JOURNAL OF PHARMACEUTICAL SCIENCES

JUNE 1982
VOLUME 71 NUMBER 6

RESEARCH ARTICLES

Factors Influencing Axial and Radial Tensile Strengths of Tablets

PAUL J. JAROSZ * and EUGENE L. PARROTT ˣ

Received June 8, 1981, from the *Division of Pharmaceutics, College of Pharmacy, University of Iowa, Iowa City, IA 52242.* Accepted for publication October 13, 1981. *Present address: Ortho Pharmaceutical Corp., Raritan, NJ 08869.

Abstract □ The axial and radial tensile strengths of compressed tablets have been measured by a tensiometer. A comparison of these strengths is indicative of the bonding strength in two directions and may be related to the tendency toward capping. The influence of compressional force, concentration of binder, and time on the tensile strengths of several materials is presented.

Keyphrases □ Tensile strength—factors influencing axial and radial tensile strengths in tablets □ Tablets—factors influencing axial and radial tensile strengths □ Compressional force—factors influencing axial and radial tensile strengths of tablets

Tablets must possess sufficient strength to withstand mechanical handling and transport. Various types of tests (abrasion, bending, indentation hardness, diametral crushing) have been used to express strength (1); however, the data from these tests seldom can be correlated in a precise manner. Even the most common strength test of diametral crushing may cause failure of the tablet by more than one type of force (2, 3). If the test method is designed so that tablet failure is a result of the application of tensile strength only, strength may be expressed precisely in terms of kilograms per square centimeter (4–7).

Most pharmaceutical tablets are anisotropic and nonhomogeneous, with the values of their properties (*e.g.*, density and strength) varying in different directions. The purpose of this investigation was to measure the axial and radial tensile strengths of tablets as influenced by compressional force, concentration of binder, and aging.

EXPERIMENTAL

Preparation of Tablets—Powders to be granulated were blended in a planetary mixer[1]. The appropriate amount of granulating solution was added and mixed for 5 min. The mass was passed through an oscillating granulator[2], collected on drying trays, and dried overnight in a forced-air oven at ambient temperature. A 16/20-mesh size fraction of the dried granulation was separated by standard sieves. Directly compressible materials were separated by standard sieves into a 60/80-mesh size fraction. An appropriate weight of the material to produce tablets from 0.3 to 0.5 cm thick was compressed by means of 1.275-cm flat-faced punches and the die fitted to a hydraulic press[3] for 5 sec at the desired compressional force. The die wall was prelubricated with 5% magnesium stearate in acetone. At least 72 hr elapsed between tablet compression and measurement of tablet strength to allow for any stress relaxation. The weight and thickness of 10 tablets were determined.

Measurement of Radial Tensile Strength—The radial tensile strength of the tablet was measured by a diametral compression test. The tensiometer[4] was modified for compression by the use of a compression device used for calibration of the mercury manometer of the tensiometer. Steel bolt heads served as platens for the radial compression test. To ensure that the tablet failed in tension, a padding, consisting of three layers of manila computer cards 1 mm thick, was used (5, 6, 8). The length of each paper strip was sufficient to extend over the edge of the bolt head. The pad was replaced after ~200 tablets had been fractured. The tablet was strained at the rate of 0.299 cm/min. The maximum force for tablet failure resulting from tensile stress (3, 4) was determined, and the force–displacement profile was recorded. The maximum tensile failure force F_σ of 10 tablets was determined, and the average was used to calculate the radial tensile strength (σ_x) by the relationship:

$$\sigma_x = \frac{2F_\sigma}{\pi Dt} \qquad \text{(Eq. 1)}$$

where D is the diameter (1.275 cm) and t is the thickness of the tablet (9).

Measurement of Axial Tensile Strength—The tablet was linearly aligned and fixed between the machined heads of two 1.275 × 2.54-cm steel bolts by means of a cyanoacrylate resin adhesive[5]. The adhesive was cured at room temperature for at least 36 hr prior to testing. By use of a pair of adapters, the bolt–tablet–bolt assemblage was fitted horizontally into the tensiometer. The tablet was strained at the rate of 0.229 cm/min. The tensiometer allowed the recording of the stress component against the extension, proportional to the distance moved by the crosshead beam. The distance traveled by the crosshead beam was magnified 16 times and recorded on the drum chart paper. The value of the maximum force was recorded only if failure was due to tension stresses. Tablet failure occurred in the body of the tablet and not near the tablet–bolt interface. The av-

[1] KitchenAid, Hobart Corporation, Troy, Ohio.
[2] Type FGS, Erweka-Apparatebau, GmbH, Heusenstamm Kr., Offenbach Main, West Germany.
[3] Carver press, model C, Menomonee Falls, Wis.
[4] Hounsfield Tensiometer, Type W, Tensiometer Ltd., Croydon, England.
[5] Eastman 910 Adhesive, Eastman Kodak, Kingsport, Tenn.

0022-3549/82/0600-0607$01.00/0

Table I—Density of Materials and Granulations

Material	Density, g/cm³
Microcrystalline cellulose[a]	1.34
Benzoic Acid	1.36[b]
Dibasic calcium phosphate[c]–povidone[d] (1.0%)	2.45
Dibasic calcium phosphate[c]–povidone[d] (7.0%)	2.43
Dibasic calcium phosphate[e]–starch (1.2%)	2.13
Dibasic calcium phosphate[e]–starch (4.5%)	2.12
Heptane, normal	0.679
Hydrous lactose[f]–povidone (1.0%)	1.44
Hydrous lactose[f]–povidone (9.0%)	1.44
Hydrous lactose[f]–starch (1.9%)	1.46

[a] Avicel PH 102, FMC Corp., Marcus Hook, PA 19061. [b] S. Shah, Ph.D. Thesis, The University of Iowa, Iowa City, Ia., 1975. [c] Ruger Chemical Co., Inc. [d] Plasdone K 29–32, GAF Corp., New York, NY 10020. [e] Emcompress, Edward Mendell Co. [f] USP, Humko-Sheffield, Memphis, TN 38101.

erage maximum force of axial tensile failure of 10 tablets was used to calculate the axial tensile strength by the relationship (10):

$$\sigma_z = \frac{4F_a}{D^2} \qquad \text{(Eq. 2)}$$

Measurement of Density—The densities of the materials and granulations were determined by pycnometry using *n*-heptane at 25° and are given in Table I. The measured dimensions and weight of each cylindrical tablet were used to calculate the apparent density of the tablet. The relative density used in the Heckel plot is the quotient of the apparent density of the tablet and the density of the material. The values of porosity used in the Ryshkewitch relationship were calculated from the relationship:

$$\text{porosity} = (1 - \rho_{\text{apparent}}/\rho) \qquad \text{(Eq. 3)}$$

Conservation curves, rather than tables of the dimensions and calculations, are presented for each tablet.

RESULTS AND DISCUSSION

The consolidation of a powder to form a tablet proceeds through several stages during compression (11, 12). As a force is applied to a powder, interparticular rearrangement causes consolidation to the closest packing. Additional compressional force results in deformation of the particles by brittle fragmentation; plastic, nonrecoverable conformation changes; and/or elastic, recoverable conformation changes. Eventually, maximum consolidation is attained at which an increase in compressional force no longer reduces the relative volume of the tablet. It has been shown (13), in terms of density, that the distribution of compressional pressure within a tablet exists. It was previously demonstrated that the bond formation is greater in a region where, because of compressional pressure, distribution is more intense (14).

