Compressibility of Pharmaceutical Solids I

Instrumentation Employed and Preliminary Results Obtained

By JACOB VARSANO and LEON LACHMAN

A description is presented of an Instron physical testing instrument which was adapted to permit its utilization in the evaluation of the compressing characteristics of drug particles and granules. Measurements were performed on a bed of a readily and a poorly compressible solid, as well as granules of these solids made with several commonly used pharmaceutical binding agents. It was found that potassium chloride crystals and granules deformed at lower compression loads than those of potassium citrate. The influence of crystal and granule size and granulating agents on these measurements was found to be relatively small when compared with the inherent properties of each salt. The relationship between the logarithm of the load and the deformation showed a change of slope depending on load range. An attempt was made to obtain a parameter of compressibility having practical implications and leading to a better theoretical understanding of the mechanism of bonding of solids under pressure.

DURING THE past 15 years a considerable amount of research has been performed to elucidate the phenomena and mechanisms involved in the compression of pharmaceutical solids and their granulations.

Higuchi and associates (1–5), using an instrumented single-punch tablet press, were able to demonstrate that a definite relationship existed between compression force and various physical characteristics of the produced tablets, among which were hardness, density, porosity, and specific surface area.

The mechanisms of compaction of powders into pellets and the transmission of the compression forces throughout the powder bed were investigated by Train (6). He also studied the physical changes occurring in the powder undergoing compression by measuring the change of relative volume with respect to load.

Shotton and Ganderton (7) evaluated the relationships between compaction forces and crushing strength, voidage, and ejection forces. The structural changes of granules occurring at different compression levels and the mechanism of bonding were also investigated by these authors (8, 9).

Several pharmaceutical solids were studied for their stress relaxation behavior under constant strain by Shlanta and Milosovich (10). The investigators found a correlation between the relaxation properties of these materials and their bonding characteristics.

Seth and Munzel (11) postulated that particles bind among each other by the formation of surface irregularities during compression. Rumpf (12) investigated the effect of adsorbed water as a factor in the bonding of particles undergoing compression.

In recent years increasing attention has been given to the influences of crystal lattice strength on the bonding characteristics of several pharmaceutical materials. Correlations between crystal hardness and bonding have been demonstrated by Windheuser *et al.* (13). A thorough investigation into the elastic and plastic deformations of some pharmaceutical solids under compression was reported by Höfer and Gstirner (14).

The cohesion between solid surfaces depends on forces of atomic attraction which demonstrate themselves at distances slightly greater than normal interatomic spacing. There exists a direct proportionality between bonding and the contact area of the solid surfaces on which these forces play a role. Solids with a greater tendency for plastic flow will attain a greater contact area when subjected to a given load and, therefore, a higher degree of bonding would result (15). Consequently, the plasticity of the crystal lattice would be a major factor contributing to the bonding of pharmaceutical solids, regardless of the other mechanisms involved.

Although previous reports have considered the importance of this aspect, there is still a need for a systematic evaluation as to the effect of relative crystal and granule hardness on the compression bonding of particulate solids. In light of this, a study was designed to perform hardness measurements on a bed of crystals and granules and determine the effect that particle size and granulating additives have on these measurements. Data accruing from such a study should contribute to the development of

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crystal and granule hardness specifications of materials used in tableting, their relative grading in respect to hardness, and permit an estimation of the compressibility characteristics of new drugs before formulation work is initiated.

This report describes the instrumentation and techniques employed toward achieving the aforementioned objectives and presents the preliminary data obtained on two pharmaceutical solids, potassium chloride and potassium citrate. Previous experience obtained with these salts during formulation work indicated that satisfactory tablets could be obtained by direct compression with potassium chloride but not with potassium citrate. These results led to the selection of potassium chloride and potassium citrate for this study as representative of a readily and a poorly compressible solid.

