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The Effect of Temperature on Diametral Compression Strength of δ-Phenylbutazone and Barbital (Form II) Tablets

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The effects of storage temperature on the diametral compression strength of δ-phenylbutazone and barbital (form II) tablets and on the drug dissolution rate were examined.

For δ-phenylbutazone, it was found that the diametral compression strength, σ, increased but the specific surface area, S_w, decreased at high storage temperature. The dissolution rate showed a sharp decrease above 70 °C. When the diametral compression strength, σ, was plotted against the rate of decrease in the specific surface area for phenylbutazone, a good linear relationship was observed. These findings can be explained by the sintering mechanism.

In the case of barbital (form II), σ decreased and the dissolution rate increased at high temperatures. The specific surface area, S_w, however, exhibited no significant change with storage temperature. Barbital does not appear to exhibit extensive sintering and the main mechanism involved is polymorphic transition.

Keywords——δ-phenylbutazone; barbital; diametral compression strength; sintering mechanism; polymorphic transition

Since most pharmaceuticals have relatively low melting points, it is considered to be of importance to know the effect of temperature on the adhesive and cohesive properties of drug powder. It is well known that mechanical properties such as flowability and compressibility are influenced by the elevation of temperature during handling of the powders, even below the melting point. Recently, York and Pilpel[1] and Danjo *et al.*[2] studied the tensile strength of organic powder beds as a function of temperature. Otsuka *et al.*[3] investigated the effect of temperature on the adhesive force between organic powder particles and a glass substrate by means of the impact separation method.

In the case of certain drugs, changes in storage temperature are also considered to influence their physical properties, including tablet strength. δ-Phenylbutazone, which has a relatively stable crystal structure, and barbital (form II), which is liable to exhibit polymorphic transition, were chosen as samples. Flat-faced tablets of these drugs were prepared, and the diametral compression test and determination of specific surface area were carried out, using heat-treated and untreated samples. Drug dissolution profiles were also examined with the same tablets.

Experimental

Samples——Table I lists the physical characteristics of the samples used. δ-Phenylbutazone was provided by Ciba-Geigy Japan and was used after being passed through a 100-mesh sieve. Barbital form II was of JPX grade and was used after being passed through a 100-mesh sieve.

Measurement of Diametral Compression Strength——Compression was conducted using a universal tension and compression tester (Minebea, model TCM 5000C). Phenylbutazone and barbital were compressed under 255 and 318 kg/cm^2 pressure, respectively. The resultant model tablets were heat-treated (for 10 and 5 h for phenylbutazone and barbital tablets, respectively), followed by a diametral compression test using the universal tension and

TABLE I. Physical Properties of Material Powders Used

Material	Average particle diameter[a] (μm)	Particle density (g/cm³)	Melting point (°C)
δ-Phenylbutazone	4.9	1.19	103
Barbital form II	13.8	1.30	189

a) Obtained by means of the krypton adsorption method.

compression tester after standing at room temperature for 12 h. The test consisted in applying a load diametrically, measuring the maximal load P at the fracture of the tablet, and calculating the diametral compression strength, σ, using the following equation:

$$\sigma = 2P/(\pi Dt) \quad (1)$$

where D is the diameter of the tablet and t is the tablet thickness.

Measurement of the Specific Surface Area——On the same tablets as used in the diametral compression test, the specific suface area was measured in terms of adsorption of krypton gas at the boiling point of liquid nitrogen by using a Shimadzu-Micromeritics model 2100D specific surface area pore distribution analyzer. The mean particle diameters listed in Table I were estimated from the specific surface area values thus obtained.

Measurement of Specific Permeability—— Specific permeability of the compressed tablets in term of air permeation was measured with a Shimadzu powder surface area determinator (model SS-100).

Dissolution Rate Measurement——The dissolution rate was measured by the rotating disk method (Toyama Industries, model NTR-VS). The dissolution medium was circulated with a pump at a constant flow rate of 200 ml/min through the flow cell, and the drug concentration was determined with a UV-spectrophotometer (Hitachi, model 200-20).

