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Effect of Moisture and Crushing Strength on Tablet Friability and *In Vitro* Dissolution

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Abstract □ The friability and dissolution of a formulation of compressed tablets were studied by varying the granulation moisture and tablet crushing strength. A general quadratic response surface model was used to analyze the data. The response surface contour plots of tablet friability consisted of a series of ellipsoidal curves. The optimum friability corresponding to a granulation moisture content and a tablet crushing strength was a simple minimum. The *in vitro* dissolution contour plots showed a stationary ridge system. Along the ridge, a large number of combinations of tablet crushing strength and granulation moisture represented 100% drug dissolution. The contour overlays of friability and dissolution contour plots showed a region where both the friability and dissolution requirement could be met. The analysis of the data by means of multiple linear regression was helpful in understanding the role of granulation moisture and tablet crushing strength on tablet friability and *in vitro* dissolution.

Keyphrases □ Dissolution—*in vitro*, effect of moisture and crushing strength, tablet friability □ Crushing strength—effect on tablet friability and *in vitro* dissolution □ Friability—tablets, effect of moisture and crushing strength

Previous studies (1–3) from these laboratories discussed the interrelationships between moisture, crushing strength, and *in vitro* drug dissolution in compressed tablets. Another physical parameter of importance to the tablet formulators, especially in coating and packaging operations, is friability of compressed tablets. The friabilator[1] (4) provides falling as well as frictional abrasion to the tablet sample and is used to measure the resistance to abrasion or attrition of tablets. The loss of weight is measured after a fixed number of revolutions of a drum rotating at a controlled rate. In the development of tablet dosage forms, formulation factors are generally checked to reduce comparative loss in friability testing. Two types of friabilator[1,2] apparatuses were compared (5) using 10 tablet formulations differing in method of granulation or choice of binder. In all instances the percentage of weight loss was higher with friabilator A[1], the differences ranging from 6.2 to 39.7%, depending upon the formulation. After 25 years of use, it was concluded (6) that the weight loss of not more than 0.8% by friabilator A was valid for the control of most pharmaceutical tablets.

Although friability is generally considered important in the development of tablet formulations, factors affecting friability have not been fully explored. The present report describes a study of the interdependence of tablet friability and *in vitro* drug dissolution on granulation moisture content and tablet crushing strength. The data were analyzed using a general quadratic response surface model and the analysis suggested that rational specifications on the in-process variables such as the granulation moisture and initial tablet hardness could ensure proper control of the tablet friability and *in vitro* dissolution.

EXPERIMENTAL

Materials—The drug, ticlopidine hydrochloride[3], 5-(*o*-chlorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-*c*]pyridine hydrochloride was at least 99.0% pure. The excipients used were microcrystalline cellulose[4] NF, povidone[5] USP, citric acid[6] USP, stearic acid powder[7] NF, corn starch[8] NF, and lactose[9] USP.

Granulation—The formulation used in this study contained 64.1% drug, 22.4% microcrystalline cellulose, 10% starch, 1% citric acid, 2% povidone, and 0.5% stearic acid. The drug and microcrystalline cellulose were mixed together in a small planetary mixer for 10 min. Povidone and citric acid were dissolved in water and the powder mixture was granulated with the binder solution. The wet granulation was mixed for 10 min and passed through a 1.4-mm aperture and dried in a forced-air oven at 60°

[1] Roche type friabilator A.
[2] Erweka Friability Apparatus B.

[3] Sanofi Research Co. Inc. New York, NY 10019.
[4] Avicel pH 101, FMC Corp., Philadelphia, PA 19103.
[5] GAF Corp. New York, NY 10020.
[6] Mallinckrodt, Inc., St. Louis, MO 63147.
[7] Emery Industries, Inc., Cincinnati, OH 45232.
[8] Staley Manufacturing Co., Decatur, IL 62525.
[9] Regular grade, Foremost Co., San Francisco, CA 94104.

