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Review

Fundamentals of Powder Compression. I. The Compactibility and Compressibility of Pharmaceutical Powders[1,2]

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In spite of the widespread use of tablets, the theoretical understanding of the tableting process has been limited. During the last decades considerable research has been done in the field of powder technology and compaction. A survey of the literature and compression equations reveals many studies on the characterization of powder properties, most of which relate to volume reduction under pressure, i.e., to the compressibility of the powder bed. For practical purposes, however, it is also important to know the compactibility of a powder bed, i.e., the ability of a powdered material to be compressed into a compact of specified strength. This strength has to be defined, e.g., as radial tensile strength or deformation hardness. Thus the first part of this review comprises the theory of powder compression of individual substances, compression parameters, compression equations, and mechanical properties of compacts, including compact strength tests and compact hardness tests.

KEY WORDS: powder compression; compression equations; compactibility; compressibility; compression equations; compact hardness tests.

COMPRESSION EQUATIONS

Compression Parameters

Powdered drugs are not generally used alone when formulating solid dosage forms. A variety of excipients, such as diluents, disintegrants, binding agents, and lubricants, the vast majority in powder form, is included for particular functions. They are then processed into convenient forms for drug administration. While full chemical profiles of drugs and additives are generally well defined for quality assurance purposes, it is important to characterize their fundamental powder and processing properties, since in principle all factors influencing the final properties of the compact depend upon them (1–4).

The powder materials may be characterized by their physicotechnical properties, e.g., flowability, compressibility, compactibility, etc. However, compressibility and compactibility bear a direct relationship with the tableting performance of the particulate solids. The term "compressibility" is defined as the ability of a powder to decrease in volume under pressure, and the term "compactibility" is defined as the ability of the powdered material to be compressed into a tablet of specified strength (i.e., radial tensile strength or deformation hardness) (3, 5). These properties characterize the tabletability of individual components and mixtures.

Compression of Particulate Solids

The compression of powdered or granular material into a cohesive mass during the formation of a pharmaceutical tablet is a complex and irreversible dynamic process, in contrast to its apparent simplicity (6). During compressive operations, the stress applied to bulk solid pharmaceutical formulations gives rise to a change in bed density, progressively confining it to a diminishing volume, ultimately reaching that of the completed tablet.

The first attempts at an interpretation of pressing phenomena were made by Balshin (7), Rakovski (8), and Walker (9). However, Seeling and Wulff (10) were the first to elucidate the behavior of a powder system under pressure. They suggested that powder compaction proceeded in three main stages, i.e., (a) particle rearrangement and closer packing, (b) elastic and plastic deformation, and (c) cold working, with or without fragmentation. The existence of several stages of consolidation during the compaction of powders was later studied by various authors (11–14) visualizing other substages of the process. These stages may be enumerated as follows:

(i) interparticular slippage, leading to closer packing;
(ii) formation of temporary truts, columns, and vaults, which protect small voids and support the imposed load;
(iii) failure of the particles by plastic or elastic deformation;
(iv) cold working, with or without fragmentation; and
(v) development of a structure that supports the ap-

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plied load, so that any further reduction in volume involves the normal compressibility of the solid material.

In the case of ceramics, metals, and other materials, the stages and substages of compaction have also been suggested on the basis of distinction between porous (16) and nonporous materials (13, 17–19).

It must, however, be emphasized that these steps do not follow each other in sequence; on the contrary, in practice these phenomena usually overlap each other, and at least one of them may be absent under many conditions, as the stages of packing and deformation may occur concurrently (10, 14, 20). The significance of any of these phases depends to a large extent on the plasticity of the powder used (10).

The attempts that have been made to quantify the consolidation of particulate matter have been adequately reviewed by Kawakita and Tsutsumi (21).

Mechanism of Consolidation (Fig. 1)

In tableting operations, the initial situation at zero pressure consists of a certain quantity of powder material or granules in the die. At the onset of compression, particles within the bulk solid bed are likely to undergo some rearrangement in their packing state such that particle–particle contact distances are reduced without excessive deformation, and the bigger holes are filled. This process is monitored by the slipping of particles past each other and is influenced largely by surface characteristics, frictional properties, and the size of the particles (1., 22–28); the smaller the particles, the greater the number of particle contacts per unit volume and the greater the likelihood of fragile arching systems being developed in the loosely compacted powder.

For highly cohesive systems, this reduction in interparticle separation may yield a compact of adequate strength for transfer to capsule shells without any major particle deformation. However, the inherent cohesive properties of most drugs and excipients are unlikely to be sufficient to form tablets with adequate strength for subsequent handling.

As the applied stress rises, elastic and plastic deformation of the particles occurs, resulting in a squashing of particles, a reduction in inter- and intraparticulate voids, and a consequent increase in overall compact density (29–31). At this stage, the interparticular bonding takes place, and a coherent mass is formed.

As the stress progresses, particle fracture and rebonding may occur, and an excessive deformation may result in work hardening.

In some cases, however, a further increase in stress may result in undesirable phenomena such as capping and lamination (32) and, in specific cases, in work softening (34, 35). Capping and lamination are attributed to the inability of compacts to relieve localized internal stress without failure. This failure can emanate from a flaw within the tablet which, when subjected to high stress, extends by crack propagation (36, 37).

Work hardening is an effect caused by cold working of the material, following an extensive deformation at the contact points during compaction, rendering the specimen increasingly resistant to further deformation (38–40). On the contrary, work softening is a phenomenon, observed in easy deformable plastic materials, in which compact hardness first attains the maximum value and then decreases. Jetzer and Leuenberger (35) observed the work softening effect with sodium chloride, potassium chloride, and hexamine. These authors expressed the view that this is due to a decrease in lattice defects in the polycrystalline compact under applied pressure.

In practice, since drugs and excipients rarely exist in equidimensional particulate form, may contain intraparticulate pores, and possess different deformation/failure properties, a rigorous analysis of the changes in density during compaction is difficult (33).

The mechanism of compaction not only depends on the powder properties (41) but also is influenced largely by

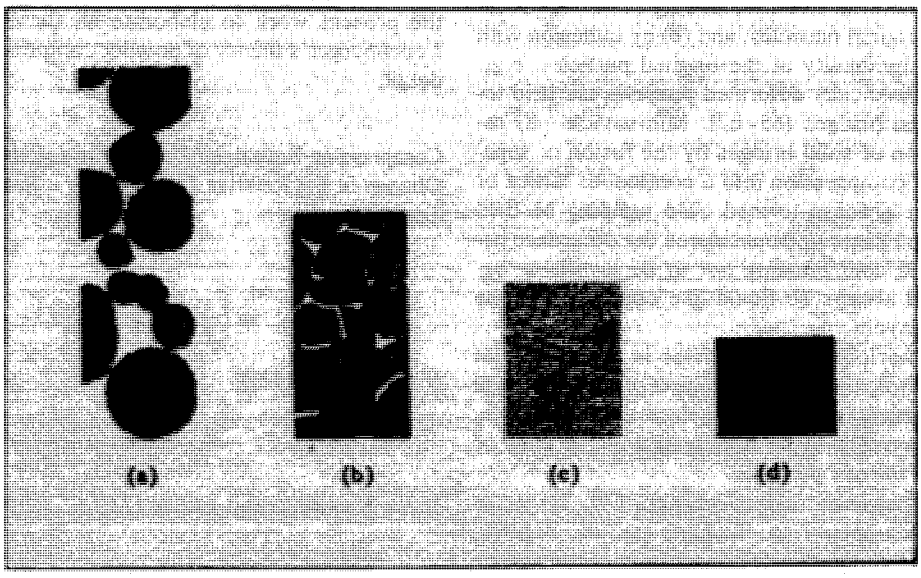

Fig. 1. Stages of the consolidation process.

various factors such as particle size (12, 42–47) and shape (48–52) as well as experimental conditions, e.g., applied pressure (53) and rate of compaction (42).

