The Derivation of an Equation Describing Powder Compaction Behavior in Terms of Void Volume

by

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A thesis submitted in partial fulfillment
of the requirement for the degree of

Master of Science
(Pharmacy)

at the
University of Wisconsin
1988

ACKNOWLEDGEMENT

I wish to thank Professor Jens T. Carstensen for his patience and kindness in helping me achieve my goal of a Master's Degree in Pharmacy. He is a true gentleman and a scholar.

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I. INTRODUCTION

Tablets are one of the oldest dosage forms available and they have been greatly studied. Aside from being relatively inexpensive, they are one of the easiest dosage forms to use and they also have a fairly high compliance rate compared to other dosage forms such as injections. Another advantage with tablets is that they deliver accurate amounts of drug to the user.[1]

There are three basic approaches to making tablets, all of which depend on the mechanical properties of the compounds. The simple compression of a powder with the addition of few additives is known as direct compression. This method is used for compounds which show good flow and compression characteristics.[1]

The second method is known as wet granulation. This method is used for compounds which compress and flow poorly. It also helps to uniformly distribute drug throughout the mix. Here, powders are mixed in a mixer and blended. Then, a granulating solution is added followed by coarse milling of the wet granulate. Drying and milling are next with tableting last. Much more could be said concerning wet granulation but it is not the purpose of this work and so it will not be commented on further.[1]

The last method is known as slugging.[1] Here a powder is compressed in large dies simply to increase particle size. Then, these large compacts are milled to a size larger than the initial particle size. In

this way, the flow of the powder is improved.

Extra ingredients are added to drugs to improve their mechanical properties. For example, the addition of talc to a formulation will improve the flow properties of the drug. In this case, talc is used as a glidant. Lubricants reduce the force necessary to eject a tablet from the die while excipients, such as lactose, are used to increase the bulk volume of drugs used in small quantities.[1] It would be difficult to accurately compress a powder into a tablet with only two milligrams of drug such as is the case with diazepam 2 mg tablets.

To help the tablet disintegrate in the body, disintegrants such as alginic acid or starch are added to the formulation. These help the release of drug from the tablet by swelling, creating space so that drug can diffuse out of the tablet.[1]

Often, compounds show poor bonding characteristics when compressed; therefore, by adding a binder such as starch paste, one can improve such binding properties.[1]

Now that the powders have been prepared, they are ready for compression. Many industrial tableting instruments are available and these include single punch and rotary punch machines. Single punch machines have only one punch and die set per machine. Relatively speaking, these instruments are slow, making up to only 100 tablets per minute. Rotary tablet machines have several dies contained in a circular arrangement and these may produce up to one million tablets per hour.

The basic process of die filling, powder compression and tablet ejection is the same for both types of tableting machines. First, a powder or granulation is transferred into the die cavity. Then the upper punch is lowered to compress the powder and finally the upper punch and lower punch rise to 1) release the pressure on the tablet and 2) to eject the tablet.[2] (See Figure I-1.)

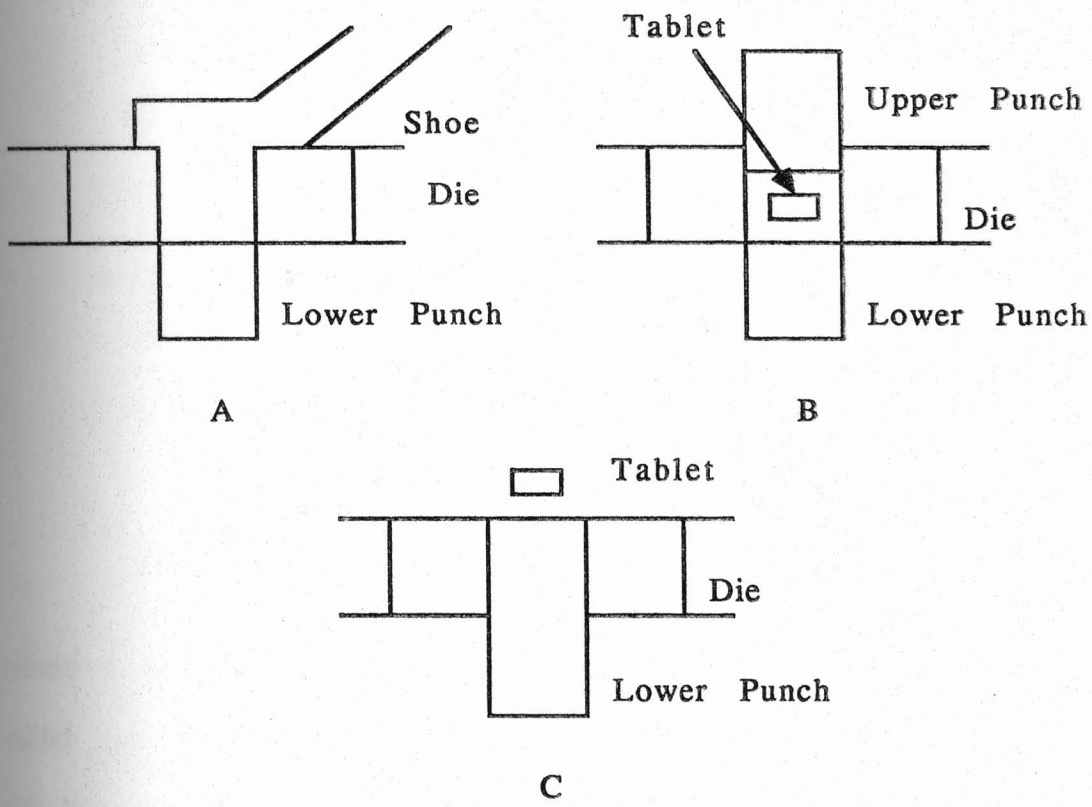


Figure I-1. A) Filling of the die with powder through the shoe. B) Compression of the powder by the upper punch. C) After the release of pressure by the upper punch, the lower punch ejects the die.

In the compression process, powders undergo mechanical stresses which are immense and depending on the material, can behave differently while compressed. The theory of the deformation of solids under compression has been reported by Leigh, et al.[3] In the case of a perfectly elastic material and below the yield stress, when the axial force is released, the radial force returns to zero as shown in Figure I-2. This behavior can be explained by the equation:

$$\tau = \nu \sigma$$

where σ is the axial force, τ the radial force and ν the Poisson ratio. Beyond point A of Figure I-2, deformation begins and the slope is equal to unity for the line segment AB. Now,

$$\tau = \sigma - s$$

where s is the yield value. At point B the axial force is released and the radial force decreases at a rate ν. Here the line segment BC is parallel to the line segment OA. At point C, the radial force decreases moreso, at a rate equal to one. The equation to describe this relation is now

$$\tau - (\sigma_1 + s) = \sigma - \sigma_1$$

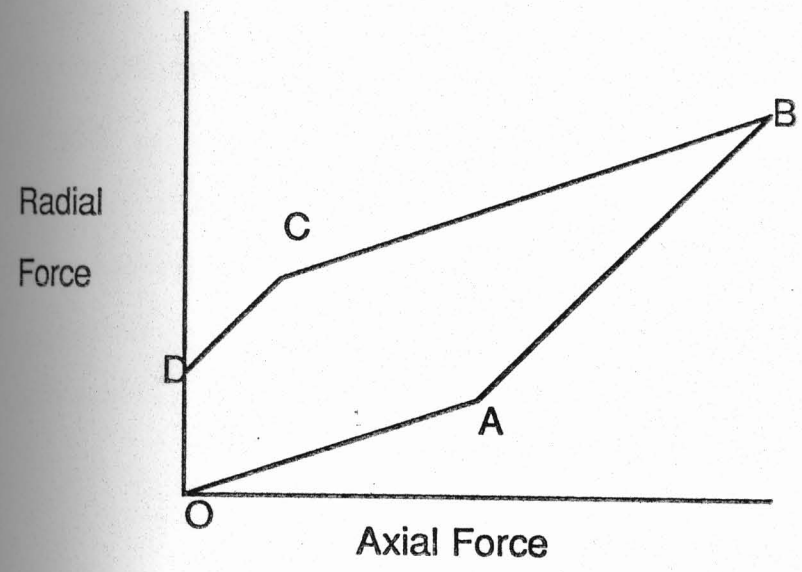


Figure I-2. Expected compression cycle when a constant yield stress occurs.

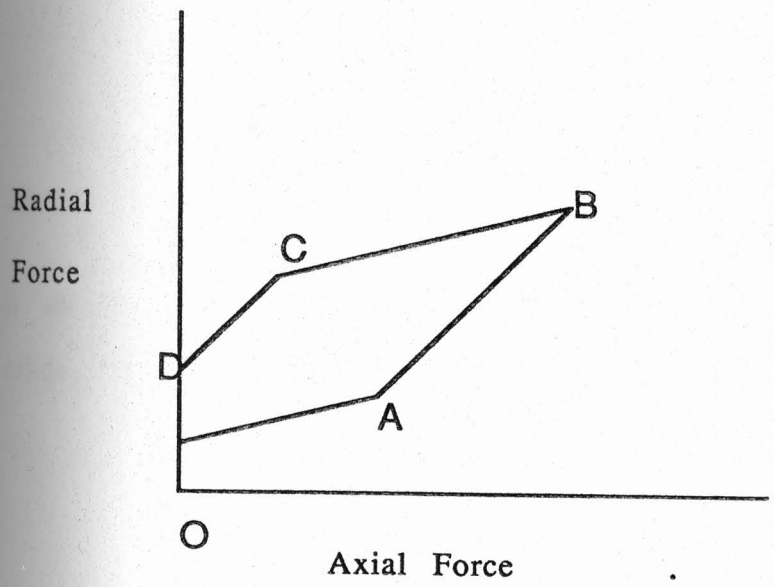


Figure I-3. Expected compression cycle for a Mohr body.

(σ_1 is the axial force at point C). Therefore, a force s is exerted against the die wall at zero axial force after compression. However, B may be so low that C is never reached.[3,4]

Mohr-type bodies (Figure I-3) are a more commonly observed phenomenon.[5] Here, similar behavior is observed up to point A, where yield occurs. From point A to B

$$\tau_1 = \sigma + \sigma_N \mu$$

where τ_1 is the shear stress in the slip plane, σ_N is the normal stress on the plane and μ is a friction term. Once the axial force is released at point B, again the radial force decreases at a rate ν and beyond C, the slope is now

$$(1+\mu) / (1-\mu).^3$$

It should be remembered that these equations are restricted to isotropic solids and do not apply to granular materials which contain void spaces.

Tablet hardness is an important consideration and Kennon and Swintosky (1958)[6] have shown that tablet hardness is a function of compression pressure. Tablet hardness will increase with compression pressure until the fracture point of the tablet is reached. Beyond this point, the tablets simply crumble.

