ELSEVIER

International Journal of Pharmaceutics 106 (1994) 187–200

international journal of pharmaceutics

Deformation kinetics of acetaminophen crystals

Meng-Chih Lin [a], Wendy C. Duncan-Hewitt [b,*]

[a] *Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ontario M5S 2S2, Canada,*
[b] *Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ontario M5S 2S2, Canada*

(Received 23 December 1992; Modified version received 11 August 1993; Accepted 20 October 1993)

Abstract

We hypothesize that if the kinetics of tablet compression for materials such as acetaminophen are more fully understood and quantified, the parameters that emerge may be used in rational approaches to understand and solve time-dependent problems such as capping. The objective of our work was to obtain two deformation kinetic parameters for the predominant barrier to deformation of acetaminophen crystals, the activation volume (V_{act}) and the activation energy (E_{act}) from the results of tablet stress relaxation by using intervening models which relate single crystal behavior to the behavior of the compact. The stress relaxation of acetaminophen was monitored at varying temperatures using an Instron stress strain analyser and single crystal hardness values were determined by microindentation. V_{act} was determined to be $5b^3$ for acetaminophen from two different sources. The E_{act} for flow was determined to be 660 kJ mol^{-1}. It is probable that the predominant deformation mechanism is climb which is a thermally activated process requiring mass transport by diffusion. Diffusion itself is expected to be extremely slow relative to that observed in many engineering materials because of the larger Burgers vector and the directional intermolecular hydrogen bonds. The difference between the relative densities of two sources probably is a result of their different particle shapes as observed by SEM. The measured relationship between hardness and temperature was linear.

Key words: Acetaminophen; Deformation kinetics; Non-linear three-element mechanical model; Stress relaxation; Microindentation; Activation volume; Activation energy

1. Introduction

Capping problems arise during the compaction of acetaminophen and other materials from the consequences of many factors. It is generally accepted that the amount of air trapped in the tablet during processing, lot-to-lot variation of compression materials and particle sizes and particle shape play crucial roles during tablet compaction. Excess air trapped in a tablet could be a driving force for capping. Materials from alternative sources may have similar chemical compositions, however, they also may exhibit different physical properties (e.g., particle size and shape). Particle behavior in processing and compaction is a function of particle size, shape, density and surface. These interact in a complex manner to give the total particle behavior pattern (Fell and

* Corresponding author.

SSDI 0378-5173(93)E0328-N

Newton, 1971; Pilpel and Walton, 1974; Lieberman and Lachman, 1981). In this theoretical study, it is conjectured that, all things being equal, capping may result from a combination of the viscoelastic properties of the particles and poor interparticle bonding. The net interparticle bond strength is assumed to be the product of the strength of adhesion and the true interparticle contact area, the latter resulting from plastic deformation under compression. The release of elastic strain of the particles during decompression tends to disrupt the interparticle bonds. The relative amounts of permanent (plastic) and reversible (elastic) deformations are time dependent and excessive elastic recovery may arise from the too rapid movement of the punch in the compression and decompression stages, therefore, the quantitation of viscoelastic parameters of pharmaceutical materials is a crucial first step in any attempt to predict capping. Once the important kinetic parameters for a material are defined and measured, they can be used in more elaborate models of tablet compaction that, by considering bonding and time-dependence, could be used to predict capping.

Many different approaches have been used to study the process of tablet compaction in an attempt to develop a parameter, an equation, or a model to evaluate the time dependence of the process and to predict or prevent the problem of capping. These include acoustic emission (Tetelman et al., 1972; Waring et al., 1987), residual die wall pressure and compression cycles (Carless and Leigh, 1974; Obiorah and Shotton, 1976; Doelker and Shotton, 1977; Obiorah, 1978), axial and radial tablet tensile strength (Fell and Newton, 1968; Nyström et al., 1978; Alderborn and Nyström, 1984), tablet densification behavior (Heckel, 1961a,b; Hersey and Rees, 1970; Fell and Newton, 1971; Humbert-Droz et al., 1983; Duncan-Hewitt, 1988), tablet stress relaxation (Cole et al., 1973; David and Augsburger, 1977; Rippie and Danielson, 1981; Sheikh Salem et al., 1984; Casahoursat et al., 1988; Yu et al., 1989), capping indices (Krycer et al., 1982), elastic recovery/plastic compression or elastic recovery/stress relaxation ratios (Bangudu and Pipel, 1984; Malamataris et al., 1984; Esezobo and Pilpel, 1986; Yu et al. 1988), indices of tableting performance (Hiestand and Smith, 1984; Hiestand, 1991) and single particle models of tablet compaction (Britten and Pilpel, 1978; Arzt, 1983; Duncan-Hewitt and Weatherly, 1989a,b; Papadimitropoulos, 1990). With the exception of the approach used by Duncan-Hewitt and Weatherly (1989a,b) and Papadimitropoulos (1990), existing methods to quantify viscoelasticity of pharmaceutical materials provide empirical fitted parameters that do not take tablet porosity into account and which have not been validated by alternate means.

The goal of our work is to obtain parameters which can be used to predict tableting kinetics from single particle parameters. The activation energy (E_{act}) and the activation volume (V_{act}) derived from the stress relaxation test are such fundamental parameters that can be inserted into the final kinetic expressions associated with single-particle based models of tablet compaction. The stress relaxation of metallic single crystals, polymeric materials and compacts of sodium chloride and potassium bromide have been studied extensively and quantified in this manner, but no investigations have been undertaken for organic crystalline materials. Acetaminophen, widely used in the pharmaceutical field, is an excellent organic model. During tablet manufacture of this material, capping is a frequent problem which may occur either while the tablet is ejected from the die or during further processing and handling. This problem is solved empirically by modifying the granulation process or by decreasing the rate of compression during in-process control, however, these methods do not solve the problem directly; furthermore, they will affect tablet quality and increase the cost of manufacturing. The work described in this paper provides the information that will form the basis of a more fundamental approach to the solution of capping problem.

Two models are used to link the microscopic activation parameters with the kinetics of tablet stress relaxation:

(i) According to the microscopic point of view provided by Krausz and Eyring (1975), deformation kinetics at high stress levels is con-

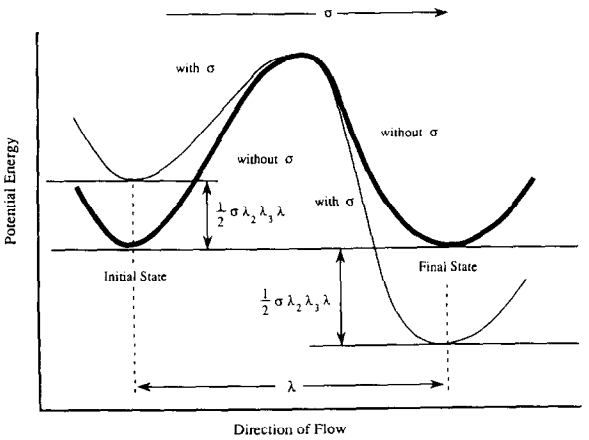

Fig. 1. An illustration of how an applied stress alters the potential energy barrier for viscoelastic flow: σ, applied stress; λ, dislocation distances in each dimension (Krausz and Eyring, 1975).

trolled by activation in the forward direction over a single energy barrier (Fig. 1). This analysis considers the motion of one deformation unit: a molecule, a dislocation, or groups of dislocations depending upon the circumstances. The behavior of one such unit is connected to the macroscopic behavior of an entire crystal using the Halsey-Eyring three element model of stress relaxation.

