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COMPRESSION BEHAVIOR OF PHARMACEUTICAL POWDERS

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SUMMARY

The compression behavior of 4 pharmaceutical powders of widely different particle size distribution and shape was studied by measuring the height of the compressed powder bed at different pressures. The data were analyzed by the Heckel equation and by the Cooper and Eaton equation. The values of the three-stage densification process, D_0, D_a, and D_b, and the material constant, K, obtained from the Heckel plots were in excellent agreement with the coefficients of the Cooper and Eaton equation. These coefficients describe two nearly independent probabilistic processes involving the filling of large holes and the filling of small pores. The results of this study suggest the usefulness of this method in studying the compression behavior of pharmaceutical powders.

INTRODUCTION

Some relationships describing the compression behavior of powders are physically meaningful only if compression is achieved by a single process (Smith, 1948; Seelig, 1947). Three mechanisms were suggested (Seelig and Wulff, 1946) to explain the compression that occurs in dry pressing: (1) packing of particles; (2) elastic and plastic deformation; and (3) cold working and fragmentation. The compression of metal powders through density–pressure curves was analyzed as a 3-stage process – die filling, individual particle motion and gross compact deformation (Heckel, 1961). The Heckel equation may be written as:

$$\ln \frac{1}{1-D} = KP + A \qquad (1)$$

where D is the relative density of a powder compact, P is the applied pressure and K and A are determined analytically from the slope and intercept respectively of the extrapolated linear region of a plot of ln (1/1 – D) vs P. The slope and the intercept are identi-

fied respectively with the reciprocal yield pressure of the material and with the movement of particles during initial stages of compression.

The Heckel equation was applied to pharmaceutical powders and powder mixtures (Fell and Newton, 1971; Kurup and Pilpel, 1978; Hersey and Rees, 1971). It was recently states (Rue and Rees, 1978) that caution should be observed when classifying powder compression behavior with respect to particle size on the basis of the Heckel equation, since the type of plot obtained will vary depending on the experimental technique employed. The Heckel plot for a granular form of microfine cellulose exhibited a continual decrease in slope. Since a linear section was not obtained, it was not possible to determine a value of the yield pressure of microfine cellulose from those results.

Two broad processes occurring during compression were assumed in deriving another equation (Cooper and Eaton, 1962). The first process is the filling of holes of the same order of size as the original particles. This occurs primarily by particles sliding past one another, which may require elastic deformation or even slight fracturing or plastic flow of particles. The second process is associated with the filling of voids that are substantially smaller than the original particles. These can be filled by plastic flow or by fragmentation. Based on the probability density of hole filling, the following equation was derived:

$$V^* = \frac{V_0 - V}{V_0 - V_\infty} = a_1 \exp(k_1/P) + a_2 \exp(k_2/P) \qquad (2)$$

where V^* is the fractional volume compaction; V_0 is the initial total volume when no holes are filled, i.e. at zero pressure; V is the compact volume; V_∞ is the compact volume when all holes of all types are filled, i.e. the volume at theoretical compression; a_1 and a_2 are dimensionless coefficients indicating a fraction of theoretical compression that would be achieved at infinite pressure by each particular process; k_1 and k_2 are coefficients with units of pressure indicating the magnitude of the pressure where the particular process has the greatest probability density; and p is the applied pressure. The compression of 4 ceramic powders was adequately explained (Cooper and Eaton, 1962) by the two nearly independent probabilistic processes described above.

In the present investigation, the compression behavior of pharmaceutical powders of widely different particle size distribution and shape was studied by measuring the height of the compressed powder bed at different pressures. The data were analyzed by the Heckel equation and by the Cooper and Eaton equation. Excellent agreement between the 3-stage densificaton process described by the Heckel equation and the two independent probabilistic processes involving filling of large holes and small pores described by the Cooper and Eaton equation showed the usefulness of this method in studying the compression behavior of pharmaceutical powders.

MATERIALS AND METHODS

Materials

The drugs, tromethamine salt of (±)-5-benozyl-1,2-dihydro-3H-pyrrolo(1,2-a)pyrrole-

1-carboxylic acid (I) and naproxen (D-2-(6-methoxy-2-naphthyl) propionic acid) (II) were obtained from the Institute of Organic Chemistry (Syntex Research, Palo Alto, Calif.) with a purity of at least 99%. The excipients used in this study were spray-dried lactose USP (Foremost, San Francisco, Calif.), crystalline lactose USP (regular grade, Foremost, San Francisco, Calif.) and magnesium stearate USP (Mallinckrodt, Chemical Works, St. Louis, Mo.).

