Comparison of Granule Strength and Tablet Tensile Strength

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Abstract □ The granule strength (crushing load) of lactose granulated with 1–9% povidone was measured initially and at intervals during a 1-year period. The granule strengths of dibasic calcium phosphate dihydrate granulated with various concentrations of starch and povidone were measured. The axial and radial tensile strengths of tablets compressed from these granules were determined and related to concentration of binder and granule strength. The effect of compressional force on the integrity of granules in a tablet matrix is shown in scanning electron photomicrographs of the fractured tablets which had undergone a diametral compression test. It appears that the compressional force and the concentration of binder contribute more than granule strength to tablet tensile strength.

Keyphrases □ Tablet compression—comparison of granule and tensile strength, lactose, povidone □ Granule strength—tablet compression, comparison with tensile strength, lactose, povidone □ Tensile strength—tablet compression, comparison with granule strength, lactose, povidone

Most materials require pretreatment to ensure tablet formation and free flow in the tablet machine. Granulation is the process by which fine powders are converted to granules with these properties to ensure a uniform fill of the die cavity, formation of a tablet, and easy ejection of the finished tablet. Granulation also facilitates handling, prevents segregation in the formulation blend, and minimizes dust. Granule strength and friability are important as they affect changes in particle size distribution of granulations and, consequently, compressibility into cohesive tablets, and also unit dose precision in some tablet formulations. They may be useful as quality control parameters so that reproducible granulations can be manufactured (1). Granule strength is usually greater as the concentration of binder is increased (2–7). For a given lot, the larger granules have a greater strength than the smaller granules (5, 8, 9).

The compression process of particulate material into a tablet and the fate of the granule in the tablet have been studied (6, 10–12). Most investigations have considered the external dimensions of the tablet, although these may not reflect the situation within the tablet matrix (13). It seems that granular integrity is progressively lost during compression.

The present study was conducted to compare the granule strength with the axial and radial tensile strengths of tablets compressed from the granules. Scanning electron microscopy was used in an attempt to visualize the granule within the tablet matrix.

Table I—Effect of Humidity on the Crushing Load of 16/20-Mesh Granules of Lactose Monohydrate Granulated with 5.0% Povidone

	Relative Humidity, %				
	0	20	45	70	90
Exposure, days	14	5	6	4	11
Loss on drying, %	5.2	5.4	6.4	5.9	7.5
Crushing load, g	773.4	873.8	496.7	796.6	241.6
	678.3	667.7	274.4	523.9	712.1
	386.1	241.2	491.8	575.3	367.0
	568.5	830.6	458.4	438.3	143.7
	425.3	842.3	590.7	411.2	466.8
	655.4	422.4	472.7	418.5	583.6
	496.4	214.4	418.5	378.6	489.7
	352.9	190.3	184.1	640.1	778.4
	374.9	373.4	512.7	726.0	540.2
	465.6	326.3	120.4	396.3	207.9
Average crushing load, g	513.7	498.3	402.0	530.5	453.1
SD, g	137.5	277.1	155.1	148.9	212.7

EXPERIMENTAL

Preparation of Granules and Measurement of Crushing Strength—All materials were USP or NF grade. A 60/80-mesh size fraction of all materials was used. An appropriate quantity of aqueous granulating liquid was added to the powder in a planetary mixer[1] and blended for 5 min. The wet mass was then passed through an appropriate screen in an oscillating granulator[2] operating at slow speed and collected on drying trays. The granulation was dried overnight in a forced-air oven at ambient temperature. Size classification of the dried granules was carried out by shaking for 5 min with a sieve shaker[3].

The technique used to measure the crushing strength of a granule was essentially that from a previous study (14) using 50- and 100-ml glass

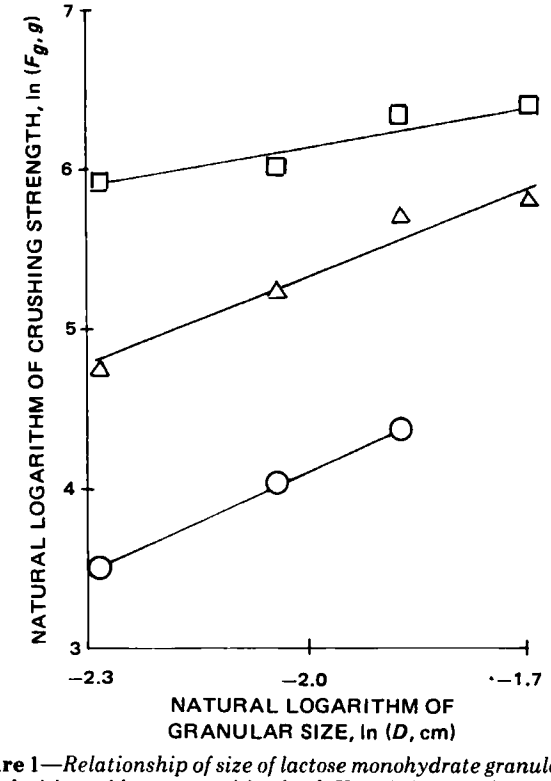

Figure 1—*Relationship of size of lactose monohydrate granules granulated with povidone to crushing load. Key: (○) 1.0%; (△) 3.0%; and (□) 7.0% povidone.*

[1] KitchenAid, Hobart, Troy, Ohio.
[2] Type FGS, Erweka-Apparatebau, GmbH., Heusenstamm Kr., Offenbach/Main.
[3] Cenco-Meinzer, Central Scientific Co., Chicago, Ill.