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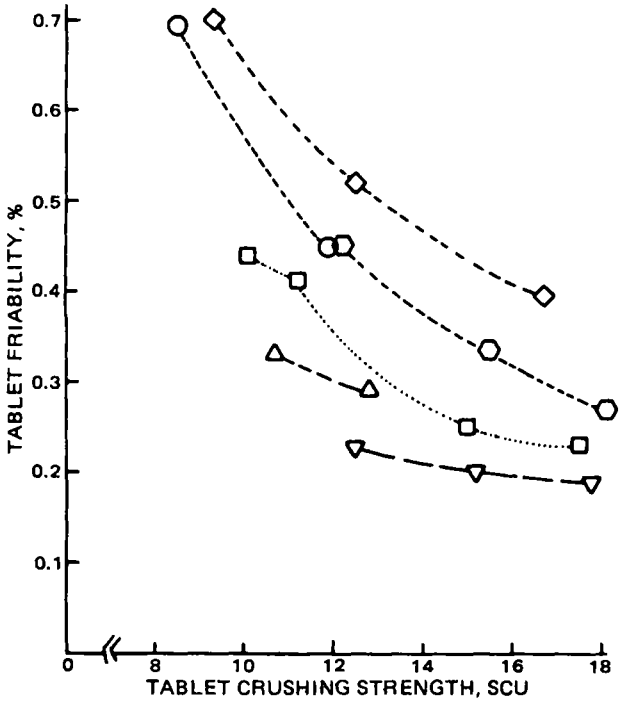

Figure 1—*Plots of tablet friability* versus *tablet crushing strength at different granulation moisture contents. The moisture contents in the granulation at the time of compression were: (○) 0.9%; (△) 1.6%; (▽) 2.0%; (□) 3.0%; (○) 3.6%; (◇) 4.3%.*

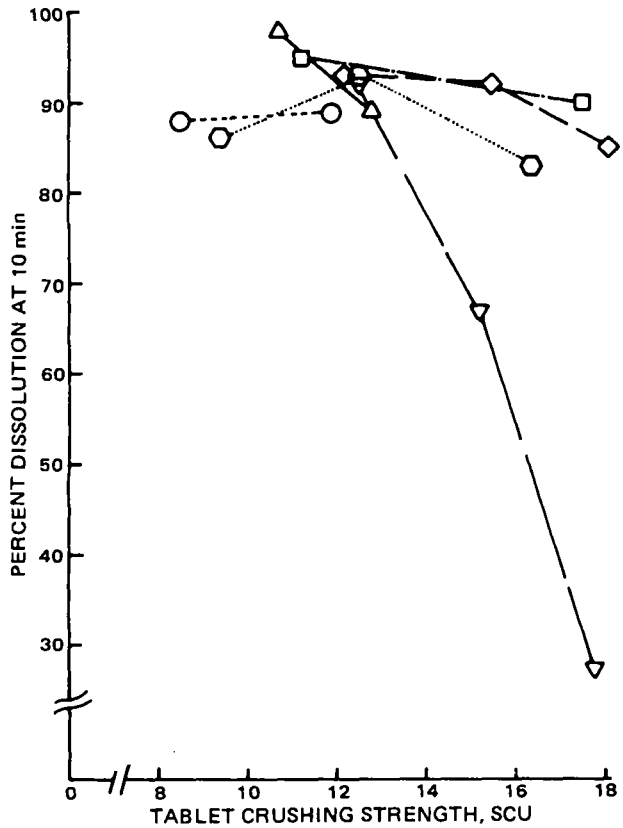

Figure 2—*Plots of percent* in vitro *drug dissolution at the 10-min time point as a function of the tablet crushing strength at different granulation moisture contents. The moisture contents at the time of compression were: (○) 0.9%; (△) 1.6%; (▽) 2.0%; (□) 3.0%; (◇) 3.6%; (○) 4.3%.*

Table I—Results of Multiple Linear Regression Analyses

Coefficients	Factors > Interactions	Regression Coefficient Values Tablet Friability, Y_1	Dissolution, Y_2
b_0	—	2.0186	79.8802
b_1	X_1	−0.2844	−11.4638
b_2	X_2	−0.1808	6.8757
b_3	X_1^2	−0.06228	−4.6829
b_4	X_1X_2	−0.000093	3.3677
b_5	X_2^2	0.005389	−0.7470
Multiple correlation coefficient		0.9407	0.7256