In addition, the properties of the resulting compact can be affected by the physicochemical properties of the starting materials, such as crystallization and milling conditions as well as the presence of a lubricant (54–57) and binder (58, 59).

Mechanisms of Bonding

The process by which the consolidated powders are bonded together under pressure is not well understood. However, it is generally accepted that compact formation by pressure occurs because of forces acting at the areas of true interparticle contact. Rumpf and his co-workers (60–64) have distinguished five different bonding mechanisms acting between particulate solids:

(i) solid bridges;
(ii) interfacial forces and capillary pressure at freely movable liquid surfaces;
(iii) adhesive and cohesive forces at non-freely movable binder bridges;
(iv) attraction between solid particles, principally by van der Waals forces; and
(v) mechanical interlocking.

The authors stated that molecular forces (van der Waals forces) are an important mechanism in the compression of drug particles. Under high compression pressures, the powder particles in a compact are forced into contact, and extensive areas of true contact between particles are formed. As the forces are typically short-range forces and are adequate to provide strong bonds, one might expect all materials to form strong intact compacts after being subjected to high compression. These forces are influenced by the particle size of the powder as their magnitude is increased by a reduction of interparticle distance.

The materials that undergo plastic deformation under pressure can be bonded in two different ways: (a) by sintering as an effect of plastic flow, caused by the extreme nonhomogeneous material stresses, leading to the loss of individuality of the original particles; and (b) by cohesion with retention of the individuality of the original particles, e.g., starch, where the plastically deformed particles are held together by hydrogen bridges (65–67). Milosovich (68) revealed the formation of solid bridges by the fusion of separate crystals under compression into a continuous lattice or a single crystal, a process termed cold welding or cold bonding. However, Führer (69) considered the difference between sintering and cold bonding not to be justifiable because there should always be liquid-like conditions in the particle boundary layer.

Mechanical interlocking of particles is an effect that does not play a significant role. The extent of the effect will depend on the particle shape and surface characteristics, and one would expect it to be manifested in the case of needle-shaped and fibrous particles.

Recently, Hüttenrauch and co-workers (70, 71) introduced the activation theory to elucidate particle bonding mechanisms. Under compaction pressure part of the energy should be absorbed by crystals as increased dislocation density and, thus, stored in the form of lattice defects. As a result of this mechanical activation, the particle surface is made amorphous, acquires a high reactivity, and tends toward releasing its excessive energy by the formation of interparticulate, sintering-like reactions, combined with partial elimination of lattice disorder.

Mathematical Models of Powder Compression

A survey of the literature reveals that more than 15 mathematical expressions have been suggested that deal with the characterization of tablet dimensions and changes in terms of the mechanisms involved in the densification process. These equations have been critically reviewed and compiled in the literature (1, 17, 72, 73).

Despite the fact that, in the pharmaceutical industry, it is more important to be able to obtain a tablet of adequate strength than to obtain a specific volume reduction, only a few equations include a prediction of the strength of the compact. Moreover, most of these equations involve the use of constants with an obscure physical significance and suffer limitations of applicability within specified conditions, e.g., compression pressure, consolidation behavior of powder. Furthermore, none of them accounts for and quantifies physical interactions taking place between the homogeneous and the heterogeneous particles in a multicomponent system.

Leuenberger and co-workers (1–3), however, suggested a novel approach by correlating the deformation hardness of the tablet as a function of the compression stress during preparation and its relative density. This equation determines the plasticity of the material, which is a practical measure of tabletability. This equation holds for pure substances as well as for binary mixtures. Moreover, since this equation is derived from the basic concept of bonding and nonbonding contact points present in a compact, it is capable of accounting for any physical interaction taking place between the components of a binary powder system.

A selection of the equations describing volume reduction–compression stress and tablet strength–compression stress profiles is given below. Since it is beyond the scope of the present work to elaborate all these expressions, only Leuenberger's theory of powder compression is described in detail.

Compression Equations Describing Volume Reduction or Change in the Relative Density ρ_r of a Powder Mass Under Pressure

$$\ln\left(\frac{1}{1-\rho_r}\right) = K\sigma_c + A \tag{1}$$

[from Heckel (11)],

$$\frac{V_0 - V}{V_0} = \frac{ab\,\sigma_c}{1 + b\,\sigma_c} \tag{2}$$

[from Kawakita and Lüdde (72)],

$$\frac{V_0 - V}{V_0 - V_\infty} = a_1 \exp(-k_1/\sigma_c) + a_2 \exp(-k_2/\sigma_c) \tag{3}$$

[from Cooper and Eaton (13)], where ρ_r is the relative density of the powder compact; σ_c is the applied pressure; V_o is the initial apparent volume; V is the powder volume under applied pressure σ_c; V_∞ is the powder volume at $\sigma_c \rightarrow \infty$; and, K, A, a, b, a_1, a_2, k_1, and k_2 are constants.

Compression Equations Describing the Strength–Porosity or Strength–Compression Stress Relationship

$$\sigma_T = \sigma_{T_{max}} \exp(-b\epsilon) \tag{4}$$

[from Ryshkewitch (74)],

$$\sigma_T = a \ln \sigma_c + b \tag{5}$$

[from Higuchi and co-workers (75)],

$$\log \sigma_c = a\,\sigma_T + b \tag{6}$$

[from Shotton and Ganderton (76)],

$$P = P_{max}[1 - \exp(-\gamma\,\sigma_c\,\rho_r)] \tag{7}$$

[from Leuenberger and co-workers (1–3)], where σ_T is the tensile strength; $\sigma_{T_{max}}$ is the maximum tensile strength for porosity $\epsilon = 0$; P is the deformation (Brinell) hardness; P_{max} is the maximum deformation hardness at $\sigma_c \rightarrow \infty$ and $\rho_r \rightarrow 1$; σ_c is the compression stress applied to make the compact; γ is the compression susceptibility parameter; ρ_r is the relative density, where $\rho_r = 1\text{-}\epsilon$ and ϵ is the porosity; and a and b are constants.