Bulk density and porosity

The power was slowly sifted into a 100 ml graduated cylinder through a plastic funnel. The powder weight (w) and volume (v) were recorded to calculate the bulk density (P_b = w/v). The reported values are the average of 4 determinations. Porosity was calculated from the bulk density and the true density of the powder

$$\text{Porosity} = 1 - \frac{\text{bulk density}}{\text{true density}}$$

Density

The method of density matching (Oster and Yamamoto, 1973) used to determine the true density of the powders. A few milligrams of the powder was added to the test tubes containing different combinations of carbon tetrachloride and hexane mixtures. The powder–solvent mixture was shaken on a vortex mixer, centrifuged and allowed to stand for 30 min. The true density of the powder was the same as the density of the solvent mixture in which the powder remained suspended. The density of the solvent mixture was determined by means of a pycnometer at 23°C using water to calibrate the volume.

Compression

The drug or the excipient powder was mixed with 1% magnesium stearate. For each compression an appropriate amount of the powder was compressed by means of a hand operated Carver Laboratory Press (Model B, Fres S. Carver, Summit, N.J.). The die and punches were 7.9 mm in diameter and the punches were flat-faced. The contact time during compression was less than 5 s. For each compression the height of the compact was measured accurately and the volume and density of the compact was calculated. Three determinations were made for each datum point.

RESULTS AND DISCUSSION

The photomicrographs of the 4 powders used in this study (Fig. 1) show the widely different particle size distributions and the differences in shape and surface texture. The values of the true density, bulk density and porosity of these powders are given in Table 1.

To describe the compression properties of the powders used in this study in terms of the Heckel and Cooper–Eaton equations, it was important to use the same initial apparent volume. The initial apparent volume was kept constant at 630 mm^3 for all powders. Since it was not possible to control the rate of loading by the instrumentation used in this study, the mean values of the compact volume and the standard deviations at given pres-