(ii) An indentation model that relates tablet stress relaxation with that at interparticulate regions was adopted in our work on the basis of the assumption that the interparticulate contact area remains constant during stress relaxation. If this is so, the contact area which is measured from the microindentation test at 10 s (the standard indentation time) can be used to calculate the true contact stress from the punch stress at 10 s. If these assumptions are correct, then the procedure should normalize all stress relaxation curves for a given material. The justification is as follows: no further movement is imposed by the punch after its movement is arrested. The plastic zone is not actually in the contact area, but in a hemispherical zone beneath it. It is then assumed that for truly elastic/plastic materials (as described by Marsh, 1964) the elastic strain at the elastic/plastic boundary becomes plastic strain. The result can be pile-up distant from the contact zone itself. This may not be true for highly viscoelastic polymers with more uniformly varying strain behavior. Regardless of the final tablet porosity, the relaxation curves should become superimposable when plotted together, regardless of the maximum force applied to the punch.

2. Background

2.1. Deformation kinetic analysis

Rapid plastic deformation is governed primarily by the threshold stress for dislocation motion (the critical resolved shear stress for yield), however, if the temperature of the test is increased (> 0.4 of the absolute melting temperature), thermal activation usually influences the rate of deformation (McClintock and Argon, 1966). On average atoms or molecules in condensed phases occupy equilibrium lattice positions and are oscillating about the minimum of the free energy wells. When stress is applied work is done on the system and the potential energy of the molecules is increased and stored in a reversible (i.e., elastic) manner. Plastic flow will occur when the atoms move under the combined effect of the applied stress and thermal activation into a new equilibrium valley forming new bonds while breaking the previous bonds. This process can be compared with a chemical reaction in which the composition remains constant but the arrangement of the molecules changes.

According to the equilibrium theory established by Arrhenius, the rate of a reaction is the sum of the rates of molecules going both from reactant to product state in the forward direction and from the product state to the reactant state in the backward direction, therefore the total rate constant K can be expressed as:

$$K_f + K_b = A_f \exp(-\Delta E_f/kT) + A_b \exp(-\Delta E_b/kT) \quad (1)$$

where A_c is a frequency factor, ΔE_f and ΔE_b are empirical activation energies in the forward

and backward directions, respectively, k denotes Boltzmann's constant and T is the absolute temperature.

For an elementary, first-order deformation, the strain rate ($\dot{\gamma}$ can be derived from Orowan's equation as:

$$\dot{\gamma} = \alpha \boldsymbol{b} \rho_m K \tag{2}$$

where α is a geometrical factor relating the active slip system to the shear strain direction, $\boldsymbol{b}$ represents the Burgers vector and ρ_m is the mobile dislocation density. The constant α and $\boldsymbol{b}$ are known accurately for single crystals, while ρ_m and K are functions of stress, strain, temperature and structure. These concepts are combined as follows:

$$\dot{\gamma} = R_f \exp(-\Delta E_f/kT) + R_b \exp(-\Delta E_b/kT) \tag{3}$$

$$R_f = \alpha \boldsymbol{b} \rho_m A_f \tag{4}$$

$$R_b = \alpha \boldsymbol{b} \rho_m A_b \tag{5}$$

At equilibrium, the activation barrier is symmetrical so that $\Delta E_f = \Delta E_b = \Delta E_e$, where ΔE_e is the equilibrium barrier height. The net strain rate under these conditions is zero. If a force is applied to the system, the forward and backward barrier heights are changed by the associated work (W):

$$\dot{\gamma}_f = R_f \exp[-(\Delta E_e - W_f)/kT] \tag{6}$$

$$\dot{\gamma}_b = R_b \exp[-(\Delta E_e + W_b)/kT] \tag{7}$$

where W_f is work performed to lower the activation energy barrier in the forward direction and W_b denotes work performed to increase the activation energy in the backward direction. From the definition of work, stress and activation volume, the following relationships are obtained:

$$W = Fd \tag{8}$$

$$\sigma = F/A \tag{9}$$

$$W = Ad\sigma \tag{10}$$

$$V_{act} = Ad \tag{11}$$

$$W = \sigma V_{act} \tag{12}$$

$$W = \tau V_{act} \tag{13}$$

where F is force, σ denotes stress, A is area, d represents distance, V_{act} is activation volume and τ the shear stress. Substituting Eq. 13 into Eq. 6 and 7:

$$\dot{\gamma}_f = K_f \exp(\tau V_{actf}/kT) \tag{14a}$$

$$K_f = R_f \exp(-\Delta E_e/kT) \tag{14b}$$

$$\dot{\gamma}_b = K_b \exp(-\tau V_{actb}/kT) \tag{15a}$$

$$K_b = R_b \exp(-\Delta E_e/kT) \tag{15b}$$

Assuming that the activation volumes, activation energies and pre-exponential factors are the same in both the forward and backward directions, then:

$$\dot{\gamma}_{total} = K[\exp(\tau V_{actf}/kT) - \exp(-\tau V_{actb}/kT)] \tag{16}$$

Noting further that:

$$\sinh x = 1/[2(e^x - e^{-x})] \tag{17}$$

Eq. 16 now becomes:

$$\dot{\gamma}_{total} = K/[2 \sinh(\tau V_{act}/kT)] \tag{18}$$

At high levels of stress, the deformation is usually controlled primarily by activation over one barrier in the forward direction, so that:

$$\dot{\gamma}_{total} = \dot{\gamma}_f = R_f \exp[-(\Delta E_e - W_f)/kT] \tag{19}$$

$$\dot{\gamma}_{total} = R_f \exp(-\Delta E_e/kT + \tau V_{act}/kT)$$

$$-\dot{\gamma}_{total} = R_f \exp(\Delta E_e/kT) \exp(-\tau V_{act}/kT) \tag{20}$$

The strain rate is not measured in a stress relaxation experiment. The shear stress rate can be substituted if the relationship between the two is known. The Halsey-Eyring three-element model (consisting of a linear spring and a non-linear dashpot in a parallel configuration) often is satisfactory deformation kinetic analysis using in this model is performed as follows. In stress relaxation the strain rate of the non-linear Maxwell element of the three-element model must satisfy the condition that the total strain rate ($\dot{\gamma}_{tot}$) is equal to 0. The following relationship between

shear stress rate ($\dot{\gamma}$) and strain rate ($\dot{\gamma}$) then results:

$$\dot{\gamma}_{tot} = \dot{\gamma}_{el} + \dot{\gamma}_{visco} = 0 \quad (21)$$

$$\dot{\gamma}_{el} = -\dot{\gamma}_{visco} \quad (22)$$

$$\dot{\gamma}_{el} = \dot{\tau}/E \quad (23)$$

$$-\dot{\gamma}_{visco} = \dot{\tau}/E \quad (24)$$

$$\dot{\tau} = -E\dot{\gamma}_{visco} \quad (25)$$

where E is the apparent elastic modulus which in practice is a composite value for the material and testing system in series. Substituting Eq. 20 into Eq. 25:

$$\dot{\tau} = R' \exp(E_{act}/kT)(-\tau V_{act}/kT) \quad (26a)$$

$$R' = ER_f \quad (26b)$$

or

$$\ln(\dot{\tau}) = \ln R' + (E_{act}/kT) - \tau(V_{act}/kT) \quad (26c)$$

From Eq. 26c, the experimental activation volume (V_{act}) can be determined from the slope of the line derived by plotting −ln(shear stress rate) vs (average shear stress) at constant temperature. The experimental activation energy (E_{act}) can be calculated from the slope of the line which results from plotting ln(shear stress rate) vs the inverse of the absolute temperature at constant stress (Krausz and Eyring, 1975; Duncan-Hewitt, 1988; Papadimitropoulos, 1990).

