Granule Strength as a Formulation Factor I: Instrumentation

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Abstract □ Although it is recognized that granule strength is an important property of powders influencing pharmaceutical processes, little information has been published on the subject. This lack of information is due mainly to difficulty in obtaining quantitative measurement of granule strength and, therefore, in obtaining meaningful data. To meet this need, instrumentation was constructed. It consists of a mechanical linkage to apply a compressive load at a uniform rate and a strain-gauge instrumented cantilever beam to convert the load to a proportional millivolt response which is measured on a recorder. A granule is placed on the platform of the cantilever beam, and an overhead cam depresses a plunger which compresses the granule. The reaction of the granule is obtained on a recorder tracing from which the stress pattern is analyzed and the crushing strength calculated.

Keyphrases □ Granule strength determination—instrumentation □ Instrumentation—granule strength testing □ Diagram—granule strength testing instrument □ Compressive strength—granules

The effect of granule strength as a formulation factor is virtually unknown, and the literature contains little information on the subject to aid the industrial pharmacist in formulating solid-dosage formulations. The effects of granule strength on such factors as compressibility, tablet hardness, friability, dissolution of active ingredients, and mouthfeel of chewable tablets are but a few areas that need to be explored. The limited data available are difficult to interpret due to the variety and subjectivity of methods used to measure granule strength.

Friability has been used as a parameter to evaluate granule strength, with increased friability associated with softer granules. Granules are placed in a Roche Friabilator or shaken with a standardized shaking device; the weight of granules exceeding a specific mesh size, expressed as a fraction or percentage, serves as an index of granule strength. In a study designed to determine the effect of granule size upon the physical properties of the granules and the tablets produced from these granules (1), the degree of friability was found to be inversely proportional to the granule size. In another study to assess the manufacturing procedures for preparing granules suitable for pharmaceutical coating purposes, the authors reported that the hardness index increased as the density of the granule increased (2). In the absence of a definitive study relating friability to granule strength, it may only be assumed that resistance to abrasion data accurately reflects the strength of the granule.

A method for measuring the breaking strength of individual granules was recently reported (3). In this test, lead shot was poured onto a pan held directly on top of the granule until the granule broke. Breaking of the granule was determined visually and had to be coordinated with manually stopping the flow of lead shot at the breaking point. The study showed that the strength of granules was dependent on both their size and on their polyvinylpyrrolidone content. The authors attributed the increase in strength to solid bridges of polyvinylpyrrolidone which formed on evaporation of the granulating solution. They also reported considerable variation in granule strength and theorized that it was due to the brittle properties of polyvinylpyrrolidone in the solid state.

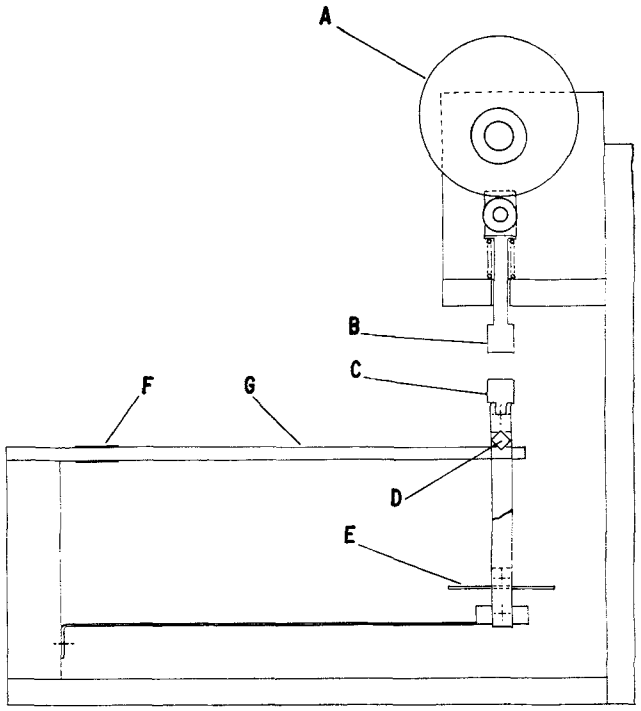

Figure 1—*Instrumentation for measuring granule strength. Key: A, motor-driven cam; B, upper jaw; C, lower jaw or anvil; D, steel pivot; E, weight platform for calibration; F, strain gauges; and G, cantilever beam.*

In another recent study (4), the authors used a simple crushing test with a spatula and observed that an increase in the amount of granulating solution increased the strength of the granules.