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Table II—Crushing Strength of Several Size Fractions of Granules of Lactose Monohydrate Granulated with Various Concentrations of Povidone

Fraction Size	D, cm	Crushing Strength, g, Percent Povidone 1	3	5	7	9
10/12	0.184	39.0	333.0	383.4	600.6	904.7
12/14	0.154	79.6	305.4	672.5	571.7	529.5
14/16	0.130	56.9	189.0	436.6	409.7	877.4
16/20	0.102	33.9	116.0	358.8	376.6	726.7

hypodermic syringes[4]. The modification included the removal of the tip of the syringe barrel and the top end of the plunger. The barrel was then used as a hollow support and guide tube with close-fitting tolerances to the plunger. The hollow plunger with one open end served as a load cell to which mercury could be added. A window was cut into the barrel to facilitate placement of the granule on the base platen. The plunger acted as the movable platen and was set directly on the granule positioned on the lower platen. As the rate of loading may effect crushing load (9), mercury was introduced from a reservoir into the upper chamber at the rate of 10 g/sec until the single granule failed. Loading time was <3 min. The total weight of the plunger and the mercury required to fracture a granule was the crushing load. A minimum of 10 granules were tested, and the average load in grams was taken as the crushing strength, F_g. In the figures only the upper standard deviation bar for granule strength is shown.

The sensitivity of crushing strength to humidity was considered for hydrous lactose granulated with 5% povidone. The granules were stored in humidity chambers at 0, 20, 45, 70, and 90% relative humidity (15) for various lengths of time as shown in Table I. The percent loss on drying was determined by a moisture balance[5] after 20 min of IR exposure at

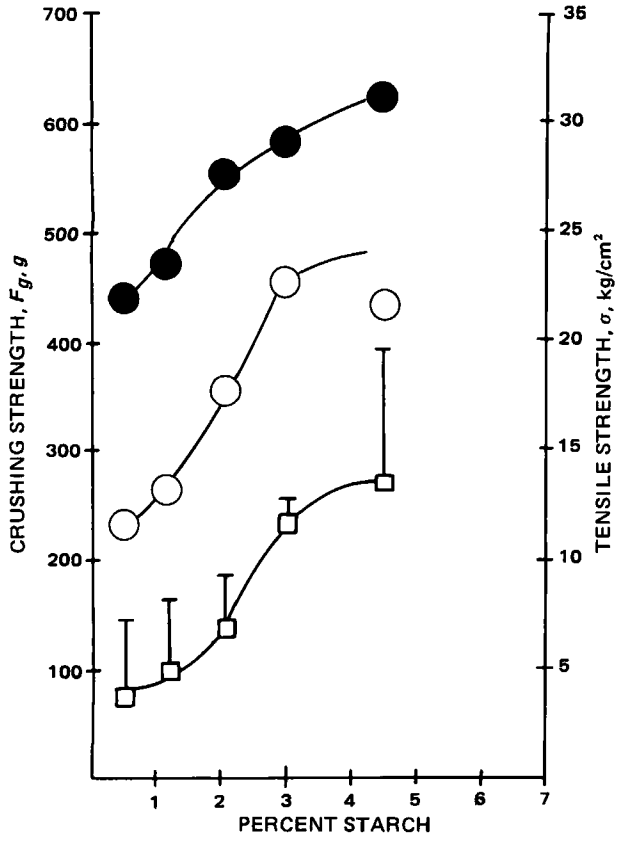

Figure 2—*Relationship of binder concentration to granule strength and tensile strengths of tablets compressed at 2268 kg from granules of dibasic calcium phosphate dihydrate granulated with starch. Key: (□) granule strength; (○) axial tensile strength; and (●) radial tensile strength.*

[4] Yale Luer-Lok, Becton Dickenson and Co., Rutherford, N.J.
[5] Ohaus Scale Corp., Florham Park, N.J.