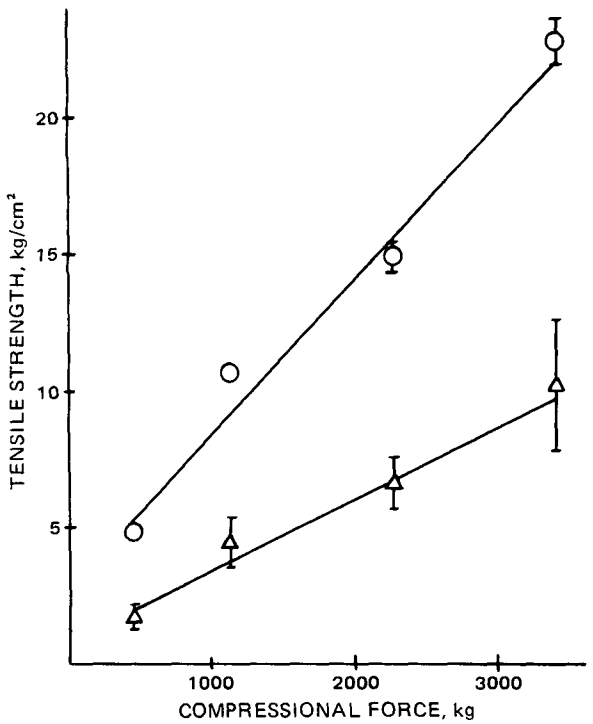


Figure 1—*The influence of compressional force on tensile strengths of tablets compressed of 60/80-mesh size dibasic calcium phosphate dihydrate*[6]. *Key: (△) axial; (○) radial.*

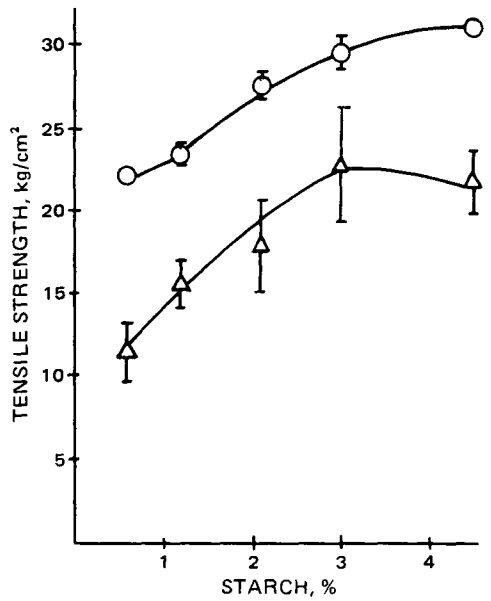


Figure 2—*The influence of starch on the tensile strengths of tablets of dibasic calcium phosphate dihydrate*[6] *compressed at 2268 kg. Key: (△) axial; (○) radial.*

For an isotropic, homogeneous tablet, the radial and axial tensile strengths should be equal. The distribution of compressional force, differences in density within a tablet, and the mixture of materials contribute to the nonhomogeneity of the tablet and to the nonuniformity of tensile strengths. To demonstrate this, the axial and radial tensile strengths were measured experimentally. Typical results for several materials are given in Table II in which there is a difference in the axial and radial tensile strengths for each material.

As shown in Table II, the variance of radial tensile strength is less than the variance of the axial tensile strength. The experimental conditions

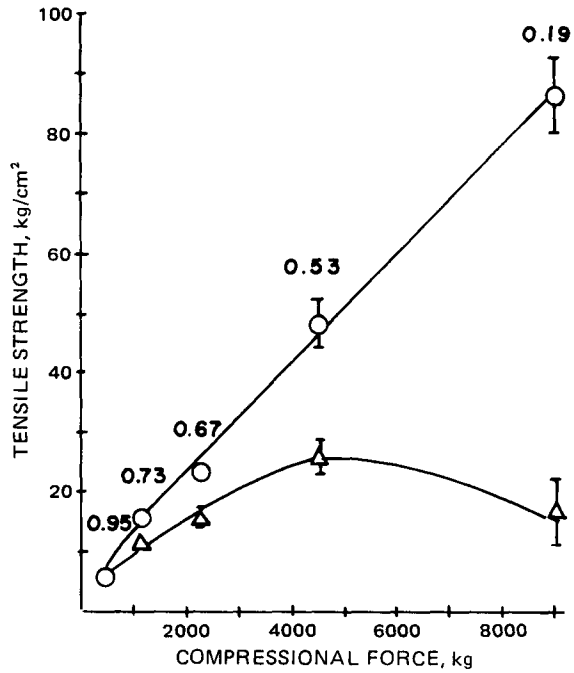


Figure 3—*The influence of compressional force on tensile strengths of tablets of dibasic calcium phosphate dihydrate*[6] *granulated with 1.2% starch. At each compressional force the value is given for* σ_z/σ_x. *Key: (△) axial; (○) radial.*

Table II—Strength Characteristics of 1.275-cm Diameter Cylindrical Tablets of Several Directly Compressible Materials

Material	Compressional Force, kg	Mean Force of Axial Tensile Failure, kg[d]	Axial Tensile Strength, σ_z, kg/cm^2	Mean Force of Radial Tensile Failure, kg[d]	Thickness, cm[d]	Radial Tensile Strength, σ_x, kg/cm^2	$\frac{\sigma_z}{\sigma_x}$
Dibasic calcium phosphate dihydrate[a]	454	2.2 (0.8)[e]	1.7 (0.4)[f]	4.6 (0.2)[e]	0.479 (0.005)[e]	4.8 (0.1)[f]	0.35
	1134	5.6 (1.6)	4.4 (0.9)	9.5 (0.4)	0.443 (0.004)	10.7 (0.3)	0.41
	2268	8.4 (1.6)	6.6 (0.9)	12.4 (0.6)	0.414 (0.001)	14.9 (0.5)	0.44
	3402	13.0 (4.2)	10.2 (2.4)	18.5 (0.9)	0.404 (0.003)	22.8 (0.8)	0.45
Lactose, anhydrous[b]	907	15.1 (3.0)	11.8 (1.6)	12.9 (0.5)	0.428 (0.001)	15.1 (0.4)	0.78
Microcrystalline cellulose[c]	454	19.6 (1.4)	15.4 (0.8)	28.4 (0.4)	0.429 (0.007)	33.0 (0.4)	0.47
Aspirin	1361	14.0 (1.9)	11.0 (1.1)	13.4 (0.6)	0.437 (0.002)	15.3 (0.5)	0.72
Benzoic acid	454	14.2 (1.4)	11.1 (0.7)	16.2 (1.0)	0.494 (0.012)	16.4 (0.7)	0.68
	1134	15.2 (1.2)	11.9 (0.6)	17.4 (0.6)	0.482 (0.013)	18.0 (0.4)	0.66
	3402	17.0 (3.0)	13.3 (1.6)	14.0 (1.2)	0.479 (0.008)	14.7 (0.9)	0.90

[a] Emcompress, Edward Mendell Co., Carmel, N.Y. [b] Lactose Direct Tabletting, Humko-Sheffield. [c] Avicel PH 102, FMC Corp. [d] Average of 10 tablets. [e] Standard deviation. [f] Confidence interval at 95% probability.

of the diametral compression (radial) test are specifically controlled to ensure tablet failure only because of tension stresses. The axial test has the disadvantage of requiring the adapter–bolt–tablet assemblage to be placed horizontally in the tensiometer. Bending stress due to the mass of the adapter and the torsion stress due to loading are present in each sample. These additional stresses add to the deviation in applied tension stress required to cause failure of the tablet. A similar set of experimental values using another apparatus has been reported (15).