Leuenberger's Theory of Powder Compression

The compression equation derived by Leuenberger relates two indices of powder compression—compactibility, i.e., the compact hardness specific parameter, and compressibility, which is the specific parameter of relative density or porosity (1–3). This theory is based on the concept of effective bonding contact points across the cross-sectional area of a compact. Leuenberger assumed that the cross-sectional area A of a cylindrical tablet contains a number N_+ of bonding contact points and a number N_- of nonbonding contact points:

$$A = (N_+ + N_-)\,a = N_o a \tag{8}$$

$$N_o = N_+ + N_- \tag{9}$$

where A is the cross-sectional area of the compact, a is the unit area per bonding point (e.g., molecular unit contact points with the dimensions 20–30 Å^2), N_o is the total number of contact points in the cross-sectional area A, N_+ is the number of bonding points, and N_- is the number of nonbonding points.

As a first approximation, it is only the bonding points N_+ that contribute to the compact hardness. The nonbonding points N_- exhibit a passive role and therefore do not show any effect on hardness. Further, the deformation hardness P is postulated to be proportional to the number of bonding points N_+:

$$P = \lambda\,N_+ = \lambda\,(N_o - N_-) \tag{10}$$

where λ is the proportionality constant.

When the relative density ρ_r of the substance reaches its maximum, i.e., $\rho_r \rightarrow 1$, the number of nonbonding points N_- is reduced to zero. Therefore, all the contact points N_o are available as bonding points N_+ contributing maximum possible hardness P_{max} to the compact:

$$P_{max} = \lambda N_{+max} = \lambda\,N_o \tag{11}$$

where P_{max} is the maximum possible deformation hardness of the compact at $\sigma_c \rightarrow \infty$ and $\rho_r \rightarrow 1$, and σ_c is the compression stress used to make the compact.

Leuenberger further assumed that the relative decrease in the nonbonding points dN_-/N_- changes in proportion to the externally applied compression stress σ_c and the change in relative density $d\rho_r$. This leads to the following simple differential equation:

$$\frac{dN_-}{N_-} = -\gamma\,\sigma_c\,d\rho_r \tag{12}$$

where λ is the proportionality constant.

Incorporating the limiting conditions that when $\rho_r = 0$, there are only nonbonding points ($N_- = N_o$), and integrating, one obtains

$$N_- = N_o \exp(-\gamma\,\sigma_c\,\rho_r) \tag{13}$$

The expression obtained for the deformation hardness P is then

$$P = \lambda\,[N_o - N_o \exp(-\gamma\,\sigma_c\,\rho_r)] \tag{14}$$

or

$$P = \lambda\,N_o\,[1 - \exp(-\gamma\,\sigma_c\,\rho_r)] \tag{15}$$

Substituting Eq. (11) in Eq. (15), one obtains the following expression for powder compression:

$$P = P_{max}[1 - \exp(-\gamma\,\sigma_c\,\rho_r)] \tag{7}$$

where P is the deformation (Brinell) hardness (MPa), P_{max} is the magnitude of P at $\sigma_c \rightarrow \infty$ and $\rho_r \rightarrow 1$ (MPa), σ_c is the compression stress applied to make the compact (MPa), ρ_r is the relative density, and γ is the compression susceptibility (MPa^{-1}).

This equation quantifies two parameters: P_{max} and γ. P_{max} denotes the theoretical maximum deformation hardness that would be attained as σ_c approaches infinity. P_{max} consequently describes the *compactibility*. A low P_{max} value shows a relatively poor compactibility, for even with high compression stress this limiting value cannot be exceeded.

The parameter γ, termed the compression susceptibility, specifies the rate—which varies according to the material—at which the compact hardness P builds up with an increase in the applied compression stress σ_c. A high value of the compression susceptibility parameter indicates that the limiting value of hardness ($P \cong P_{max}$) and a sharp decrease in compact porosity may be attained with relatively low compression stress. This parameter consequently represents *compressibility*.

These two parameters allow one to characterize the deformation of a substance under pressure and to judge the binding behavior of particles. Jetzer *et al.* (77) have presented a classification of the deformation behavior and evaluation of the bonding properties of substances on the basis of numerical values of these two parameters (Tables I and II).

Table I. Approximate Values of P_{max} and γ Observed in Plastic and Brittle Materials (the Values Shown Are Orders of Magnitude) (77)

	Type of deformation under stress	
Parameter	Plastic	Brittle
Compactibility	Small	Large
P_{max} (MPa)	$0-10^2$	10^2-10^3
Compressibility	Large	Small
γ (MPa^{-1})	10^{-2}	10^{-3}

MECHANICAL PROPERTIES OF COMPACTS

The compaction properties of pharmaceutical materials are commonly assessed by characterizing their mechanical properties. Although a number of tests are performed, hardness, measured by indentation method, and tensile strength, measured by tensile stress determination, bear a direct relationship with the compactibility of the material. The indentation hardness describes the "local" plasticity of the material, and the tensile strength describes the "global" strength of the compact (78). These two measurements can be used to formulate dimensionless parameters that characterize the relative tableting performance of individual components and mixtures (79).

Compact Strength Rates

Various types of tests, e.g., abrasion, bending, diametral crushing, fatigue strength, etc., have been used to express compact strength (80); however, the data from these tests can seldom be correlated in a precise manner (81).

In pharmaceutical practice, tablet strength is commonly measured by diametral compression involving tensile failure of tablets. This test is a measurement of the force required to fracture the tablet. However, instead of an ideal fracture, complicated fracture patterns may occur with some materials, which may lead to inaccurate determinations (82). The determination of tensile strength, therefore, depends upon the correct state of stress developing within the compact (83).

If the test method is designed so that the tablet failure is a result of the application of tensile stress only, strength can be calculated by the relationship (84)

$$\sigma_x = \frac{2F}{\pi DT} \tag{16}$$

Table II. Relationship Between the Bonding Properties of a Material and Its Compression Parameters (the Specified Values Are Orders of Magnitude) (77)

Compactibility parameter P_{max} (MPa)	Compressibility parameter γ (MPa^{-1})	Bonding properties
Low ($1-10^2$)	Low (10^{-3})	Poor to very poor
High (10^2-10^3)	Low (10^{-3})	Moderate
Low ($1-10^2$)	High (10^{-2})	Good
High (10^2-10^3)	High (10^{-2})	Very good

where σ_x is the tensile strength, F is the force needed to cleave the tablet, D is the diameter of the tablet, and T is the tablet thickness.

In practical terms, to obtain tensile strength failure of a constant magnitude, the conditions of the test must ensure that the maximum length of the load diameter is under constant tensile stress, associated with the maximum value for shear and compressive stresses, below the loading area (83). In addition, various factors, e.g., elastic and plastic properties of the material, the fracture behavior of the material, the homogeneity of the compact, adhesion conditions between the compact and its support, the properties of the tensile apparatus, may influence the tensile strength measurements (85–87).

Some authors (87, 88), however, suggest the determination of axial tensile strength because of the sensitivity of radial tensile strength measurements to crack propagation variations. In the axial tensile strength test, the tablet cleaves in a plane along its axis. It is measured by straining the face of the tablet, mounted between a pair of adapters, and determining the maximum force required to cause failure due to tensile stresses. The axial tensile strength is calculated by the relationship (89)

$$\sigma_z = \frac{4F}{D^2\pi} \tag{17}$$

where σ_z is the axial tensile strength, F is the force required to cleave the tablet, and D is the diameter of the tablet.