X-Ray Diffraction Analysis——The instrument used for this purpose was a JEOL DX-GE-2F X-ray powder diffraction analyzer. The X-ray source was Cu K_α with an Ni filter, at a voltage of 15 kV, a current of 10 mA and a scanning speed of 2°/min.

Measurement of Melting Point——The melting point was taken as the point of intersection of the maximum gradient of the endothermic peak to the base line, measured with a DSC apparatus (Rigaku Denki, type 8085E1).

Measurement of Density——Density was measured with a Shimadzu-Micromeritics type 1302 helium–air hydrometer.

Results

Identification of Polymorphic Transition

X-Ray diffraction patterns of the original δ-phenylbutazone and that stored at 80 °C for 10 h are presented in Fig. 1a, b, respectively. The patterns obtained were identical,[4] indicating that no transition occurred in this temperature range. Figure 2 shows the X-ray diffraction patterns for barbital stored at various temperatures for 5 h. The diffraction patterns show an abrupt change at a temperature of 130 to 140 °C, the transition temperature of form II to form I.[5,6]

Effect of Storage Temperature on Diametral Compression Strength

Figure 3 shows the relationship between storage temperature (abscissa) and diametral compression strength, σ (ordinate), for δ-phenylbutazone. The abscissa T/T_m (homologous temperature) denotes the ratio of storage temperature to melting point in terms of absolute temperature. The diametral compression strength, σ, increased starting from around 50 °C. Figure 4 shows the results obtained for barbital. In this case, T/T_m was calculated by using the melting point of form II. Little change occurred in diametral compression strength, σ, below a storage temperature of 100 °C, and σ exhibited a remarkable reduction above 120 to 130 °C.

Effect of Storage Temperature on Specific Surface Area

The specific surface area of each sample was measured and the effect of storage

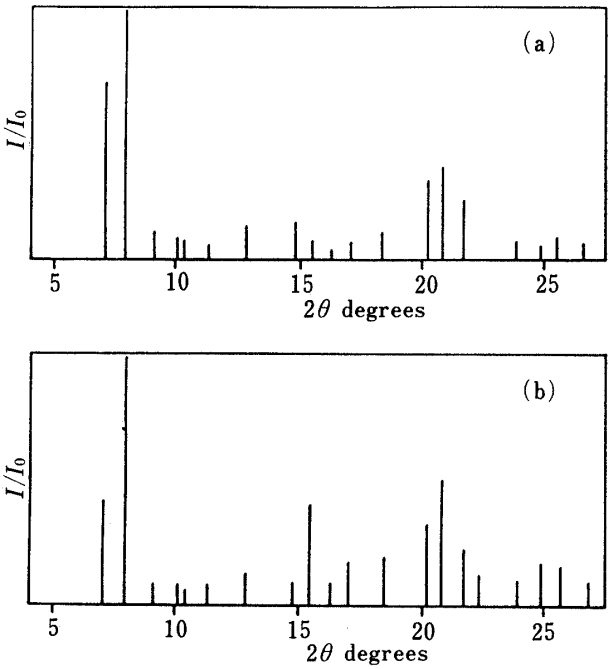

Fig. 1. X-Ray Diffraction Patterns of δ-Phenylbutazone
(a) 25 °C; (b) 80 °C.