There are several tablet defects that can occur, two of which are capping and splitting. Capping is the separation of the crown from the remainder of the compact. Both capping and splitting may be caused by 1) excess pressure, 2) too many fines (very fine particles), 3) too weak a granule, 4) too dry a granulation, 5) unfavorable polymorphs or crystal habits or 6) an excessively high compression rate.[1]

Spotting is another kind of defect. It is the presence of impurities on the surface of the tablet and it may be due to the presence of dirt, chemical reactions (changes) or mold growth in the case of high moisture formulations.[1]

Finally, picking is a situation where part of the surface of the tablet is missing. It may be caused by too wet a granulation, poorly polished punches, too much play between punch and die or insufficient lubricant.[1]

Theory

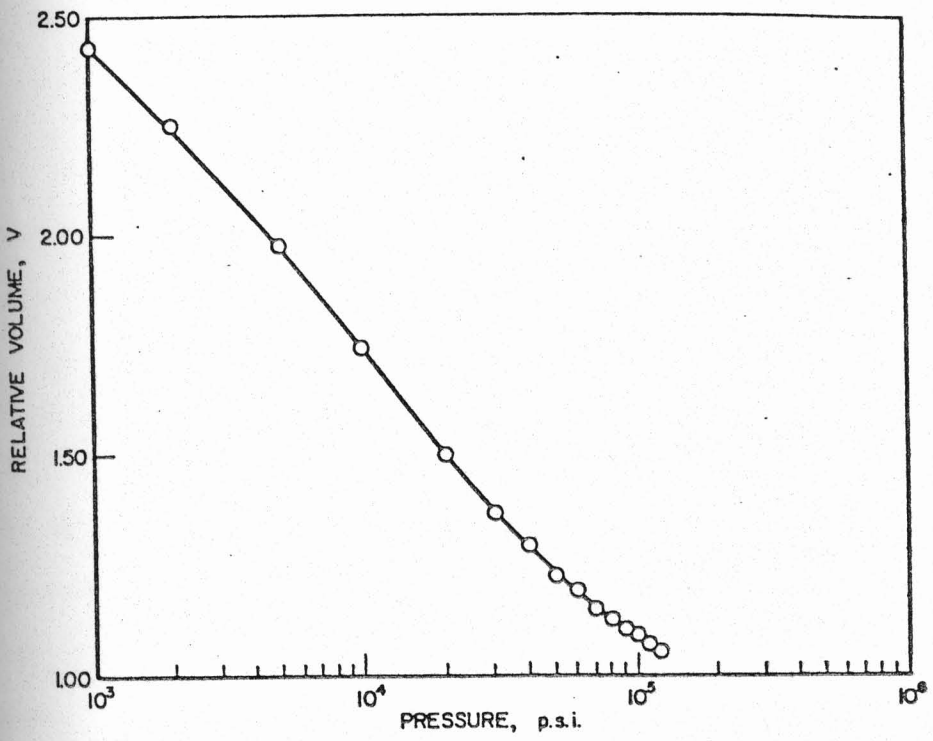
The mechanical properties of tableted dosage forms are, of course, important. The tablet must be sufficiently hard to prevent breakage during transportation. If not hard enough, the tablet will simply break within the container, before it can be consumed. The harder one makes a tablet, the more resistant it is to external strain. However, a harder tablet is less porous which, in turn, leads to a decrease in disintegraton/ dissolution rates.[7] Therefore, the manufacture of a tablet involves a careful balance of compression pressures, not too high and not too low, in order to achieve the most practical solution.

Several attempts have been made to relate the pressure exerted in making a compact to either its relative volume[8] or its density.[9,10,11] Balshin[8] proposed the following equation relating the applied pressure (P) on a compact to its relative volume (V).

$$\ln P = -LV + C$$

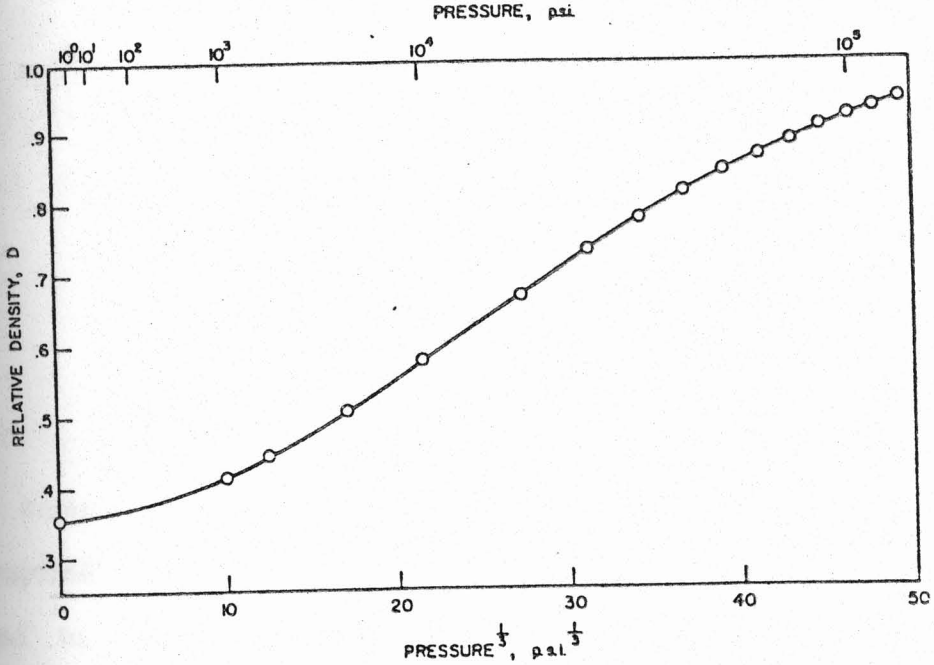
where L is called the modulus of pressing and C is a constant. As seen in Figure I-4, the relationship is not linear over the entire pressure range and this analysis is also insensitive to variations in pressure at high pressure ranges.

Smith[9] suggested the following density-pressure relationship



—Volume-pressure relationship of Balshin for −200 +250 mesh iron (A) powder.

Figure I-4.[8]



—Density-pressure relationship of Smith for −250 +250 mesh iron (A) (electrolytic).

Figure I-5.[9]

$$C_f = (\rho - \rho_0)/P^{1/3}$$

where C_f is the "compressibility factor," ρ is the compact's density, ρ_0 is the apparent density of the powder and P is the applied pressure. The use of this equation, as seen in Figure I-5, is justified only at intermediate pressures and it is not indicative of what occurs at both low and high pressures.

Ballhausen[10] suggested that

ln D/(1-D) is proportional to P

where P is the applied pressure and D is the relative density of the compact. This relation holds at intermediate and high pressures but not below 50,000 psi for the metals used. Konopicky[11], on the other hand, suggested that

ln 1/(1 - D) is proportional to P.

This relation held for high and intermediate pressures as well but it also held to compression pressures as low as 20,000 psi for the same metals it was compared to. Therefore, Heckel expanded on Konopicky's equation. He attempted to relate the density of a compact to the pressure used in making that compact. If a relationship could be found, predictions of

compact density could be made by knowing the pressure used in making the compact.

The Heckel equation[12,13,14] has been used successfully for many years to describe powder compacts. It comprises the following concepts. If a tablet is made in a die and expelled, it will contain a certain amount of void space characterized by its porosity:

$$E = 1 - D'/D \quad \text{(Eq. 1)}$$

where D' is the apparent density of the compact (g/cm^3), D is the true density of the compact (g/cm^3) and E is the porosity.

Heckel proposed that the change in density relative to pressure is proportional to the void volume (1 - D*). Here, D* is the relative density (D'/D).

$$dD^*/dP = b(1 - D^*)$$

which upon rearrangement and integration gives

$$\ln [1/(1 - D^*)] = bP + \ln [1/(1-D^*_0)] \quad \text{(Eq. 2)}$$

where D^*_0 is the relative apparent density. This equation can then be rewritten as

$$-\ln E = bP + A \quad \text{(Eq. 3)}$$

where

$$E = -\ln (1-D^*_o) \text{ and } A = \ln (1/(1-D^*_o)).$$

Since A is representative of densification due to individual particle motion and densification by die filling, equation 3 represents a three-stage process. The first step is filling of the die which is followed by increased densification due to particle movement and rearrangement. The last step is increased density due to particle deformation after appreciable bonding between particles has taken place. Here, b is related to the deformability of the compact which, in turn is related to the yield strength.

It is noted that, at best, the Heckel equation is quasi-theoretical. Heckel (1961)[14] experimentally found the value of b to be approximately equal to $1/3\theta$ where θ is the yield strength. (By knowing the yield strength of some materials, Heckel was able to back calculate an equation relating the known yield strength of those materials to that derived from the slope of the Heckel equation.) Hersey and Rees later expanded this to imply b being the reciprocal of the yield pressure (1970).[15] It is thus possible to obtain information about the strength of a material by means of Heckel plots.

Figure I-6 shows a plot of the natural log of 1/porosity versus compression pressure for all pressures. The Heckel equation, it should be said, applies only to compression pressures above the yield strength and

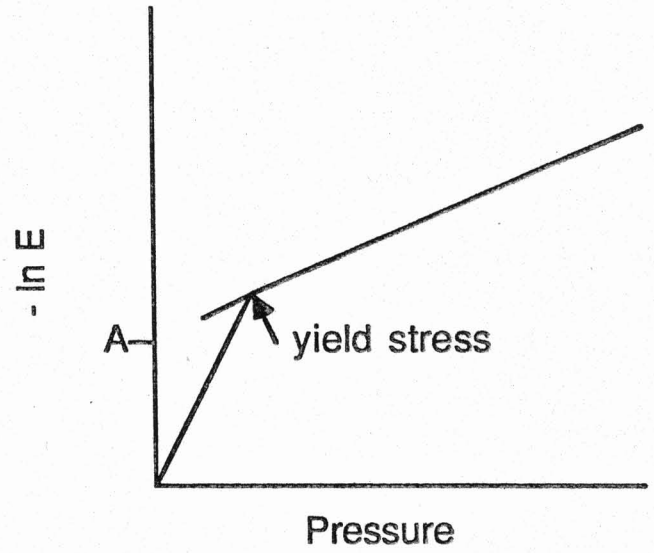


Figure I-6. A plot of the natural log of 1/porosity vs pressure. The Heckel equation applies only to pressures above the yield strength. It should be stated that the break at the yield strength is not sharp but smooth.

its intercept is not equal to zero but equal to A as shown. And the transition at the yield stress is smooth and not sharp as shown in the diagram.

The strength of a compact is intimately related to the pressure used in making that compact. At moderate pressures an increase in the force of compression leads to a harder compact. But, at a critical pressure, capping or lamination of the compact is seen. It is one of the purposes of this thesis to investigate whether the capping point is associated with a critical porosity. Acetaminophen is used as a model system.

In actual compression, at the point where compression starts is the point where the *first event* of surpassing the yield pressure, 3θ, at individual contact points occurs. Since consolidation would take place at certain points, and failure at others, a tablet may be formed, with bonds at some contact points, and non-bonds at others. If a powder bed, for instance, were such that each particle had n contact points, and if there were N particles present, then there is the potential for $N \cdot n/2$ bonds. It is visualized here, that the Heckel region does not start until all *possible* bonds have been formed. This number may be less than $N \cdot n/2$ because complete consolidation may never be achievable. In the range between the "first compression" or the "first pair of particles bonding" and the point where the maximum number of bonds have been formed will there be a region of non-linearity, when the data are plotted according to Heckel. It is a point in this writing that most pharmaceutical powders and granulations fall into this category.

If a pharmaceutical powder or granulation is not really in the Athy-Heckel range, then if it is treated linearly by the Athy-Heckel equation, a situation such as shown in Figure I-7 occurs.