The Burgers vector $\boldsymbol{b}$ is the unit deformation distance and often equals the dimensions of the unit cell. It is customary to express the activation volume of a deformation mechanism in Burgers vector units. The activation volume is associated with the size of the deformation region, for example, if deformation occurs by molecular diffusion, it may be on the order of the molecular size.

2.2. Microindentation

Microindentation tests measure the resistance of a material to plastic deformation in a contact configuration. In this procedure a diamond indenter of specific geometry [pyramidal symmetrical (Vickers) and rhombic-based asymmetrical (Knoop)] is pressed at right angles into the surface of the material under a given load, then removed from the surface. Subsequently the area of the permanent impression is determined (Westbook and Conrad, 1973; Duncan-Hewitt, 1988). The hardness or mean confined yield stress of materials is usually calculated from P/A, where P is the applied load and A represents the true area of contact or the projected area of contact. The Vickers Hardness Number (VHN, 136° pyramid) is calculated from the mean length of the diagonals of an indentation and is equal to the mean stress across the true area of contact.

$$\text{VHN} = \text{load}/\text{area of contact} = 1.854\, P/d^2 \text{ MPa} \quad (27)$$

where P is the applied load (in N) and d denotes the mean indentation diagonal (in mm).

Since microindentation tests can be used to obtain the hardness of crystals with very small loads, it is particularly useful for studying the plastic deformation of small, brittle crystals such as many pharmaceutical materials, including acetaminophen. Indentation parameters are particularly useful in the present case because the contact area derived from the hardness of single crystals can be used to correlate tablet stress relaxation with deformation kinetic analysis.

It is assumed that a material yields in the contact configuration according to the Von Mises yield criterion with an added elastic constraint factor. The Von Mises yield criterion assumes that yielding occurs by slip or twinning and that these are caused by the shear components of stress (McClintock and Argon, 1966). The constraint factor is a function of the geometry of the contact.

The constraint factor for the indentation of acetaminophen was found to be ~ 2.39 (Duncan-Hewitt, 1988). Therefore, the relationship between the hardness and the shear stress adopted in our model is as follows:

$$H = F/A \quad (28)$$

$$\tau = H/(2.39\sqrt{3}) \quad (29)$$

where τ is the shear stress, H denotes the hardness and $\sqrt{3}$ arises from the Von Mises yield criterion (McClintock and Argon, 1966).

Because tablet stress relaxation results from contact deformation of randomly oriented particles, It is impossible to obtain a precise estimate of the yield behavior of individual slip systems, but the activation parameters remain valid.

3. Materials and experimental methods

3.1. Stress relaxation

Two lots of very fine crystalline acetaminophen powder (Rhône-Poulenc Santé, RIC No. 11622801, MI No. F-05136, and RIC No. 11622801, MI No. F-02815, made in the U.S.A. and France, respectively) were used as received.

An Instron stress strain analyzer (Model 4201) equipped with Series IX computer software (Version 4.01C) and a printer (Hewlett Packard R, Think Jek 2225C) was used for tablet compaction and stress relaxation measurement. Two kinds of 13 mm stainless-steel dies and punches (square and cylindrical shapes), were used to make the compacts. Compacts were made at temperatures ranging from -20 to $+70$°C. For temperatures above 25°C, a 13 mm square stainless-steel die surrounded with an environmental chamber equipped with controlling heater was used. For temperatures below 25°C, a 13 mm stainless-steel cylindrical die equipped with a 100 Ω platinum thermocouple was employed. The temperatures were controlled by a mechanical cooling accessory (Dupont R, No. 990476–907,623) and were monitored by an electronic detector (Canlab R TT4003). Compact thickness was measured using a digital micrometer (Mitutoyo R Digimatic Indicator). Data analysis was performed using a Macintosh LC computer.

Prior to each compression the die and punches were cleaned with methanol and dried, the die wall and upper and lower punch surfaces were lubricated with a 1% suspension of magnesium stearate in acetone, then the die was with filled about 0.7 g of acetaminophen crystalline powder which was accurately weighted. The Instron was recalibrated prior to each compression and the material was compacted using the compression program. The rate of punch displacement was 1 mm/min during compaction. At maximum punch travel (at loads of 2.5, 3.5 or 4.5 kN) the movement of the cross-head was arrested and stress relaxation was monitored for 2 min. At least two runs were performed at each stress level. Compacts were also made at temperatures ranging from -20 to $+70$°C, since stress relaxation was monitored at various temperatures to permit the calculation of the activation energy.

3.2. The Vickers hardness test

Acetaminophen, received as a fine crystalline powder (Rhône-Poulenc Santé, RIC No. 11622801, MI No. F-05136, made in U.S.) was recrystallized from a 50% acetone solution to produce crystals which were sufficiently large (2–5 mm) for microindentation experiments.

Microindentation testing was performed using a Tukon miniload microindentation hardness tester (Model 300) equipped with a 136° Vickers diamond pyramid indenter and a microscope unit. For the temperatures above and below 25°C, a microscope heating stage (Leitz 350) was installed on the tester and connected with a temperature controlled bath (Ultratem 2000, VC thermostat circulation). The temperature were monitored using an Omega thermocouple which was connected directly to a stainless-steel disc placed under the crystals. Since water will deposit on the crystal at temperatures below the dew point, high purity (not less than 99.5%) nitrogen was passed continually through the stage.

An acetaminophen crystal was mounted in a thermally conductive aluminum oxide paste (Wakefield thermal compound No. 120-2) with the surface ({210}) to be indented oriented normal to the indentation direction. This was achieved by maximizing the intensity of light reflected from the surface when the crystal was viewed under the microscope attachment. The $10\times$ objective was used to select an indentation site and the $50\times$ objective was used to observe the indentation.

The indenter was cleaned with acetone and allowed to dry. It was then lowered slowly onto the surface of the crystal by a hydraulic mechanism over a period of 15 s and the full load was

maintained for 10 s. The indenter was subsequently raised automatically. At these loads, at least one diagonal of the indentation was usually clearly defined. A 136° diamond pyramid indenter (Vickers) (depth/breadth/length = 1 : 4.29 : 30.53) was employed and indentations were measured using the scale in the eyepiece of microscope which was calibrated daily. The mean diameters of six indentations was used to calculate the average hardness value. The tests were performed at temperatures varying from −20 to +70°C to assess the role of temperature-dependent flow.