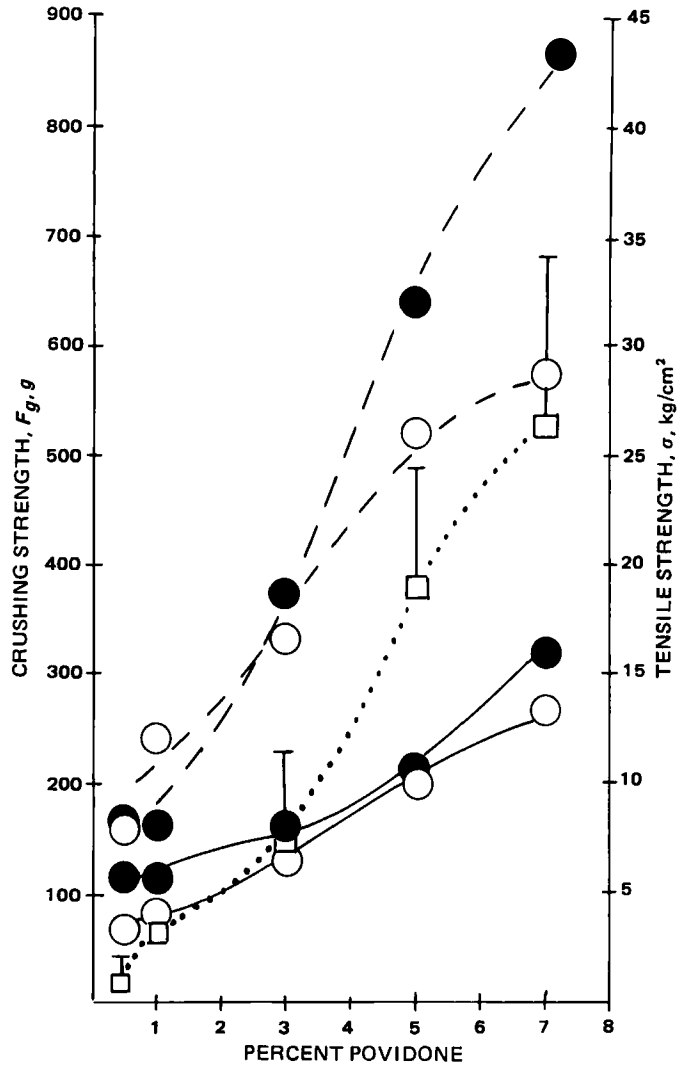

Figure 3—*Relationship of binder concentration to granule strength and tensile strengths of tablets compressed at 2268 (—) and 4536 (- - -) kg from granules of dibasic calcium phosphate dihydrate granulated with povidone. Key: (□) granule strength; (○) axial tensile strength; (●) radial tensile strength.*

an input of 12 W. The load at which a granule failure occurs may be difficult to experimentally observe, since a granule may deform plastically or a high point on its surface may fracture without failure of the entire granule. Thus, there is considerable variance in the crushing loads, as shown in Table I and as previously reported (5). Within the precision of the apparatus used, it does not appear that humidity significantly affected the strength of the granule. Although the relative humidity ranged from 0 to 90%, the moisture content of the granules was from 5.2 to 7.5%.

Preparation of Tablets and Measurement of Tensile Strength—An appropriate weight of 16/20-mesh size fraction of granules was compressed for 5 sec at the desired force by 1.275 cm diameter punches and die-fitted to a hydraulic press[6]. At least 72 hr elapsed between tableting and tablet evaluation to allow for any stress relaxation within the tablet. The weight and thickness of a minimum of 10 tablets were determined. The method of measurement of the axial tensile strength (σ_z) and the radial tensile strength (σ_x) of tablets by a tensiometer has been described (16). The mean force of tensile failure of 10 tablets was used to calculate the tensile strength.

RESULTS AND DISCUSSION

Mechanical Strength of Granules—The crushing strength of granules of lactose monohydrate granulated with povidone solution is

[6] Carver model C, Monomonee Falls, Wis.

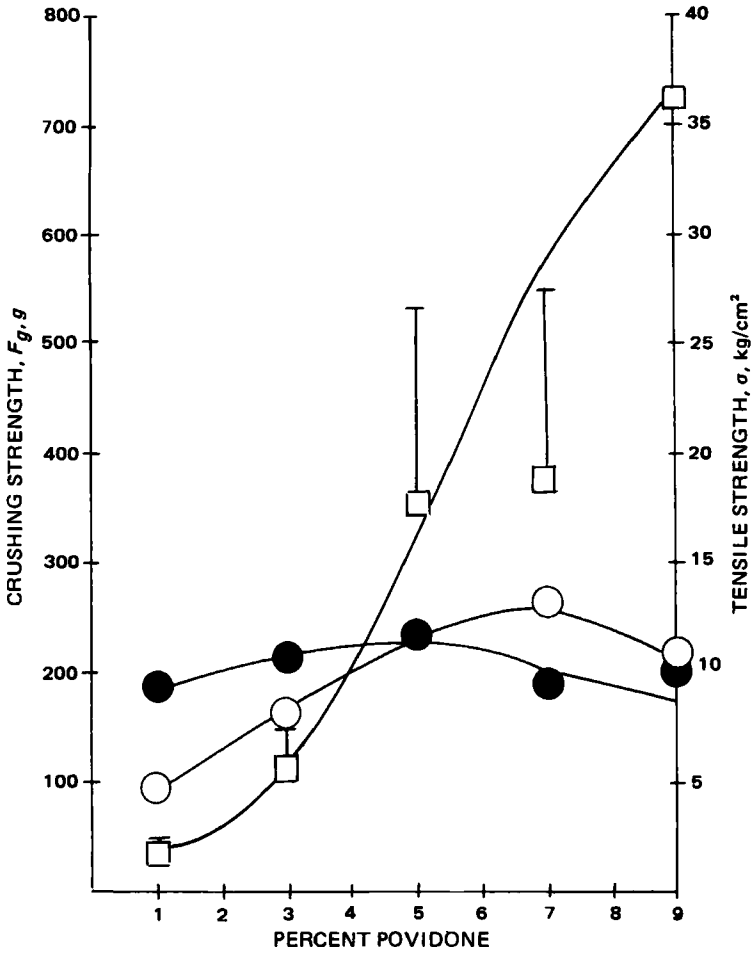

Figure 4—*Relationship of binder concentration to granule strength to tensile strengths of tablets compressed at 1134 kg from lactose monohydrate granules granulated with povidone. Key: (□) granule strength; (○) axial tensile strength; and (●) radial tensile strength.*