EXPERIMENTAL

Instrumentation.—The Instron Universal testing instrument TM-M, table model[1] shown in Fig. 1 was utilized for this study. This equipment permits an evaluation of the stress-strain characteristics of materials under selected loads applied at varying rates and patterns. The major considerations for selecting the instrument were its accuracy, versatility, operational convenience, and relative compactness. These qualities make it a valuable tool for both investigational and routine measurements.

A brief description of the operational principles of this instrument follows. The vertically moving crosshead (A) is driven by a synchronous system exerting a compression force at constant rates independent of load. A set of interchangeable gears provides a selection of crosshead speeds. The load cell (B) is a bonded wire strain gauge system excited by a stabilized oscillator and is temperature compensated. The load cell output is amplified and fed to the potentiometer-type strip chart recorder (C), driven synchronously with the crosshead at variable speed ratios. The actuation of the crosshead and its direction of motion is controlled from a panel (D) either manually or automatically by preset conditions.

To allow the measurements of deformation occurring in particulate solid beds under varying stress levels, the special fixture shown in Fig. 2 was designed for the instrument. It consisted of two punches and a die resembling a single-punch tablet press. The upper punch (A) was attached to the moving crosshead. The lower punch (B) was seated on a flange (C) which was fastened by set screws to the load sensitive table of a compression load cell (D). A threaded bushing (E) containing the lower punch provided a means for regulating its height. The die (F) was placed on a metal plate (G) which slides vertically along a pair of sturdy steel rods (H) attached to the base of the instrument. The surface of the rods had inscribed scales in 1-mm. increments to allow the positioning of the die plate at desired heights which in turn is

Fig. 1.—Instron universal testing instrument equipped with compression fixture. Key: A, crosshead; B, load cell; C, recorder; D, control panel; E, fixture.

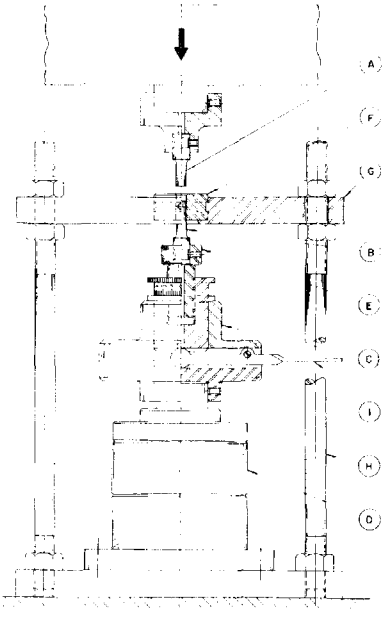

Fig. 2.—Fixture for compressing particulate solids. Key: A, upper punch; F, die; G, metal plate; B, lower punch; E, threaded bushing; C, flange holding lower punch; I, lifting lever; H, steel rods; D, compression cell.

held in place by set screws. A lever (I) served to extrude the compressed compacts from the die by lifting the bushing containing the lower punch. The flat-faced punches employed in this study were of $^{11}/_{32}$-in. diameter. The die and punches were chromium plated to reduce sticking and friction.

The instrument equipped with the fixture described above permitted an evaluation of the deformation properties of solids undergoing compression from the relationship of upper punch travel and the compression force exerted on the lower punch.

Materials Used.—Potassium chloride (Schuylkill

[1] Instron Corp., Canton, Mass.

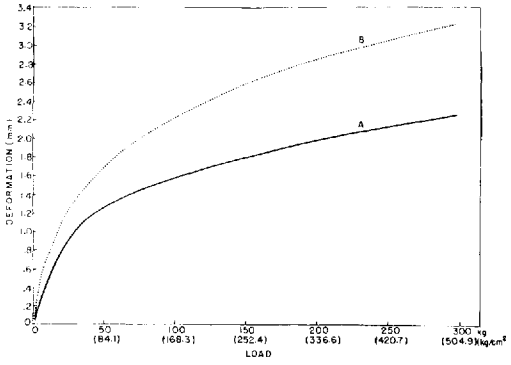

Fig. 3.—Deformation of crystals at varying loads. Key: A, potassium citrate crystals; B, potassium chloride crystals.