If all the point on such a plot are obviously linear, then the Athy-Heckel equation obviously is obeyed. However, if *some* of the points are not in the linear region, then they can be discarded, particularly if it can be shown that they were obtained at pressures below 3θ. This can be internally checked, because the slope of the Heckel plot may be $k = 1/(3\theta)$. If one now discards e.g. the point at the lowest pressure, then a new line is drawn, k is obviously different, so a new value of 3θ is obtained, which

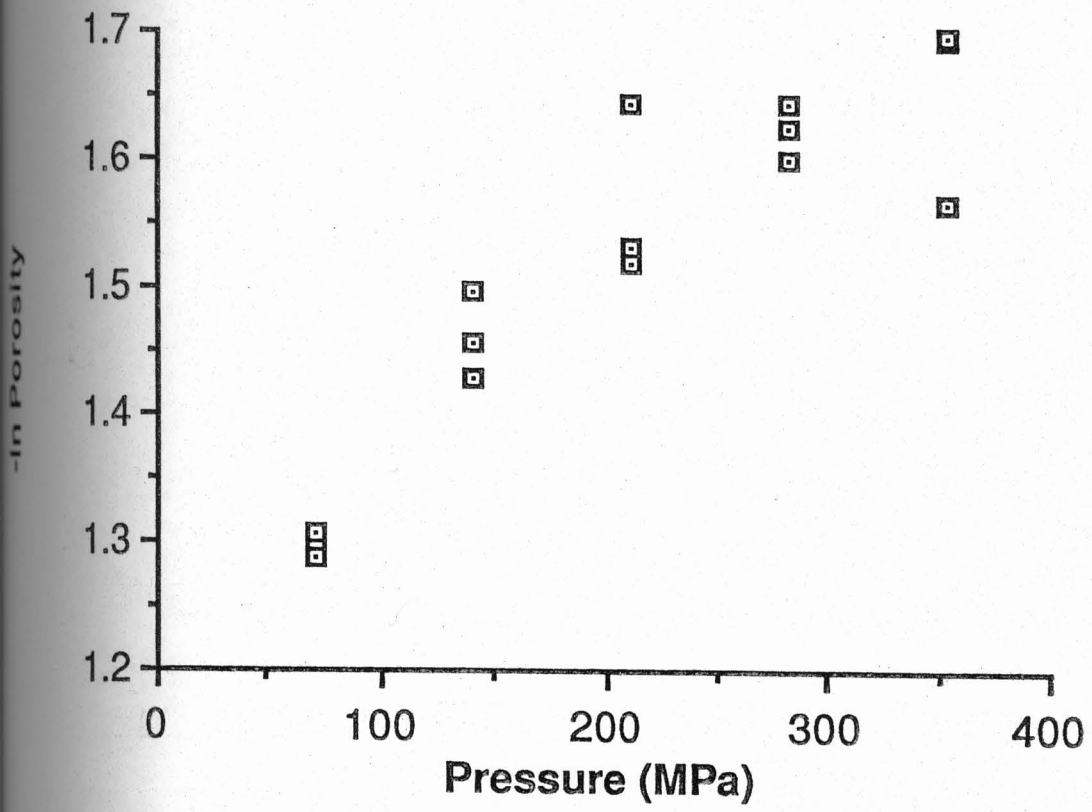


Figure I-7 . A representation of curvature in a 1.27 cm die at 30% apap concentration when plotting -ln porosity vs pressure.

may justify discarding yet another point on the line. In this range it is the totally empirical equation by Cooper and Eaton[15] which is most widely used:

$$(V-V_t)/(V_o-V_t) = Fe^{-\alpha/P} + F'e^{\gamma/P} \quad \text{Eq. 4}$$

V-symbols are, here, apparent volumes, and subscript zero refers to the apparent volume of a cascaded or tapped dense powder), V_t is the asymptotic value of the powder at high pressure, and F, F', α and γ are constants. It is noted that this is a five parameter equation, and that, furthermore, it does apply only to a one component systems.

To date two possible mechanisms for the capping of acetaminophen have been described by Shotton and Ganderton[17], Obiorah and Shotton[18], Doelker and Shotton[19] and Hiestand et al.[20] The first possibility is that strong interparticulate bonds fail when the stress on the compact is removed[17]. The second possibility is that the tablet is allowed to expand in only one direction upon the release of the force of compression; the tablet expands uniaxially. And, because of the low plastic flow, the tablet then caps or laminates[18,19,20]. This suggests that strong bonds would eliminate rather than cause tablet fracture. Carstensen, Alcorn, Hussain and Zoglio (1985)[21] showed that the Hiestand principle is applicable. (If relaxation is three dimensional instead of uniaxial, capping can be prevented by three-dimensional relaxation of the applied force.) Actually,

the real reason for capping and lamination is probably an interplay of both of the mechanisms and it is probably impossible to associate capping with one mechanism as opposed to another. Therefore, it cannot be related to anything including Heckel plots.

Another purpose of the thesis is to determine if different results are obtained with different die sizes. Berg (1969)[22] showed that within a die, there is some ordering along the walls of the die and Train (1959)[23] and Ridgeway and Tarbuck (1966)[24] have shown that the porosity of a tablet varies positionally within the die. In Figure I-8, the first layer of spheres lines itself up against the wall simply because of geometry. Here the porosity is equal to one because the spheres touch the wall only as a point and occupy no surface area on the die wall. The second layer of spheres aligns itself according to the first layer. This process continues until it becomes totally random. Ridgeway and Tarbuck (1966)[24], using a radial voidage distribution, were able to show that the ordering of spheres along a die wall was up to five sphere diameters thick (See Figure I-9). The first minimum occurs at a distance approximately equal to the radius of the

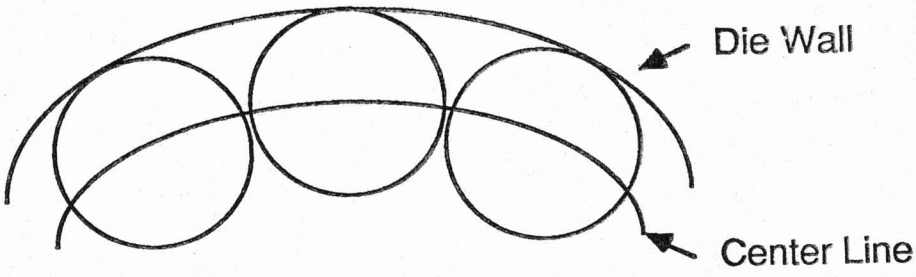
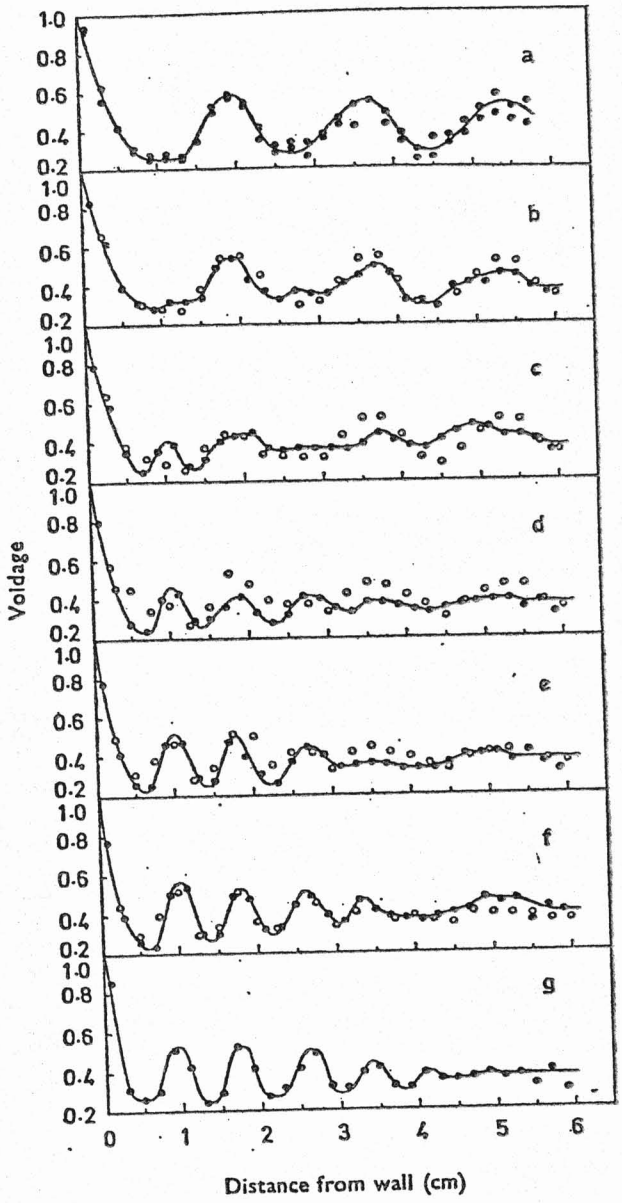


Figure I-8. Diagram showing how the porosity varies along a die wall within the first layer of spheres. Notice the high voidage along the die wall and the low voidage at the center line of the spheres.



Radial voidage distribution for mixtures of 10 and 20 mm spheres in a cylindrical container. ●, experimental. ○, calculated by suitably weighting values for the individual components. Mixture composition (% 10 mm by number): a, 0; b, 33·3; c, 58·4; d, 85·7; e, 95·3; f, 99·1; g, 100.

Figure I-9 .23

first layer of spheres with the first maximum occurring at approximately one sphere diameter. Gradually, the function is damped because of the increasing amount of randomness. It should be remembered that this applies only to hard spheres. Roblee et al. (1958)[25] have shown that for cylindrical powders, the ordering occurs for only three particle diameters. Therefore, it is possible that die diameter does affect tablet porosity where Heckel plots are concerned. (See Figure I-10.)

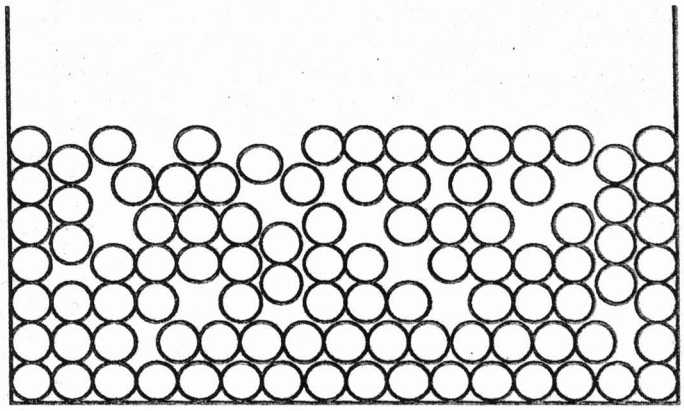


Figure I-10. Arrangement of an ideally spherical powder formulation about a die cavity. Notice the ordered arrangement along the die walls and the randomness of arrangement in the bulk.