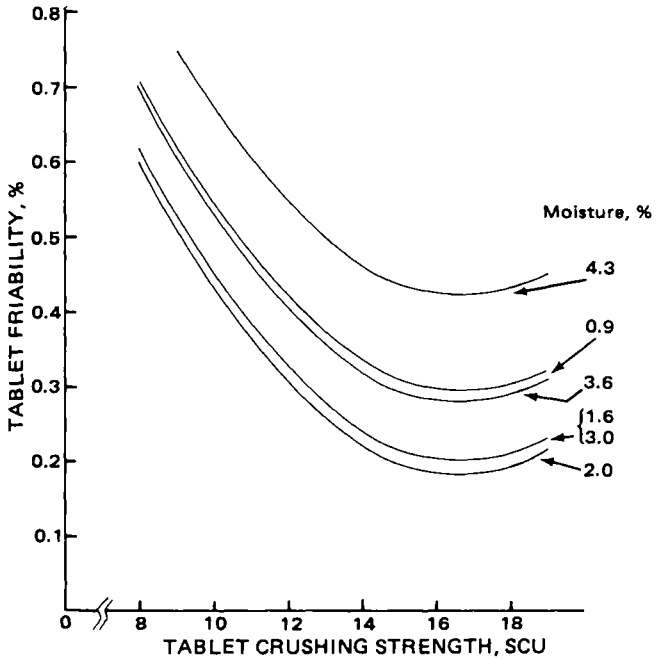

Figure 3—*Calculated plots of tablet friability* versus *tablet crushing strength at different granulation moisture contents using Eq. 1.*

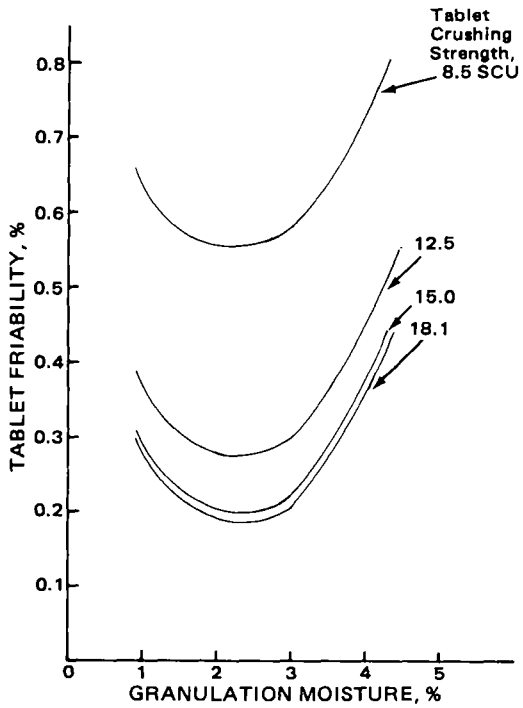

Figure 4—*Calculated plots of tablet friability* versus *percent granulation moisture at different tablet crushing strengths using Eq. 1.*