Chemical Co.); potassium citrate (Chas. Pfizer and Co., Inc.); cornstarch U.S.P.; acacia U.S.P.; and polyvinylpyrolidone (PVP) (Antara Chemicals).

Procedure.—The potassium chloride and potassium citrate were milled on a Fitzpatrick machine, and granulations of these salts were prepared with water, cornstarch paste 20% w/v, acacia solution 20% w/v, and PVP solution 20% w/v. For each granulation system the ratio of binder to salt was kept at 1.4%. The granulations and the untreated crystalline solids were screened on U. S. standard sieves to obtain the following size fractions:

	Sieve Classification, Mesh
Potassium chloride, crystalline	40–60, 60–80, 80–100, 100–120
Potassium citrate, crystalline	40–60, 60–80, 80–100, 100–120
Granulations	18–20, 20–40, 40–60, 60–80, 80–100

The screened fractions and unscreened material were dried in a 65°-oven until the Karl Fischer test indicated no measurable amount of water.

Compression.—The die wall was dusted with magnesium stearate, and a 300-mg. sample was accurately weighed and fed into the die cavity through a specially designed glass funnel. In order to insure uniform packing of the particles in the die, the funnel was suspended on a vibrating arm operating at a constant frequency.

The instrument was operated on automatic load cycling at a downward crosshead motion of 1 cm./min. until a 300-Kg. (504.9 Kg./cm.^{2}) load was exerted on the lower punch. When this maximum load was reached, the instrument automatically reversed the direction of the crosshead at a speed of 50 cm./min. The ratio of the downward crosshead speed to that of the recorder chart was 1:50. For each screened fraction, five measurements were made, and their mean values were used in subsequent calculations. Corrections were made for the amount of deflection due to the instrument and the fixture.

RESULTS AND DISCUSSION

Figure 3 presents a typical load deformation relationship as replotted from the recorder. It

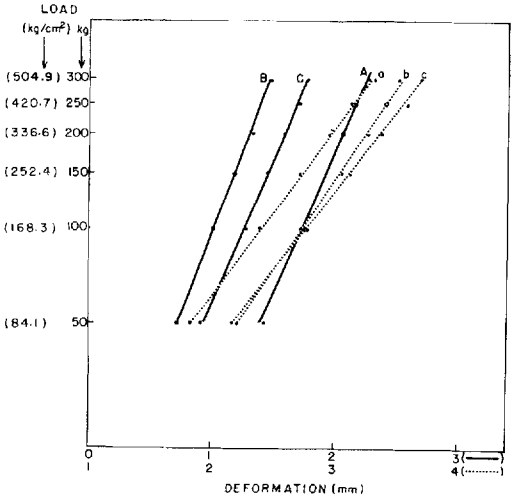

Fig. 4.—Compression curves of potassium citrate and potassium chloride crystals at varying particle sizes. Key: (potassium chloride) a, on 100; b, on 60; c, not screened; (potassium citrate) A, on 100; B, on 60; C, not screened.

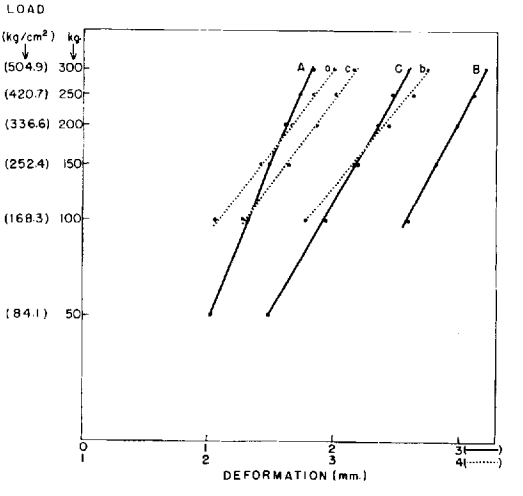

Fig. 5.—Compression curves of potassium citrate (on 80) and potassium chloride (on 80) granulated with several agents. Key: (potassium citrate) A, crystalline; B, starch paste granulation; C, acacia granulation; (potassium chloride) a, crystalline; b, starch paste granulation; c, acacia granulation.