Other investigators (5) modified a microtensile testing machine to measure compressive strain. They calculated the elastic moduli for sodium chloride, sucrose, hexamine, salicylamide, and aspirin. Diffi-

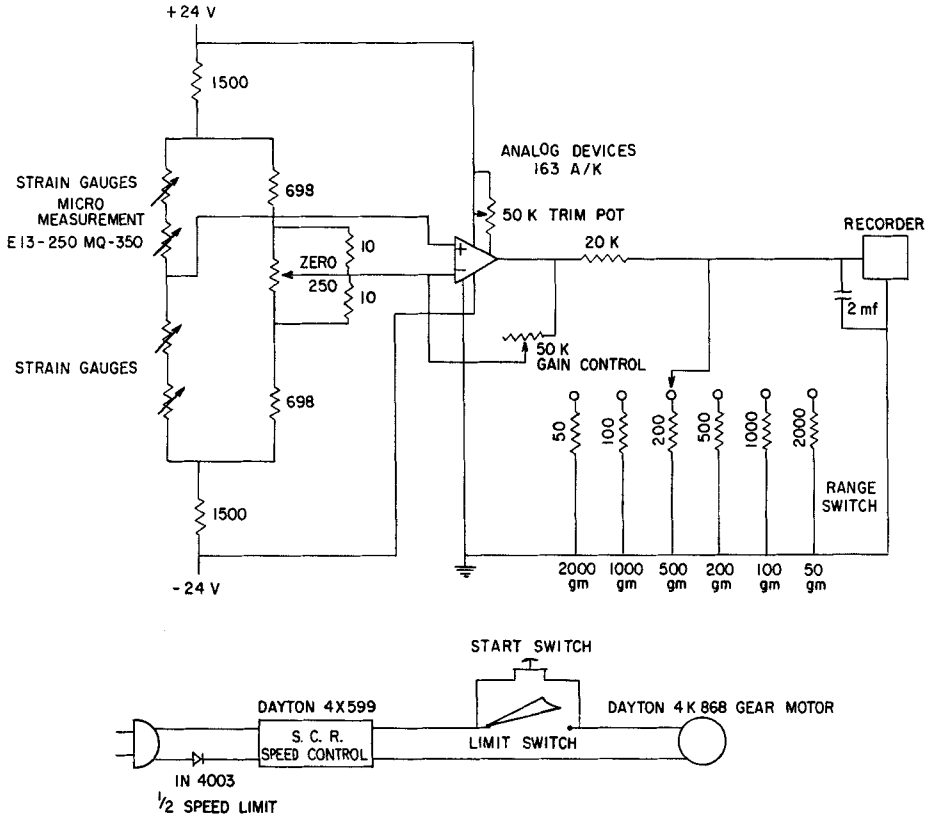

Figure 2—*Electrical diagram of strain-gauge instrumented cantilever beam and motor-driven cam.*

culties were encountered in determining the elastic modulus due to crystal defects, misorientation, slip, and cracking under load, which contributed to a scattering of results. The scattering of results was also reported in a study of tensile strength measurement on moist granules (6).

At the present time, there is no generally accepted method for measuring granule strength nor is there a method suitable for the desired purposes. The immediate objective of this study was the development of instrumentation that would yield basic information on granule strength and be practical for use in an industrial setting. This report describes the instrumentation developed.

EXPERIMENTAL

Description of Instrument—The instrumentation (Fig. 1) consists of a mechanical linkage to supply the load at a uniform rate, a strain-gauge instrumented cantilever beam to convert the compressive load to a proportional millivolt response, and a recorder to measure the millivolt response.

A single granule is selected at random from within a mesh size range and is placed on the anvil (C). The cam (A) is then rotated at a uniform rate, which may be varied from 12 sec. to 3.5 min. per revolution. Rotation of the cam, controlled by a link chain, gear motor[1], and speed control switch[2], causes the plunger to descend, compressing the granule against the anvil. The compressive load bends the cantilever beam, thereby deforming the strain gauges. By arranging a hardened steel pivot (D) in a parallelogram arrangement, the load is applied with low friction at one point on the beam. The millivolt response across the strain-gauge bridge circuit is proportional to the compressive load on the granule and is measured on the horizontal axis of a recorder. A tracing is obtained of increasing compressive load with time, with a break in the tracing indicating the compressive load at fracture. Twenty measurements are made, and the average breaking load and standard deviation are calculated.

The electrical diagram (Fig. 2) shows the strain gauges connected in series as a voltage divider, with the center point between the upper and lower gauges being fed to an operational amplifier and compared with a point on another voltage divider fed from the same power source. All components have low temperature coefficients to reduce thermal drift, and the power supply uses an integrated circuit voltage regulator with regulation of 0.025%.