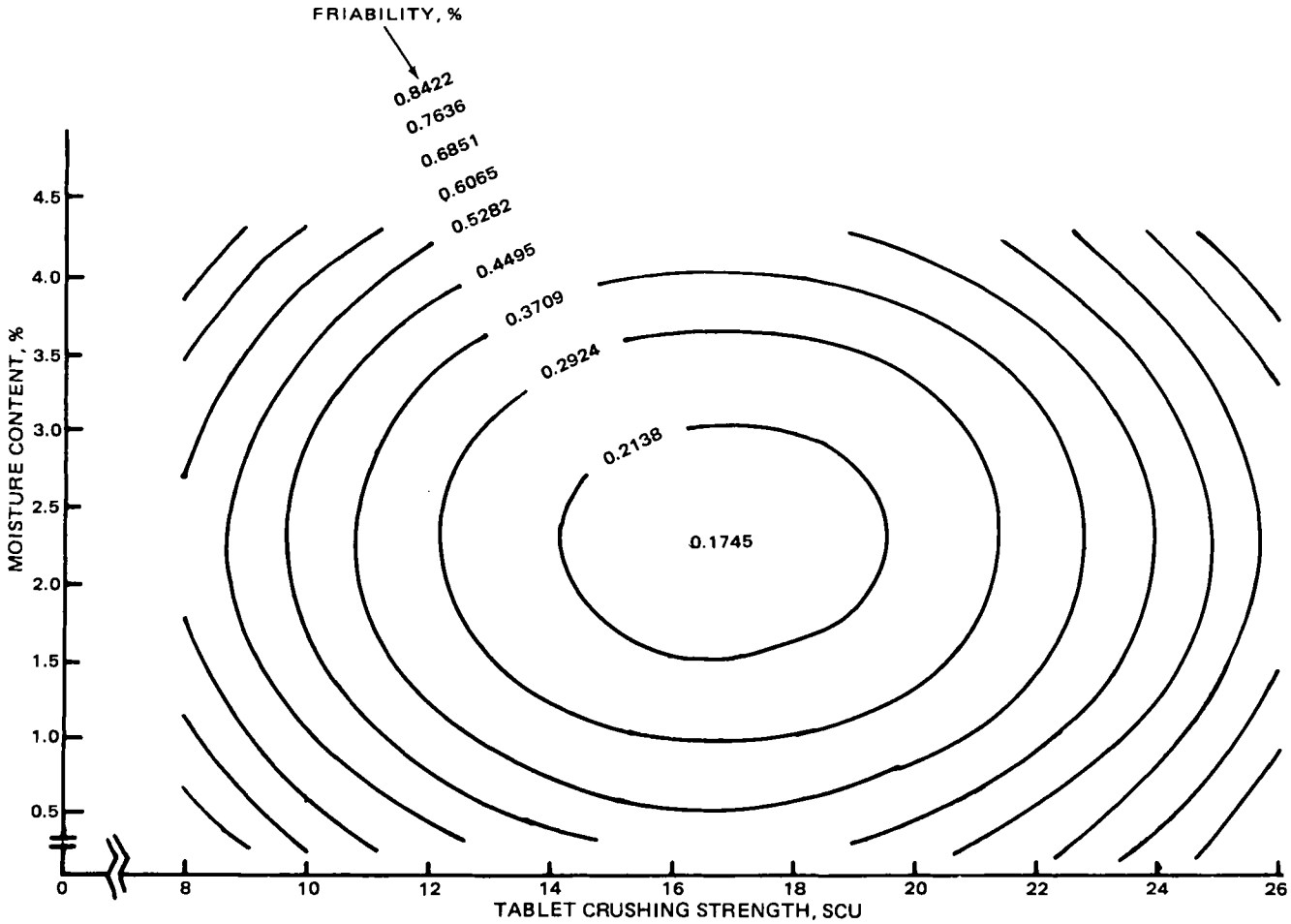

Figure 5—*Response surface contour plots of a two variable system, tablet crushing strength, and granulation moisture content and a response variable, friability.*

until the desired moisture levels were obtained. The dried granulations were screened through a 1.2-mm aperture. Starch and stearic acid were then blended with the granulations for 5 min. The granulations were stored in tightly closed jars. The moisture content of the final granulations were determined prior to compression.

Compression—Tablets were compressed with a rotary tablet machine[10] to a targeted crushing strength. The punches and dies were 10.32 mm in diameter, and the punches were standard concave in shape.

Moisture Determination—The granulation moisture was determined with a moisture balance[11] by exposure to a 125 W IR lamp for 15 min at the 90 V setting. The percent weight loss on drying was read directly from the instrument.

Tablet Crushing Strength—The initial tablet crushing strength was determined[12] immediately after compression. For each determination 10 tablets were tested and the mean calculated.

Friability Determination—At least 20 tablets were brushed with a soft camel hair brush to remove all adhering particles and placed in a friabilator[1]. After accurate weighing, the tablets were placed in the drum. The drum was rotated for 4 min or 100 revolutions. At the end of 4 min, the tablets were removed, brushed to remove adhering particles, and accurately weighed. The loss of weight was calculated. The test was run in duplicate and the mean percent friability was calculated.