A comparison of radial and axial tensile strengths is indicative of the bonding strength in two directions and may be related to the tendency toward capping (81, 90). Jetzer and Leuenberger (78) reported a relationship between the deformation hardness and the radial tensile strength of the tablet to predict the capping tendency of materials.

Compact Hardness Tests

In technical terms, hardness may be defined as the resistance of a solid to local permanent deformation (91). It is related primarily to the plasticity and therefore assesses a number of fundamental material properties. Deformation hardness is usually measured by a nondestructive indentation or scratch test. The techniques of hardness testing can be divided into two groups:

(a) tests that determine hardness by the static impression method, e.g., the Brinell, Vickers, and Rockwell hardness tests; and
(b) tests that determine hardness by dynamic or rebound methods.

The most widely used methods in determining the hardness of solids are static indentation methods. These involve the formation of a permanent indentation on the surface of the material to be examined; the hardness being determined by the load and size of the indentation formed is usually expressed as force per unit area.

In the Brinell hardness test a hard spherical indenter of diameter D is pressed under a fixed normal load F onto the smooth surface of the material under examination (Fig. 2). When equilibrium has been reached, the load and the in-

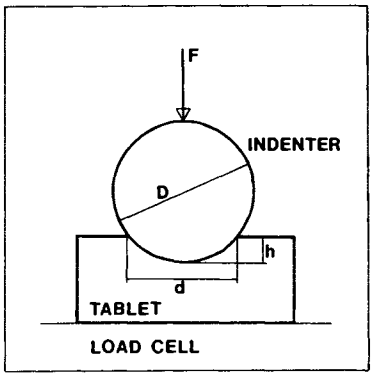

Fig. 2. Brinell hardness test.

denter are removed. The resulting indentation diameter d and depth h are measured. The Brinell hardness number (BHN) is expressed as the ratio of the load to the diameter of the indentation and can be calculated from the relationship (92)

$$\text{BHN} = \frac{2F}{\pi D\,(D - \sqrt{D^2 - d^2})} \tag{18}$$

In most cases, the Brinell hardness number is not a constant for a given material but depends upon the load and diameter of the indenter (91).

Dynamic tests differ from static ones in that the test object is exposed not to gradually and regularly increasing stress loads, but to an abrupt impact stress. In dynamic methods, either a pendulum is allowed to strike from a known distance or an indenter is allowed to fall under gravity onto the surface of the test material. The hardness is then determined from the rebound height of the pendulum or the volume of the resulting indentation.

The volume of the indentation so formed is directly proportional to the kinetic energy of the indenter. It, therefore, implies that the material offers an average pressure of resistance to the indenter equal to the ratio

$$\frac{\text{energy of impact}}{\text{volume of indentation}} \tag{19}$$

This has the dimensions of pressure and is sometimes referred to as the dynamic hardness number.

Hiestand *et al.* (93) described a novel dynamic or impact test for estimating the hardness of compressed tablets. They allowed a steel sphere, arranged as a pendulum, to swing onto the flat face of a rigidly held tablet. Since energy E consumed during the impact is used in doing pressure–volume work, this energy divided by the volume of the indentation provides an estimate of the mean deformation pressure.

In pharmaceutical practice, Spengler and Kaelin (94) and Nutter-Smith (95) were the first to determine the tablet hardness by the indentation method. Afterward, considerable work was reported on hardness profiles across tablet surfaces and elastic recovery of tablets using Brinell (96–102) and Vickers (103, 104) hardness tests.

Leuenberger (1) developed a semistatic method to determine tablet hardness. He used a 1.76-mm-diameter steel sphere, pressed into the compact by an Instron universal testing instrument under a known load. The diameter of the dent was measured by photomicrograph, and the Brinell method of calculating hardness was used.

In the area of crystallography, indentation methods have found use in determining crystal hardness (105–107). Ridgway *et al.* (108) determined the crystal hardness of substances using the Vickers hardness test. Jetzer (34) compared the crystal hardness of substances of pharmaceutical importance with their compactibility parameter P_{max} by the Brinell hardness test.

Deformation (Brinell) Hardness Determination

The deformation or Brinell hardness of tablets was determined using a universal testing instrument (Model TT-DM, Instron Ltd., High Wycombe, England), equipped with an Instron load cell (Type CCM), by a quasi-static method developed by Leuenberger (1, 3).

The measurements were accomplished using an upper punch fitted with a steel sphere (see Fig. 3) that was pushed at a constant rate into the center of the upper surface of the tablet until the desired load was reached. The diameter of the dent left on the tablet surface was measured by scanning electron micrograph (see Fig. 4).

Since the plastic materials varied in softness and, consequently, in their resistance to indentation load, it became inevitable to use a different load for different material and its binary mixtures with caffeine. Therefore, two indentation loads, i.e., 3.924 N for magnesium stearate and 9.81 N for polyethylene glycol (4000), sodium lauryl sulfate, and sodium stearate, were used. The selection of the indentation load was made on the basis of its optimum compatibility with components in the binary mixture.

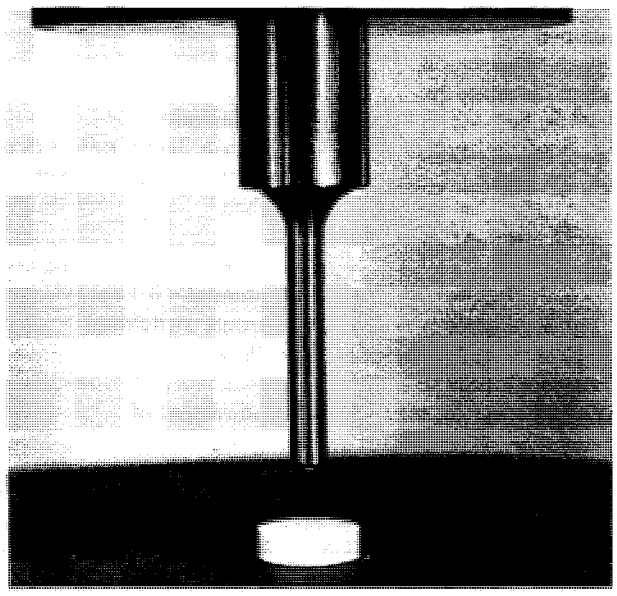

Fig. 3. Deformation hardness test [after Leuenberger (1, 3)].