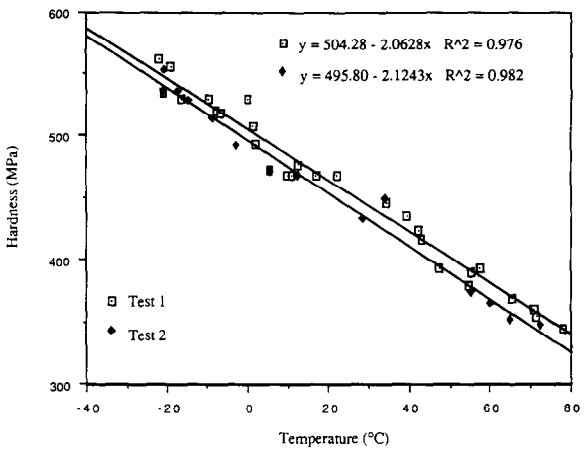

Fig. 2. The temperature vs hardness plot for acetaminophen crystals from lot F-05136.

4. Results

The hardness values obtained between −20 and + 70°C decreased linearly with increasing the temperature (Fig. 2).

4.1. Activation volume

The activation volumes, calculated from plots of −(ln shear stress rate) vs shear stress (Fig. 3 and 4) using Eq. 26c were $5 \pm 0.8b^3$ (SE = 0.302, $p = 0.0001$) and $5 \pm 1.0b^3$ (SE = 0.408, $p = 0.0001$), respectively, for the acetaminophen from the two different sources (Table 1). It is probable that the predominant deformation mechanism is climb which is a thermally activated process requiring mass transport by diffusion. This activation volume is comparable with that found for

Table 1
Summary of deformation kinetic data at 298 K for acetaminophen lot F-0536 and F-02815

Source	Sample	Maximum load (kN)	Weight (g)	Thickness (mm)	Density (g cm^{-3})
F-05136 (U.S.A.)	ACE1.2.3	2.5	0.768 ± 0.004	5.937 ± 0.027	0.976 ± 0.005
	ACE7.8	3.5	0.767 ± 0.003	5.843 ± 0.022	0.993 ± 0
	ACE13.14	4.5	0.765 ± 0.006	5.703 ± 0.0720	1.012 ± 0.005
F-02815 (France)	ACE4.5	2.5	0.759 ± 0.004	6.220 ± 0.023	0.920 ± 0.001
	ACE10.11	3.5	0.757 ± 0.004	6.001 ± 0.030	0.950 ± 0
	ACE16.17	4.5	0.757 ± 0.013	5.882 ± 0.073	0.970 ± 0.006

Sample	Maximum load (kN)	Relative density	Slope (s^{-1})	r^2	V_{act} (b^3)
ACE1.2.3	2.5	0.755 ± 0.004	2.802 ± 0.181	0.832	5 ± 0.6
ACE7.8	3.5	0.768 ± 0	2.697 ± 0.536	0.901	5 ± 1.4
ACE13.14	4.5	0.783 ± 0.004	2.506 ± 0.284	0.821	5 ± 0.7
ACE4.5	2.5	0.712 ± 0.001	3.072 ± 0.334	0.823	6 ± 0.7
ACE10.11	3.5	0.735 ± 0	2.294 ± 0.438	0.805	5 ± 0.7
ACE16.17	4.5	0.750 ± 0.004	2.032 ± 0.945	0.524	4 ± 0.7

Lot no. F-05136: ACE1.2.3, ACE7.8 and ACE13.14; true density 1.293; $V_{act} = 5 \pm 0.8\ b^3$; lot no. F-02815: ACE4.5, ACE10.11 and ACE16.17; true density 1.293; $V_{act} = 5 \pm 1.0\ b^3$.

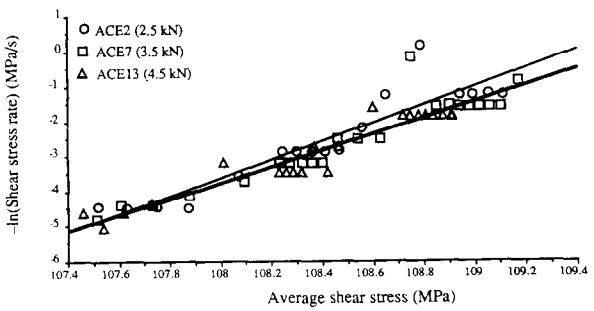

Fig. 3. The −ln(shear stress rate) vs (average shear stress) plots for acetaminophen lot F-05136 compacts compressed at a maximum load of 2.5, 3.5 and 4.5 kN at room temperature.

sucrose ($2b^3$) under similar conditions (Duncan-Hewitt, 1988). A relatively higher activation volume such as that found for sodium chloride ($54b^3$) probably is associated either with a Peierls-Nabarro or cross slip mechanism of dislocation motion. The data are summarised in Table 2.

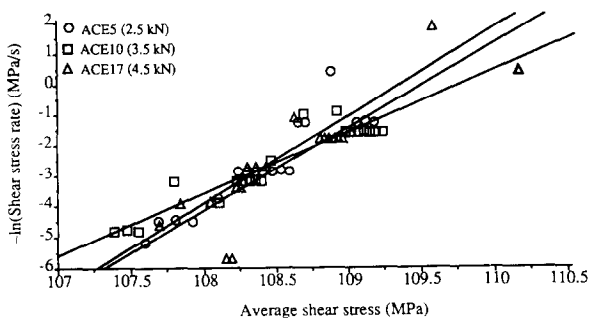

Fig. 4. The −ln(shear stress rate) vs (average shear stress) plots for acetaminophen lot F-02815 compacts compressed at a maximum load of 2.5, 3.5 and 4.5 kN at room temperature.

Table 2
Properties of the material used in this study compared with those of sucrose and sodium chloride

Material	Hardness (MPa)	Activation volume (b^3)	Activation energy) (kJ/mol)	E (MPa)	T_m (°C)
Sucrose [a]	645	2	106	27000	190
Sodium chloride [b]	213 [a]	54	120	43000 [c]	797
Acetaminophen	445	5	658	8400 [a]	170

[a] From Duncan-Hewitt (1988).
[b] From Papadimitropoulos (1990).
[c] From Lawn and Wilshaw (1975).

4.2. Activation energy

The slopes of the plots of ln(shear stress rate) vs $1/T$ (Fig. 5) were used to calculate the activation energy (660 ± 130 kJ mol^{-1}, $n = 39$, SE = 0.07, $p = 0.02$).