The radial tensile strength is greater than the axial tensile strength with a brittle material (dibasic calcium phosphate dihydrate[6]). The difference may be a reflection of the number of clean particle bonds and of original particle bonds oriented in the axial and radial direction. In brittle fracture, clean surfaces are formed during compression, and two fresh, clean surfaces bond to form the strongest bond. A newly formed surface may bond to an original surface of another particle, whereas two original surfaces, which bond during compression, probably form the weakest bond.

When a brittle material is compressed along the vertical (axial) axis, the stress upon each particle does not necessarily compress the particle along the axial direction because of the random packing and alignment of the particles toward each other during the stages of compression; however, a greater potential exists for vertical stress on the particles during the relocation and fragmentation stages due to the movement of the punch. The overall result is that more clean surfaces are created when they are normal to the radial than to the axial direction. As the compressional force is increased, a brittle fracture results in a stronger, radial tensile strength than axial tensile strength (Fig. 1). The slope (0.00577, $r = 0.990$) of the radial tensile strength–force line is twice that of the slope (0.00275, $r = 0.993$) of the axial tensile strength–force line.

The Griffith fracture theory (16) proposes that failure results from the existence of flaws or cracks within the sample. If more bonds are formed in the radial direction, the potential for the presence of a flaw or crack is greater in the axial than the radial direction. This concept appears to be supported by the results shown in Fig. 1.

Influence of Compressional Force and Concentration of Binder—In tableting technology, a blend of pharmaceutical powders is commonly granulated with a granulating or binding solution. The incorporation of the binder increases the adhesiveness of the formulation. As shown in Fig. 2, the radial tensile strength of tablets compressed at 2268 kg of force from dibasic calcium phosphate dihydrate[6] granulated with starch paste is increased as the concentration of starch is increased. The axial tensile strength is increased to its greatest value at 3% starch and is not increased by an additional increase in the starch concentration.

The effect of compressional force on the tensile strength of tablets compressed from dibasic calcium phosphate dihydrate[6] with 1.2% starch is shown in Fig. 3. For the given concentration of binder, the axial tensile strength is increased to a maximum value at 4536 kg of force and is not increased at greater compressional forces.

The tensile strengths of tablets compressed from dibasic calcium

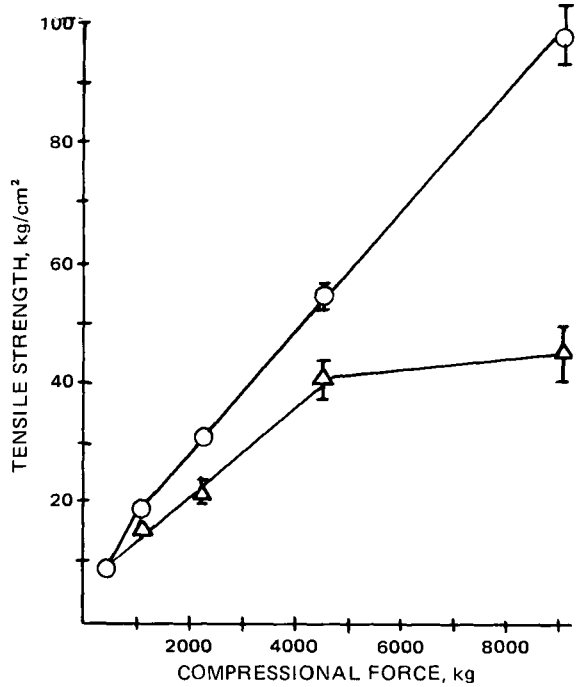


Figure 4—*The influence of compressional force on the tensile strengths of tablets compressed of dibasic calcium phosphate dihydrate[6] granulated with 4.5% starch. Key: (△) axial; (○) radial.*

[6] Emcompress, Edward Mendell Co., Carmel, N.Y.

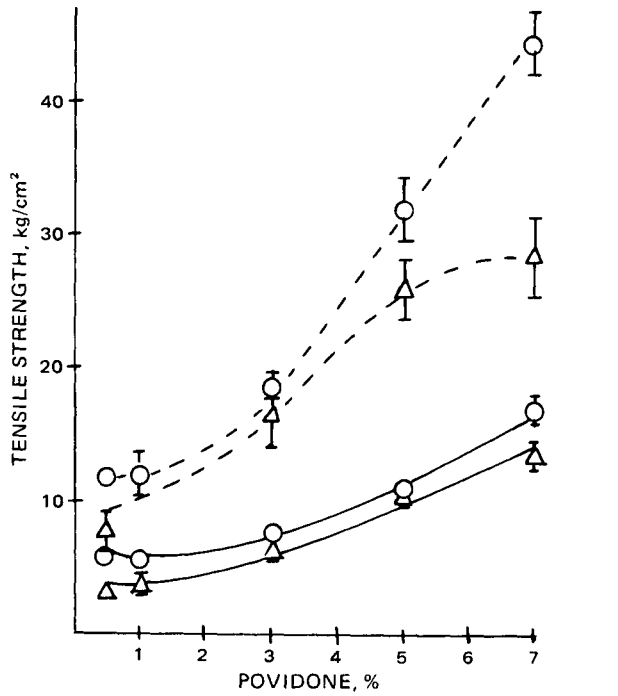


Figure 5—*The influence of povidone on the tensile strengths of tablets of dibasic calcium phosphate dihydrate[7] compressed at 2268 (——) and at 4536 kg (- - - -). Key: (△) axial; (○) radial.*

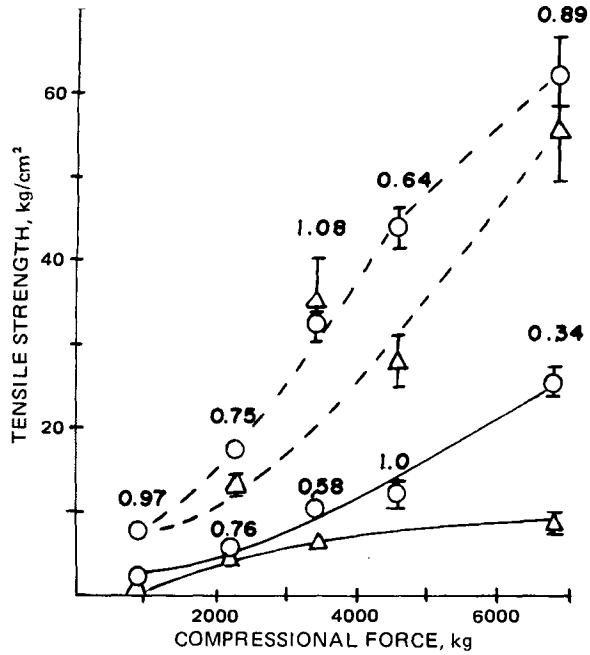


Figure 6—*The influence of compressional force on the tensile strengths of tablets of dicalcium phosphate dihydrate granulated with 1.0 (—) and with 7.0% (- - - -) povidone. At each compression force the value is given for σ_z/σ_x. Key: (△) axial; (○) radial.*

phosphate dihydrate[6] with 4.5% starch are shown in Fig. 4. The rate of increase of radial tensile strength with an increase in compressional force is essentially the same as that of the tablet containing 1.2% starch. The maximum axial tensile strength is attained at the same compressional force as for the tablet containing 1.2% starch, but there is no decrease in axial strength as the compressional force is increased further. This difference in the axial and radial tensile strength–force profiles indicates that consolidation is not uniform throughout the entire tablet mass.