When tablets are compressed, there is a correlation between the applied tableting pressure, and the hardness and thickness of the resulting compact. These qualities are obviously important, hardness because it (if in the proper range) assures that the tablets may withstand the

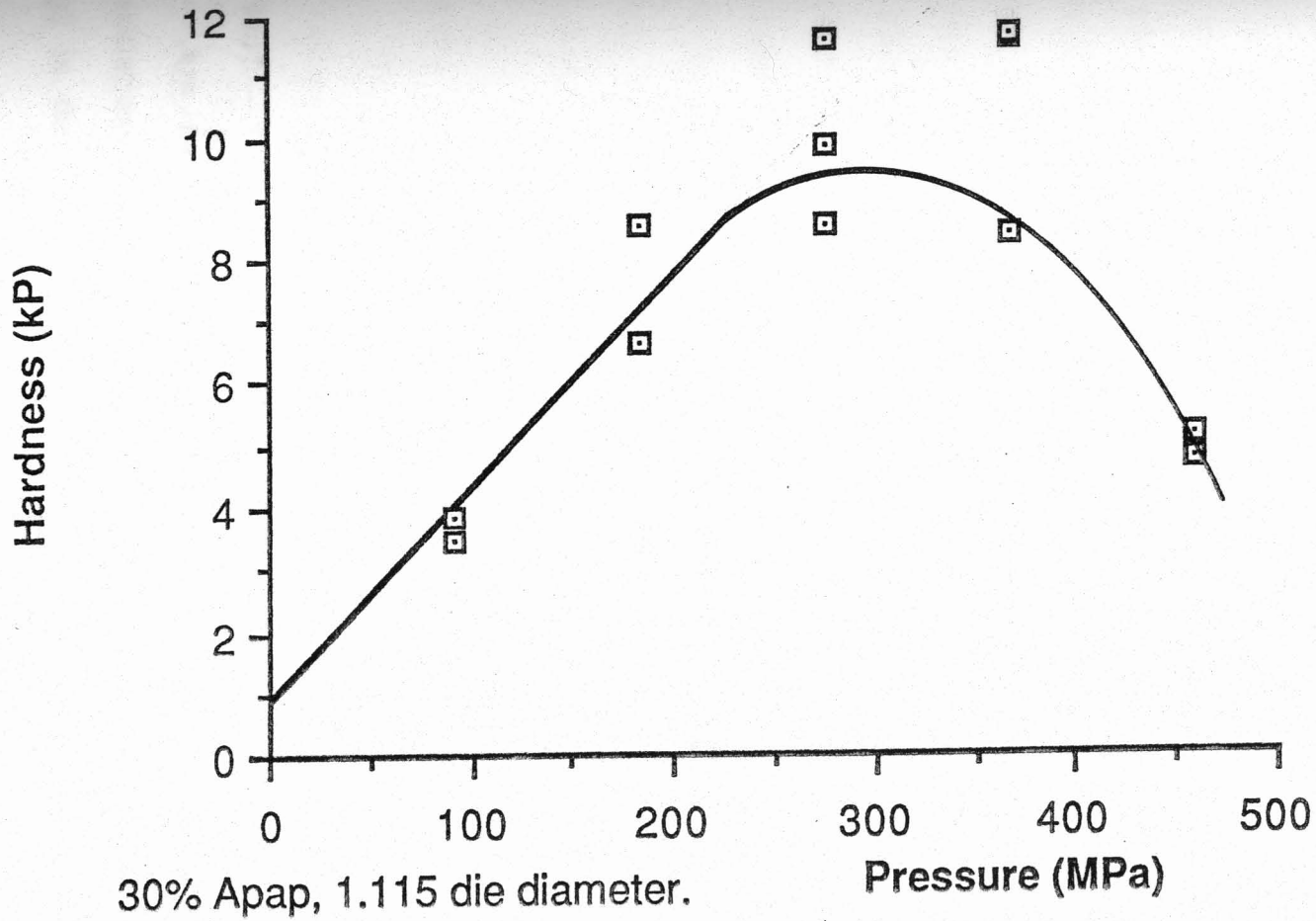


Figure I-11 Plot of hardness vs pressure for apap at 30% concentration.

vicissitudes of transportation. Dimensions are important because the solid dosage form is destined to be filled into bottles of given volumes, using machinery at particular settings, and gross deviation in thickness from batch to batch is troublesome from a manufacturing point of view.

The most conventional method of such recording in industrial pharmacy is a plot of thickness (and hardness) as a function of applied tableting pressure. From a more fundamental point of view, the use of porosity as a function of applied pressure is more meaningful.

Figure I-11 shows a plot of tablet hardness vs compression pressure for 30% acetaminophen in a 1.115 cm die. It is seen that the plots are not linear. This can be explained by the fact that at higher pressures and acetaminophen concentrations, capping is observed. When this occurs, tablet hardness decreases. Also, Heckel plots become curved because the porosity is increased with capping. (Figure I-7) Therefore, curvature in Heckel plots is expected at high acetaminophen concentrations and at high forces of compression.

Several questions arise:

1. Do the intercepts of Heckel plots, as predicted by prevailing theories, correspond to the negative logarithm of the porosity of a closed packed bed?

2. Are the relatively low pressures used in compressing pharmaceutical granulations and powders (as opposed to the pressures used in metallurgy) in the linear region of a Heckel plot, or only apparently so?

3. Is it possible, rationally, to eliminate the points that are not in the linear regon? This could be visualized as the points below the failure region. If not, how can they be described mathematically and does this apply to binary mixtures?

4. Do capping tendencies show their effects below the yield strength?

5. Are there differences between die sizes when examining tablet compression? If they are, then it would be difficult to compare results from different authors when comparing Heckel plots.

The work to be described in the following attempts to answer these questions.

II. EXPERIMENTAL

The objectives of this work included the determination of tablet porosity at different compression pressures and also at different drug concentrations. It is known that acetaminophen is a poorly compressible drug[25] and so as one increases its concentration to high levels (i.e. 30% of tablet weight), tablet hardness decreases at high pressures (See Figure II-1.)[20]

The materials used in this study consisted of acetaminophen (CPC R&D, Lot No. 8103094), magnesium stearate (Fischer Scientific Company, Lot No. 785331) and dicalcium phosphate dihydrate (Stauffer

Chemical, unmilled).

Particle size is an important factor during tableting. It affects flow rates, dissolution and, important to this work, porosity. Sieve analyses were therefore performed on the materials used.

Sieve analyses of dicalcium phosphate dihydrate (Di-Tab) and acetaminophen were conducted with the results shown in tables II-1 and II-2. Also done was a sieve analysis for the combinations of 15%, 20%, 25%, and 30% acetaminophen. The data for 20% are presented in table II-3. Data for the other concentrations are consistent with those of 20% apap. Before mixing the powders, each was passed through a No. 12 sieve.

The tableting apparatus consisted of a Carver hydraulic press (Carver Press, Menomonee Falls, WI, USA) set at a speed of compression of 10 seconds and a dwell time of 30 seconds.

Dicalcium phosphate dihydrate was mixed with 0.5% magnesium stearate in a mortar and pestle for 10 minutes. This mixture, then, was compressed in a 1.27 cm die (flat-faced, non-beveled punch, 0.9 gm) with a force of compression of 8.92 kN. Three of these tablets were made. Then forces of compression of 17.92, 26.88, 35.84 and 44.80 kN were applied to the same mixture. Again, at each force of compression, three tablets were made.

Acetaminophen in concentrations of 5, 10, 15, 20, 25 and 30% was mixed with dicalcium phosphate dihydrate and 0.5% magnesium stearate. This mixture was compressed in the same fashion as the dicalcium phosphate dihydrate.

All of this was then repeated for die diameters of 0.635 cm (0.27 gm samples), 0.95 cm (0.6 gm samples) and 1.115 cm (0.7 gm samples). Forces of compression in excess of 26.88 kN were not done for the die of 0.635 cm diameter for safety reasons. (Excessively high pressures are reached above this force of compression.)

Heckel plots were made and their slopes determined using linear regression.

Lastly, the hardness of each tablet was determined on a Schleuniger Hardness Tester which uses a diametrical failure test and hardness vs compression force plots were made.

Particle Diameter (μm)	No. of particles larger than diameter	Percent of particles larger than diameter
840	0	0
420	8.2×10^{5}	2.0 x 10-3
250	1.47×10^{10}	4.05
177	7.13×10^{10}	19.52
149	1.98×10^{11}	54.38
<149	3.65×10^{11}	100.00

Table II-1. Sieve analysis data of dicalcium phosphate dihydrate.

Particle Diameter (μm)	No. of particles larger than diameter	Percent of particles larger than diameter
2000	0	0
840	2.6×10^{7}	7.6 x 10-4
420	1.9×10^{9}	5.4 x 10-2
250	1.9×10^{12}	54.79
177	2.0×10^{12}	57.27
149	2.3×10^{12}	66.94
<149	3.5×10^{12}	100.00

Table II-2. Sieve analysis of acetaminophen before mixing with dicalcium phosphate dihydrate.

Particle Diameter (μm)	No. of particles larger than diameter	Percent of particles larger than diameter
840	0	0
420	2.5×10^{5}	1.0 x 10-5
250	1.8×10^{10}	0.75
177	4.3×10^{11}	1.79
149	3.9×10^{11}	16.20
<149	2.4×10^{12}	100.00

Table II-3. Sieve analysis of 20% acetaminophen, 0.5% magnesium stearate and 79.5% dicalcium phosphate dihydrate after sieving and mixing in a mortar and pestle.

III. RESULTS AND DISCUSSION

By knowing the true densities (D, g/cm^3) of the acetaminophen (1.294, Merck Index, pg. 537, 7th edition) and the dicalcium phosphate[27], one can calculate the true density of the mixtures. (Magnesium stearate was not included because it is constant in concentration throughout and its contribution to the total weight of the tablet is very small, affecting the density only slightly.) The volume of the tablet can then be calculated by the use of the equation for the volume of a cylinder ($\pi r^2 h$). Here, r is the radius of the die (cm) and h is the thickness of the tablet (cm). From the weight and volume of the tablet , the apparent density is easily calculated (apparent density = weight / volume).

Now that the apparent and true densities are known, one can calculate the porosity of the tablets by using equation 1. The Carver Press used exerts a force on the compressed tablet and this force can be converted into pressure by the following equation:

$$\text{Pressure} = \text{Force} / \text{Area} \qquad \text{(Eq. 5)}$$

where the force is measured in Newtons and the area is measured in square meters. This, then, gives a pressure in Pascals. By taking the negative natural log of the porosity, one can then plot this value versus the applied pressure to determine b, θ and A, the other three parameters involved in this equation.

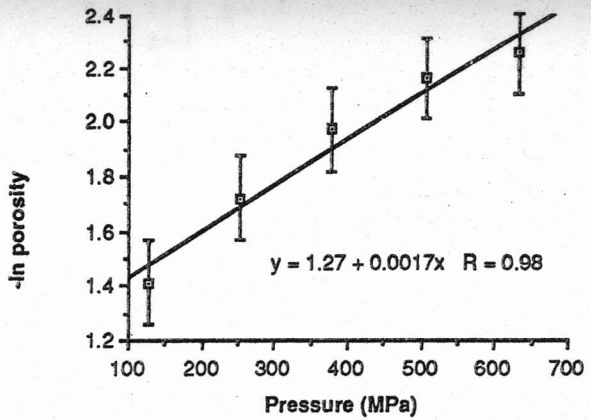


Figure III-1. Heckel plot of dicalcium phosphate dihydrate in 0.95 cm die.

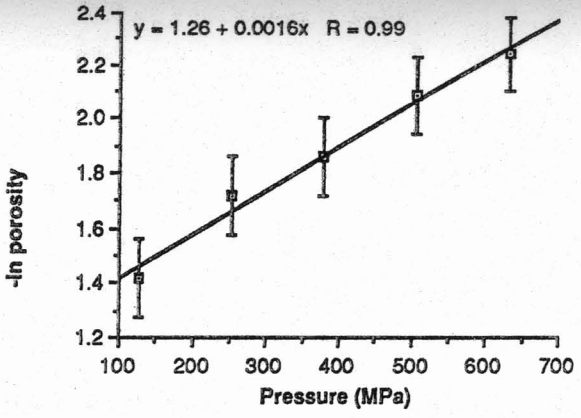


Figure III-2. Heckel plot of 5% acetaminophen in 0.95 cm die.