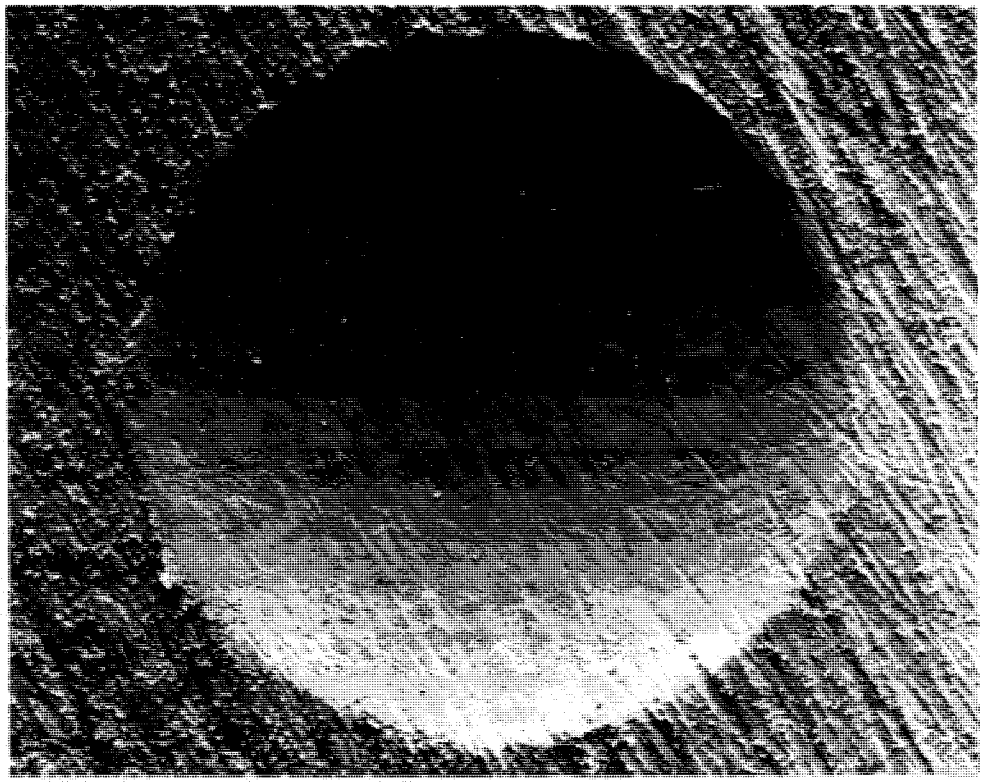

Fig. 4. Scanning electron micrograph of the dent left on the magnesium stearate tablet. 100×.

Experimental Conditions Observed in the Determination of Deformation (Brinell) Hardness

The following parameters were kept constant.

Storage conditions of tablets	Room temperature (25 ± 1°C) Relative humidity, 50 ± 10%
Lag time allowed for post-compression changes	8 days
Indentation load	3.924 and 9.81 N
Number of tablets tested for each observation	6
Indentation rate	0.05 cm/min
Stress-relief rate	0.05 cm/min
Pressure transducer	Instron load cell (Type CCM) at lower tablet surface
Dwell time at maximum stress	Duration of pressure constant at <0.1 sec (via electronic switching)
Diameter of indenter sphere	1.761 mm

Scanning Electron Microscopic Measurement of Indentation Diameter

The tablet to be examined was mounted on an aluminium stub using colloidal carbon and sputtered (SCD 030, Balzers-Union AG, Balzers, Fürstentum Liechtenstein) in high vacuum with a thin layer (20 nm) of gold.

The dent on the tablet was examined in a scanning electron microscope (Stereoscan Mark 2A, Cambridge Scientific Instruments, Cambridge, England) at an accelerating voltage of 10 kV and the image formed on the CRT was photographed (see Fig. 4).

Determination of the Effect of the Indentation Load on the Hardness Value and on Compression Parameters P_{max} and γ

The hardness values (Brinell, Meyer, Vickers, etc.) depend upon experimental variables, e.g., indentation load, dwell time of load, load rate, size of indenter, etc., and vary with them. It is, therefore, necessary to keep these variables constant for a set of experiments in order to make the results comparable. However, since the plastic materials varied in their resistance to the indentation load, it became inevitable to use a different load for different material and its binary mixtures with caffeine. It was, therefore, necessary to determine the effect of this variable on compression parameters.

Meyer (109) found for a sphere of given diameter that, for most substances, the relation between the indentation load F and the diameter of the dent d may be expressed by

$$F \propto d^n \tag{20}$$

or

$$F = kd^n \tag{21}$$

where k is the index of specific hardness and is a material-specific constant, and n is a coefficient representing the rate of hardness increase as indentation proceeds. In the limiting case that $d \ll$ the diameter of the indenter sphere and $n = 2$, the Meyer hardness number (MHN) is equal to the Brinell hardness number (BHN) and is given by

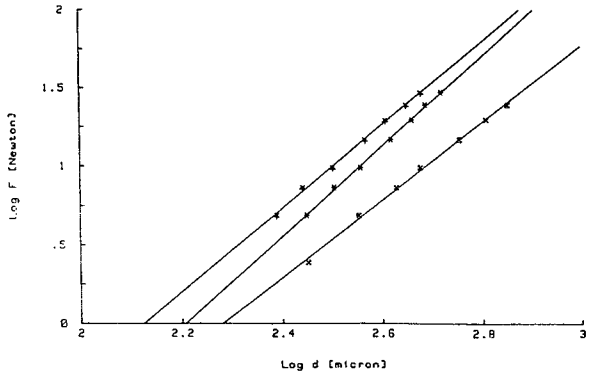

Fig. 5a. Relation between the logarithm of indenter load and the logarithm of dent diameter for caffeine (anh.) tablets compressed at various stresses. Compression stress: (⊠) 51.61 MPa, $Y = 2.456x - 5.602$, $r = 0.9987$; (*) 154.84 MPa, $Y = 2.863x - 6.317$, $r = 0.9993$; (★) 258.07 MPa, $Y = 2.649x - 5.625$, $r = 0.9990$.

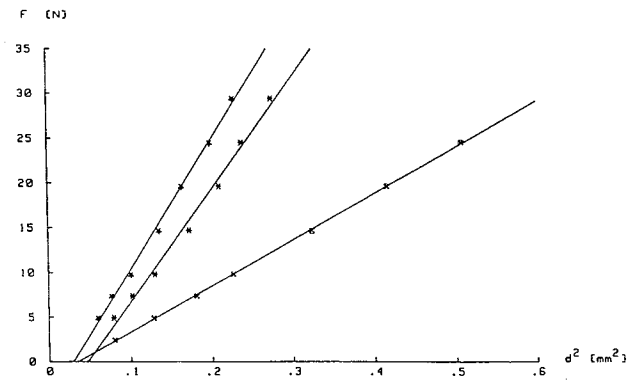

Fig. 6a. Relation between indenter load (F) and square of dent diameter (d^2) for caffeine (anh.) tablets compressed at various stresses. Compression stress: (⊠) 51.61 MPa, $Y = 51.542x - 1.801$, $r = 0.9999$; (*) 154.84 MPa, $Y = 125.840x - 5.900$, $r = 0.9958$; (★) 258.07 MPa, $Y = 145.673x - 4.258$, $r = 0.9984$.

$$\text{BHN} \cong \text{MHN} = \frac{F}{\pi\,(d/2)^2} \tag{22}$$

In this case, Eq. (21) can be written as

$$F = kd^2 \tag{23}$$

or

$$k = \frac{F}{d^2} \tag{24}$$

Theoretically, the value of k, which represents the specific hardness of a material, is directly proportional to the Meyer and Brinell hardness numbers.

Method

In order to determine the effect of the indentation load on the hardness values and on the compression parameters, P_{max} and γ, caffeine tablets were prepared at various compression stresses, i.e., 51.61, 103.23, 154.84, 206.45, 258.07, and 309.68 MPa. These tablets were indented under a series of loads ranging between 2.45 and 29.43 N. The dent left on the tablet was measured by photomicrographs.