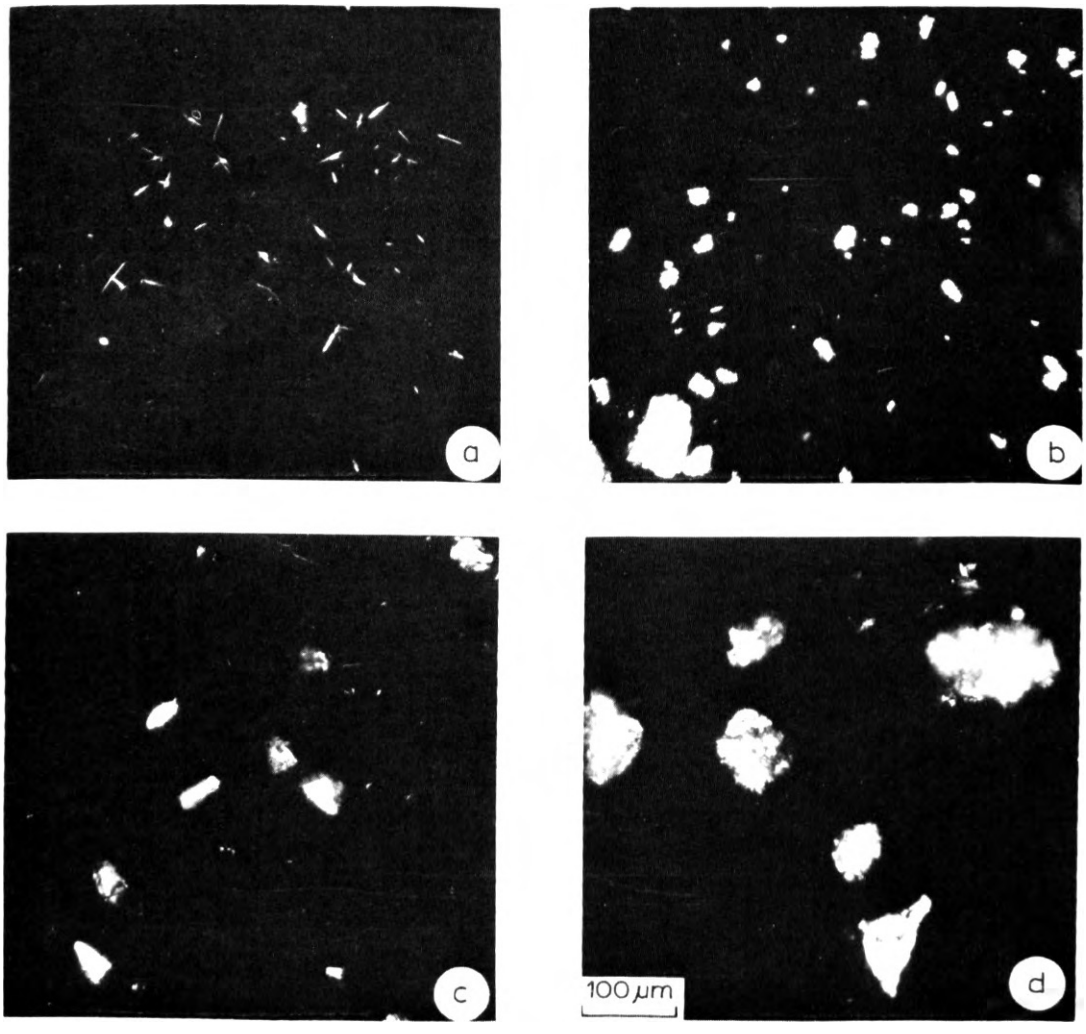

Fig. 1. Photomicrographs of powders used in this study. (a) Drug I, (b) Drug II, (c) crystalline lactose, (d) spray-dried lactose.

TABLE 1

DENSITY AND POROSITY OF POWDERS USED IN THIS INVESTIGATION

Powders	Density (g/ml)	Bulk density (g/ml)	Porosity
Drug I	1.328	0.182	0.863
Drug II	1.263	0.397	0.686
Lactose crystalline	1.520 [a]	0.649	0.573
Lactose spray-dried	1.520 [a]	0.658	0.567

[a] From literature.

TABLE 2

MEAN VOLUMES OF COMPRESSION AT GIVEN PRESSURES

Pressure (kg/cm^2)	Volume, mm^3 (mean ± S.D.)			
	Drug I	Drug II	Lactose crystalline	Lactose spray-dried
229	130 ± 4	243 ± 1	358 ± 4	361 ± 3
458	118 ± 1	228 ± 1	338 ± 3	342 ± 1
687	114 ± 0.0	220 ± 0	327 ± 1	331 ± 1
916	109 ± 0.0	218 ± 1	319 ± 1	322 ± 1
1,374	104 ± 0.0	212 ± 1	307 ± 1	313 ± 0.0
1,832	102 ± 0.0	210 ± 2	302 ± 1	304 ± 0.0
2,290	101 ± 0.0	207 ± 1	297 ± 0.0	302 ± 3
2,749	99 ± 0.0	207 ± 1	292 ± 0.0	295 ± 0.0
3,665	98 ± 0.0	207 ± 1	289 ± 1	289 ± 1

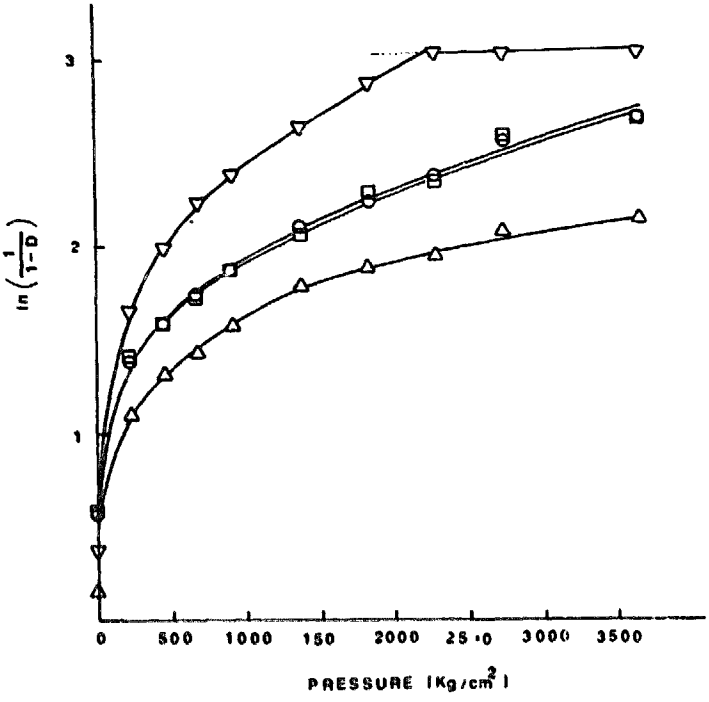

Fig. 2. ln (1/1 − D) vs pressure plots for powders used in this investigation. Key: ▽, Drug I; △, Drug II; ○, crystalline lactose; □, spray-dried lactose.