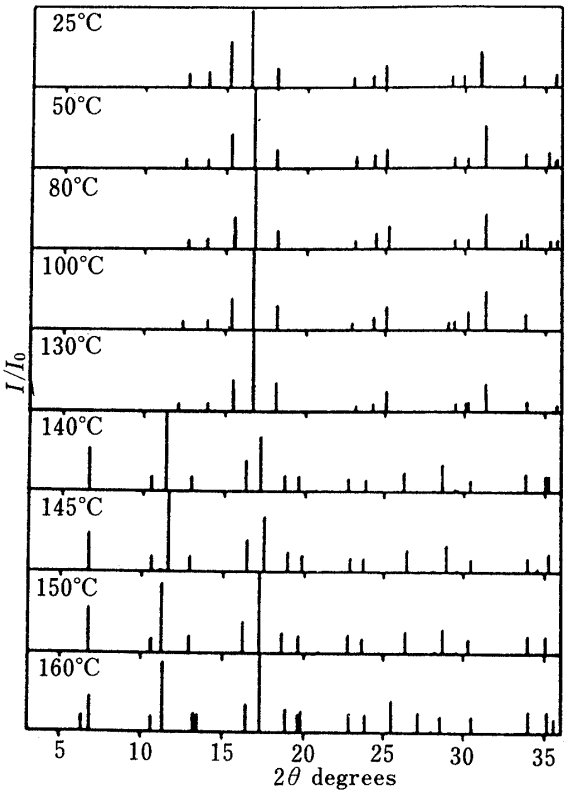

Fig. 2. X-Ray Diffraction Patterns of Barbital Polymorphs

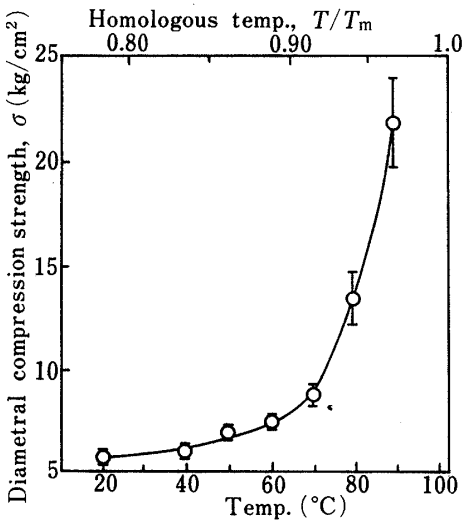

Fig. 3. Diametral Compression Strength (σ) as a Function of Temperature for δ-Phenylbutazone Tablets

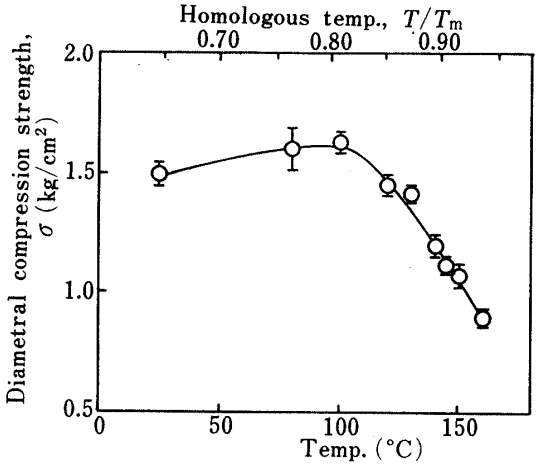

Fig. 4. Diametral Compression Strength (σ) as a Function of Temperature for Barbital Tablets

temperature was examined. Figure 5 shows the results obtained for δ-phenylbutazone. As the storage temperature rose, specific surface area, S_w, gradually decreased. An abrupt reduction occurred in the vicinity of 70 to 80 °C. Figure 6 gives the results for barbital; no significant change was noted with change of temperature.

Effect of Storage Temperature on Dissolution Rate

Each tablet was subjected to dissolution test. The Noyes–Whitney equation was applicable to the data obtained.