***In Vitro* Dissolution**—The USP Method II was used. For each sampling point six tablets were tested. The apparatus consisted of USP paddles driven by a multiple-spindle drive with a variable speed control[13], 1-liter round-bottom plastic flasks[14], and a water bath. The dissolution medium was 700 ml of deaerated water equilibrated at 37° and stirred at 50 rpm. The dissolved drug was analyzed by recording the absorbance at 236 nm using an automated monitoring system consisting of a peristaltic pump[15], 1-mm spectrophotometer flow cells, and automatic sample changer/spectrophotometer[16]. The absorbances were plotted on a recorder every minute until complete dissolution was achieved.

The dissolution apparatus was calibrated using USP dissolution calibrator tablets (prednisone 50 mg). The mean dissolution and the standard deviations were within the required range.

RESULTS AND DISCUSSION

The effects of granulation moisture and tablet crushing strength on tablet friability are given in Fig. 1. The results suggest that the tablet friability depends on moisture content and tablet crushing strength (controllable variables). It is possible to reduce tablet friability at higher crushing strengths and at optimum moisture contents.

Figure 2 gives the results of drug dissolution at the 10-min time point *versus* tablet crushing strength at different moisture contents. At lower moisture contents (1.6 and 2.0%), the drug dissolution is strongly dependent on tablet crushing strength. The higher the tablet crushing strength, the lower the percent drug dissolved and *vice versa*. However, at higher moisture contents (3.0, 3.6, and 4.3%), the dissolution of the drug shows very little dependency on crushing strength of the tablets.

A general multiple linear regression analysis of the results was performed using a program package[17], RSREG, on a computer[18]. The RSREG procedure fits the parameters of a complete quadratic response surface and then determines critical values to optimize the response with respect to the factors in the model. A general quadratic response surface

[10] Model B-2, Stokes.
[11] Cenco, Central Scientific Co. Chicago, IL 60623.
[12] Schleuniger-2E Hardness Tester, Vector Corp., Marion, IA 52303.
[13] Model 72 R, Hanson Research Corp., Northridge, Calif.
[14] Elanco, Indianapolis, Ind.
[15] Model 1210, Harvard Apparatus, Millis, Mass.
[16] Model 25, Beckman Instruments, Fullerton, Calif.
[17] SAS Institute Inc, Cary, NC 27511.
[18] IBM 3033.