shown in Table II. For a given concentration of povidone the strength of a granule is a function of its size. It was suggested previously that (17):

$$F_g = q\,D^n \qquad \text{(Eq. 1)}$$

where D is the diameter of the granule and q and n are constants for a material. Using the natural logarithmic form of Eq. 1:

$$\ln F_g = q' + n \ln D \qquad \text{(Eq. 2)}$$

the constants may be evaluated by plotting as shown in Fig. 1. The slopes are 2.10, 1.90, and 0.88 for 1.0, 3.0, and 7.0% povidone, respectively. The decrease of the slope as the concentration of binder is increased suggested that particle size influences the granule resistance to crushing to a lesser extent than the concentration of the binder (18–21).

The strength of dibasic calcium phosphate dihydrate[7] granules containing 0.6–4.5% starch is shown in Fig. 2. At low concentrations of starch, the granule resistance to crushing is weak. As the concentration of binder is increased (2–3%), there is a considerable increase in the granule strength, and further increases in the concentration of binder only slightly increase the granule strength. The inflection in Fig. 2 may represent the binder concentration just sufficient to encase the granule surface under the conditions of preparation. A further increase of binder will fill in the porous openings of the granule, continuing, but to a lesser extent, to increase the granule resistance to crushing (18).

The effect of concentration of povidone on the strength of granules of dibasic calcium phosphate dihydrate[8] is shown in Fig. 3. The relationship is similar to that obtained with starch, and in the range of 3–6% povidone in the granules there is the greatest increase in strength.

The effect of concentration of povidone on the strength of granules of lactose monohydrate is shown in Fig. 4. Again the range of 3–6% povidone in the granules provides the greatest increase in strength of the granule.

[7] Encompress, Edward Mendell Co., Carmel, N.Y.
[8] USP, Ruger Chemical Corp., Irvington, N.J.

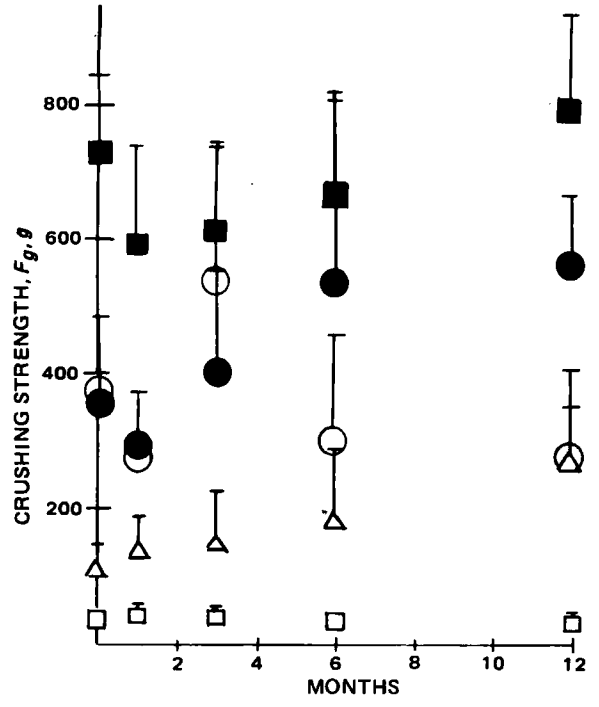

Figure 5—*Effect of time on the granule strength of 16/20-mesh granules of lactose monohydrate granulated with various concentrations of povidone. Key: (□) 1%; (△) 3%; (●) 5%; (○) 7%; and (■) 9% povidone.*

Aging has been reported to affect the mechanical properties of compressed tablets (22). Lactose granules containing 1–9% povidone were stored at 40–45% relative humidity and at ambient temperature, and the crushing load was measured initially and at 1, 3, 6, and 12 months. The data are plotted in Fig. 5. Within the variance of the experimental apparatus aging does not appear to markedly affect the crushing strength of the granule.

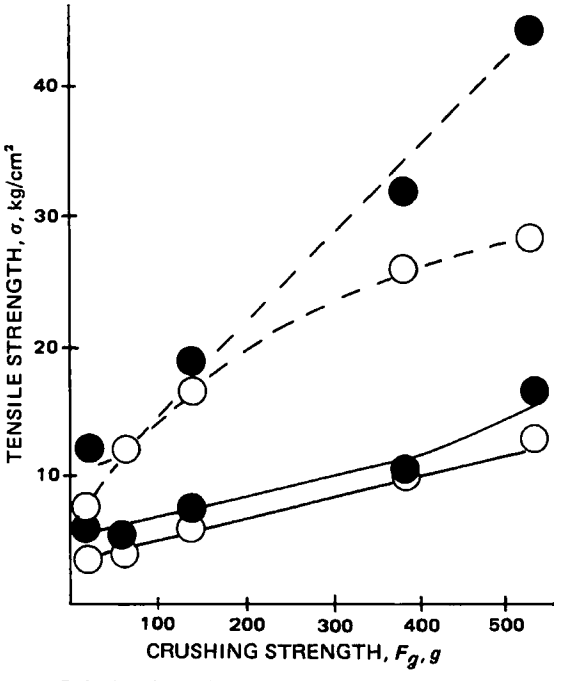

Figure 6—*Relationship of granule strength to tensile strengths of tablets compressed at 2268 and 4536 kg from dibasic calcium phosphate dihydrate granulated with povidone. Key: (○) axial and (●) radial tensile strengths; (—) 2268 kg; and (- - -) 4536 kg.*