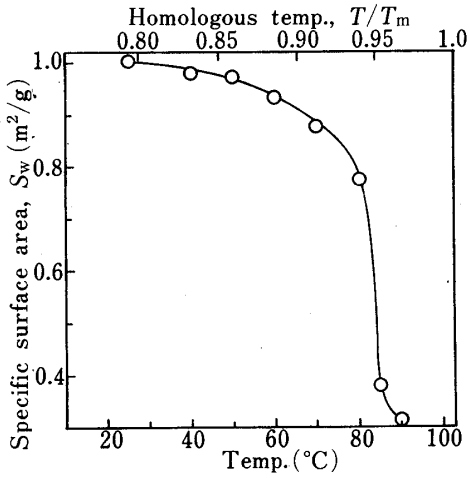

Fig. 5. Specific Surface Area (S_w) as a Function of Temperature for δ-Phenylbutazone

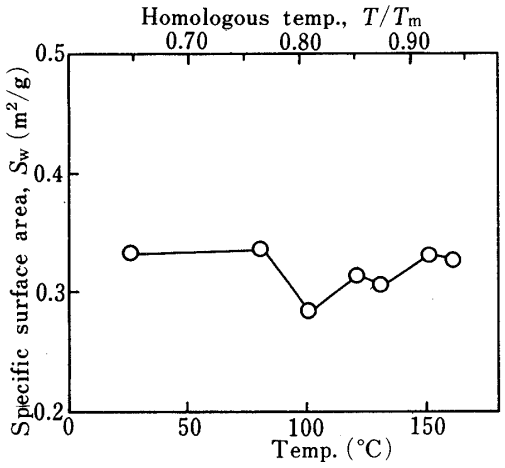

Fig. 6. Specific Surface Area (S_w) as a Function of Temperature for Barbital

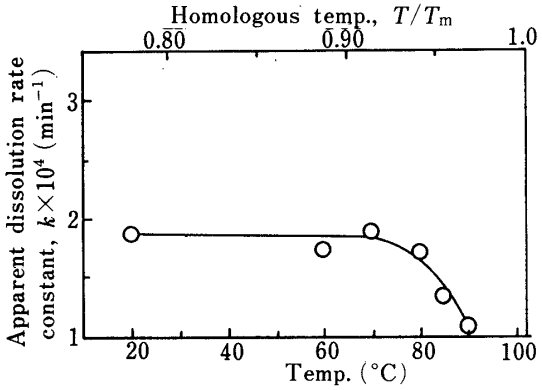

Fig. 7. Relationship between Apparent Dissolution Rate Constant (k) and Temperature for δ-Phenylbutazone

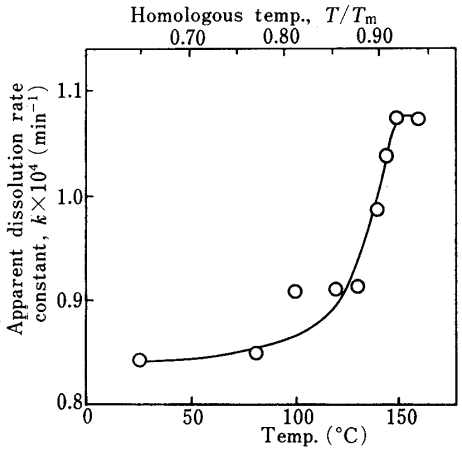

Fig. 8. Relationship between Apparent Dissolution Rate Constant (k) and Temperature for Barbital

$$\ln(C_s/(C_s-C))=kt \qquad (2)$$

Where C_s is the solubility and C is the concentration of the solution at time t. The constant k values, corresponding to apparent dissolution rate, were plotted against storage temperature. In the case of phenylbutazone (Fig. 7) k decreased sharply above 70 °C, but it increased above 100 °C in the case of barbital (Fig. 8).

Discussion

The temperature-induced change in diametral compression strength, σ, and specific surface area, S_w, may be interpreted as follows. Jernot and Coster[7] suggested the following equation which relates surface area to the contact area of two spheres in the case of sintering.

$$S_w/S_{w0}=1-(N/4)(x/a)^2 \qquad (3)$$

Where S_{w0} and S_w are specific surface area per unit mass before and during sintering, respectively, N is the coordination number of a particle, x is interparticulate neck radius, and a is the particle radius.