Calibration of Instrument—To calibrate the instrument, weights are added to the platform and the recorder response is noted. The magnitude of the change in potential was found to be directly pro-

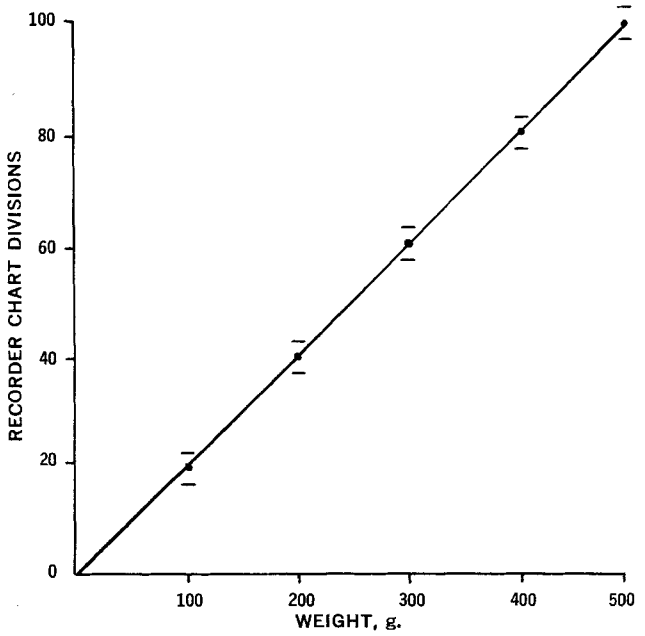

Figure 3—*Calibration curve relating weight in grams to recorder response.*

[1] Model 4K868, Dayton Electric Mfg. Co., Chicago, Ill.
[2] Model 4X599, Dayton Electric Mfg. Co., Chicago, Ill.

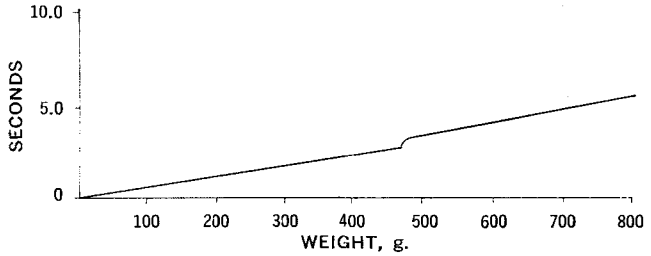

Figure 4—*Typical recorder tracing of an aspirin granule, indicating the magnitude of the breaking point and its breaking pattern.*

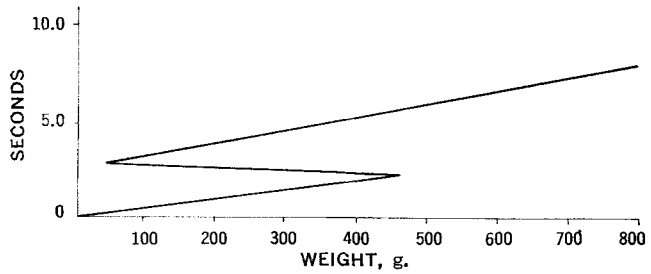

Figure 5—*Typical recorder tracing of a sugar–starch pellet, indicating the magnitude of the breaking point and its breaking pattern.*

portional to the weight added to the platform of the cantilever beam. The linear relationship for the 0–500-g. range is shown in Fig. 3; the same linear relationship was found to exist over a range of 0–2000 g. Each point represents the average of 20 measurements, and the horizontal lines above and below each point are the 95% confidence limits. The points are connected by a line calculated by the method of least squares.

Materials—Commercially available materials of either USP, NF, or pharmaceutical grade were used. Granules of lactose and dicalcium phosphate dihydrate were prepared by the following wet granulation procedure. Eleven kilograms of material was passed through a No. 12 screen on an oscillating granulator and placed in a 1.8-cu. ft. Stokes mixer. The granulating solution at room temperature was added in four equal volumes at 2-min. intervals until 2000 ml. was added. The wet mass was mixed for 20 min., wet-sieved through a No. 6 screen on an oscillating granulator, dried at 54.4° (130°F.) for approximately 20 hr., and dry-sieved through a No. 12 screen. The granules were separated into a 14–16-mesh size, using the Ro-Tap testing sieve shaker with U. S. standard sieves. Granules of aspirin[3] and pellets of sugar–starch[4] were purchased. Aspirin granules were separated into 10–12-, 14–16-, 16–18-, and 20–25-mesh ranges, and sugar–starch pellets were separated into a 14–16 range.