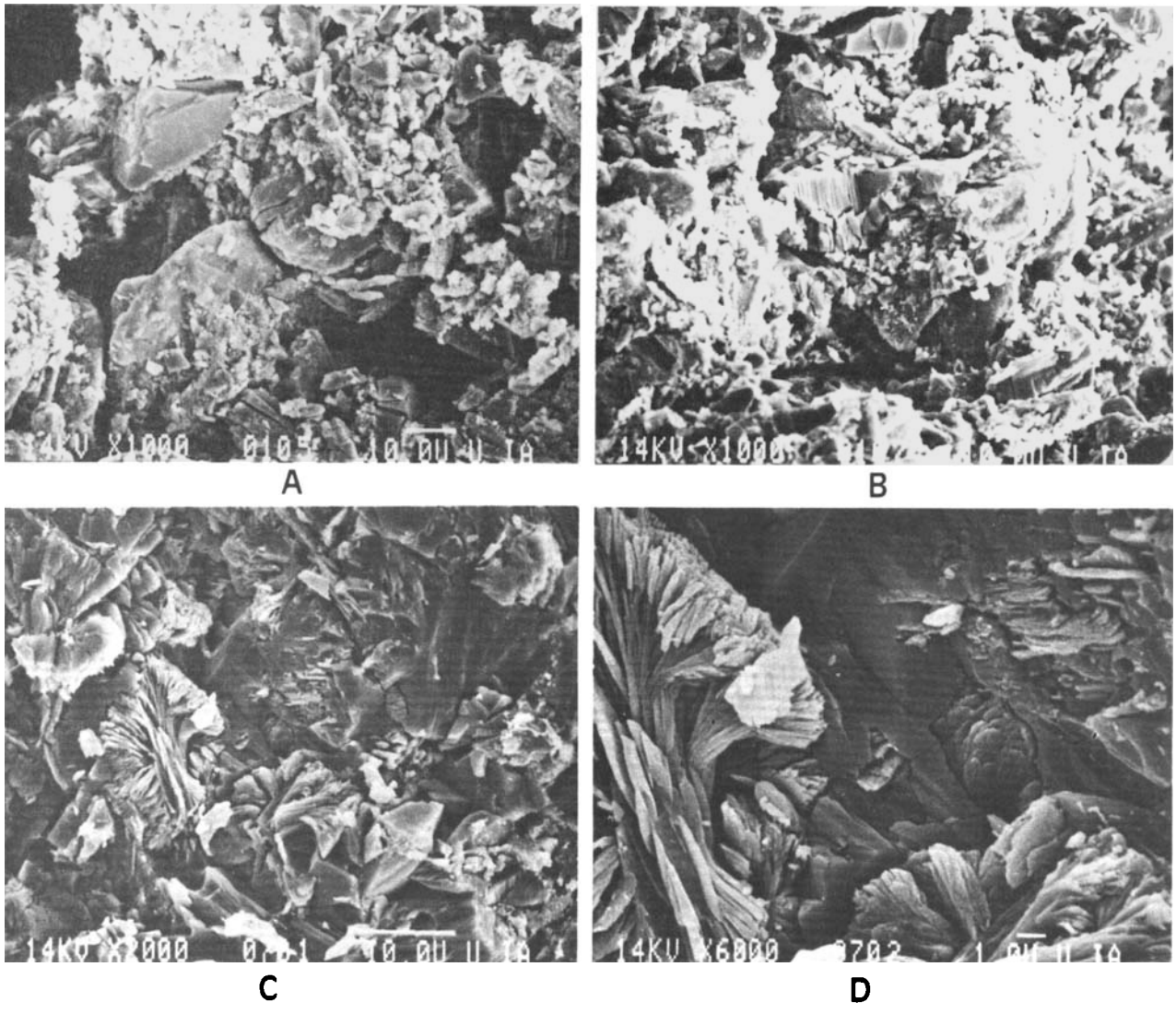

Figure 7—*Scanning electron photomicrographs of tablets of dibasic calcium phosphate dihydrate and starch. Key: (A) location above center of tablet, compressional force 454 kg, starch 1.2%, original magnification 1000×; (B) location near axial and radial tablet surface, same tablet as (A); (C) location near center of tablet, compressional force 1134 kg, starch 4.5%, original magnification 2000×; and (D) same as (C) but original magnification 6000×.*

Relationship of Granule Strength to Tablet Tensile Strength—A 16/20-mesh size fraction of granule was selected for investigation, since this is a tablet granulation size often used in commercial production. The relationship of the axial and radial tensile strengths of tablets compressed at 2268 and 4536 kg of force to the crushing strength of granules of dibasic calcium phosphate dihydrate[8] granulated with povidone is shown in Fig. 6. For the various granules compressed at a given force, the tensile strength of the tablet is increased as the resistance to crushing is increased. The granule strength is increased as the concentration of binder is increased; therefore, the effect of granule strength on tensile strength is probably inseparable from the effect of concentration. The form of a plot of tensile strength against concentration of binder is similar to that of the granule strength against concentration, as shown in Fig. 3.