In accordance with Eq. (21), log F was plotted against log d and, as the value of Meyer's work-hardening index n was expected to be ~2, load F against d^2. The Brinell and Meyer hardness values were calculated using Eqs. (18) and (22), respectively. Subsequently, the compression parameters, P_{max} and γ, were computed from the Brinell hardness values using a nonlinear regression analysis program. The values of the compression parameters were computed for the series of indentation loads used.

RESULTS AND DISCUSSION

Indentation diameters were obtained with a series of loads, and the plots of log F against log d and load F against d^2 are shown in Figs. 5a and 5b and 6a and 6b, respectively.

The plots of log F against log d and of F against d^2 for all compression stresses are straight lines with regression coefficient better than 0.99. This shows that Meyer's relationship, originally empirically derived for solid materials, can be applied satisfactorily to highly consolidated tablets.

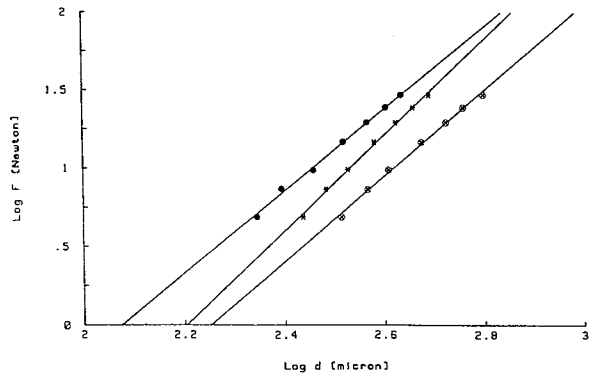

Fig. 5b. Relation between the logarithm of indenter load and the logarithm of dent diameter for caffeine (anh.) tablets compressed at various stresses. Compression stress: (⊗) 103.23 MPa, $Y = 2.724x - 6.133$, $r = 0.9982$; (*) 206.45 MPa, $Y = 3.053x - 6.727$, $r = 0.9988$; (●) 309.68 MPa, $Y = 2.617x - 5.426$, $r = 0.9987$.

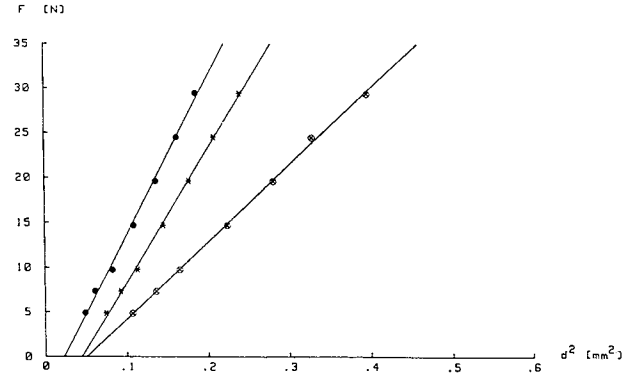

Fig. 6b. Relation between indenter load (F) and square of dent diameter (d^2) for caffeine (anh.) tablets compressed at various stresses. Compression stress: (⊗)103.23 MPa, $Y = 85.750x - 4.320$, $r = 0.9995$; (*) 206.45 MPa, $Y = 149.265x - 6.656$, $r = 0.9994$; (●) 309.68 MPa, $Y = 176.409x - 4.052$, $r = 0.9985$.

Table III. P_{max} and γ Values of Caffeine (Anh.) Powder with Various Indentation Loads[a]

Indentation load (N)	P_{max} (MPa)	95% confidence intervals	γ, 10^2 (MPa^{-1})	95% confidence intervals	N	SS-min (MPa^2)	(SS-min/N)$^{1/2}$ (MPa)
29.43	219.90	137.97 . . . 301.84	0.67	0.16 . . . 1.17	6	372.07	7.87
24.53	203.27	131.06 . . . 275.49	0.73	0.17 . . . 1.29	6	393.66	8.10
19.62	199.86	122.08 . . . 277.64	0.68	0.14 . . . 1.22	6	355.56	7.70
14.72	184.97	182.36 . . . 187.57	0.68	0.66 . . . 0.70	6	490.60	9.04
9.81	158.31	76.58 . . . 240.04	0.74	−0.08 . . . 1.56	6	511.26	9.23
4.91	138.03	24.81 . . . 251.25	0.65	−0.41 . . . 1.71	6	645.24	10.37

[a] Average value of compressibility parameter $\gamma = (0.69 \pm 0.04) \times 10^{-2}$ MPa^{-1}. N, number of observations; SS-min, minimum sum of squared residuals (sum of squared deviations of the experimental from the calculated values); (SS-min/N)$^{1/2}$, mean deviation per observation (square root of sum of the squared residuals divided by the number of observations).

These straight lines do not pass through the origin, indicating that the specific hardness index k is directly proportional, but not equal, to the Meyer or Brinell hardness numbers as expressed by Eq. (24). The value of Meyer's work-hardening index n obtained for various compression stresses does not exhibit a regular pattern. As the tablets become harder, the value of n initially increases from ~2.5 to 3.1 and then decreases. This shows that caffeine, unlike many other brittle materials reported by Aulton and Marok (38), consolidates very well at medium stresses, and maximum consolidation approaches at a compression stress of ~200 MPa. Above this compression stress, the hardness continues to rise with increasing compression stress; however, the value of n falls from ~3.1 to 2.6 as work-hardening continues, presumably because of the reduction of the compact's capacity for further work-hardening.

The results for the compression parameters, P_{max} and γ, are given in Table III.

The results for the hardness values show an excellent agreement between the Brinell and the Meyer hardness relationships. However, it is observed that hardness is not a single-valued quantity but, rather, varies in relation to the indentation load; there is an increase in the observed hardness with increasing load, because a large indentation produced by a given sphere will involve greater plastic strains than a small one, a corresponding increase in the representative yield stress, and therefore an appreciable increase in the observed hardness.

Consequently, the results for the compression parameters show that the compactibility parameter P_{max} is not a constant value but, rather, varies with the load. In contrast, the compression susceptibility or compressibility parameter γ is a constant value within the limits of the experimental error and is independent of experimental variables (refer to Table III). This is not unexpected, as P_{max} is determined from the hardness values, which are variable dependent,

$$P = P_{max} [1 - \exp (-\gamma \sigma_c \rho_r)] \tag{7}$$

whereas γ is a function of the ratio P/P_{max}, which is constant,

$$\exp (-\gamma \sigma_c \rho_r) = 1 - \frac{P}{P_{max}} \tag{25}$$

or

$$-\gamma = \frac{1}{\sigma_c \rho_r} \ln \left(1 - \frac{P}{P_{max}}\right) \tag{26}$$

where P is the deformation hardness of the compact (MPa), P_{max} is the magnitude of P at $\sigma_c \to \infty$ and $\rho_r \to 1$ (MPa), γ is the compression susceptibility (MPa^{-1}), σ_c is the compression stress applied to make the compact (MPa), and ρ_r is the relative density.