TABLE 3

VALUES OF K, A, D_0, D_a, and D_b FOR POWDERS STUDIED IN THIS INVESTIGATION

Powder	K $(kg/cm^2)^{-1}$	A	D_0	D_a	D_b
Drug I	1.50×10^{-4}	1.622	0.137	0.802	0.655
Drug II	4.97×10^{-4}	1.929	0.314	0.855	0.541
Lactose crystalline	2.69×10^{-4}	1.761	0.427	0.828	0.401
Lactose spray-dried	2.77×10^{-4}	1.734	0.433	0.823	0.390

sures are given in Table 2. The small variability in the data suggests that the decompression due to elastic recovery is significantly less important in the overall compression process of these powders.

The relative density vs pressure data for these powders was plotted as $\ln(1/1 - D)$ vs P (Fig. 2). These plots were analyzed in terms of Eqn. 1. Table 3 gives the values of K and A obtained from the plots given in Fig. 2. Drug II on compression approached its true density when the applied pressure was 2200 kg/cm^2. Further increase in pressure resulted in a break in the curve and the data points resulted in a straight line with a zero slope. The true density of Drug II obtained from this plot was 1.202 which is close to the value given in Table 1.

The experimental values of D_0 and the calculated values of D_a and D_b are also given in Table 2. As shown earlier (Heckel, 1961), D_a was calculated from Eqn. 3,

$$D_a = 1 - e^{-A} \tag{3}$$

and D_b was calculated from Eqn. 4,

$$D_a = D_0 + D_b \tag{4}$$

The needle-shaped small particles of Drug I compared to the large, nearly spherical particles of spray-dried lactose resulted in a smaller apparent relative density, D_0 and larger D_b value which is the density contribution from individual particle movement and rearrangement. This could be due to the material difference and the large difference in shape and size of the particles.

The values of the material constant, K, vary widely depending upon the powder being compressed. The values range from 1.5×10^{-4} $(kg/cm^2)^{-1}$ to 4.97×10^{-4} $(kg/cm^2)^{-1}$. The two types of lactose gave similar material constant values, indicating that they behave similarly in their ability to deform. Drug I gave the lowest K value, indicating that the material is hard and less plastic and higher pressure is needed to deform this material. The higher material constant value for Drug II indicates that the powder is soft and plastic and deforms readily.

The values obtained for crystalline and spray-dried lactose do not agree well with those previously reported (Fell and Newton, 1971; York, 1979). It is important to point out

that in order to quantify compression parameters for powders, it is essential to take into account a large number of experimental conditions. These properties are markedly influenced by the impurities and imperfections in the crystal and are not intrinsic properties of the specific crystal structure of the chemical entity. The history of the powder, level and type of lubrication, level of absorbed or adsorbed moisture, rate of compaction, contact time, initial apparent volume, dimensions of the die, the technique used to estimate compact dimensions all play an important role on compression behavior. Furthermore, unless machine instrumentation is of high accuracy and standarized, data obtained in different laboratories are unlikely to be comparable. At best, under a given set of conditions, the values of the parameters provide a comparative evaluation of the compression behavior of powders under study.

The plots of the fractional volume compression vs pressure plots for the 4 powders are given in Figs. 3–6. Excellent fit between the experimental and calculated results using Eqn. 2 were obtained. Table 4 summarizes the values of the coefficients a_1, a_2, k_1 and k_2. Large values of coefficients a_1 were obtained for all powders, compared to a_2, indicating that a large percentage of compression was achieved by filling large holes. There is also a good relationship between the bulk density and the coefficients a_1 and a_2. The larger the bulk density, the smaller the coefficient a_1 and the larger the coefficient a_2.

The sum of the dimensionless coefficients a_1 and a_2 should be equal to unity provided that the compression process could be achieved simply by the filling of large holes and by the filling of small pores. The sum of a_1 and a_2 obtained from the experimental results for the 4 powders were 0.993, 0.997, 1.003 and 0.992 suggesting that the compression of these powders can be simply explained by two mainly independent probabilistic processes.