The relationship of concentration of binder to granule strength and to tensile strengths of dibasic calcium phosphate dihydrate tablets granulated with starch and compressed at 2268 kg is shown in Fig. 2. The plot of granule strength against concentration of binder is similar to that of the plot of tablet tensile strength against concentration.

The relationship of concentration of binder to granule strength and to tensile strengths of lactose monohydrate tablets granulated with povidone and compressed at 1134 kg is shown in Fig. 4. Again, the form of the granule strength–concentration curve and the tensile strength–concentration curve is similar.

Visualization of Granule Fate—The fate of a granule in the tableting process has been followed by several investigators (10, 13, 23). It has been reported (11) that within a given range of compression the integrity of an individual granule in a compact may be demonstrated. Another report (12) showed that at low compressional force there was no apparent change in volume because interparticulate slippage shortens the granule, but its diameter increased as it was flattened. At intermediate forces, plastic deformation and consolidation continued to flatten the granule, but solid bridges were formed without the diameter of the granule increasing, so that a reduction of volume occurred. Finally, at high compressional force, a structure was formed that could support the applied force without further consolidation.

The effect of compressional force on the deformation of granules within a tablet may be visualized by scanning electron microscopy of the surface produced by fracture of the tablet in the diametral compression test. Differences in porosity within a compact have been reported (13). In Fig. 7A the photomicrograph is of a porous region immediately above the less porous center of a dibasic calcium phosphate dihydrate tablet compressed at 454 kg from granules containing 1.2% starch. In Fig. 7B the photomicrograph is of a denser region near the surface of the same tablet.

The structure of a dibasic calcium phosphate dihydrate tablet compressed at 1134 kg from granules containing 4.5% starch is shown in Fig. 7C and D. Two pockets of starch may be seen within the matrix of the tablet. It may be that the pockets occur because the amount of starch is greater than that amount required to just encase the granule (18). At higher compressional forces these starch structures become indistinguishable.

The porosity of a compressed tablet is decreased as compressional force is increased (24, 25). Photomicrographs of the center of tablets of dibasic