Similarly, for tablets compressed at 2268 and 4536 kg of force from dibasic calcium phosphate dihydrate[7] granulated with povidone, the tensile strengths are increased as the concentration of povidone is increased (Fig. 5). The influence of compressional force on tensile strength of tablets of dibasic calcium phosphate dihydrate[7] and povidone is illustrated in Fig. 6. As the compressional force is increased, the slope of the radial tensile strength *versus* percent of binder increases more rapidly than the slope of the axial tensile strength. A maximum axial tensile strength is attained at 5–6% povidone when compressed at 4536 kg.

The influence of compressional force on the tensile strengths of tablets

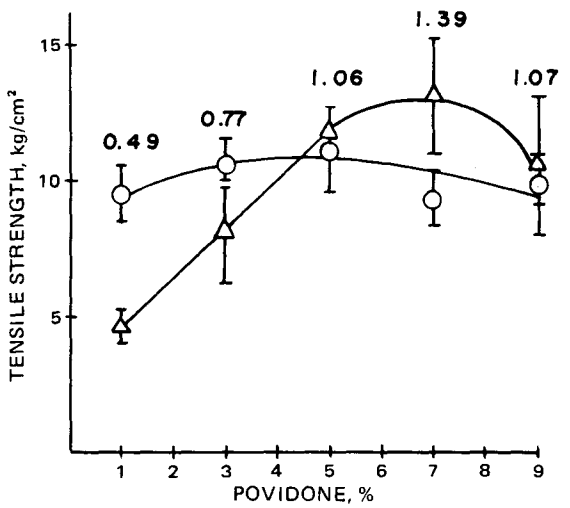


Figure 7—*The initial influence of povidone on the tensile strengths of tablets of hydrous lactose compressed at 1134 kg. At each compressional force the value is given for σ_z/σ_x. Key: (△) axial; (○) radial.*

[7] Ruger Chemical Co., Irvington, N.J.

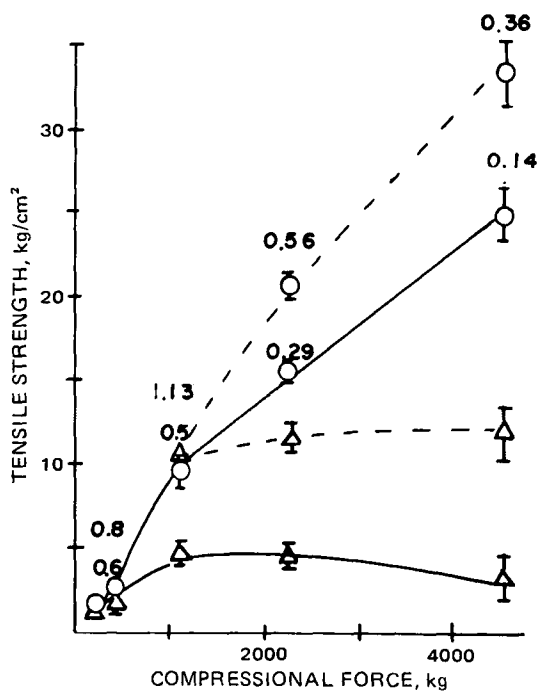


Figure 8—*The influence of compressional force on the tensile strengths of tablets of hydrous lactose granulated with 1 (—) and 9.0% (- - - -) povidone. At each compressional force the value is given for σ_z/σ_x. Key: (△) axial; (○) radial.*

of dibasic calcium phosphate dihydrate[7] granulated with 1.0 and 7.0% povidone is shown in Fig. 6. The strength of tablets compressed from dibasic calcium phosphate dihydrate[6] is increased only moderately with an increase in compressional force. At low concentrations of binder, the effect of compressional force on dibasic calcium phosphate dihydrate[7] is moderate, but at high concentrations, 7% of binder, the tensile strength is significantly increased with an increase in compressional force (Fig. 6).

The influence of povidone concentration on the tensile strength of hydrous lactose tablets compressed at 1134 kg of force is shown in Fig. 7. The concentration of povidone has little effect on the radial tensile strength. As the concentration of povidone is increased, the axial tensile strength is increased rapidly to values that exceed the radial tensile strength. Thus, povidone axially strengthens a tablet of hydrous lactose to a greater extent than a tablet of dibasic calcium phosphate dihydrate.

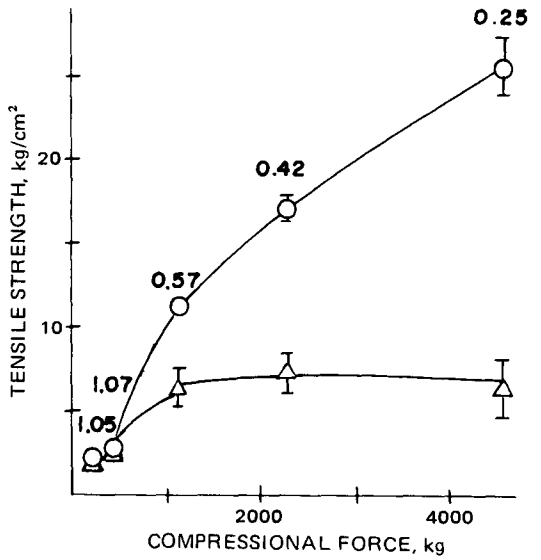


Figure 9—*The influence of compressional force on tensile strengths of tablets of hydrous lactose granulated with 1.9% starch. At each compressional force the value is given for σ_z/σ_x. Key: (△) axial; (○) radial.*

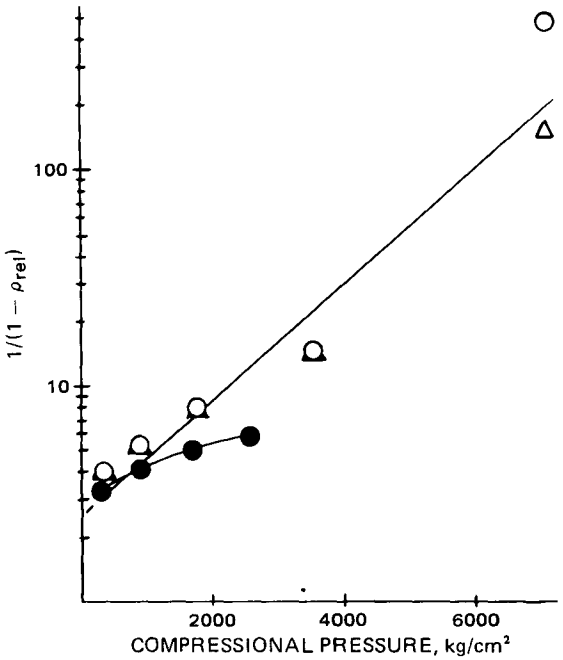


Figure 10—*Density–compressional pressure relationship according to Heckel plot. Key: (●) dibasic calcium phosphate dihydrate[6]; (○) with 1.2% starch; (△) with 4.5% starch.*

Since the granulating solvent was water, in which lactose is soluble, the lactose may have partially dissolved at the surface of the granules and upon drying formed bridges, which mechanically strengthened the tablet (17, 18).