Moreover, the dimension of γ is equal to the ratio volume/energy, and its reciprocal, i.e., $1/\gamma$, can be interpreted as the volume-specific mean activation energy E_a required to induce plastic deformation or fragmentation in the material. Since the mean activation energy E_a is a material-specific constant, the compressibility parameter γ is expected to be independent of any experimental variable (see Table IV). It has thus been shown that the mean activation energy E_a of a powder material is proportional to its compactibility parameter P_{max}.

Table IV. Values of Compressibility Parameter γ and Mean Activation Energy E_a of Individual Materials (per Unit Volume)

Material	γ value, 10^2 (MPa^{-1})	Mean activation energy E_a or $1/\gamma$ per unit volume (MPa)
Caffeine (anh.) powder	0.69 ± 0.04[a]	144.89 ± 7.30
Magnesium stearate	4.75	21.0
Polyethylene glycol (4000)	4.22	23.70
Sodium lauryl sulfate	14.87	6.72
Sodium stearate	4.70	21.28

[a] See Table III.

REFERENCES

1. H. Leuenberger. *Zur Theorie der Pulverkompression,* Habilitationsschrift, University of Basle, Basle, 1980.
2. H. Leuenberger, E. N. Hiestand, and H. Sucker. *Chem.-Ing.-Tech.* 53:45–47 (1981).
3. H. Leuenberger. *Int. J. Pharm.* 12:41–55 (1982).
4. P. York. *Int. J. Pharm.* 14:1–28 (1983).
5. H. Leuenberger and W. Jetzer. *Powder Technol.* 37:209–218 (1984).
6. E. G. Rippie and D. W. Danielson. *J. Pharm. Sci.* 70:476–481 (1981).
7. M. Y. Balshin. *Vestnik. Metalloprom.* 18:124–137 (1938).

8. V. S. Rakovski. *Fundamental Considerations in the Production of Hard Alloys,* Onti, Moscow, 1935.
9. E. E. Walker. *Trans. Faraday Soc.* **19**:73–83, 614 (1923).
10. R. P. Seeling and J. Wulff. *Trans. Am. Inst. Min. Metall. Eng.* **166**:492–505 (1946).
11. R. W. Heckel. *Trans. Metall. Soc. AIME* **221**:671–675, 1001–1008 (1961).
12. C. L. Huffine and C. F. Bonilla. *Am. Inst. Chem. Eng. J.* **8**:490–493 (1962).
13. A. R. Cooper and L. E. Eaton. *J. Am. Ceram. Soc.* **45**:97–101 (1962).
14. J. A. Hersey and J. E. Rees. The effect of particle size on the consolidation of powders during compaction. Particle Size Analysis Conference, Bradford, England, 1970.
15. K. A. Khan and C. T. Rhodes. *J. Pharm. Sci.* **64**:444–447 (1975).
16. J. van der Zwan and C. A. M. Siskens. *Powder Technol.* **33**:43–52 (1982).
17. G. Bockstiegel and J. Hewing. *Arch. Eisenhüttenwes.* **36**:751–767 (1965).
18. W. A. Gray. *The Packing of Solid Particles,* Chapman and Hall, London, 1968.
19. P. J. James. *Powder Metall. Int.* **4**:82–85, 145–149, 193–198 (1972).
20. S. Malkowska and K. A. Khan. *Drug Dev. Ind. Pharm.* **9**:331–348 (1983).
21. K. Kawakita and Y. Tsutsumi. *Bull. Chem. Soc. Jap.* **39**:1364–1368 (1966).
22. E. N. Hiestand. *J. Pharm. Sci.* **55**:1325–1344 (1966).
23. E. N. Hiestand. *Pharm. Ind.* **34**:262–269 (1972).
24. O. Molerus. *Powder Technol.* **28**:135–145 (1981).
25. W. D. Jones. *Fundamental Principles of Powder Metallurgy,* Edward Arnold, London, 1960, pp. 245–260.
26. S. Clyens and W. Johnson. *Mater. Sci. Eng.* **30**:121–139 (1977).
27. C. Führer. *Acta Pharm. Tech.* **12**:143–153 (1966).
28. C. A. Rogers. *Packing and Covering,* Cambridge University Press, Cambridge, 1964.
29. A. Broese van Groenou. *Powder Technol.* **28**:221–228 (1981).
30. E. Shotton. *Pharm. Ind.* **34**:256–262 (1972).
31. G. K. Bolhuis and C. F. Lerk. *Acta Pharm. Tech.* **23**:13–20 (1977).
32. A. Ritter and H. B. Sucker. *Pharma. Technol.* **4**(3):57–65, 128 (1980).
33. E. Doelker. Developments in compression. Compressional tests as an aid in tablet formulation. In D. D. Breimer and P. P. Speiser (eds.), *Topics in Pharmaceutical Sciences 1983,* pp. 371–385.
34. W. Jetzer. *Verpressbarkeit und Kompressibilität von pharmazeutischen Wirk- und Hilfsstoffen unter Berücksichtigung binärer Mischungen,* Ph.D. thesis, University of Basle, Basle, 1982.
35. W. Jetzer and H. Leuenberger. *Powder Technol.* **42**(2):137–144 (1985).
36. E. N. Hiestand, J. E. Wells, C. B. Peot, and J. F. Ochs. *J. Pharm. Sci.* **66**:510–518 (1977).
37. S. Leigh, J. E. Carless, and B. W. Burt. *J. Pharm. Sci.* **56**:888–892 (1967).
38. M. E. Aulton and I. S. Marok. *Int. J. Pharm. Tech. Prod. Mfr.* **2**:1–6 (1981).
39. J. E. Rees and P. J. Rue. *J. Pharm. Pharmacol.* **30**:601–607 (1978).
40. J. E. Rees and P. J. Rue. *Drug Dev. Ind. Pharm.* **4**:131–156 (1978).
41. T. M. Jones. *Pharm. Ind.* **39**:469–476 (1977).
42. J. T. Fell and J. M. Newton. *J. Pharm. Sci.* **60**:1866–1869 (1971).
43. A. McKenna and D. F. McCafferty. *J. Pharm. Pharmacol.* **34**:347–351 (1982).
44. H. R. Gregory. *Trans. Inst. Chem. Eng.* **40**:241–251 (1962).
45. A. Sheak. Ph.D. thesis, University of London, London, 1975.
46. C. C. Harris. *Trans. AIME* **238**:17–30 (1967).
47. K. Kendall. *Nature* **272**:710–711 (1978).
48. M. P. Summers, R. P. Enever, and J. E. Carless. *J. Pharm. Sci.* **66**:1172–1175 (1977).
49. E. Shotton and B. A. Obiorah. *J. Pharm. Sci.* **64**:1213–1216 (1975).
50. E. Shotton and B. A. Obiorah. *J. Pharm. Pharmacol. Suppl.* **25**:37P–43P (1973).
51. J. Jaffe and N. E. Foss. *J. Am. Pharm. Assoc. (Sci. Ed.)* **48**:26–29 (1959).
52. R. Rupp and J. Healy. *Acta Pharm. Tech.* **21**:191–194 (1975).
53. I. M. Jackson, F. Ridgway, and M. H. Rubinstein. Compression characteristics of mixtures of elastic, plastic and brittle materials. *3rd International Conference on Pharmaceutical Technology,* APGI, Paris, 1983, Vol. III, pp. 67–74.
54. E. Shotton and C. J. Lewis. *J. Pharm. Pharmacol. Suppl.* **16**:111T–120T (1964).
55. K. S. Manudhane, A. M. Contractor, H. Y. Kim, and R. F. Shangraw. *J. Pharm. Sci.* **58**:616–620 (1969).
56. P. J. Jarosz and E. L. Parrott. *Drug Dev. Ind. Pharm.* **10**:259–273 (1984).
57. A. H. De Boer, G. K. Bolhuis, and C. F. Lerk. *Powder Technol.* **20**:75–82 (1978).
58. E. Doelker and E. Shotton. *J. Pharm. Pharmacol.* **29**:193–198 (1977).
59. C. Nyström, J. Mazur, and J. Sjögren. *Int. J. Pharm.* **10**:209–218 (1982).
60. E. Turba and H. Rumpf. *Chem.-Ing.-Tech.* **36**:230–240 (1964).
61. W. Pietsch. *Chem. Tech.* **19**:259–266 (1967).
62. H. Rumpf. *Chem.-Ing.-Tech.* **46**:1–46 (1974).
63. H. Schubert. *Chem. Ing. Tech.* **51**:266–277 (1979).
64. H. Rumpf, K. Sommer, and K. Steier. *Chem.-Ing.-Tech.* **48**:300–307 (1976).
65. C. Führer und J. Ghadially. *Acta Pharm. Suec.* **3**:201–207 (1966).
66. C. Führer. *Sci. Pharm.* **34**:142–146 (1966).
67. C. Führer and G. Erikson. *Pharm. Zentralhalle* **107**:641–645 (1968).
68. G. Milosovich. *Drug Cosm. Ind.* **92**:557–558, 656, 662–669 (1963).
69. C. Führer. *Chem.-Ing.-Tech.* **43**:849–853 (1971).
70. R. Hüttenrauch and I. Keiner. *Pharmazie* **31**:651–652 (1976).
71. R. Hüttenrauch. *Acta Pharm. Tech. Suppl.* **6**:55–127 (1978).
72. K. Kawakita and K.-H. Lüdde. *Powder Technol.* **4**:61–68 (1970/1971).
73. M. A. Kehinde. *Mechanical Properties and Behaviour of Compacted Metal Powders Containing Lubricants,* M.Sc. thesis, Loughborough University of Technology, U.K., 1975.
74. E. Ryshkewitch. *J. Am. Ceram. Soc.* **36**:65–68 (1953).
75. T. Higuchi, L. N. Elowe, and L. W. Busse. *J. Am. Pharm. Assoc. (Sci. Ed.)* **43**:685–689 (1954).
76. E. Shotton and D. Ganderton. *J. Pharm. Pharmacol. Suppl.* **12**:87T–96T (1960).
77. W. Jetzer, H. Leuenberger, and H. Sucker. *Pharm. Technol.* **7**(4):33–39 (1983).
78. W. Jetzer and H. Leuenberger. *Pharm. Acta Helv.* **59**:2–7 (1984).
79. E. N. Hiestand and D. P. Smith. *Powder Technol.* **38**:145–159 (1984).
80. F. W. Goodhart, J. R. Draper, D. Dancz, and F. C. Ninger. *J. Pharm. Sci.* **62**:297–304 (1973).
81. P. J. Jarosz and E. L. Parrott. *J. Pharm. Sci.* **71**:607–614 (1982).
82. J. M. Newton, G. Rowley, J. T. Fell, D. G. Peacock, and K. Ridgway. *J. Pharm. Pharmacol. Suppl.* **23**:195S–201S (1971).
83. J. T. Fell and J. M. Newton. *J. Pharm. Sci.* **59**:688–691 (1970).
84. J. T. Fell and J. M. Newton. *J. Pharm. Pharmacol.* **20**:657–659 (1968).
85. H. Schubert. *Powder Technol.* **11**:107–119 (1975).
86. W. A. Nash. *Schaum's Outline of Theory and Problems of Strength of Materials,* 2nd ed., McGraw-Hill, New York, 1972, pp. 105–154.
87. S. T. David and L. L. Ausberger. *J. Pharm. Sci.* **63**:933–936 (1974).
88. B. W. Müller, K. J. Steffens, and P. H. List. *Acta Pharm. Technol.* **22**:91 (1976).
89. C. Nyström, W. Alex, and K. Malmqvist. *Acta Pharm. Suec.* **14**:317–320 (1977).