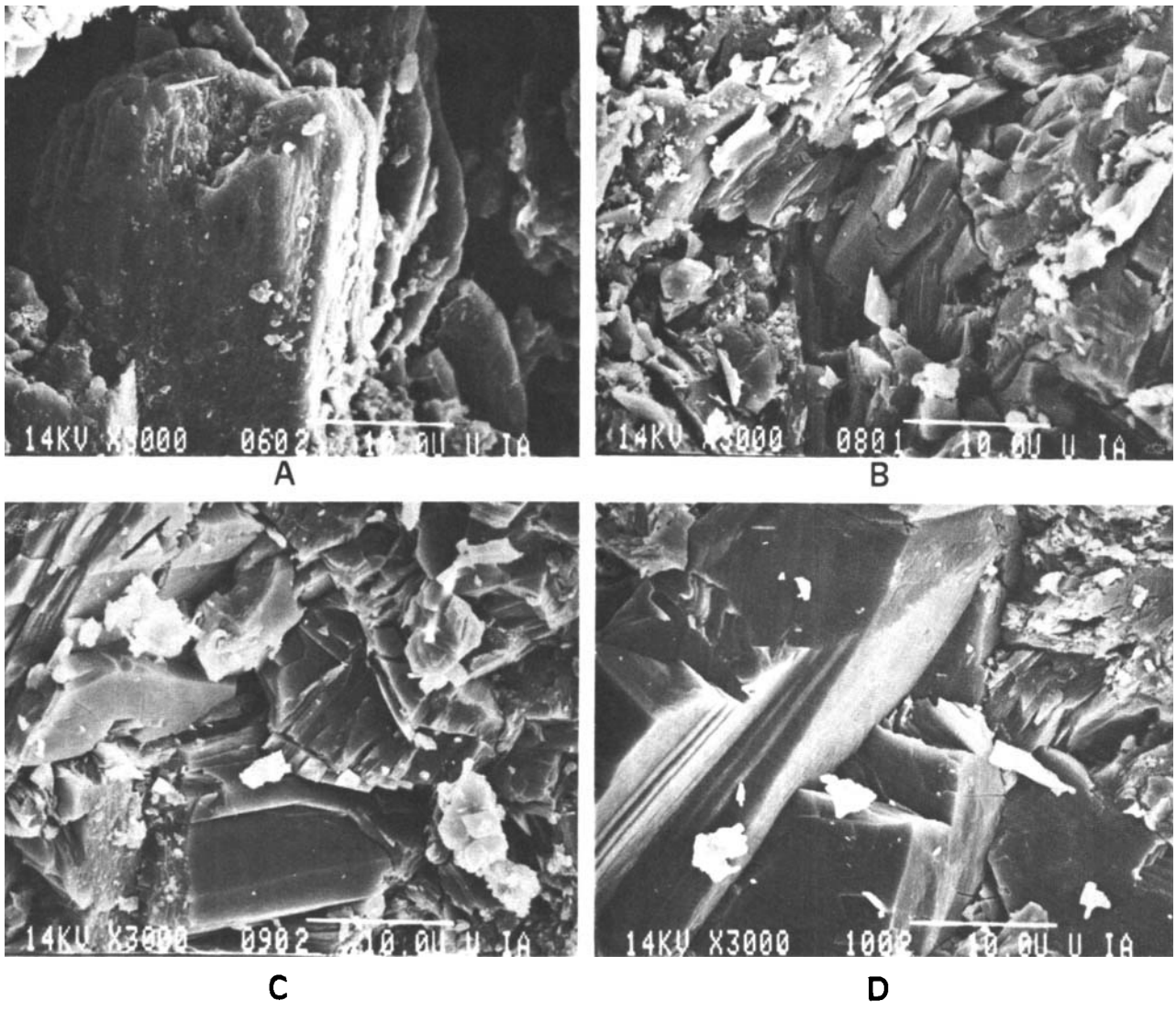

Figure 8—*Scanning electron photomicrographs of center of tablet of dibasic calcium phosphate[7] and 4.5% starch. Original magnification 3000×. Key: compressional force (A) 454; (B) 2268; (C) 4536; and (D) 9402 kg.*

calcium phosphate dihydrate compressed at 454, 2268, 4536, and 9402 kg from granules containing 4.5% starch are shown in Fig. 8. In Fig. 8A, at a low compressional force of 454 kg, the original granule may be distinguished. As the compressional force is increased, the granule is fractured, and no original granules can be seen because consolidation has occurred (Fig. 8B–D). This agrees with the general thought that they should break down on compaction in the die (26).

As shown in Fig. 6, as the compressional force is increased from 2268 to 4536 kg, the tablet tensile strength is increased. Although the crushing strength of granules is important in the handling of the granulation in the tablet process and in tablet reproducibility, the compressional force and the concentration of binder appear to be more basically related to the tablet tensile strength.

REFERENCES

(1) D. E. Fonner, N. R. Anderson, and G. S. Banker, in "Pharmaceutical Dosage Forms: Tablets, Volume 2," H. A. Lieberman and L. Lachman, Eds., Dekker, New York, N.Y., 1981, p. 216.

(2) B. M. Hunter and D. Ganderton, *J. Pharm. Pharmacol.*, **25**, 71P (1973).

(3) W. L. Davis and W. T. Gloor, *J. Pharm. Sci.*, **61**, 618 (1972).

(4) N. A. Armstrong and G. A. March, *ibid.*, **65**, 198 (1976).

(5) C. F. Harwood and N. Pilpel, *ibid.*, **57**, 478 (1968).

(6) D. Ganderton and A. A. Selkirk, *J. Pharm. Pharmacol.*, **22**, 345 (1970).

(7) K. T. Jaiyeoba and M. S. Spring, *ibid.*, **31**, 192 (1978).

(8) A. M. Marks and J. H. Sciarra, *J. Pharm. Sci.*, **57**, 497 (1968).

(9) G. Gold, R. N. Duvall, B. T. Palermo, and R. L. Hurtle, *ibid.*, **60**, 922 (1971).

(10) W. A. Strickland, Jr., E. Nelson, L. W. Busse, and T. Higuchi, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 51 (1956).

(11) E. Shotton and D. Ganderton, *J. Pharm. Pharmacol.*, **12**, 93T (1960).

(12) M. H. Rubinstein, *J. Pharm. Sci.*, **65**, 376 (1976).

(13) D. Train, *J. Pharm. Pharmacol.*, **8**, T45 (1956).

(14) W. Erni and W. A. Ritschel, *Pharm. Ind.*, **39**, 82 (1977).

(15) "Handbook of Chemistry and Physics," R. C. Weast, Ed., 55th ed., CRC Press, Cleveland, Ohio, 1974, p. E-46.

(16) P. J. Jarosz and E. L. Parrott, *J. Pharm. Sci.*, **71**, 607 (1982).

(17) C. E. Capes, in "Proceedings of Powtech '71," A. S. Goldberg, Ed., Powder Advisory Centre, London, England, 1971, p. 151.

(18) K. Nishimura, N. Ikeda, and T. Fukazawa, *Yakuzaigaku*, **38**, 190 (1978).

(19) W. O. Opakunle and M. S. Spring, *J. Pharm. Pharmacol.*, **28**, 508 (1976).

(20) W. O. Opakunle and M. S. Spring, *J. Pharm. Pharmacol.*, **28**, 806 (1976).

(21) W. O. Opakunle and M. S. Spring, *J. Pharm. Pharmacol.*, **28**, 915 (1976).

(22) A. S. Alam and E. L. Parrott, *J. Pharm. Sci.*, **60**, 263 (1971).

(23) R. J. Rue, H. Seager, J. Ryder, and I. Burt, *Int. J. Pharm. Tech. Prod. Mfr.*, **1**, 2 (1980).

(24) T. Higuchi, A. N. Rao, L. W. Busse, and J. V. Swintosky, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 194 (1953).

(25) S. A. Shah and E. L. Parrott, *J. Pharm. Sci.*, **65**, 1784 (1976).
(26) E. Shotton, J. A. Hershey, and P. E. Wray, in "The Theory and Practice of Industrial Pharmacy," 2nd ed., L. Lachman, H. A. Lieberman, and J. L. Kanig, Eds., Lea & Febiger, Philadelphia, Pa., 1976, p. 309.