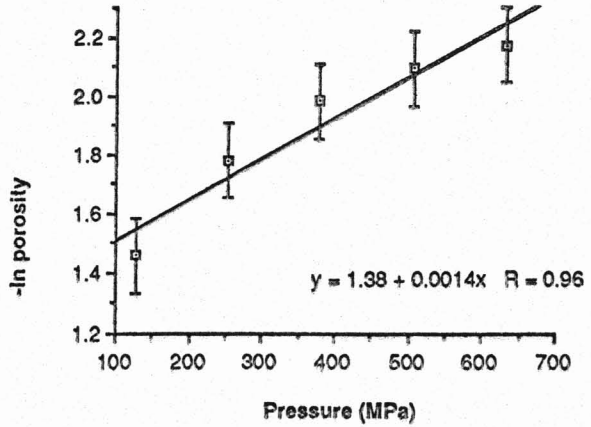


Figure III-3. Heckel plot of 10% acetaminophen in 0.95 cm die.

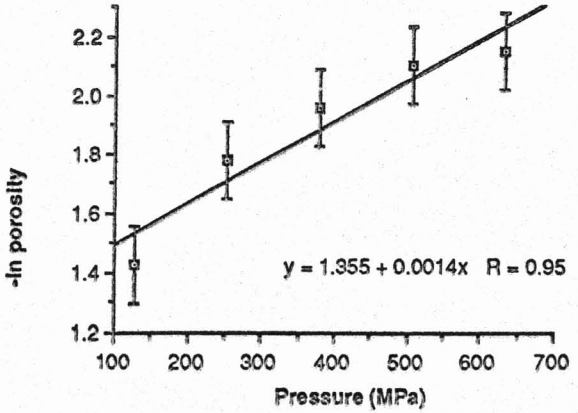


Figure III-4. Heckel plot for 15% acetaminophen in 0.95 cm die.

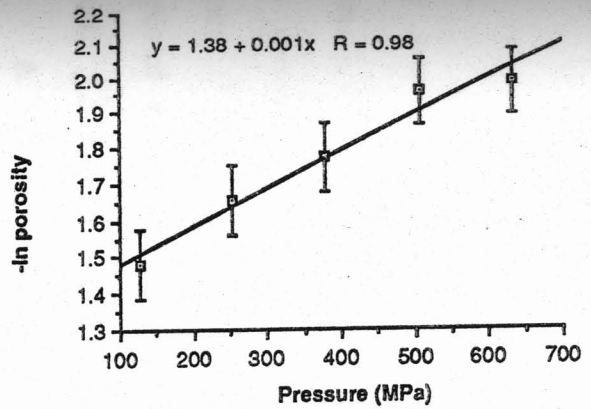


Figure III-5. Heckel plot of 20% acetaminophen in 0.95cm die.

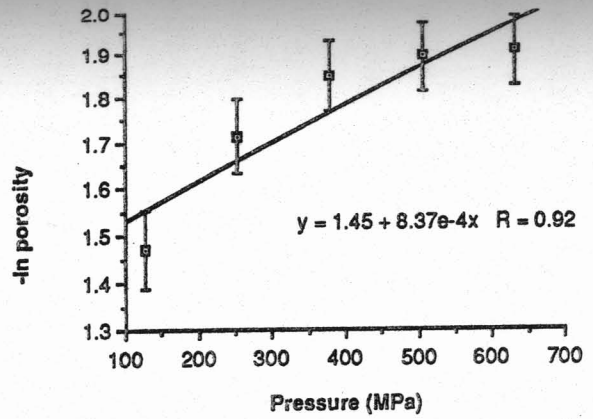


Figure III-6. Heckel plot of 25% acetaminophen in 0.95 cm die..

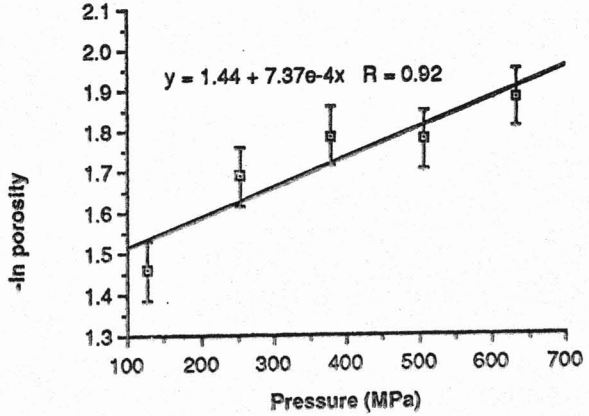


Figure III-7. Heckel plot of 30% acetaminophen in 0.95 cm die.

Figures III-1 to III-7 show the Heckel plots in a 0.95 cm die for acetaminophen concentrations of 0-30% and Tables III-1 through III-4 show b and A values for the four different die sizes and each drug concentration. The figures show good linearity especially in those figures with low drug concentrations. These plots were made in the pharmaceutically traditional way; that is, all points of pressure were included. There are pitfalls associated with such plotting since, as mentioned earlier, the Heckel equation applies only to intermediate pressures.

The first consideration involves the low pressure region. Because the Heckel equation applies to pressures only above the yield strength, one cannot include those pressures below the yield strength. Therefore, from the empirical relation

$$b = 1/3\theta$$

one can calculate to a rough approximation the yield strength. For example, in Figure III-1, $b = 0.0017$. Therefore $\theta = 1/3b = 196$ MPa and any pressure below 196 MPa should not be included in the Heckel plot (see Figure III-8). The deletion of such a data point, of course, changes the slope of the line and a better approximation for the yield strength can be made.

A second consideration involves points of measurement at high pressures. Because of the basic differences in physical properties of metals

% Apap	b	A	Correlation Coefficient
0	0.0011	1.34	0.96
5	0.0014	1.49	0.96
10	0.0012	1.55	0.97
15	0.0011	1.51	0.92
20	0.00082	1.59	0 93
25	0.00073	1.58	0.93
30	0.00062	1.56	0.93

Table III-1. The Heckel slopes and y-intercepts for the punch with a 0.635 cm diameter.

% Apap	b	A	Correlation Coefficient
0	0.0017	1.27	0.95
5	0.0016	1.26	0.97
10	0.0014	1.37	0.96
15	0.0014	1.36	0.94
20	0.0011	1.37	0.95
25	0.00084	1.45	0.90
30	0.00074	1.44	0.88

Table III-2. The Heckel slopes and y-intercepts for the punch with a 0.95 cm diameter.

% Apap	b	A	Correlation Coefficient
0	0.0020	1.13	1.00
5	0.0021	1.26	0.92
10	0.0019	1.21	0.96
15	0.0013	1.33	0.91
20	0.0015	1.27	0.93
25	0.0015	1.24	0.94
30	0.0011	1.34	0.89

Table III-3. The Heckel slopes and y-intercepts for the punch with a 1.115 cm diameter.

% Apap	b	A	Correlation Coefficient
0	0.0023	1.16	0.97
5	0.0019	1.20	0.97
10	0.0017	1.22	0.98
15	0.0018	1.20	0.96
20	0.0013	1.27	0.93
25	0.0083	0.99	0.92
30	0.0012	1.26	0.92

Table III-4. The Heckel slopes and y-intercepts for the punch with a 1.27 cm diameter.

versus pharmaceuticals, metals do not show capping tendencies. However, most powders of pharmaceutical interest do show capping properties. Therefore, there must be, associated with drugs, a critical capping pressure. The problem then lies in the fact that a compact which has capped has a higher porosity than one that has not and this then contributes to the curvature sometimes seen in Heckel plots. The question then is to determine above what pressure do we not include data points? It is possible that the linear region in the Heckel plots is very short because capping occurs shortly after plastic deformation begins.

Another possibility is that the yield strength of the material has not yet been reached and, therefore, a pressure high enough to exhibit the linear region in the Heckel plot has not yet been reached. Indeed this may be the case as can be seen from tables III-5 to III-8. The dashed lines in the tables indicate data whereby yield strengths could not be determined with the available data because pressures high enough to reach the yield strength had not been used (i.e. safety reasons). Yet at some of the higher pressures used, cappers were observed. This will be commented on later. From what is known about the true plot of -ln E vs pressure, the inclusion of a pressure below the yield point increases the Heckel slope, decreasing the yield strength since they are inversely related. In other words, including low pressure data underestimates the value of the yield strength. These data show, then, that cappers can be observed below the yield strength of a binary mixture.

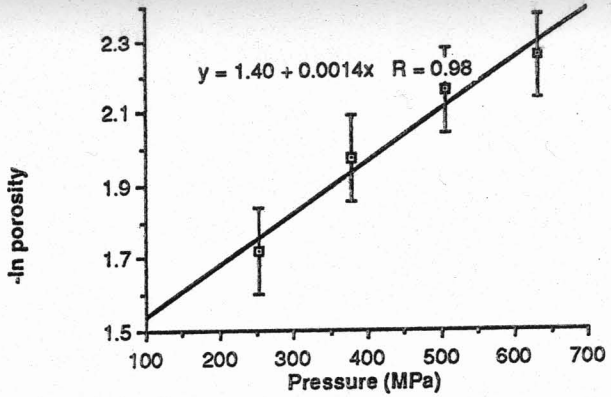


Figure III-8. Adjusted data for dicalcium phosphate dihydrate.

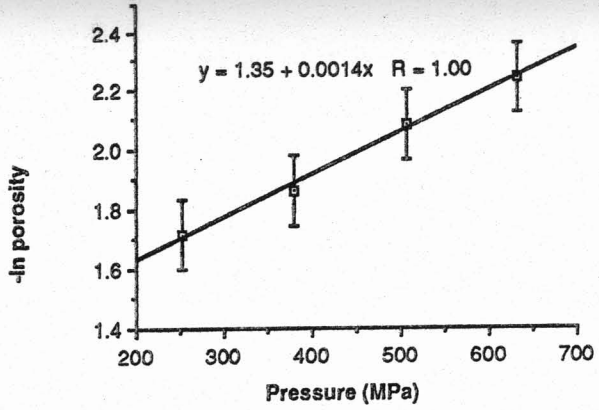


Figure III-9. Adjusted data for 5% acetaminophen.

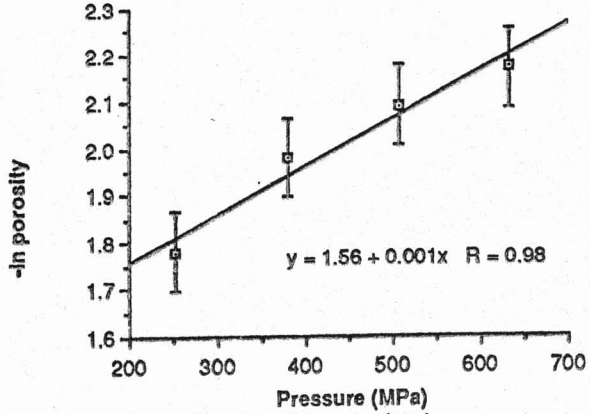


Figure III-10. Adjusted data for 10% acetaminophen.

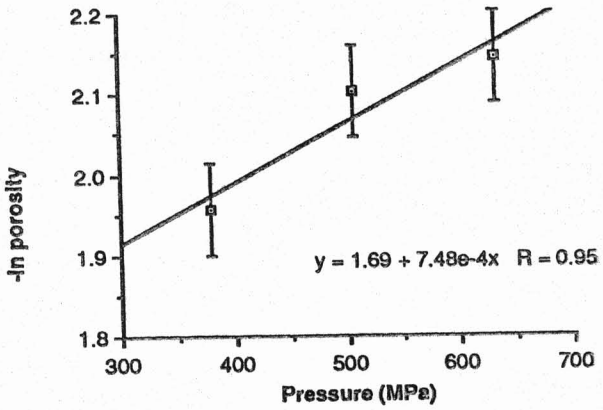


Figure III-11. Adjusted data for 15% acetaminophen.