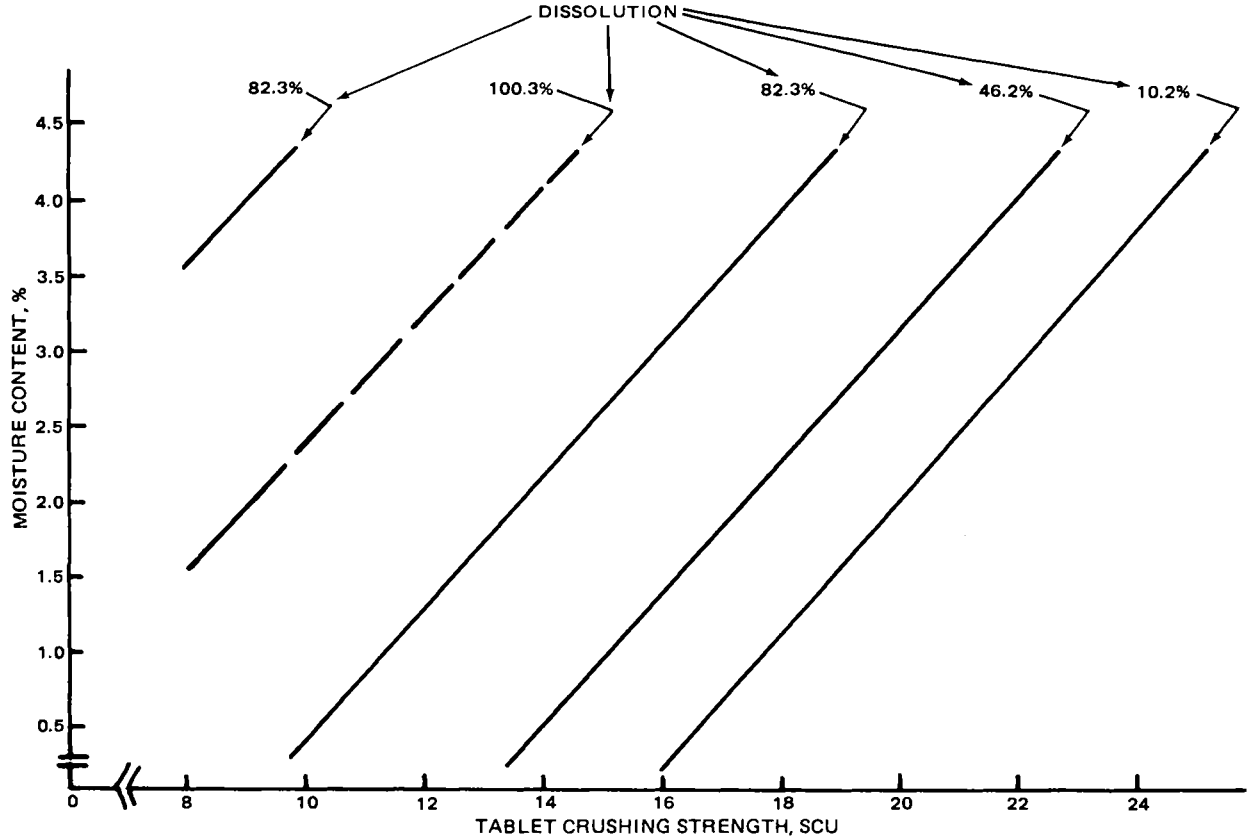

Figure 6—*Response surface contour plots of a two variable system, tablet crushing strength, and granulation moisture content and a response variable, dissolution (at 10 min).*