The influence of compressional force on the tensile strengths of tablets composed of hydrous lactose with 1.0 and 9.0% povidone is shown in Fig. 8. There is a maximum axial tensile strength attained at a low concentration of binder with an observed tendency for capping at high compressional forces. Lactose behaves as a Mohr body (19) and is known to be prone to capping (20). A similar result is shown in Fig. 9 for tablets of hydrous lactose granulated with 1.9% starch.

Behavior of Material—Heckel (21, 22) characterized the behavior of materials during compression by the relationship:

$$\log \frac{1}{1-\rho_{rel}} = \frac{KP}{2.303} + A \qquad \text{(Eq. 4)}$$

where ρ_{rel} is the relative density, P is the compressional pressure, and K and A are constants. The slope (K) has been related to the reciprocal of the mean yield pressure, which is the minimum pressure required to cause

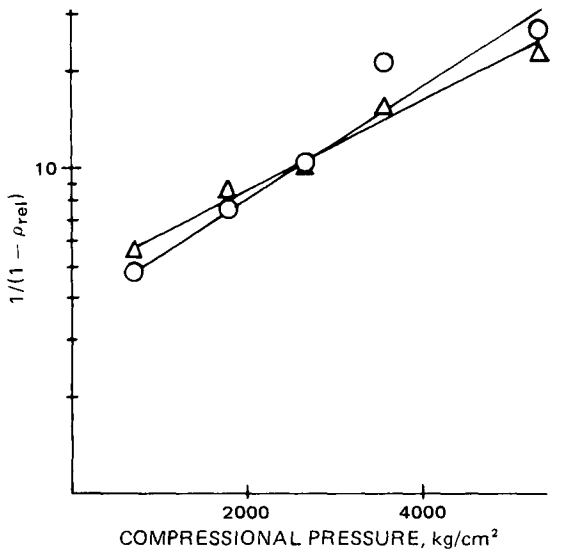


Figure 11—*Density–compressional pressure relationship according to Heckel plot for dibasic calcium phosphate dihydrate[7] granulated with povidone. Key: (△) 1.0% povidone; (○) 7.0% povidone.*

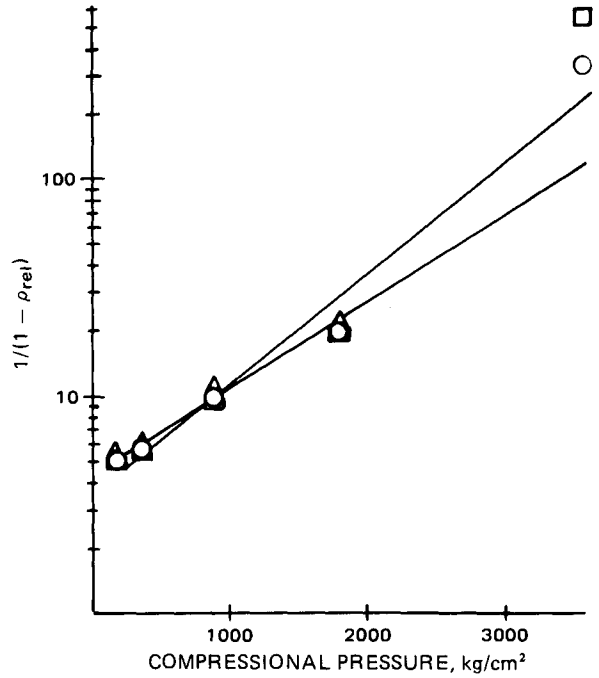


Figure 12—*Density–compressional pressure relationship according to Heckel plot of hydrous lactose granulated with povidone and starch. Key: (△) 1.0% povidone; (○) 9.0% povidone; (□) 1.9% starch.*

deformation of the material undergoing compression (23). The intercept of the curved portion of the curve at low pressure represents a value due to densification by particle rearrangement. The intercept obtained from the slope of the upper portion of the Heckel plot is a reflection of the densification obtained during consolidation. A large value of the slope indicates the onset of plastic deformation at relatively low pressures (24). A Heckel plot for tablets of dibasic calcium phosphate dihydrate[6] is shown in Fig. 10. The small value of the slope indicates consolidation of dibasic calcium phosphate dihydrate is not by plastic deformation but primarily by brittle fracture (25).

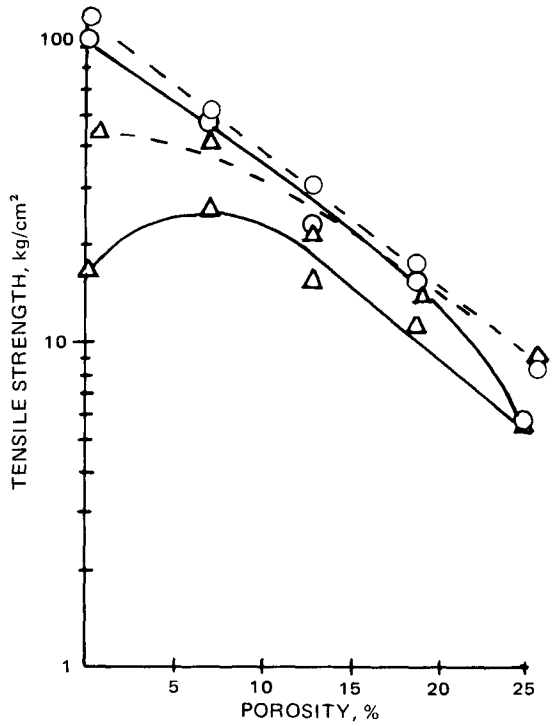


Figure 13—*Tensile strengths–porosity relationship of logarithmic form of the Ryshkewitch equation for dibasic calcium phosphate dihydrate[6] granulated with 1.2 (——) and 4.5% (- - - -) starch. Key: (△) axial; (○) radial.*