5. Discussion

The difference between the relative densities of the two sources of acetaminophen (Table 1) probably is a result of the particle shape as observed by (SEM) at $2000\times$ and $500\times$ magnifications (Figs. 6 and 7). While the particle shape and therefore the initial packing and compactability are different for the two lots of acetaminophen, the activation parameters (V_{act} and E_{act}) are the same, indicating that the underlying deformation behavior is identical. For a given level of stress the contact deformations of the materials are identical, which suggests that the former differences probably arise from differences in the function which relates particle shape and coordination number (Jones and Pilpel, 1966a–; Pilpel and Walton, 1974; Lieberman and Lachman, 1981). These results differ from those reported by Duncan-Hewitt and Weatherly (1989a,b) who found that the compaction of brittle materials is independent of particle size. This difference may arise from the fact that relatively low maximum compaction forces were employed, so that fracture did not yet essentially equalize the average particle size of the two lots.

The hardness of materials is a measure of the constrained resistance to plastic deformation which is thermally activated. Increasing the temperature causes the average internal energy of the molecules to increase, so that more molecules overcome the activation energy for flow. We compared the normalized relationships of hardness and temperature using the $\log(H/E)$ vs T/T_m plot (Fig. 8), where H is the hardness, E denotes the elastic modulus, T is the temperature and T_m the melting temperature, for several materials [alumina, silicon (ceramic materials), sodium chloride, ice, acetaminophen and sucrose]. For this purpose, the values of the hardness and

elastic modulus for the first four materials were taken from Frost and Ashby (1982) and those for the last two materials from Duncan-Hewitt (1988).

The error for the elastic moduli for acetaminophen and sucrose is about 50%, because the values were derived by a depth of focus measure-

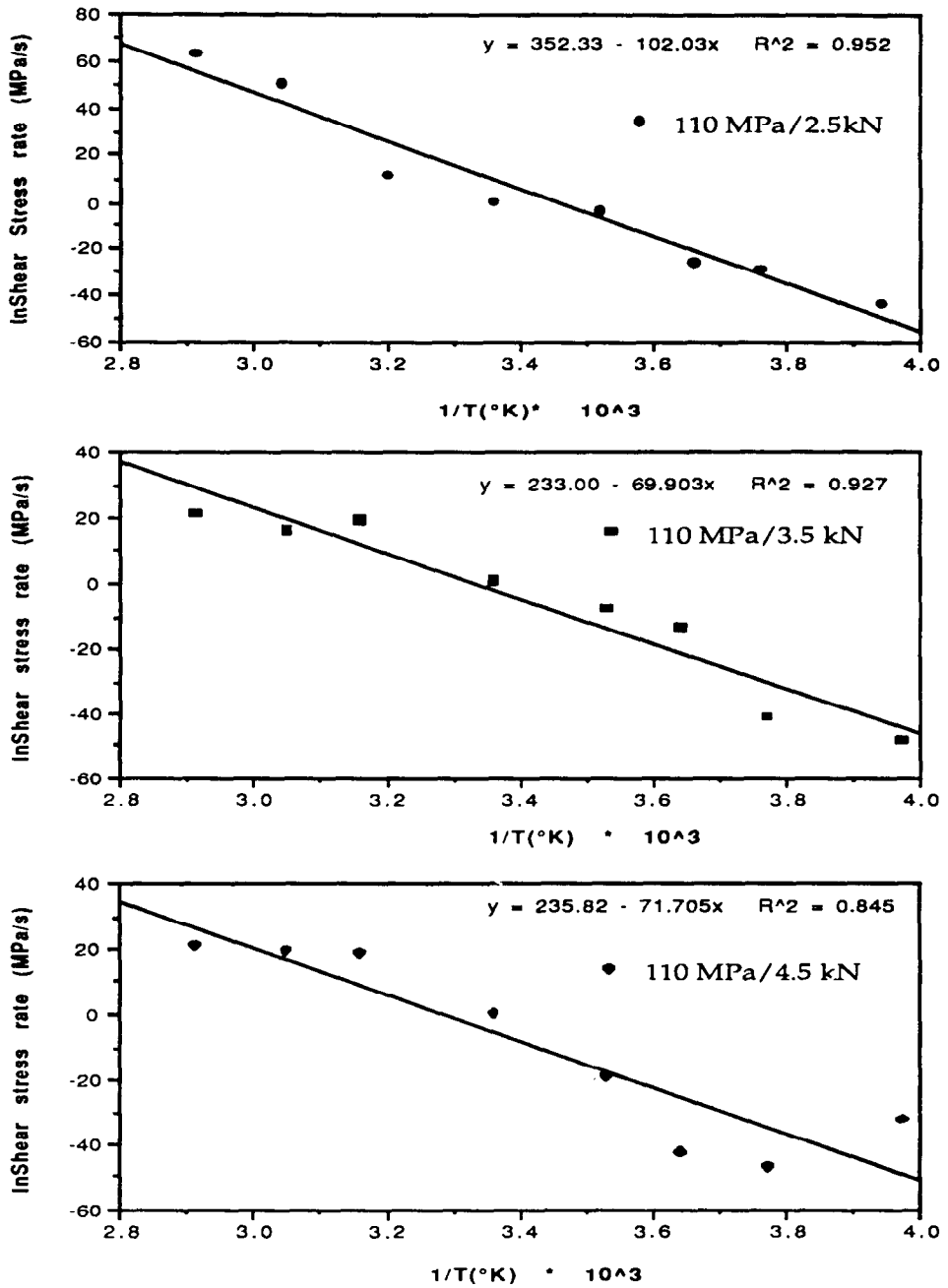

Fig. 5. Arrhenius plots for acetaminophen lot F-5136 used for the activation energy determination (E_{act} = 660 kJ mol^{-1}, n = 39, SE = 0.07, p = 0.02).