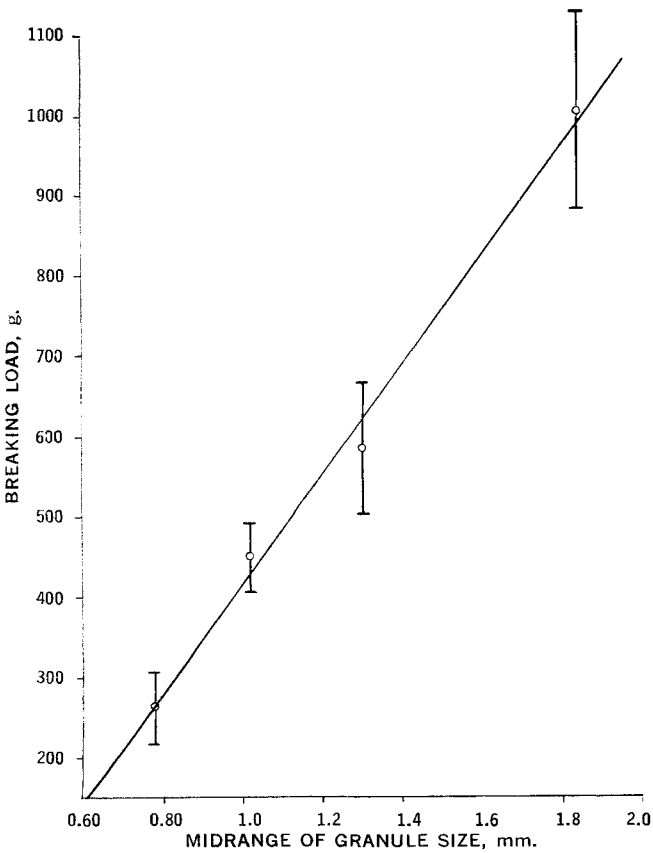

Figure 6—*Plot showing relationship of strength of aspirin granules to granule size.*

Table I—Breaking Load[a] and Standard Deviation of 14–16-Mesh Granules

Granule	Breaking Load, g.	*SD*
Aspirin with 10% starch	466.1	169.6
Sugar–starch pellets	336.0	142.5
Lactose granulations		
Water	62.4	27.0
20% Polyvinylpyrrolidone	196.3	85.5
10% Methylcellulose, 15 cps.	134.9	66.6
Dicalcium phosphate granulations		
Water	11.9	5.14
10% Methylcellulose, 15 cps.	152.9	51.1

[a] Average of 20 measurements.

RESULTS AND DISCUSSION

A typical recorder tracing for a 14–16-mesh aspirin granule is shown in Fig. 4; the horizontal axis is the compressive load and the vertical axis is the time. The break occurred at 475 g. Compressive strength may be defined as the maximum compressive load causing fracture and should not be confused with hardness, which is a measure of the resistance to indentation. Consequently, in this example the compressive strength of the granule is 475 g.

The loading rate is extremely important and is readily calculated from the tracing. As the loading rate increases, it approaches an impact load rather than a compressive load, causing the granule to exhibit different properties. It is also important that the compressive load be applied at a uniform rate to enable the granule to respond with a characteristic stress. In Fig. 4 the reciprocal of the slope of the line, 165 g./sec., is the rate at which the weight is being applied.

The pattern of the break indicates the reaction of the granule to the compressive load. The break that is characteristic for aspirin granules shows that the granule is capable of supporting additional compressive load after fracture. Examination of the fractured granule reveals that it remains intact. This is in contrast to sugar–starch pellets where the breaking pattern (Fig. 5) is characterized by a sharp break with a long backswing. The break occurs at 460 g. at a loading rate of 165 g./sec., and a backswing develops from the breaking point to 40 g. The backswing is significant because it provides insight as to the ability of the fractured particle to support a load. In this case, the fractured pellet does not retain its spherical form but rather disperses into fine particles. In effect, there is a collapse of the spherical particle. The backswing develops because the compressive load on the cantilever beam is abruptly relieved and the release in tension allows the beam to rise until the anvil makes contact with the descending plunger. In the case of aspirin granules (Fig. 4), the fractured granule remains intact between the plunger and anvil and continues to transmit the compressive load. In addition to the breaking pattern, the tracing provides a quantitative measurement of granule strength.