90. C. Nyström, K. Malmqvist, J. Mazur, W. Alex, and A. W. Hölzer. *Acta Pharm. Tech. Suppl.* 7:57–60 (1979).
91. D. Tabor. *The Hardness of Metals,* Oxford University Press, Amen House, London, 1951.
92. DIN Taschenbuch 19. *Materialprüfnormen für metallische Werkstoffe I Herausgeber,* DIN Deutsches Institut für Normung Beuth Verlag GmbH, Berlin, Köln, 1978.
93. E. N. Hiestand, J. M. Bane, and E. P. Strzelinski. *J. Pharm. Sci.* 60:758–763 (1971).
94. H. Spengler and A. Kaelin. *Acta Pharm. Helv.* 20:239–269 (1945).
95. A. Nutter Smith. *Pharm. J.* 163:477–483 (1949).
96. P. L. Seth and K. Münzel. *Pharm. Ind.* 22:7–10 (1960).
97. K. Ridgway, M. E. Aulton, and P. H. Rosser. *J. Pharm. Pharmacol. Suppl.* 22:70S–78S (1970).
98. M. E. Aulton, H. G. Tebby, and P. J. P. White. *J. Pharm. Pharmacol. Suppl.* 26:59P–60P (1974).
99. M. E. Aulton and H. G. Tebby. *J. Pharm. Pharmacol. Suppl.* 27:4P (1975).
100. M. E. Aulton and H. G. Tebby. *J. Pharm. Pharmacol. Suppl.* 28:66P (1976).
101. M. E. Aulton. *Pharm. Acta Helv.* 56:133–135 (1981).
102. M. E. Aulton. *Pharm. Acta Helv.* 56:332–335 (1981).
103. K. Ridgway, J. Glasby, and P. H. Rosser. *J. Pharm. Pharmacol. Suppl.* 21:24S–29S (1969).
104. R. Crawford, D. Paul, and Y. Adeebnia. *Eur. Polymer J.* 16:401–405 (1980).
105. J. W. Mullin. *Crystallisation,* Butterworths, London, 1972.
106. R. Mitsche and E. M. Onitsch. *Mikroskopie* 3:257–384 (1948).
107. K. Ridgway and M. E. Aulton. *J. Pharm. Pharmacol. Suppl.* 23:111S–120S (1971).
108. K. Ridgway, E. Shotton, and J. Glasby. *J. Pharm. Pharmacol. Suppl.* 21:19S–23S (1969).
109. K. Meyer. *Physikalisch-chemische Kristallographie,* 2nd ed., VEB Deutscher Verlag für Grundstoffindustrie, Leipzig, 1977.