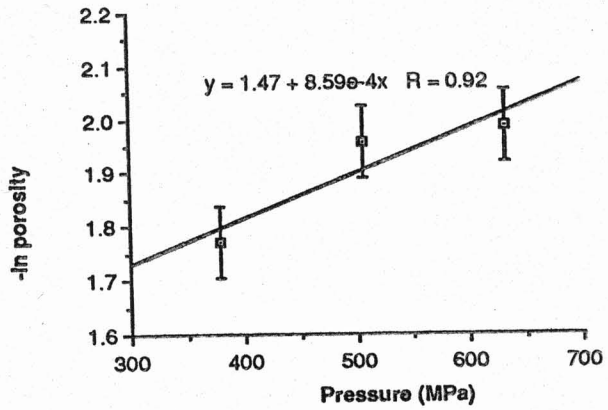


Figure III-12. Adjusted data for 20% acetaminophen.

Figures III-8 through III-12 show the Heckel plots of dicalcium phosphate dihydrate with acetaminophen concentrations of 0-20% in a 0.95 cm die as adjusted according to the above discussion.

In discussing the values of A one would expect that at zero pressure, A represents the negative natural log of the tapped density, the density of closest packing. If this were true then one would have the point at zero pressure without actually compressing the powder and it would also be a valid data point, determined below the yield strength. Simple experiments whereby tapped densities were determined by dropping a No. 8 rubber stopper onto a graduated cylinder containing the powder showed that this is not so. Table III-9 shows the values of the tapped densities of these powders for each of the different drug concentrations. Therefore, the negative natural log of the tapped density should not be included in Heckel plots.

Concentration	b	A
0	0.0016	1.34
5	0.0014	1.49
10	0.0012	1.55
15	0.0011	1.51
20	-	-
25	0.00035	1.87
30	0.00034	1.77

Table III-5. b and A values for a die of 0.635 cm diameter at various acetaminophen concentrations.

Concentration	b	A
0	0.0017	1.29
5	0.0014	1.35
10	0.0010	1.56
15	0.0013	1.46
20	0.00090	1.45
25	-	-
30	-	-

Table III-6. b and A values for a die of 0.95 cm diameter at various acetaminophen concentrations.

Concentration	b	A
0	0.0018	1.16
5	0.0023	1.28
10	0.0016	1.30
15	0.0018	1.48
20	-	-
25	0.0016	1.25
30	-	-

Table III-7. b and A values for a die of 1.115 cm diameter at various acetaminophen concentrations.

Concentration	b	A
0	0.0021	1.20
5	-	-
10	0.0017	1.23
15	0.0014	1.31
20	-	-
25	-	-
30	-	-

Table III-8. b and A values for a die of 1.27 cm diameter at various acetaminophen concentrations.

We must address the effect of die diameter on Heckel plots. Figure III-13 is a plot of the Heckel slopes for each drug concentration for each die diameter. Though the data are linear for die diameters of 0.635 cm and 1.27 cm, they are not so linear for the die diameters of 0.95 cm and 1.115 cm, exemplified by the poor correlation coefficients. These data are inconclusive in determining whether Heckel plots are affected by die diameter but they do suggest that more research should be done in this area.

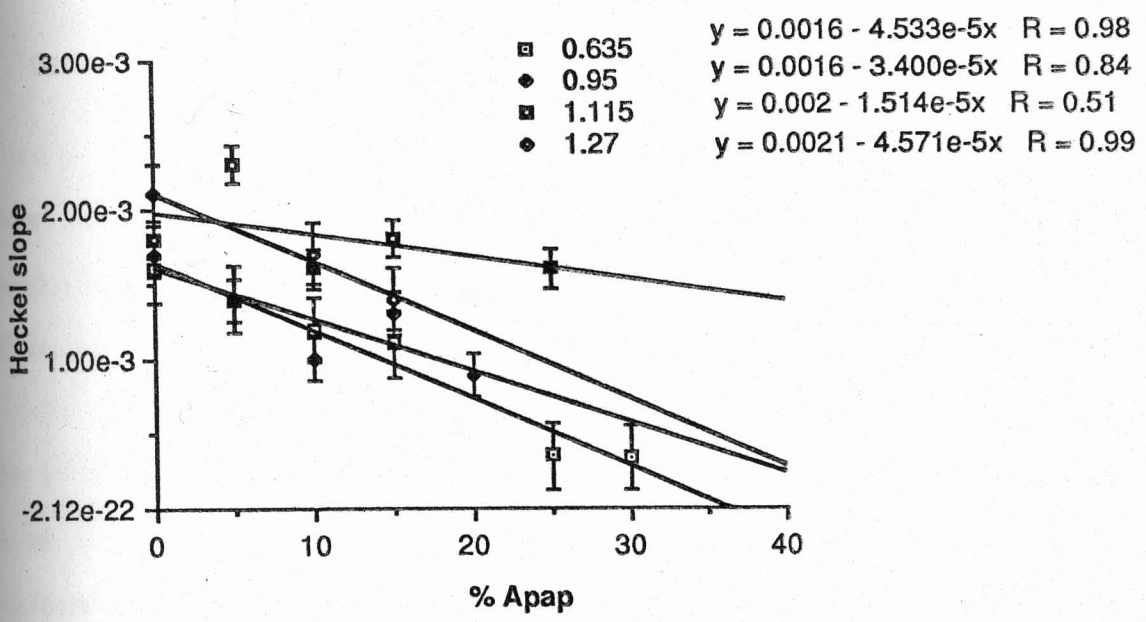


Figure III-13. Plots of Heckel slopes vs % apap for all 4 die diameters. Data are from tables III-5 to III-8.

As evidence of the occurence of capping, Figure I-7 is presented. Here one can clearly see a decrease in the Heckel slope at higher compression force, which is what occurs when the porosity of a tablet is higher. Therefore, curvature is seen and it occurs below the yield pressure. This occurs at high pressure for the other die sizes as well (not shown).

The porosity data are listed in Table III-9. Although there may be some difference in data obtained in the different size dies, these differences are not significant on the 95% level. The data from the different punches have therefore been pooled in the following (with a possible slight loss of precision).

A set of data plotted according to the Heckel equation is shown in Fig. III-14. Once again, it is seen that there is curvature.

It will be assumed in the following that the volume of air in the powder bed/compact is a quantity which will decrease exponentially with increasing pressure. It is noted that bond formation may start in certain regions of the bed, while the powder in other areas are still in the process of consolidation. This is depicted in Fig. III-15.

It is noted in Fig. III-15 that the closest packing is not necessarily the theoretically closest packing. Wall effects (as pointed out by both Berg et al.[22] and Tarbuck and Ridgway[24] will distort the arrangement, and "defects" will be present, when the powder is confined in a finite vessel (like the die). The space in between particles 1,2,3 and 4 does not correspond to the theoretical closest packing, and, this progressing with the

downwards stroke of the upper punch, the "final porosity" in such a pharmaceutical tablet may not necessarily be zero.

Once the closest packing for the particular compression event has been reached in a certain region of the powder bed, then further pressure will start to distort particles in that volume region, first below the elastic range, then, after the elastic limit has been reached (at which point a bonded tablet starts forming) by either plastic deformation or by brittle fracture. This is depicted in Fig. III-15. It is noted that it is probable that particles in certain regions reach closest packing (and hence start distorting) sooner than in others. This, in turn, may lead to inclusion of voids, which, within a reasonable pressure range, would be impossible to eliminate. A case in point is that when tablets are made on a high speed compression machine, then the porosity at a given pressure is larger than when the tablet is made on a hydraulic press. This is, in part, due to the different consolidation in a vibrating system[28], but also due to the view stated above, that compression starts in some regions before consolidation is complete in an over-all sense.

A one component system will first be dealt with, and it will be assumed (without loss of generality) that the amount in question is one gram. The smallest volume possible usually considered to be the true (void-less) solids volume, V^*, given by

$$V^* = 1/D_A \quad \text{Eq. 6}$$

Table III-9. - Data of Porosity Versus Pressure and Dies Used

Pressure (MPa)	Die	Porosity			
		% APAP			
		0%	10%	15%	20%
Q_A			0.817	0.760	0.691
71	1.27 cm	0.284(0.004)	0.267(0.001)	0.279(0.001)	0.270(0.003)
142		0.212(0.003)	0.223(0.001)	0.226(0.003)	0.227(0.005)
212		0.193(0.004)	0.203(0.001)	0.200(0.002)	0.201(0.004)
283		0.169(0.007)	0.189(0.005)	0.187(0.007)	0.189(0.002)
354		0.143(0.004)	0.157(0.005)	0.165(0.006)	0.184(0.005)
92	1.12 cm	0.273(0.003)	0.262(0.002)	0.258(0.004)	0.270(0.003)
184		0.222(0.005)	0.206(0.002)	0.196(0.002)	0.199(0.002)
275		0.191(0.002)	0.167(0.002)	0.167(0.002)	0.173(0.005)
367		0.159(0.004)	0.153(0.004)	0.156(0.002)	0.166(0.002)
459		0.132(0.001)	0.130(0.010)	0.157(0.005)	0.152(0.002)
126	0.95 cm	0.243(0.002)	0.233(0.002)	0.239(0.005)	0.227(0.003)
253		0.180(0.010)	0.169(0.002)	0.169(0.002)	0.191(0.009)
379		0.139(0.003)	0.138(0.003)	0.141(0.001)	0.170(0.006)
506		0.115(0.001)	0.124(0.007)	0.122(0.005)	0.142(0.008)
632		0.106(0.012)	0.114(0.002)	0.117(0.004)	0.136(0.003)
283	0.65 cm	0.168(0.004)	0.158(0.002)	0.169(0.005)	0.169(0.002)
566		0.108(0.005)	0.101(0.002)	0.111(0.003)	0.117(0.003)
849		0.069(0.001)	0.082(0.005)	0.096(0.008)	0.106(0.005)

Porosity Measurements are Averages of 3 determinations. Figures in Parentheses are Standard Errors of the Mean.