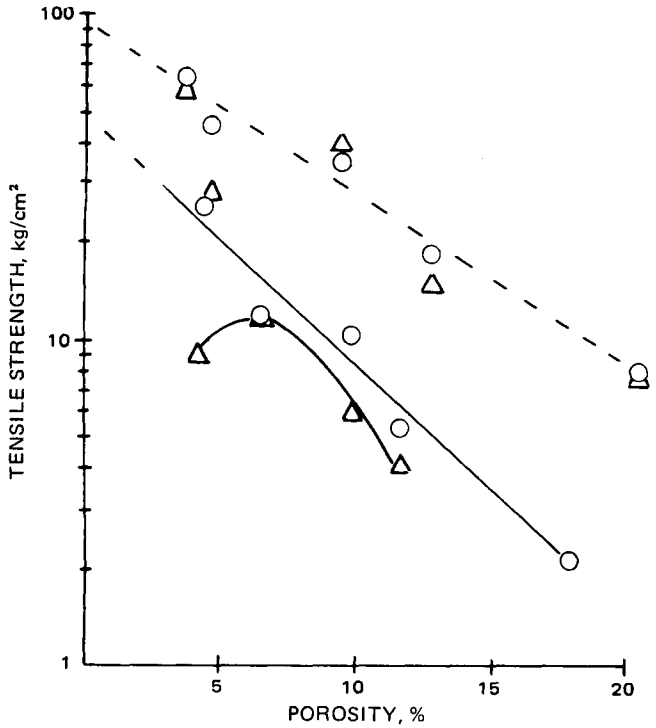


Figure 14—*Tensile strengths–porosity relationship of logarithmic form of Ryshkewitch equation for dibasic calcium phosphate dihydrate[7] granulated with 1.0 (—) and 7.0% (- - - -) povidone. Key: (△) axial; (○) radial.*

The effect of the addition of starch to dibasic calcium phosphate dihydrate[6] is shown in Fig. 10. The lower mean yield pressures (1442 and 1904 kg/cm^2 with 1.2 and 4.5% binder, respectively) for dibasic calcium phosphate[6] granulated with starch, than the mean yield pressure (4303 kg/cm^2) for dibasic calcium phosphate dihydrate indicate that the addition of starch confers some plastic property to the mass. The density–compressional pressure relationship of dibasic calcium phosphate dihydrate[7] granulated with povidone is plotted in Fig. 11. The lower mean yield pressure (2535 kg/cm^2) for dibasic calcium phosphate dihydrate[7] granulated with 7.0% povidone than the mean yield pressure (3282 kg/cm^2) with 1.0% povidone indicates the onset of plastic deformation with an increase in concentration of the binder.

The Heckel plots for lactose granulated with povidone and for lactose granulated with starch are shown in Fig. 12. The mean yield pressure is

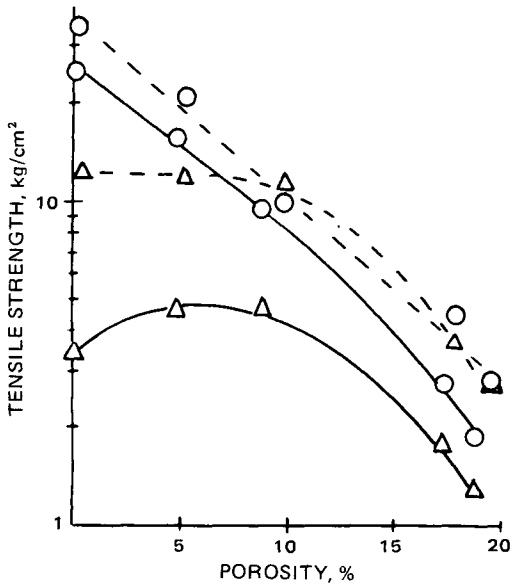


Figure 15—*Tensile strengths–porosity relationship of logarithmic form of the Ryshkewitch equation for hydrous lactose granulated with 1.0 (—) and 9% (- - - -) povidone. Key: (△) axial; (○) radial.*

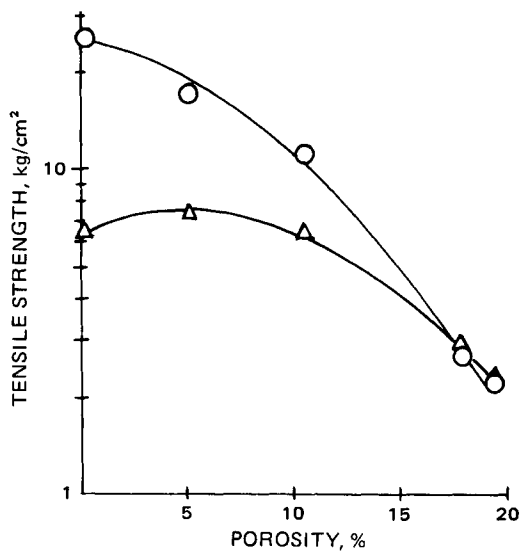


Figure 16—*Tensile strengths–porosity relationship of logarithmic form of Ryshkewitch equation for hydrous lactose granulated with 1.9% starch. Key: (△) axial; (○) radial.*

decreased as the concentration of plastically deformed povidone is increased. The addition of a plastic binder to an excipient tends to confer some plasticity to the excipient.

Ryshkewitch (26) observed that:

$$\log \sigma_x = \log \sigma_{max} - bp \qquad \text{(Eq. 5)}$$

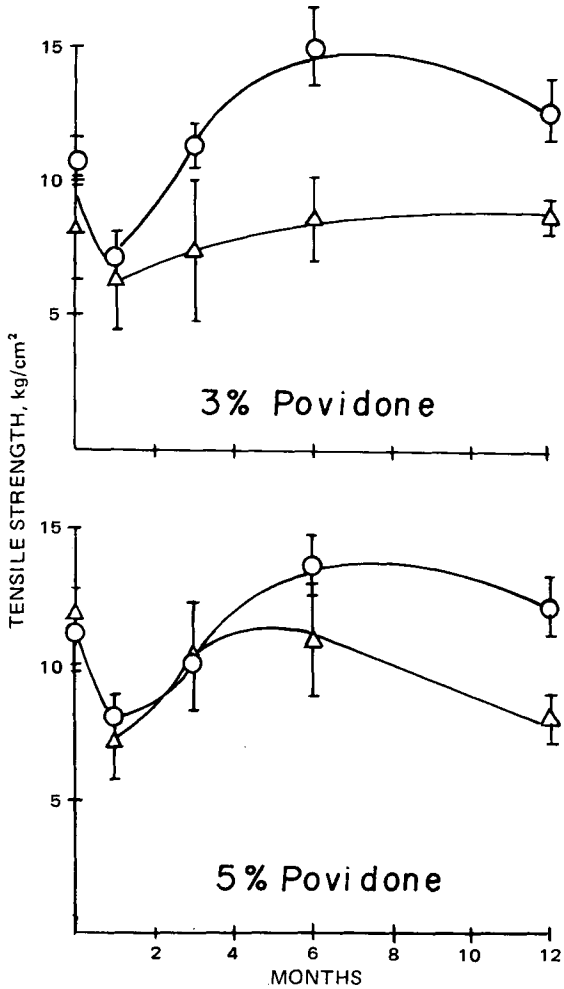


Figure 17—*The influence of time on the tensile strength of tablets of hydrous lactose granulated with 3 and 5% povidone. Key: (△) axial; (○) radial.*

Table III—Values of Constants b and σ_{max} of the Ryshkewitch Equation

	b	σ_{max}	r
Lactose granulated with 1.9% starch	5.7	31.8	0.981
Lactose granulated with 1.0% povidone[a]	5.5	27.4	0.996
Lactose granulated with 9.0% povidone	5.3	36.1	0.996
Dibasic calcium phosphate dihydrate[b] granulated with 1.0% povidone	7.6	48.2	0.979
Dibasic calcium phosphate dihydrate[b] granulated with 7.0% povidone	5.1	89.3	0.991
Dibasic calcium phosphate dihydrate[c] granulated with 1.2% starch	4.6	95.4	0.993
Dibasic calcium phosphate dihydrate[c]	4.1	106.6	0.999

[a] Regression of four points only. [b] Ruger Chemical Co. [c] Emcompress, Edward Mendell Co.

where σ_x is the radial tensile strength, σ_{max} is the theoretical radial tensile strength at zero void, b is a constant, and p is porosity.