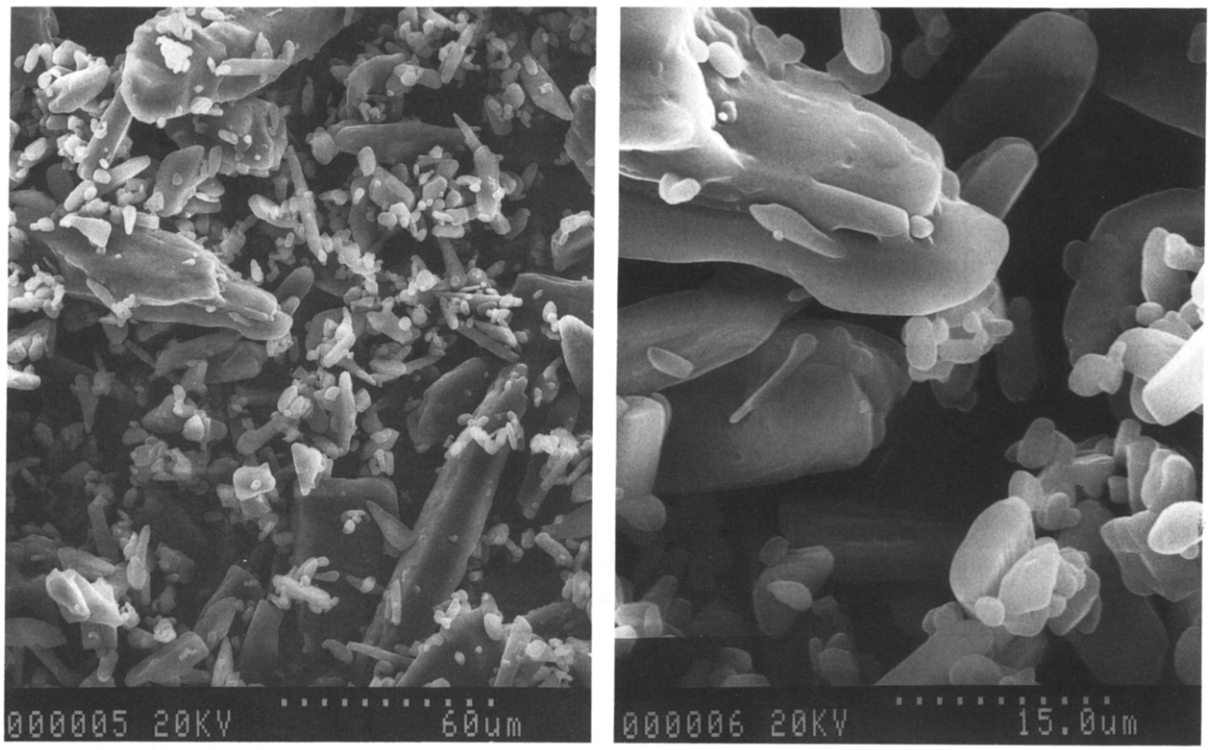

Fig. 6. Scanning electron micrographs at 500 × (left) and 2000 × (right) magnifications for acetaminophen lot F-05136.

ment of microindentations. The logarithmic scale is used to permit comparison with deformation mechanism maps (Frost and Ashby, 1982). We concluded that: (1) pharmaceutical materials behave in a manner similar to that of several common ceramic materials if one takes the relative bond strengths into account; and (2) of the materials shown, acetaminophen resists deformation the most. This is due, in part, to the relatively small elastic modulus with which the hardness value is normalized. When stress is applied, reversible deformation behavior is favored highly which provides the driving force for capping.

Plastic flow in crystalline solids is influenced by lattice structure and the type of bonding present, intrinsic lattice defects (e.g., vacancies, interstitials, voids) and extrinsic lattice defects (e.g., impurities). The first factor, the lattice structure and type of bonding, is the most important in that it establishes the base behavior of brittle materials.

Dislocations are the primary source of of plasticity in a crystal. The energy associated with the dislocation varies with the width of the dislocation, the area over which the lattice distortion is spread (Fig. 9 adapted from Davidge, 1979). In ductile metals or ionic crystals, the total distortion is spread over a relatively large volume and the variations in energy (as a function of distance from the centre of the dislocation) are small as is the total barrier height. For example, the E_{act} of pure nickel is 284 kJ mol^{-1} and the E_{act} of sodium chloride is 120 kJ mol^{-1} (Frost and Ashby, 1982). Conversely, in covalent crystals or other crystals formed by highly directional bonds, the total deformation is highly localized over a relatively small volume and the energy density associated with the dislocation is large. For example, silicon has an activation energy of approx. 500 kJ mol^{-1} (Frost and Ashby, 1982) and acetaminophen crystals, assembled by hydrogen bonds, possesses an E_{act} for flow of 660 kJ mol^{-1}. It is this

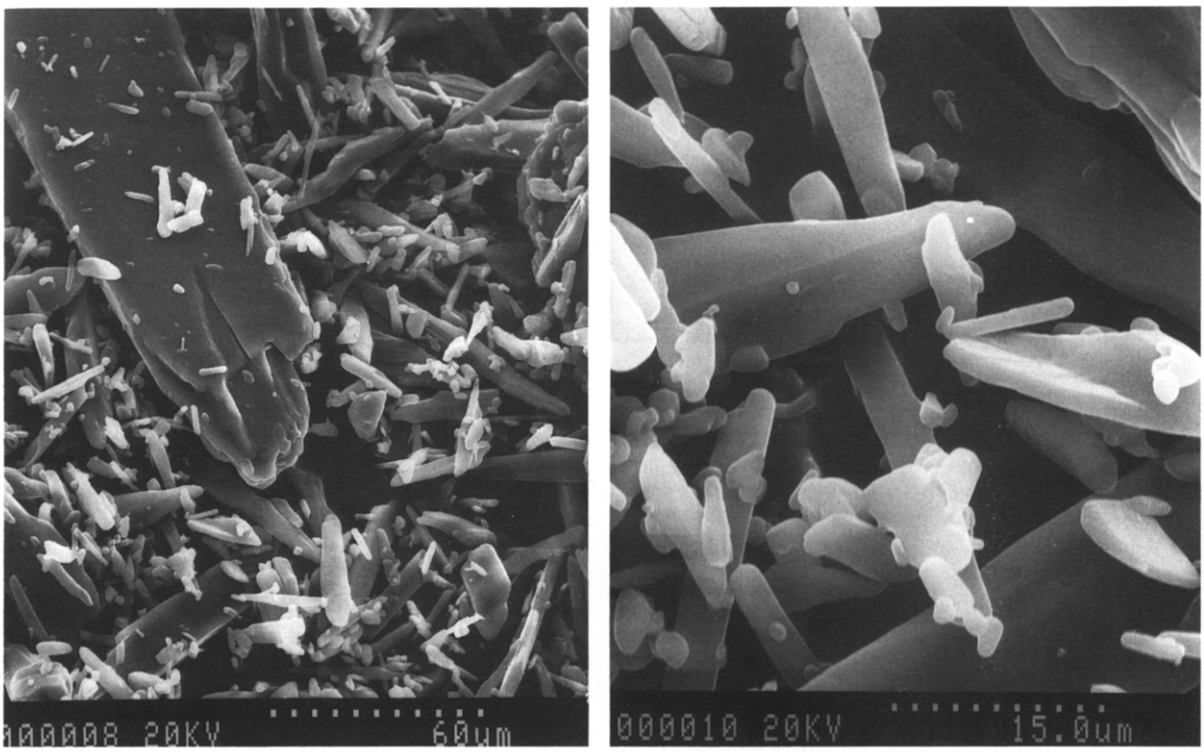

Fig. 7. Scanning electron micrographs at 500 × (left) and 2000 × (right) magnifications for acetaminophen lot F-02815.

energy that must be overcome if flow is to occur. When the activation parameters of acetaminophen are compared with those of other materials, the effects of the directional hydrogen bonds on flow are apparent. For materials such as these, fracture is likely to occur before significant flow can take place.

If the mechanism of flow truly is climb (as demonstrated by V_{act}), then the E_{act} should be similar to that for self-diffusion. Therefore, the type of future experiment suggested by the data is a measurement of self-diffusion which normally is performed by radiolabelling techniques. However, in the present case, the diffusion in acetaminophen crystals might be expected to be slow because of the following reasons: (1) the acetaminophen molecule is quite large. From a materials' standpoint, the flow unit must consist of the entire acetaminophen molecule unless decomposition occurs, so that the Burger's vector is also large ($a = 1.3688$ nm, $b = 1.0000$ nm, $c = 1.5103$ nm), i.e., the diffusion distance is longer; (2) acetaminophen crystals form primarily by intermolecular hydrogen bonding which links the molecules to each other to form a pleated sheet parallel to the xz plane and the sheets are stacked along the y direction by van der Waals forces to form a rough and thick molecular structure. As a result, there will be higher entropic components to the free energy for diffusion.