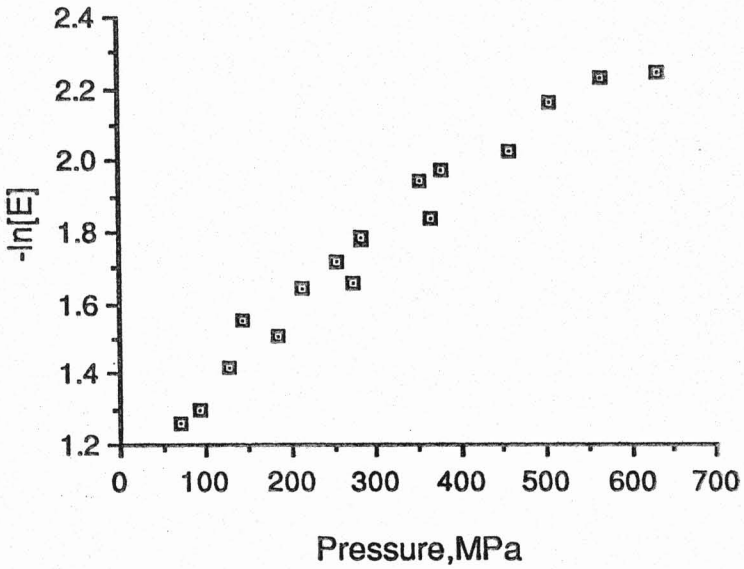


Fig. III-14 Data from Dicalcium Phosphate Dihydrate in the Tested Pressure Range

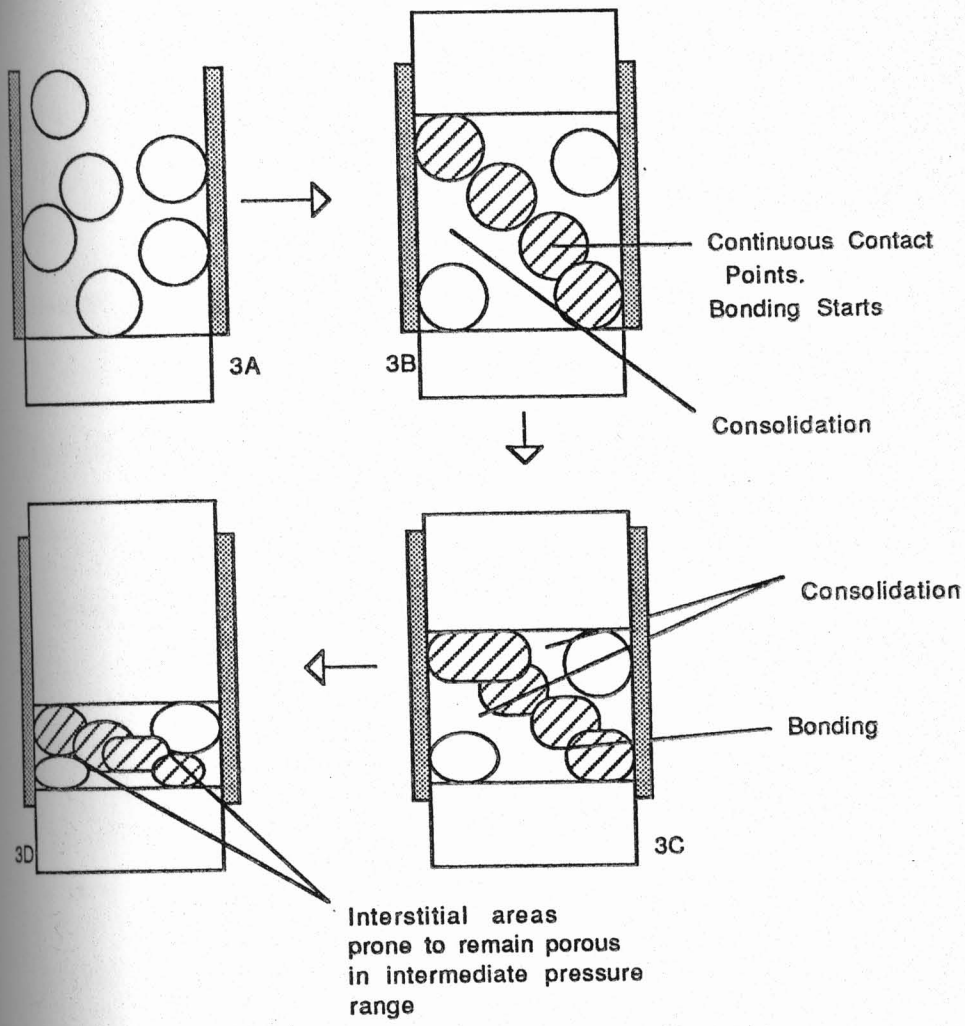

3A
3B
Continuous Contact
Points.
Bonding Starts
Consolidation
3C
Consolidation
Bonding
3D
Interstitial areas
prone to remain porous
in intermediate pressure
range

Fig. III-15

where D_A is the true (non-porous) density of the solid.

At the time when compression/consolidation starts, the apparent specific *void volume* (i.e. the volume of air) is V_A, and it is assumed that the apparent specific *volume of the powder bed*, V_p, will decrease, with increasing pressure, P, by the formula:

$$V_p = V_S + V_A \cdot e^{-aP} \quad \text{Eq. 7}$$

where a is the compression parameter. V_S is the solids volume at infinite pressure and would equal V^* $(= 1/D_A)$ if the compact at high pressure were free of void space, a point not necessarily true in pharmaceutical tablet compression. This is shown schematically in Fig. III-16.

It is noted that the assumption leading to Eq. 7 is different from the one made by Heckel.[13,14] In that treatment it is assumed that the *porosity*, E, decreases exponentially with pressure, i.e. that

$$E = V_A/[V_A+V^*] = Ae^{-bP} \quad \text{Eq. 8}$$

whereas in the view presented here, it is simply V_A which decays exponentially with pressure. It will be seen that (a) this view seems to apply over the pharmaceutical pressure range, and (b) it allows meaningful interpretation of the terms of the ensuing least squares fits, and that

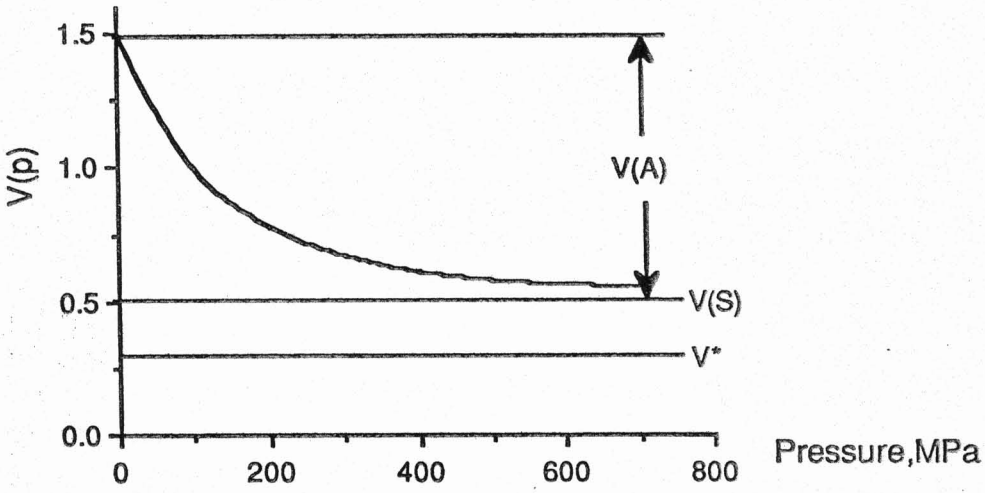


Fig. III-16 Schematic of volume behavior

finally (c) it allows for logical extension from one-component to binary (and multinary) systems.

The void volume (at pressure P) which is subject to exponential decay in pressure is $V_A \cdot e^{-aP}$, so the total volume is the solids volume at infinite pressure, V_S, plus $V_A \cdot e^{-aP}$, i.e. the total volume is given by equation 7.

The actually *measured* porosity, E, is the true void volume, divided by the total volume, and is given by:

$$1-E = V^*/V_p = (1/D_A)/[V_S + V_A \cdot e^{-aP}] \quad \text{Eq. 9}$$

This may be stated more conveniently in inverse form:

$$1/[1-E] = V_S D_A + V_A \cdot D_A e^{-aP} \quad \text{Eq. 10}$$

Table III-10 Example of the Selection of the Best Value of J.

%APAP	J	R
0	1.035	0.9870
0	1.04	0.9876
0	1.045	0.9870
10	1.065	0.9821
10	1.07	0.9832
10	1.075	0.9819
15	1.09	0.978
15	1.095	0.983
15	1.10	0.974
20	1.08	0.962
20	1.085	0.965
20	1.09	0.966
20	1.095	0.965
20	1.10	0.961

or

$$\ln[\{1/(1-E)\}-J] = -aP + \ln[V_A \cdot D_A] \quad \text{Eq. 11}$$

where

$$J = V_S D_A \quad \text{Eq. 12}$$

In cases of complete compression, J should equal one, but, depending on circumstances, J might be larger than one.

Fig. III-17 shows data from pure dicalcium phosphate dihydrate (Ditab™) and they seem to follow Eq. 11 fairly well when V_S is set equal to V^* ($=1/D_A$), i.e. when the density to which the powder tends on increased pressure equals the true density. However, using larger values of J, by iteration, gives better fits and judging the best value to be the one giving the highest correlation coefficient yields J = 1.04 as being the best value. This procedure is exemplified in Table III-10. It is seen that a given value of J gives a maximum in the correlation coefficient, but that the sensitivity is only about 0.5. This should be kept in mind during the part of the following where interpretations of slopes and intercepts are being discussed.

Figs III-18, 19, and 20 show the data in this presentation mode for the three mixtures containing APAP. The least squares fit parameters are shown in Table III-11.