In Fig. 13 the logarithms of tensile strengths are plotted against the porosity of tablets compressed from dibasic calcium phosphate dihydrate[6] granulated with 1.2 and 4.5% starch, and the increase in starch increases the radial tensile strength 47%, even though the porosity remains at 25%. The increase in starch increases the radial tensile strength only 12% as zero void is approached.

The Ryshkewitch relationship of tensile strength to the porosity of dibasic calcium phosphate dihydrate[7] granulated with 1.0 and 7.0% povidone is shown in Fig. 14. The maximum axial tensile strength occurs at 6–7% porosity, which is the same porosity as for dibasic calcium phosphate dihydrate[6,7] and starch.

Similarly, the Ryshkewitch relationships for hydrous lactose with 1.0 and 9.0% povidone are plotted in Fig. 15. A nine-fold increase in concentration of povidone causes a 58% increase in radial tensile strength near 20% porosity and only a 34% increase near zero void. The Ryshkewitch relationship for hydrous lactose with starch is shown in Fig. 16. Values for the constants of the Ryshkewitch equation are given in Table III.

It appears that the concentration of the binder has a greater influence in more porous tablets than in those approaching zero void. As compressional force is increased and the porosity of the tablet is decreased, the interparticular distances through which adhesive forces operate are shorter. Thus, the adhesive forces of the material are stronger at lower porosity, and a lesser amount of binder would be required to produce a tablet of the desired strength.

Index of Capping—The elastic property of a material is responsible for the capping or failure of a tablet perpendicular to its compressional axis. When the compressional force is removed, shear deformation occurs as the elastic material rebounds (27). Strains are magnified about regions of low density, and upon release of the force, there may be a mechanical failure.

Binders are added to materials having poor adhesive property to strengthen intergranular binding and, thus, reduce the tendency to cap. For elastic materials the elastic energy released, when the punch pressure is relieved, overcomes the bonds present between particles in that region and capping occurs. Binders are plastic materials, and under compression these materials undergo plastic deformation. The total energy of compression is dissipated throughout the entire material being compressed. A greater part of the total energy of compression is absorbed by the binder at greater concentrations, and less energy is stored elastically by the elastic deformation of the other materials of the formulation. Upon removal of the compressional force, there is less elastic recovery and a reduced tendency toward capping.

A weak axial tensile strength has been associated with capping (1, 10, 28). A comparison of Figs. 3 and 4 shows that the maximum axial tensile strength for a tablet of dibasic calcium phosphate dihydrate[6] containing 4.5% starch is reached at the same compressional force as for a tablet containing 1.2% starch, but there is no decrease in axial strength after reaching the maximum value for the tablet containing 4.5% starch. The slopes of the radial tensile strength–force curves are nearly identical. The difference in axial and radial tensile strengths indicates that the tablet is not as strongly bonded in the axial direction as in the radial direction. As the axial and radial tensile strengths are measures of bonding, it appears that the ratio σ_z/σ_x could be used as an index of capping. The ratio would be unity for a homogeneous tablet and would decrease toward zero as the homogeneity became progressively less.

The data presented in Fig. 6 for the tablets of dibasic calcium phosphate dihydrate[7] with 1.0 and 7.0% povidone support the statement that an increase in concentration of binder reduces capping. At the highest compressional force (6804 kg) the ratio σ_z/σ_x is 0.34 and 0.89 for 1.0 and 7.0% povidone, respectively. Capping does not occur as the dibasic calcium phosphate dihydrate is a brittle material, and fragmentation occurs and is the mode of consolidation.

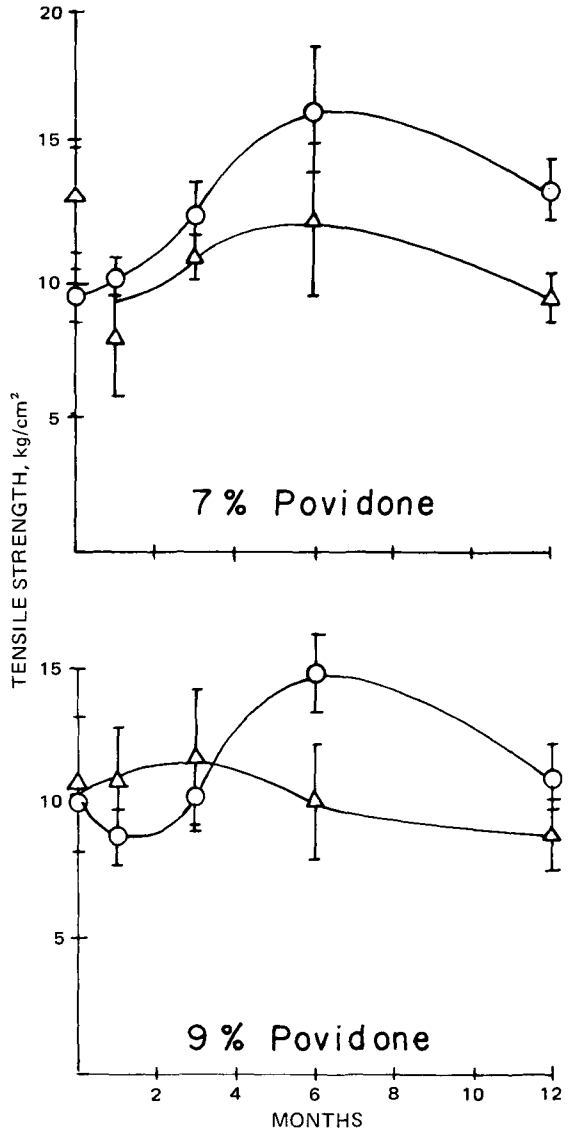


Figure 18—*The influence of time on the tensile strength of tablets of hydrous lactose granulated with 7 and 9% povidone. Key: (△) axial; (○) radial.*

With nonbrittle materials, considerable consolidation may be due to elastic bonding. As elastic rebound will occur when the compressional force is removed, the tablet will have a capping tendency. For such materials, a low value for σ_z/σ_x indicates that capping is likely. To properly evaluate the probability of capping, the mechanism of bonding or consolidation and the ratio of the axial and radial tensile strengths must be considered. Hydrous lactose with povidone attains a maximum axial tensile strength at a low concentration of binder with a tendency for capping at high compressional forces. At the highest compressional force (4536 kg) for hydrous lactose tablets, containing 1.0 and 9.0% povidone, the ratio σ_z/σ_x is 0.14 and 0.36, respectively.