Eq. 30, derived from the Krausz and Eyring expression, can be used to compare the strain rates of sodium chloride and acetaminophen at different levels of stress:

$$\dot{\tau} = -\epsilon'\dot{\gamma} = -\epsilon' A \exp(\tau V_{act}/kT) \qquad (30)$$

If it is assumed that the system is much stiffer than the materials being tested, then the elastic modulus values of approx. 40 000 for sodium chloride and 8000 for acetaminophen can be used. The resultant plot of ln(strain rate) vs shear stress is shown in Fig. 10. Under the conditions of the

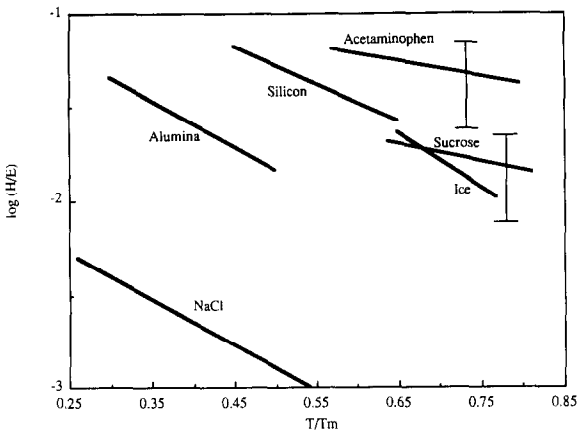

Fig. 8. Normalized hardness vs temperature plots for sodium chloride, silicon, ice, alumina, acetaminophen and sucrose. The values for the first four materials were taken from Frost and Ashby (1982) and those for the last two materials from Duncan-Hewitt (1988). The error for the elastic moduli of acetaminophen and sucrose is about 50%, because the values were derived by a depth of focus measurement of microindentations. The logarithmic scale is used to permit comparison with deformation mechanism maps (Frost and Ashby, 1982).

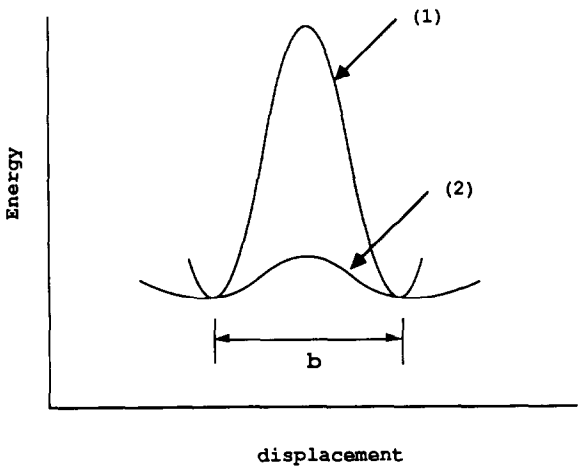

Fig. 9. The energy associated with a dislocation varies with the width of the dislocation and the area over which the lattice distortion is spread (Davidge, 1979). Curve (1) represents an energy distribution function for a deformation that is highly localized over a relatively small volume, therefore, the energy variation as a function of the Burgers length is relatively large; curve (2) represents an energy distribution function for a deformation that is spread over a relatively large volume, therefore, the energy variation as a function of Burgers vector is relatively small.

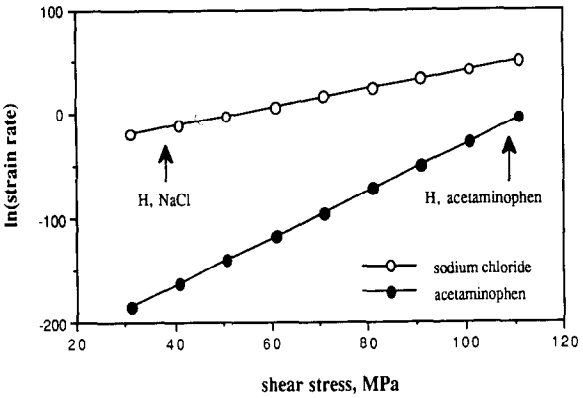

Fig. 10. The predicted plot of ln strain rate vs shear stress for sodium chloride and acetaminophen calculated using Eq. 30.

hardness test, the strain rates and therefore the self-diffusion rates for the materials are very similar. However, the strain rate of acetaminophen falls rapidly to zero as the stress level is decreased. Diffusion tests, which attempt to evaluate diffusion rates at zero stress would therefore be impracticable for the evaluation of acetaminophen.

The analyses performed in this study were developed for isotropic materials and were applied as though acetaminophen crystals, when distributed randomly in a powder bed, behaved isotropically, on average. In fact, work presently in progress suggests that this is far from true. Acetaminophen crystals are both elastically and plastically anisotropic. The deformation during compaction would tend to orient the crystals which, in turn would cause the compact to be anisotropic also. The effects of such anisotropy on the deformation kinetic analysis of tablet stress relaxation will be a primary focus of future work. The mechanisms controlling the kinetics at 10 s may not be the same as those controlling kinetics during tablet compaction where contact times are of the order of microseconds. However dislocation mechanisms usually control deformation at large strain rates. Substantiation of this awaits the development of a suitable model of tablet compaction.

6. Acknowledgements

We should like to thank Ortho Pharmaceutical (Canada) for the use of their Instron stress strain analyser. This work was supported by the Life Sciences Committee-Graduate Student Summer Program Award and in part by a National Science and Engineering Research Council of Canada Grant and a Medical Research Council of Canada Grant to W.C.D.-H.

7. References

Alderborn, G. and Nyström, C., Radial and axial tensile strength and strength variability of paracetamol tablets. *Acta Pharm. Suec.*, 21 (1984) 1–8.

Bangudu, A.B. and Pilpel, N., Effect of composition, moisture and stearic acid on the plasto-elasticity and tableting of paracetamol-microcrystalline cellulose mixtures. *J. Pharm. Pharmacol.*, 37 (1985) 289–293.

Britten, J.R. and Pilpel, N., Effects of temperature on the tensile strength of pharmaceutical powders. *J. Pharm. Pharmacol.*, 30 (1978) 673–677.

Carless, J.E. and Leigh, S., Compression characteristics of powders: radial die wall pressure transmission and density change. *J. Pharm. Pharmacol.*, 26 (1974) 289–297.

Casahoursat, L., Lemagnen, G. and Larrouture, D., The use of stress relaxation trials to characterize tablet capping. *Drug Dev. Ind. Pharm.*, 14 (1988) 2179–2199.

Cole, E.T., Rees, J.E. and Hersey, J.A., Relations between compaction data for some crystalline pharmaceutical materials. *Pharm. Acta Helv.*, 50 (1975) 28–32.

David, S.T. and Augsburger, L.L., Plastic flow during compression of directly compressible fillers and its effect on tablet strength. *J. Pharm. Sci.*, 66 (1977) 155–159.

Davidge, R.W., *Mechanical Behavior of Ceramics*, Cambridge University Press, Cambridge, U.K., 1979.