The consistently higher values of the coefficient, k_2, compared to the coefficient, k_1, indicated that the filling of small pores needs much larger pressure than is needed to fill the large holes. This is in agreement with the results of the ceramic powders reported earlier (Cooper and Eaton, 1962). The lower the bulk density or the higher the porosity of the powder, the smaller the pressure needed to fill the large holes and this is reflected in the k_1-values.

The values of the coefficient, k_2, indicate that the two types of lactose are similar in compression behavior. The large k_2-value for Drug I indicates that the particles are hard and less plastic requiring higher pressure for deformation. The smaller k_2-value for Drug II indicates that the material is soft and plastic and deforms readily.

TABLE 4

VALUES OF COEFFICIENTS a_1, a_2, k_1 AND k_2 OF POWDERS USED IN THIS INVESTIGATION

Powder	a_1	a_2	k_1 (kg/cm^2)	k_2 (kg/cm$_2$)
Drug I	0.960	0.033	9.58	1214.24
Drug II	0.957	0.040	15.83	975.00
Lactose crystalline	0.852	0.151	25.95	1133.02
Lactose spray-dried	0.839	0.153	24.81	1136.98

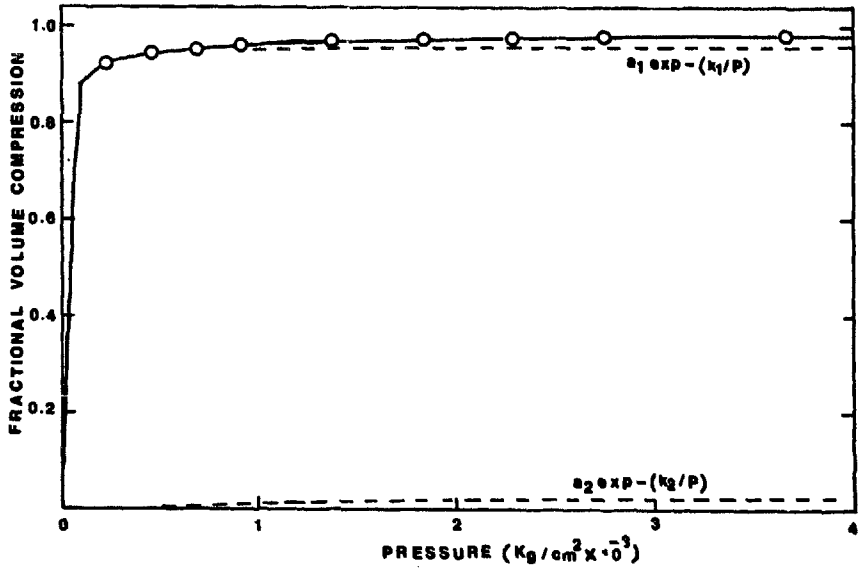

Fig. 3. Fractional volume of compression of the Drug I powder vs pressure plot. The solid line was calculated using Eqn. 2 and the circles are the experimental results.

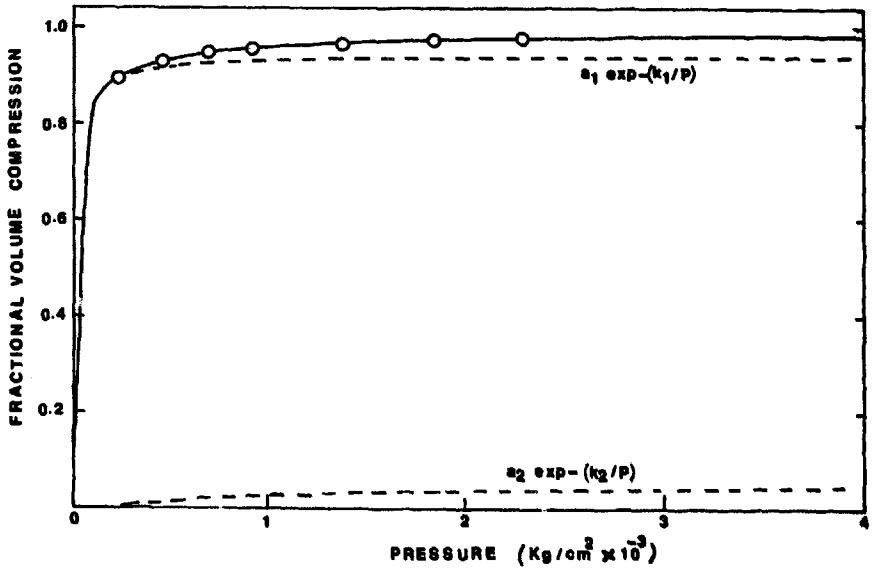

Fig. 4. Fractional volume of compression of the Drug II powder vs pressure plot. The solid line was calculated using Eqn. 2 and the circles are the experimental results.