TABLE I.—(Δ LOG LOAD/Δ DEFORMATION) OF POTASSIUM CITRATE AND POTASSIUM CHLORIDE AT VARYING PARTICLE SIZES

	Crystals	
Sieve Size	Potassium Citrate	Potassium Chloride
On 40	.96	.51
On 60	.94	.64
On 80	.90	.50
On 100	.85	.50
On 120	.94	.58
Not screened	.87	.52

TABLE II.—INFLUENCE OF GRANULATING ADDITIVES ON SLOPES (Δ LOG LOAD/Δ DEFORMATION) OF POTASSIUM CITRATE

Sieve Size	Crystals	Granulated with			
		Water	Starch Paste	Acacia	PVP
On 20	...	.87	.85	.85	.84
On 40	.96	.89	.84	.85	.90
On 60	.94	.88	.82	.80	.82
On 80	.90	.94	.79	.74	.75
On 100	.85	.86	.81	.76	.92
On 120	.94	...	...	...	...
Not screened	.87	.87	.85	.76	.89

TABLE III.—INFLUENCE OF GRANULATING ADDITIVES ON SLOPES (Δ LOG LOAD/Δ DEFORMATION) OF POTASSIUM CHLORIDE

Sieve Size	Crystals	Granulated with			
		Water	Starch Paste	Acacia	PVP
On 20	...	.54	.54	.46	.47
On 40	.51	.50	.48	.46	.46
On 60	.64	.54	.49	.40	.54
On 80	.50	.54	.41	.56	.55
On 100	.50	.54	.52	.49	.56
On 120	.58	...	...	...	...
Not screened	.52	.56	.51	.50	.54

TABLE IV.—WORK EXPENDED TO COMPRESS CRYSTALS AND GRANULATIONS OF POTASSIUM CITRATE AND POTASSIUM CHLORIDE AT VARYING PARTICLE SIZES

Sieve Size	Crystals		Starch Paste Granulation		Acacia Granulation		PVP Granulation		Water Granulation	
	K Citr.	KCl	K Citr.	KCl	K Citr.	KCl	K Citr.	KCl	K Citr.	KCl
On 20	...	...	179	300	169	283	171	280	165	254
On 40	145	230	172	281	165	283	164	270	166	265
On 60	138	212	174	277	174	309	174	254	164	250
On 80	153	242	180	261	187	230	182	248	160	243
On 100	152	245	179	252	178	259	164	241	167	242
On 120	151	272	...	...	...	...	...	...	...	...
Not screened	161	246	168	262	172	255	162	252	161	254

shows that the deformation of potassium chloride was greater than that obtained with potassium citrate.

Plotting the logarithm of the load against deformation produced a linear relationship over a load range from approximately 50 to 300 Kg. for both potassium citrate and potassium chloride as shown in Figs. 4 and 5. Because of particle reorganization occurring at the load range below 50 Kg., deviation from linearity takes place in the above relationship. The slopes of the plots in Figs. 4 and 5 (Δ log load/Δ deformation), are an index of the relative ease with which the solid bed undergoes deformation.

The compression slopes of the plots in Fig. 4 are summarized in Table I. It is evident from the data in this table that within each salt, the slope values are for the most part of the same magnitude, independent of particle size. However, a comparison of the slopes of the two salts reveals a significant difference between them.

The effect of granulating additives at a constant particle size on the slopes is demonstrated by the plots in Fig. 5. The slopes of such plots are presented in Tables II and III. It can be seen that the slopes of each salt are essentially unaffected by granule size and granulating agent at concentrations normally used in tablet technology.