The average breaking load for several different strength, 14–16-mesh materials is summarized in Table I. Each value represents an average of 20 measurements. Results varied from a high granule strength of 466.1 g. for aspirin granules with a standard deviation of 169.6 to a granule strength of 11.9 g. for dicalcium phosphate

[3] Marketed as aspirin 10% starch granulation, white, 12–15 mesh, by the Monsanto Co., St. Louis, Mo.

[4] Marketed as white pellets by the Raymond Confectionery Co., Niles, Ill.

granules with a standard deviation of 5.14. The relatively high standard deviation indicates intergranule variability in strength. To meet the requirement of statistical significance, the data were evaluated by Duncan's multiple-range test (7) which classifies the means into subsets. A statistical difference exists between different subsets but not between members of the same subset. The first subset is aspirin granules; the second, sugar–starch pellets; the third, lactose with 10% methylcellulose, lactose with 20% polyvinylpyrrolidone and dicalcium phosphate with 10% methylcellulose; and the fourth, lactose granulated with water and dicalcium phosphate granulated with water. The use of 20% polyvinylpyrrolidone or 10% methylcellulose in preparing lactose granules increased granule strength over those made by aqueous granulation. Also, 10% methylcellulose increased the granule strength of dicalcium phosphate over the straight aqueous granulation. The increase in strength of 20% polyvinylpyrrolidone over 10% methylcellulose for lactose granules does not have statistical significance.

Measurements were also made on 10–12-, 16–18-, and 20–25-mesh aspirin granules; the effect of granule size on the strength of these granules is shown in Fig. 6. Each value represents the average of 20 measurements, and the vertical bracketed lines are the 95% confidence limits. A linear relationship was found to exist between the strength of these granules and granule size.

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ACKNOWLEDGMENTS AND ADDRESSES

Received August 7, 1970, from the *Pharmaceutical Research and Development Laboratory, Miles Laboratories, Inc., Elkhart, IN 46514*

Accepted for publication March 1, 1971.

NOTES

Schiff Base Derivatives of Anti-Inflammatory *O*-Substituted Hydroxylamines

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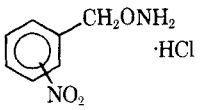
Abstract □ The synthesis of 12 azomethine (Schiff base) derivatives by the reaction of various nitrobenzaldehydes and salicylaldehydes with the anti-inflammatory compounds, *m*-nitrobenzyloxyamine hydrochloride and 4-thiazolylmethoxyamine dihydrochloride, and with congeneric *O*-substituted hydroxylamines is described. These Schiff bases, which are structurally related to the naturally occurring pyridoxal derivatives, showed no activity in the carrageenin-induced rat paw edema test. These compounds possessed no antimalarial activity and no activity against the L-1210 mouse lymphoid leukemia test system.

Keyphrases □ Hydroxylamines, *O*-substituted—synthesis of Schiff base derivatives, pharmacological screening □ Azomethine (Schiff base) derivatives—synthesis, pharmacological screening □ Anti-inflammatory hydroxylamines—synthesis, pharmacological screening of Schiff base derivatives

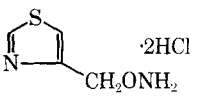
Potent anti-inflammatory activity in the carrageenin-induced rat paw edema test is shown by *m*-nitrobenzyloxyamine hydrochloride (I), *p*-nitrobenzyloxyamine hydrochloride (II), and 4-thiazolylmethoxyamine dihydrochloride (III) (1). Moreover, I, II, and III also possess powerful inhibitory activity *in vitro* against the histamine-forming enzyme, specific histidine decarboxylase (1–3).

The present work describes the synthesis and biological activity of Schiff base derivatives of these anti-inflammatory *O*-substituted hydroxylamines (I and III) and congeneric compounds. These Schiff bases are



I: *meta*

II: *para*



III

structurally related to naturally occurring pyridoxal derivatives.

Pyridoxal phosphate, the coenzyme of mammalian histidine decarboxylases, is attached to the apoenzyme by an azomethine linkage (Schiff base) with the ϵ-amino group of a lysine unit in the enzyme molecule (4). Schiff bases of pyridoxal phosphate are highly reactive and can react with an amino acid more rapidly than can the free aldehyde (5).

It is hoped that the synthetic Schiff bases described in this report might compete with pyridoxal phosphate for the amino group of apoenzyme-bound histidine.

The 12 Schiff bases synthesized are listed and their analytical data and melting points are given in Table I. The syntheses of the starting benzyloxyamines (1) (with the exception of 2-chloro-4,5-methylenedioxybenzyloxyamine hydrochloride which is described in the *Experimental* section) and 4-thiazolylmethoxyamine dihydrochloride (6) are reported in other publications. The Schiff bases were prepared by standard methods (7, 8)