Doelker, E. and Shotton, E., The effect of some binding agents on the mechanical properties of granules and their compression characteristic, *J. Pharm. Pharmacol.*, 29 (1977) 193–198.

Duncan-Hewitt, W.C., The use of microindentation techniques to assess the ability of pharmaceutical crystals to form strong compacts. Ph.D. Thesis, University of Toronto (1988).

Duncan-Hewitt, W.C. and Weatherly, G.C., Evaluating the deformation kinetics of sucrose crystals using microindentation techniques. *Pharm. Res.*, 6 (1989a) 1060–1066.

Duncan-Hewitt, W.C. and Weatherly, G.C., Evaluating the hardness, Youngs' modulus and fracture toughness of some pharmaceutical crystals using microindentation techniques. *J. Mater. Sci. Lett.*, 8 (1989b) 1350–1352.

Duncan-Hewitt, W.C. and Weatherly, G.C., Modelling the uniaxial compaction of pharmaceutical powders using the mechanical properties of single crystals: I. Ductile materials. *J. Pharm. Sci.*, 79 (1990a) 147–152.

Duncan-Hewitt, W.C. and Weatherly, G.C., Modelling the uniaxial compaction of pharmaceutical powders using the mechanical properties of single crystals: II. Brittle materials. *J. Pharm. Sci.*, 79 (1990b) 273–278.

Esezobo, S. and Pilpel, N., Effect of temperature on the plasto-elasticity of some pharmaceutical powders and on the tensile strengths of their tablets. *J. Pharm. Pharmacol.*, 38 (1986) 409–413.

Fell, J.T. and Newton, J.M., Effect of particle size and speed of compaction on density changes in tablets of crystalline and spray-dried lactose. *J. Pharm. Sci.*, 60 (1971) 1866–1869.

Fell, J.T. and Newton, J.M., The tensile strength of lactose tablets. *J. Pharm. Pharmacol.*, 20 (1968) 657.

Frost, H.J. and Ashby, M.F., *Deformation Mechanism Maps*, Pergamon, Oxford, 1982.

Heckel, R.W., Density-pressure relationships in powder compaction. *Trans. Metall. Soc. AIME*, 221 (1961a) 671–675.

Heckel, R.W., An analysis of powder compaction phenomena. *Trans. Metall. Soc. AIME*, 221 (1961b) 1001–1008.

Hiestand, E.N., Tablet bond: I. A theoretical model. *Int. J. Pharm.*, 67 (1991) 217–229.

Hiestand, E.N. and Smith, D.P., Indices of tableting performance. *Powder Technol.*, 38 (1984) 145–159.

Hiestand, E.N. and Smith, D.P., Tablet bond: II. Experimental check of model. *Int. J. Pharm.*, 67 (1991) 231–246.

Hiestand, E.N., Well, J.E., Peot, C.B. and Ochs, J.F., Physical process of tableting. *J. Pharm Sci.*, 66 (1977) 510–519.

Humbert-Droz, P., Gurny, R., Mordier, D. and Doelker, E., Densification behavior of drugs presenting availability problems. *J. Pharm. Tech. Prod. Mfr*, 4 (2) (1983) 29–35.

Jones, T.M. and Pilpel, N., Some angular properties of magnesia and their relevance to material handling. *J. Pharm. Pharmacol.*, (Suppl.) 18 (1966a) 182S–189S.

Jones, T.M. and Pilpel, N., The flow of granular magnesia. *J. Pharm. Pharmacol.*, (Suppl.) 18 (1966b) 429–442.

Jones, T.M. and Pilpel, N., The flow properties of granular magnesia. *J. Pharm. Pharmacol.*, 18 (1966c) 81–93.

Krausz, A.S. and Eyring, H., *Deformation Kinetics*, Wiley, New York, 1975.

Krycer, I., Pope, D.G. and Hersey, J.A., An evaluation of the techniques employed to investigate powder compaction behavior. *Int. J. Pharm.*, 12 (1982) 113–134.

Krycer, I., Pope, D.G. and Hersey, J.A., The prediction of paracetamol capping tendencies. *J. Pharm. Pharmacol.*, 34 (1982) 802–804.

Lieberman, H.A. and Lachman, L., *Pharmaceutical Dosage Forms: Tablets*, Vol. 2, Dekker, New York, 1981, pp. 202–216.

Malamataris, S., Baie, S.B. and Pilpel, N., Plasto-elasticity and tableting of paracetamol, Avicel and other powders. *J. Pharm. Pharmacol.*, 36 (1984) 616–617.

McClintock, F.A. and Argon, A.S., *Mechanical Behavior of Material*, Addison-Wesley, Reading, MA, 1966.

Nyström, C., Malmqvist, K., Mazur, J. and Hölzer, A.W.,

Measurement of axial and radial tensile strength of tablets and their relation to capping. *Acta Pharm. Suec.*, 15 (1978) 226–232.

Obiorah, B.A., Possible prediction of compression characteristics from press cycle plots. *Int. J. Pharm.*, 1 (1978) 249–255.

Obiorah, B.A. and Shotton, E., The effect of waxes, hydrolysed gelatin and moisture on the compression characteristics of paracetamol and phenacetin. *J. Pharm. Pharmacol.*, 28 (1976) 629–632.

Papadimitropoulos, E.A., Post consolidation behavior of two crystalline materials, sodium chloride and potassium bromide. M.Sc. Pharm. Thesis, University of Toronto (1990).

Pilpel, N. and Walton, C.A., The effect of particle size and shape on the flow and failure properties of procaine penicilline powders. *J. Pharm. Pharmacol.*, (Suppl.) 26 (1974) 1–10.

Rippie, E.G. and Danielson, D.W., Viscoelastic stress/strain behavior of pharmaceutical tablets: analysis during unloading and postcompression periods. *J. Pharm. Sci.*, 70 (1981) 476–481.

Sheikh Salem, M., Fell, J.T., Alkaysi, H.N. and Muhsin, N.A., Stress relaxation of mixtures of pharmaceutical powder. *Acta Pharm. Technol.*, 30 (1984) 312–316.

Tetelman, A.S. and Chow, R., Acoustic emission testing and microcracking process. Acoustic Emission, ASTM STP 505. *Am. Soc. Test. Mater.*, (1972) 30–40.

Westbook, J.H. and Conrad, H., The science of hardness testing and its research application. *Am. Soc. Metals*, (1973).

Waring, M.J., Rubinstein, M.H. and Howard, J.R., Acoustic emission of pharmaceutical materials during compression. *Int. J. Pharm.*, 36 (1987) 29–36.

Yu, H.C.M., Rubinstein, M.H., Jackson, I.M. and Elsabbagh, H.M., Compaction characterisation of paracetamol and Avicel mixtures. *Drug Dev. Ind. Pharm.*, 15 (1989) 801–823.

Yu, H.C.M., Rubinstein, M.H., Jackson, I.M. and Elsabbagh, H.M., Multiple compression and plasto-elastic behavior of paracetamol and microcrystalline cellulose mixtures. *J. Pharm. Pharmcol.*, 40 (1988) 669–673.