The values for work expended in compressing the

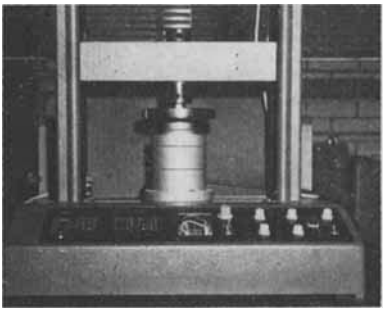

Fig. 6.—The instrument as utilized for measuring the crushing strength of compacts.

TABLE V.—OVER-ALL MEAN CRUSHING STRENGTH OF COMPACTS COMPRESSED FROM CRYSTALS AND GRANULATIONS OF POTASSIUM CITRATE AND POTASSIUM CHLORIDE

	K Citr., Kg.	KCl, Kg.
Crystals	6.15	10.94
Water granulation	5.90	10.06
Starch paste granulation	3.78	9.93
PVP granulation	2.99	9.80
Acacia granulation	10.15	13.69

materials under study over the load range from 50 to 300 Kg. were computed from the areas under the load displacement curves and are presented in arbitrary units in Table IV. The data clearly indicate that in all instances the work done in compressing potassium chloride is greater than that for potassium citrate. This is an indication that potassium chloride has undergone greater deformation at this load level than potassium citrate.

Crushing strength measurements on the compacts obtained in this study were performed on the instrument as illustrated by the photograph shown in Fig. 6. Table V presents the over-all means of these values for each granulation. It is evident from these data that greater apparent bonding was achieved with potassium chloride than with potassium citrate.

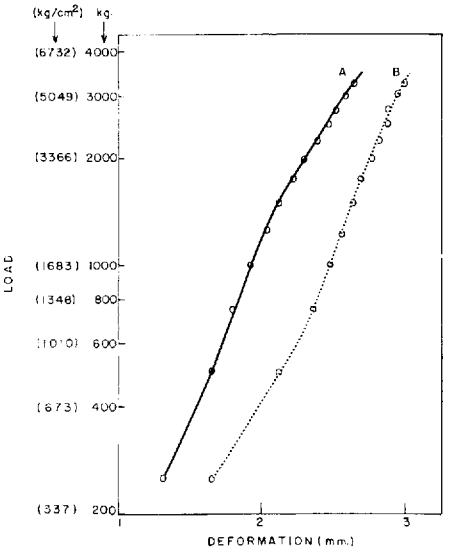

Fig. 7.—Compression curves of potassium citrate (on 80) and potassium chloride (on 80) at high loads. Key: A, potassium citrate; B, potassium chloride.

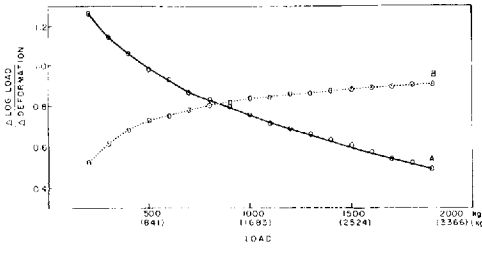

Fig. 8.—Compression slopes of 80-mesh crystals at different loads. Key: A, potassium citrate; B, potassium chloride.

In order to determine whether the slope relationship for the two substances found at lower loads would remain valid at higher loads, a floor model Instron capable of exerting a maximum load of 5000 Kg. was utilized. The data obtained were plotted in Fig. 7, and it is apparent from the nonlinearity of the plots of log load *versus* deformation that the straight line relationship found at the lower loads does not hold true over a wide load range. Because of the curvature of the plots, it is not readily possible to obtain the compression slopes of the two substances. It was felt that if the compression curves were approximated as straight lines, valuable information on the mechanism of compression would be obscured. Instead, the equation of the best fitted line was calculated on a computer by the method of least squares, using the quadratic model $\log y = A_1 + A_2X + A_3X^2$. The slope at each load level of the fitted line was then computed by differentiating the model: $d(\log y)/dx = A_2 + 2A_3X$. This analysis permitted the determination of the compression slopes at any load level. The computer program also recorded the residual sum of squares and the standard deviation. The latter represented the geometric mean of the variations about the fitted line and included both the experimental error and the inadequacy of the model.