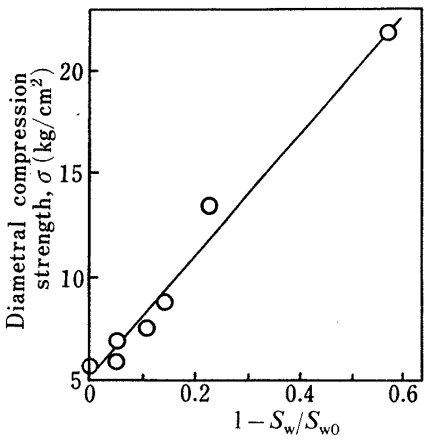

Fig. 9. Plots of Diametral Compression Strength (σ) *vs.* ($1-S_w/S_{w0}$) for δ-Phenylbutazone

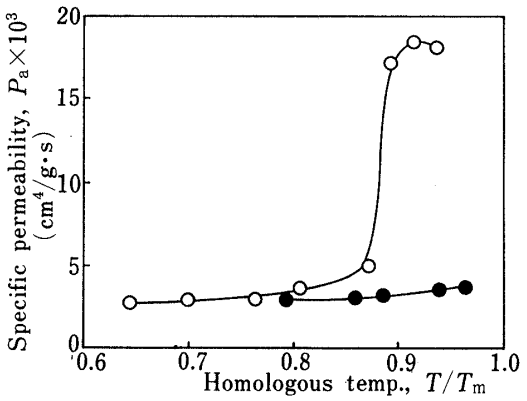

Fig. 10. Relationship between Specific Permeation (P_a) and Temperature

●, δ-phenylbutazone; ○, barbital.

The diametral compression strength, σ, was assumed to be a function of the sum of the effective contact area between particles which is proportional to the ratio of decrease in the surface area ($1-S_w/S_{w0}$) according to Eq. 3. Figure 9 shows a plot of the ratio of decrease in surface area, ($1-S_w/S_{w0}$), to the diametral compression strength, σ, for phenylbutazone. Good linearity was obtained. From these results, it appears that the increase in diametral compression strength during storage at high temperature may be considered to arise from sintering. The reduction in specific surface area is associated with that in the drug release rate. The relationship between k and storage temperature for phenylbutazone is shown in Fig. 7.

In the case of barbital, a considerable difference was noted in the temperature-dependent change in diametral compression strength, σ, specific surface area, S_w, and apparent dissolution rate constant, k, from those in the case of phenylbutazone. While σ showed a reduction above about 100°C, S_w underwent no remarkable change, and the value of k increased sharply in essentially the same temperature region. It is considered that S_w is influenced not only by sintering (reduction in the surface area), but also by transition, which may induce the micronization of particles. The apparent small change in this value may possibly have resulted from mutual cancellation of complex effects. Still, diametral compression strength decreased above 100 °C. This contradiction may be explained on the basis of intracompact fragile portions induced by distortion accompanying the crystal structure transition. The increase in the dissolution rate is considered to have resulted from cracks in the tablet, promoting liquid penetration. For verification of this supposition, air permeation was measured for each test sample. The results are shown in Fig. 10. The specific permeability, P_a, was calculated by means of the following equation:

$$P_a = QL/(\Delta PAt) \tag{4}$$

where Q is the amount of air that permeated the tablet at time t, L is tablet thickness, ΔP is the pressure difference across the thickness (L) and A is the cross-sectional area of the tablet. For barbital, the specific permeability, P_a, increases sharply above 130 °C, indicating the possible formation of some large channels within the tablet. On the other hand, for phenylbutazone, the specific permeation, P_a, was found to be approximately constant in this temperature range. These results suggested that phenylbutazone has few channels within the tablet after heating.

In conclusion, we have examined changes in the hardness of organic powder compacts induced by storage at high temperature as a result of sintering and polymorphic transition

phenomena. It is emphasizes that environmental temperature effects should be taken into consideration when discussing the physicochemical behavior of low-melting substances or substances having a transition point in the relatively low temperature range.

References and Notes

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