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High-Performance Liquid Chromatographic Determination of Vincristine Sulfate in Preformulation Studies

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Received February 19, 1982 from the *Science and Technology Division, Pharmaceutical Research and Development Division, Product Development Research Department, Bristol-Myers, Inc., Syracuse, NY 13201.* Accepted for publication May 26, 1982. Present address: *Boots Pharmaceutical, Inc., Shreveport, LA 71106. ‡American Cyanamid, Medical Research Division, Lederle Laboratories, Pearl River, NY 10965.

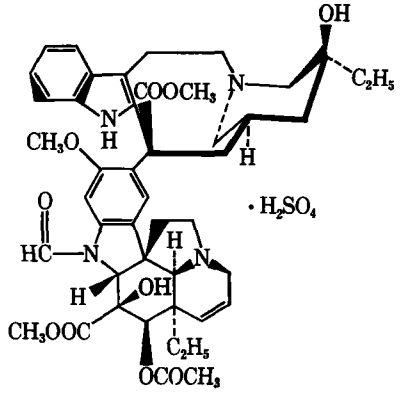
Abstract □ A fast and simple procedure was developed for the quantitative determination of vincristine sulfate for use in preformulation studies. The procedure involves the use of high-performance liquid chromatography with a reverse-phase column and a mobile phase containing the sodium salt of 1-pentanesulfonic acid for ion-pairing. The procedure has been shown to be specific for vincristine sulfate in the presence of forced degradation products of this substance, vinblastine (a structurally similar *Vinca* alkaloid), and several possible formula excipients. The procedure is linear from 10–200% of the normal injection concentration, and has an assay precision (relative 2σ) of ±1.6%. Recovery of known samples averaged 99.7%.

Keyphrases □ Vincristine sulfate—high-performance liquid chromatography, preformulation studies, degradation □ High-performance liquid chromatography—vincristine sulfate, degradation products □ Preformulation studies—vincristine sulfate, degradation products, high-performance liquid chromatography

Vincristine sulfate (I), an antineoplastic agent originally obtained from extracts of *Vinca rosea*, is structurally related to vinblastine. An analytical procedure was required for the determination of vincristine sulfate in samples resulting from preformulation studies. The procedure had to be capable of accurate and precise quantitation, specific in the presence of a number of possible excipients, and stability indicating. Because a large number of samples were to be examined, it was also necessary that the procedure be rapid and simple.

A number of assay procedures have been reported for vincristine sulfate (1); however, some are not stability indicating (direct spectrophotometric analysis), others are time consuming and complex (colorimetric analysis), and some are not sufficiently accurate and precise (TLC analysis). Several high-performance liquid chromatographic (HPLC) methods have been reported. One procedure (2) requires a 40-min gradient with a vincristine retention time of ~25 min. This was deemed too lengthy for the proposed purpose.

Another procedure (3) required the use of ammonium carbonate in the mobile phase. Since the column life might be shortened appreciably by the presence of ammonium carbonate[1], this procedure was not used. This paper reports the development of a simple and rapid HPLC procedure for the determination of vincristine sulfate stability.



EXPERIMENTAL

Reagent and Chemicals—Acetonitrile and methanol were HPLC grade[2], and were used without further purification. Water was distilled and filtered[3] prior to use. Vincristine sulfate was used as received[4]. All other reagents were ACS grade or better and used without further purification.

Equipment—A liquid chromatograph[5] was connected to an injection valve[6], a variable-wavelength detector[7], a recorder[8], and an integrator[9].

A column[10] consisting of a monomolecular layer of a phenylorganosilicone permanently bonded to polar, porous silica particles was used.

The mobile phase consisted of 30% acetonitrile and 70% aqueous solution which contained 0.02 *M* ammonium acetate and 0.005 *M* of the sodium salt of 1-pentanesulfonic acid adjusted to pH 2.0 with 10% v/v nitric acid[11]. The flow rate was 2.5 ml/min (pressure was ~2000 psi). The detector sensitivity was 0.1 AUFS at 254 nm. Chart speed was 60 cm/hr.

Internal Standard Preparation—Propyl *p*-hydroxybenzoate (~30 mg) was accurately weighed and transferred to a 100-ml volumetric flask.

[1] μ-Bondapak and μ-Porasil Liquid Chromatography Columns Care and Use Manual, Waters Associates, Milford, Mass.
[2] Burdick and Jackson Laboratories, Inc., Muskegon, Mich.
[3] Type HA, 0.45μ filter, Millipore Corp., Bedford, Mass.
[4] Gedeon Nichter Ltd., Budapest, Hungary.
[5] Model 5000 Varian Associates, Walnut Creek, Calif.
[6] Valco injection valve with pneumatic actuator, Valco Instruments, Houston, Tx.
[7] Model UV-50 Varichrom, Varian Associates, Walnut Creek, Calif.
[8] Model 9176, Varian Associates, Walnut Creek, Calif.
[9] Model CDS-111L, Varian Associates, Walnut Creek, Calif.
[10] μ-Bondapak Phenyl, Catalog No. 17198 (30 cm × 3.9-mm i.d.), Waters Associates, Milford, Mass.
[11] Beckman Model Zeromatic II, Beckman Instruments, Fullerton, Calif.

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