressure ($P \text{ N m}^{-2}$) needed to achieve $\rho_F 0.41$ versus homologous temperature. ▲ = Griseofulvin. ○ = Sucrose. ■ = Mixture M_1 . ● = Mixture M_2 . □ = Mixture M_3 .

Several authors (Bowden & Tabor 1950, 1964; Kuczynski 1950; Polke 1969; Esezobo & Pilpel 1977; Britten & Pilpel 1978) have observed that certain physical and mechanical properties of materials vary with temperature according to the Arrhenius equation:

$$\text{Property} = K e^{-E_0/R\theta} \quad (2)$$

where K = material constant; E_0 = activation energy; θ = absolute temperature (K); e = base of natural logarithm (= 2.718); R = 8.3 KJ mol⁻¹.

It was thought of interest to see whether this equation could also be applied to the present results.

Table 2. Activation energies.

Material	Activation energy E_0 KJ mol ⁻¹	
	of compression	of densification
Griseofulvin	9.8	1.0
Sucrose	5.5	0.6
Mixture M_1	7.5	1.0
Mixture M_2	8.4	1.0
Mixture M_3	7.7	1.0

Dealing first with those in Fig. 1, the values of log pressure P required to compress each material to the selected packing density of 0.41 at each temperature were plotted against the reciprocals of the temperature, $1/\theta$. Dealing next with the resistance to packing, this was arbitrarily defined as the reciprocal of the packing density achieved after 30 taps (since clearly the resistance to packing is inversely proportional to the density achieved). The values of $\log 1/\rho_{F30}$ taken from Fig. 2 were also plotted against $1/\theta$. In both cases straight line graphs were obtained with correlation coefficients greater than 0.93 and this confirmed the validity of equation (2).

The values of the activation energies of compression and of densification were obtained from the slopes of these lines and are listed in Table 2 (the estimated error being about $\pm 7\%$). As expected the former were greater than the latter and the values for griseofulvin were higher than those for sucrose, presumably because of the difference in their cohesiveness. For both materials and their mixtures activation energies were in the range of about 1 to 10 KJ mol⁻¹ showing that physical rather than chemical forces were operating between the particles.

The conclusions of this work are that the densification produced by tapping of some typical pharmaceutical powders and their compression by the

application of relatively low pressures are both facilitated by cooling them in the range of homologous temperatures from 0.7 to 0.5.

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