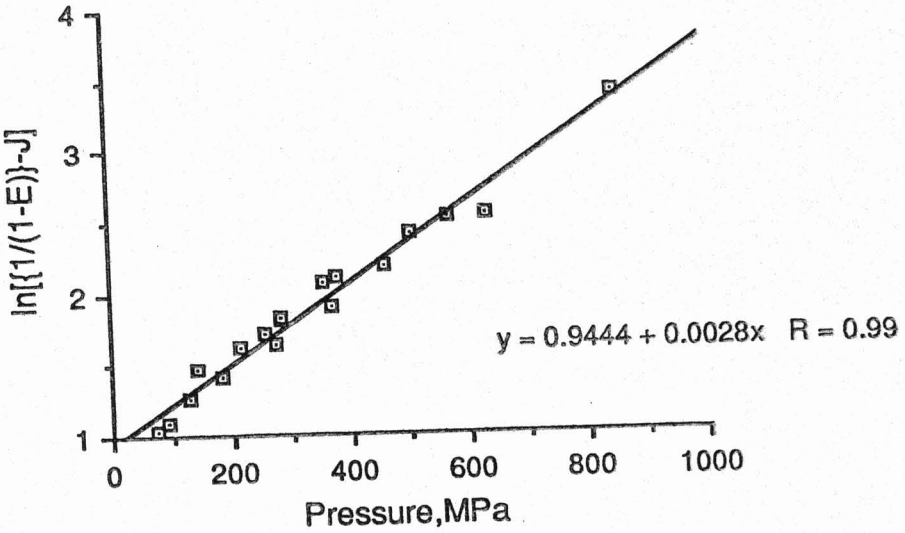


Fig. III-17. DCP data plotted according to Eq. 11 using J = 1.04

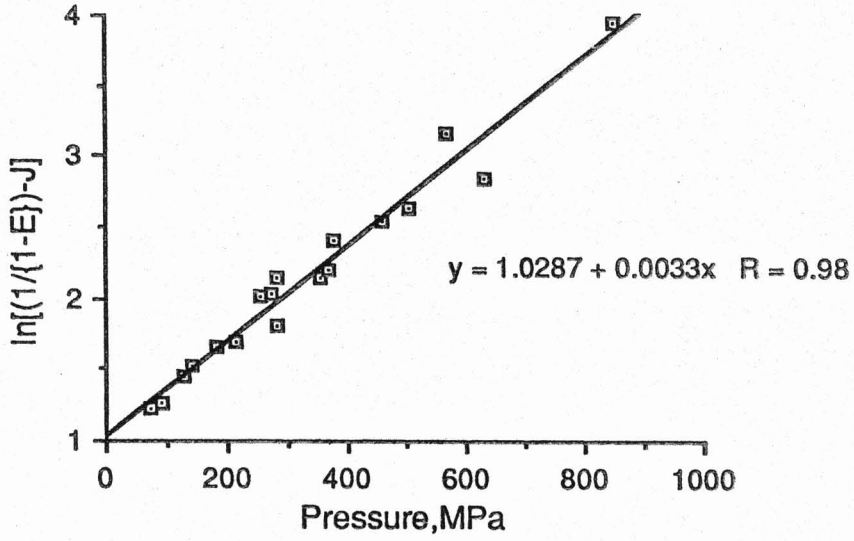


Fig. III-18. Data from 10% APAP + DCP, using J = 1.07

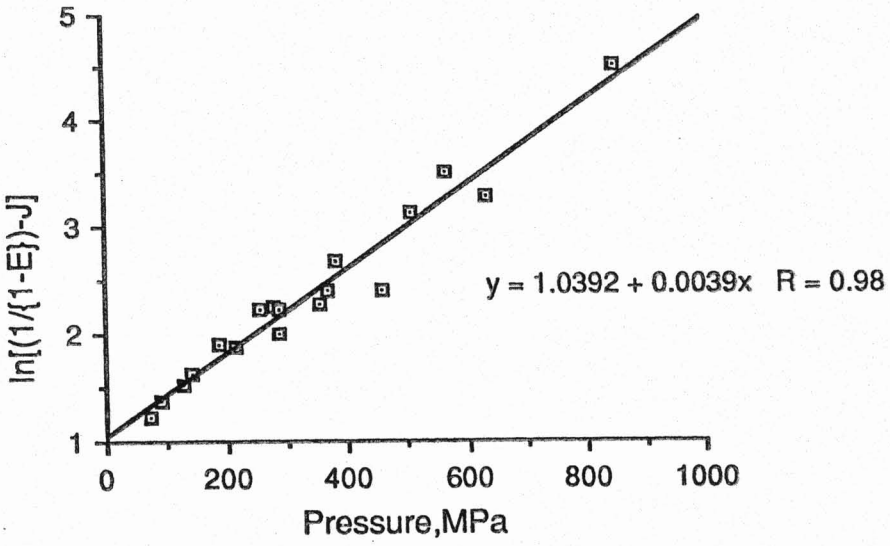


Fig. III-19. Data from 15% APAP + DCP using J = 1.095

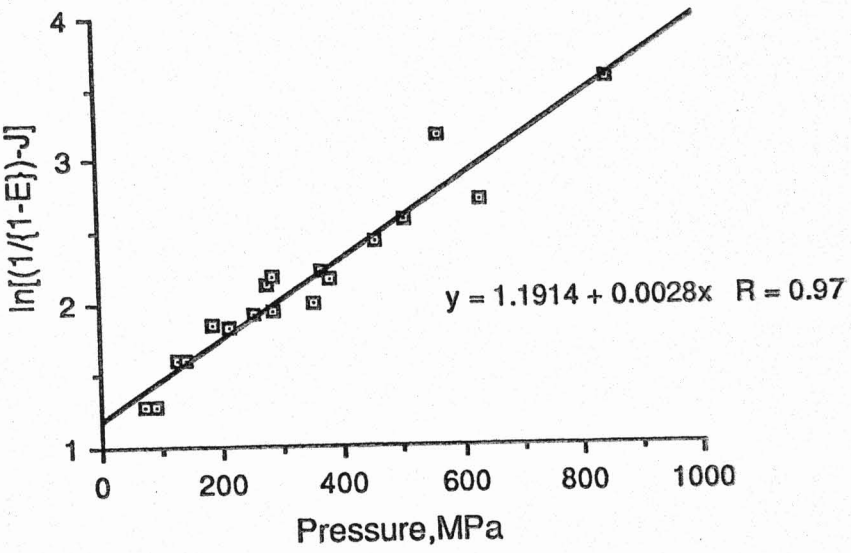


Fig. III-20. Data from 20% APAP + DCP using J = 1.09

Table III-11 Least Squares Fit Parameters for Data Treated According to Eq.11

%APAP	J	V_S cm^3/g	Slope x 10^3	Intercept	R	V_A cm^3/g	E_A
0	1.04	0.45	2.813	0.944	0.988	1.11	0.66
10	1.07	0.46	3.345	1.028	0.983	1.21	0.72
15	1.095	0.47	3.299	1.113	0.977	1.32	0.74
20	1.09	0.47	2.803	1.192	0.967	1.43	0.75

The last two columns shown the values of V_A and E_A, i.e. the volume of void of the powder bed at the time the compression starts, and the porosity at this point. The value of V_A is given by the intercept of Eq. 11:

$$V_A = (1/D_A)\cdot\exp(\text{intercept}) \quad \text{Eq. 13}$$

The value of V_S, the true solids volume towards which the data tend, is

obtained from the value of J:

$$V_S = J/D_A \quad \text{Eq. 14}$$

J, of course, is the fractional decrease in density, going from the true, non-porous solid to the solid towards which the powder bed tends upon compression in the pharmaceutical pressure range.

The porosity, E_A, is given by

$$E_A = V_A/(V_s+V_A) \quad \text{Eq. 15}$$

It is noted that the values of V_A increase with increasing percentage of APAP. This would imply that the presence of this latter keeps the dicalcium phosphate dihydrate particles from approaching one another, a point which may contribute to the capping tendencies evident with percentages higher than 20% of dicalcium phosphate dihydrate. This is demonstrated in Fig. III-21.

The compression parameter, a, on the other hand, is seemingly insensitive to the percentage of APAP, within the error of the method.

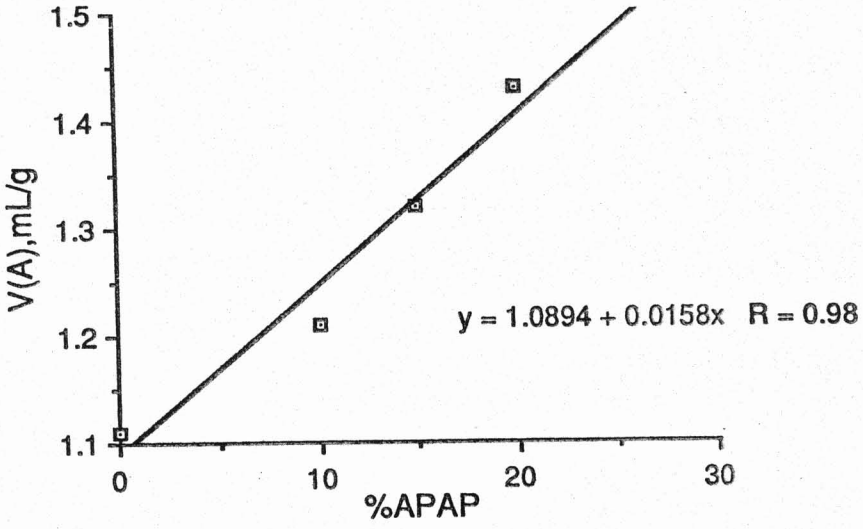


Fig. III-21. Effect of APAP content on the initial void volume

CONCLUSIONS

1. Capping of binary mixtures can occur below the yield strength of a binary mixture.

2. The tapped density does not seem to be the sole determining factor in the y-intercept, A. More work is suggested to determine the exact meaning of this data point.

3. Heckel slopes decrease with an increasing acetaminophen concentration, as expected, since acetaminophen is a poorly compressible compound and should exhibit a high yield strength.

4. A model has been developed for presenting compression data, in which the void volume decays exponentially with applied pressure, and where the final solids volume is estimated statistically.

5. This final volume is not equal to the true solid volume, i.e., in compression in the pharmaceutical pressure range, a certain amount of air is viewed to remain in the solid (i.e. the final solid will have some residual trapped porosity).

6. The treatment allows linearization over the entire compression range, rather than only the high pressure range applicable for the Athy-Heckel equation. It is felt that this latter only applies to pressures so high that they actually are not in the range of pressures applied to pharmaceutical tablets.

7. APAP causes capping in dicalcium phosphate dihydrate compacts, when its percentage is above 20%. The air volume at the time compression starts also increases as a function of APAP, and it is suggested that the two phenomena are related.

REFERENCES

1. Carstensen, J.T., Theory of Pharmaceutical Systems, Academic Press, N.Y., 1973, Vol II, 221-254.

2. Carstensen, J.T., Solid Pharmaceutics: Mechanical Properties and Rate Phenomenon, Academic Press, N.Y., 1980, 174-177.

3. Leigh, S., Carless, J.E., and Burt, B.W., J. Pharm. Sci., 1967, **56**: 888.

4. Long, W.M., Powd. Met., 1960, **6**: 173.

5. Nadai, A., Theory of Flow and Fracture of Solids, 2nd ed., Chap. 15, McGraw Hill, N.Y.

6. Kennon, L., and Swintosky, J.V., J. Amer. Pharm. Ass. Sci., 1958, **47**: 397.

7. Cruaud, O., Duchene, d., Puisieux, F., and Carstensen, J. T., J. Pharm. Sci., 1980, **69**: 607-608.

8. Balshin, M. Yu., *Vestnik Metalloprom.*, 1938, **18**: 124.

9. Smith, G.B., "Proceedings of the Fourth Annual Spring Meeting of the Metal Powder Association," 1948, 29.

10. Ballhausen, C., *Eisenhuttenw.*, 1951, **22**: 185.

11. Konopicky, K.: see H. Krainer, *Berg-huttenmanv. Monatsh.*, 1948, **93**: 62.

12. Athy, L. F., Bull. Am. Assoc. Petrol Geologist, 1930, **14**: 1.

13. Heckel, R. W., Trans. of the Metall. Soc. of AIME., Aug., 1961, **221**: 1961-1971.

14. Heckel, R. W., Trans. of the Metall. Soc. of AIME., Oct., 1961, **221**: 1001-1008.

15. Cooper, A.R. and Eaton, L.E., J. Am. Ceramic Soc., 1962, 45: 97-101.

16. Hersey, J. A. and Rees, J. E., Proc. Particle Size Analysis Conference. Bradford, England, 1970.

17. Shotton, E., and Ganderton, D., J. Pharm. Pharmacol., 1961, 13 (Suppl.): 144T-152T.

18. Obiorah, B. A. and Shotton, E., J. Pharm. Pharmacol., 1976, 28: 629-632.

19. Doelker, E., Shotton, E., J. Pharm. Pharmacol., 1977, 29: 193-198.

20. Hiestand, E. N., Wells, J.E., Peot, C.B., Ochs, J.F., J. Pharm. Sci., 1977, 66: 510-519.

21. Carstensen, J. T., Alcorn, G. J., Hussain, S. A., and Zoglio, M. A., J. Pharm. Sci., 1985, 74: 1239-1241.

22. Berg, T. G.O., McDonald, R. L., and Trainor, Jr., R. J., Powd. Tech., 1969/70, 3: 183-188.

23. Train, D. and Carrington, J.N., J. Pharm. Pharmacol., 1959, 11: Suppl. 261T-268T.

24. Ridgeway, K. and Tarbuck, K.J., J. Pharm. Pharmacol., 1966, 18: Suppl.168S-175S.

25. Roblee, L.H.S., Baird, T.M., and Tierney, J.W., A.I.Ch.E. Journal, 1958, 4: 460-464.

26. Malamataris, S., Bin Baie, S., and Pilpel, N., J. Pharm. Pharmacol., 1984, 36: 616-617.

27. Hou, X. P., and Carstensen, J. T., Int. J. of Pharm., 1985, 25: 207-215.

28. Laughlin, S.M., Van Campen, L., Takkieddin, M., Duchene, D., Puissieux, F., and Carstensen, J.T., J. Pharm. Sci., 1979, 3: 32.