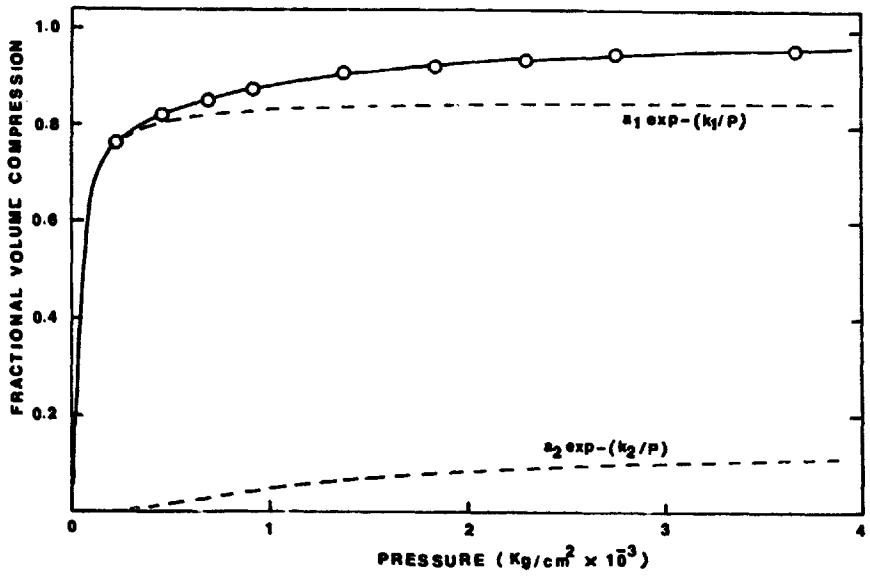

Fig. 5. Fractional volume of compression of the crystalline lactose vs pressure plot. The solid line was calculated using Eqn. 2 and the circles are the experimental results.

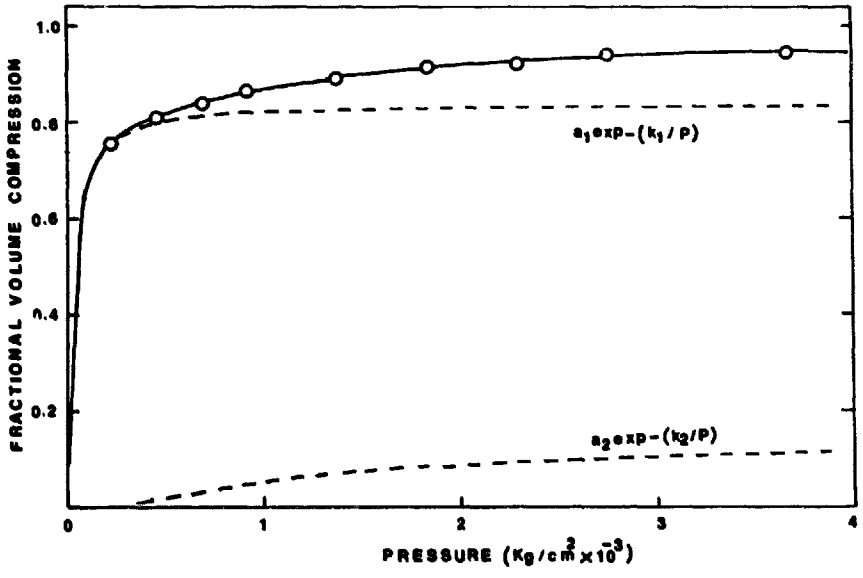

Fig. 6. Fractional volume of compression of the spray-dried lactose vs pressure plot. The solid line was calculated using Eqn. 2 and the circles are the experimental results.

The analysis of the compression behavior of these powders by the Cooper and Eaton equation shows excellent agreement with the results of the analysis using Heckel equation. This approach does provide useful information in studying compression properties of pharmaceutical powders, provided a large number of experimental variables are accounted for.

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