The slopes computed in this manner were plotted against load as shown in Fig. 8. This graphical presentation clearly illustrates the influence of varying loads on the compression slopes. From the plot of potassium chloride, it can be seen that the compression slope increases and approaches a plateau with increase in load. This relationship would indicate that the major deformation of the crystal bed took place at the lower load range. As the load increases beyond this range, a greater portion of it is being transmitted through the bed onto the load cell with little further compaction being accomplished. In contrast, for potassium citrate, the major deformation is occurring at the higher load range as evidenced by the considerable decrease in compression slope as the load increases.

The changes occurring in compression slopes at different load ranges provide valuable information about the compression characteristics of a material and permit the selection of the most appropriate load level to obtain optimal compaction. It would be expected that the grading of the relative compressibility of materials could be accomplished by determining the load range at which most active compaction is taking place.

The work expended in compressing potassium chloride and potassium citrate in the load range up

Table VI.—Cumulative Work Expended to Compress 80-Mesh Potassium Citrate and Potassium Chloride Crystals from 50 Kg. to Load Levels Given in Table

	Cumulative Work at Loads in Kg.								
	500	1000	1500	2000	2500	3000	3500	4000	4500
Potassium citrate	281	557	862	1187	1528	1882	2246	2620	3002
Potassium chloride	356	613	870	1129	1388	1647	1906	2166	2425

to 4500 Kg. is given in Table VI. It can be seen from the data in this table that more work is expended on the potassium chloride crystals up to 1500 Kg., while for potassium citrate more work is expended from 1500 to 4500 Kg. This would indicate that the potassium chloride crystals are undergoing greater deformation and compaction at the lower load range while the reverse is true for potassium citrate.

SUMMARY AND CONCLUSION

A description has been presented of a modified Instron physical testing instrument which can be used to obtain a quantitative measure of the compressibility of pharmaceutical solids. Preliminary information is given for potassium chloride and potassium citrate crystals and granulations of these salts which can be summarized as follows.

1. Potassium chloride was found to deform at lower compression loads than potassium citrate.

2. Modifying the two salts by granulating with materials commonly used in tablet technology indicated that the inherent compression properties of the salts predominated. The granulating agents employed were water, acacia, starch paste, and polyvinylpyrrolidone.

3. A linear relationship was found for log load *versus* deformation for both salts at load levels up to 300 Kg. However, at higher loads, this linear relationship did not hold true.

4. In order to permit a measure of the relative compressibility of the materials at high load levels, a computer program was prepared to determine the quadratic equation best fitting the experimental data which were subsequently used to obtain the compression slopes at each load by calculating the derivative.

5. The relationship between compression slope and load can be used to determine the load range at which maximum deformation of the solid bed is taking place.

6. The work expended at different loads can also be used to determine the load range of maximum deformation.

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Powder Flow Studies I

Instrumentation and Applications

By GERALD GOLD, RONALD N. DUVALL, and BLAZE T. PALERMO

Several methods have been used to evaluate the flow properties of pharmaceutical formulations. Although these methods give reproducible results, they often measure different factors. Consequently, it is difficult to interpret the data, and it is debatable whether correlation with actual flow of material is possible. A new approach to the measurement of powder flow is presented and involves measurement of the weight of powder per unit time flowing through a hopper orifice. The instrument, a recording powder flowometer, consists of a hopper, strain gauge balance, and recorder. The flow rate can be calculated from the recorder tracing, and in addition, the tracing serves to characterize the flow qualities of a formulation. Various sized hopper orifices with or without vibration can be used. By incorporation of an ionostat into the instrument, the static charge may also be measured concurrently with the flow rate.

FLOW PROPERTIES of pharmaceutical formulations are extremely important to the industrial pharmacist. Increasing complex manufacturing techniques and modern dosage forms require a more thorough and basic understanding of the science and technology of small particles. In tablet and capsule manufacturing, considerable effort is directed toward obtaining and improving free flowing powders and granulations. Recent compendia standards and law enforce-

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