Aging—Changes in strength of tablets have been reported to be a function of strain recovery (29), time (30), and loss of moisture (31, 32). Five formulations of tablets weighing 800 mg were prepared by compression at 1134 kg of force for hydrous lactose containing from 1.0 to 9.0% povidone. The tablets were stored in tightly closed glass containers at 43% relative humidity and ambient temperature. The axial and radial tensile strengths measured initially and at 1, 3, 6, and 12 months are shown in Fig. 17 for hydrous lactose with 3.0 and 5.0% povidone. Similar plots are shown in Fig. 18 for hydrous lactose tablets with 7.0 and 9.0% povidone. The implication is that the tensile strength did not change to a significant extent after 1 year in storage. A report (33) that the hardness

of hydrochlorothiazide tablets composed of lactose and povidone did not change after 1 year at room temperature supports this implication.

REFERENCES

(1) A. Ritter and H. Sucker, *Pharm. Tech.*, **4**, No. 9, 108 (1980).
(2) K. Ridgway, *Pharm. J.*, **205**, 709 (1970).
(3) W. C. Rudnick, A. R. Hunter, and F. C. Holden, *Mater. Res. Stand.*, **1**, 283 (1963).
(4) J. T. Fell and J. M. Newton, *J. Pharm. Sci.*, **59**, 688 (1970).
(5) P. J. F. Wright, *Mag. Concr. Res.*, **7**, 87 (1955).
(6) L. L. Simon, *Constructional Rev.*, **29**, 23 (1956).
(7) J. T. Fell and J. M. Newton, *J. Pharm. Pharmacol.*, **20**, 657 (1968).
(8) N. B. Mitchell, *Mater. Res. Stand.*, **1**, 780 (1961).
(9) M. M. Frocht, "Photoelasticity," Vol. 2, Wiley, New York, N.Y., 1948, p. 127.
(10) C. Nystrom, W. Alex, and K. Malmqvist, *Acta Pharm. Suec.*, **14**, 317 (1977).
(11) D. Train, *J. Pharm. Pharmacol.*, **8**, 74S (1956).
(12) E. L. Parrott, in "Pharmaceutical Dosage Forms: Tablets," Vol. 2, H. A. Lieberman and L. Lachman, Eds., Dekker, New York, N.Y., 1981.
(13) D. Train, *Trans, Inst. Chem. Engrs.*, **35**, 258 (1957).
(14) D. Train and J. A. Hersey, *Powder Metall.*, **6**, 20 (1960).
(15) E. Turba and H. Rumpf, *Chem. Eng. Tech.*, **36**, 230 (1964).
(16) A. A. Griffith, *Proc. 1st Int. Cong. Appl. Mech.*, **1924**, 55.
(17) W. O. Opakunle and M. S. Spring, *J. Pharm. Pharmacol.*, **28**, 915 (1976).
(18) K. T. Jaiyeoba and M. S. Spring, *ibid.*, **32**, 1 (1980).
(19) E. Shotton and B. A. Obiorah, *J. Pharm. Sci.*, **64**, 1213 (1975).
(20) N. L. Henderson and A. J. Bruneo, *ibid.*, **59**, 1336 (1970).
(21) R. W. Heckel, *Trans. Metall. Soc. AIME*, **221**, 671 (1961).
(22) R. W. Heckel, *ibid.*, **221**, 1001 (1961).
(23) R. York, *J. Pharm. Pharmacol.*, **30**, 6 (1978).
(24) P. York and N. Pilpel, *J. Pharm. Pharmacol.*, Suppl., **25**, 1P (1973).
(25) K. A. Khan and C. T. Rhodes, *J. Pharm. Sci.*, **64**, 444 (1975).
(26) E. Ryshkewitch, *J. Am. Ceramic Soc.*, **36**, 65 (1953).
(27) J. A. Seitz and G. M. Flessland, *J. Pharm. Sci.*, **54**, 1353 (1965).
(28) C. Nystron, K. Malmqvist, J. Mazur, W. Alex, and A. W. Holzer, *Acta Pharm. Suec.*, **15**, 226 (1978).
(29) M. E. Aulton, D. N. Travers, and P. J. P. White, *J. Pharm. Pharmacol.*, **25**, 79P (1973).
(30) R. P. Bhatia and N. G. Lordi, *J. Pharm. Sci.*, **68**, 896 (1979).
(31) Z. T. Chowhan and A. A. Amaro, *Drug. Dev. Ind. Pharm.*, **5**, 545 (1979).
(32) Z. T. Chowhan, *J. Pharm. Pharmacol.*, **32**, 10 (1980).
(33) A. S. Alam and E. L. Parrott, *J. Pharm. Sci.*, **60**, 263 (1971).

ACKNOWLEDGMENTS

Abstracted in part from a dissertation submitted by Paul J. Jarosz to the Graduate College, University of Iowa, in partial fulfillment of the Doctor of Philosophy degree requirements.

Determination of Octanol–Water Equivalent Partition Coefficients of Indolizine and Substituted 2-Phenylindolizines by Reversed-Phase High-Pressure Liquid Chromatography and Fragmentation Values

CLAUDIO L. K. LINS, JOHN H. BLOCK ˣ, ROBERT F. DOERGE, and GERARD J. BARNES

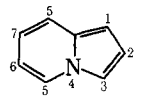
Received May 19, 1980, from the *School of Pharmacy, Oregon State University, Corvallis, OR 97331.* Accepted for publication July 27, 1981.

Abstract □ Octanol–water partition values were calculated using fragmentation values and measured rapidly by high-pressure liquid chromatography (HPLC) on bonded octadecylsilane supports. Log *P* for indolizine, π, and fragment (*f*) values for the indolizinyl substituents were determined using both methods. Good agreement was obtained for all three values.

Keyphrases □ Partition coefficient—indolizine and 2-phenylindolizines, determination by high-pressure liquid chromatography and fragmentation values □ Indolizine—substituted 2-phenylindolizines, partition coefficients determined by high-pressure liquid chromatography and fragmentation values □ High-pressure liquid chromatography—determination of partition coefficients of indolizine and 2-phenylindolizines □ Fragmentation values—determination of partition coefficients of indolizine and 2-phenylindolizine

There is considerable interest in partition coefficient determination in the area of rational drug design (1). The partition coefficient, log *P*, represents the distribution of a substance between an organic and aqueous phase. Several methods may be used to determine partition coefficients including the shake-flask method, liquid–liquid chromatography on liquid impregnated plate technique, and high-pressure liquid chromatography (HPLC).

No studies have been done on the log *P* of indolizines. Indolizine (I) is a 10π aromatic heterocyclic compound with the nitrogen at the bridge head position. It is nearly electrically neutral and weakly basic with a pKa value of 3.94 (2).



I

For the normal shake-flask method, octanol and water have been used previously as the biological lipid and aqueous phases, respectively, in partition determination (3). Due to the instability of the indolizine nucleus, measuring log *P* values of this compound by this technique has proven difficult. The shake-flask procedure (4) is a tedious, time-consuming process and subject to purity, stability, and mass-balance problems from the compounds being measured.

BACKGROUND

Liquid chromatography on paper or lipid-impregnated plates has been used as an alternative to octanol–water partition. Martin (5) derived Eq. 1 for thin-layer or paper chromatography (TLC):

0022-3549/82/0600-0614$01.00/0