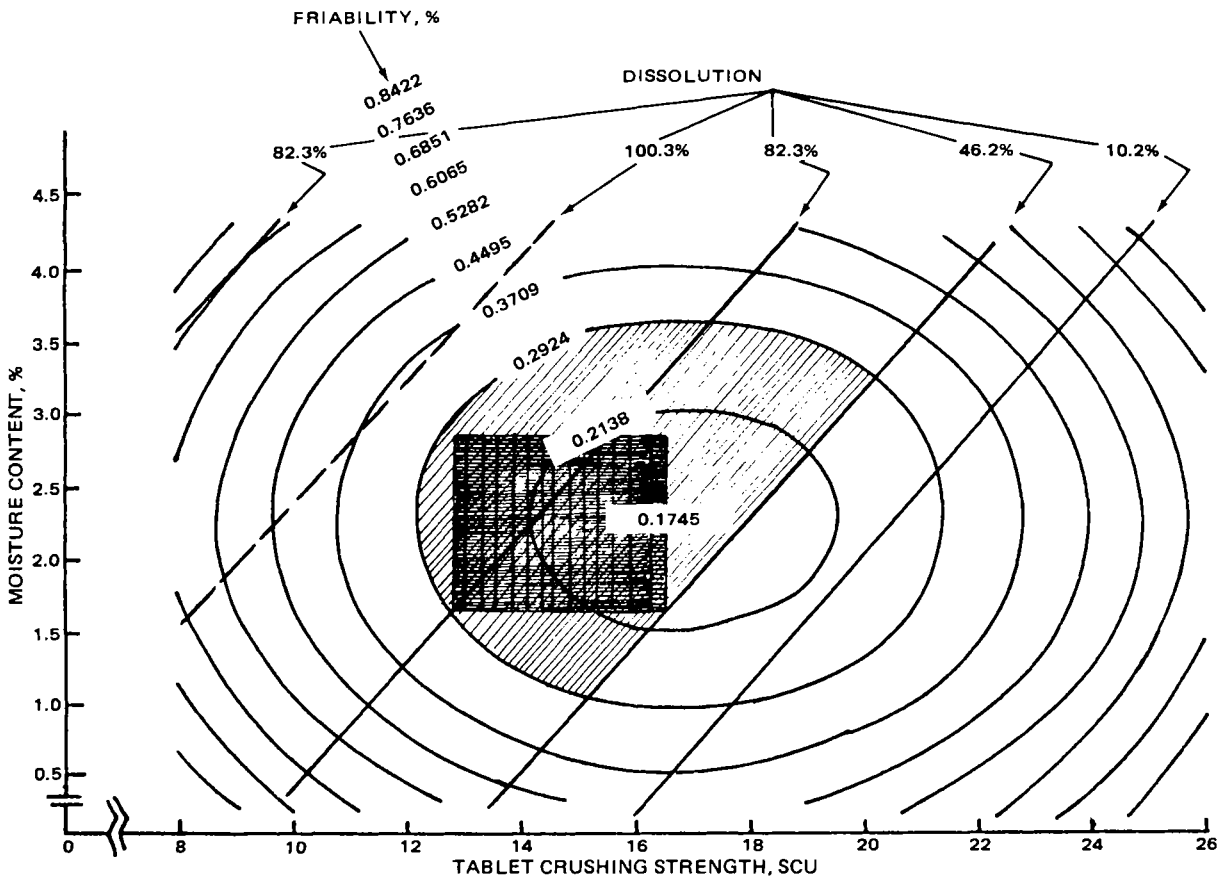

Figure 7—*Contour overlay showing the superimposed contour plots of friability and* in vitro *dissolution. The deeply shaded rectangle indicates the ranges in which in process specifications for tablet crushing strength and granulation moisture content could be set.*

model is written:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1^2 + b_4X_1X_2 + b_5X_2^2 + \text{Error} \quad \text{(Eq. 1)}$$

where Y is the response surface such as tablet friability or drug dissolution, X_1 and X_2 are controllable variables such as granulation moisture and tablet crushing strength, and the coefficients b_0, b_1, ... b_5 are the least-square regression coefficients.

The results of the regression analysis are given in Table I. The regression coefficients were substituted in Eq. 1, and by fixing the moisture content, the calculated plots of tablet friability *versus* tablet crushing strength were obtained (Fig. 3). Similarly, by fixing the tablet crushing strength, calculated plots of tablet friability *versus* moisture content were obtained (Fig. 4). These plots suggest that the moisture content in the range of ~1.5–3.0% and tablet crushing strength in the range of ~14–17 Strong Cobb units (SCU) give the least possible tablet friability. Similar conclusions could be drawn from the data given in Fig. 1.

The response surface contour plots of friability and dissolution are given in Figs. 5 and 6. The response surface contour plots illustrate the geometric relationships between the controllable variables and their responses. The predicted values of responses for a grid of the controllable variable data points can be generated. The friability contour plot consists of a series of ellipsoidal curves. The solution for optimum response indicated that the predicted value of friability at optimum was 0.17%, corresponding to a moisture content of 2.3% and a tablet crushing strength of 16.8 SCU.

In tableting, tablet crushing strengths are generally limited to between 8 and 20 SCU because of compression, friability, and dissolution limitations. From Fig. 5 one can obtain a range of crushing strengths (14.2–19.4 SCU) and a range of moisture content (1.5–3%), which gives friability in the minimum possible range of 0.17–0.21%. At a fixed tablet crushing strength of 16 SCU, friability decreases as the moisture content increases until it reaches its optimum value. Further increase in moisture content results in an increase in friability. Similarly, at a fixed moisture content of 2%, friability decreases as the crushing strength is increased until an optimum value is reached, after which time material is generally incompressible due to the tablet density approaching the calculated true density of the formulation.

The response surface contour plots of dissolution given in Fig. 6 show a stationary ridge system. The stationary ridge system has parallel straight line contours running in a direction determined by the relative effect of X_1 and X_2, which are controllable variables. The response surface contour plots using Eq. 1 can take a number of different forms depending on the coefficients b_0, b_1, ... b_5.

Within the practical limitations of tableting, there are a large number of combinations of tablet crushing strength and granulation moisture content all along the ridge which is expected to give 100% drug dissolution. At constant crushing strength, an increase or decrease in the granulation moisture content moving away from the ridge in either direction results in lower dissolution. Similarly, at constant granulation moisture content, an increase or decrease in crushing strength moving away from the ridge results in lower drug dissolution.

In this investigation, not only *in vitro* dissolution but also tablet friability were considered important and both were measured experimentally. If it was desired that the specifications for dissolution in 10 min were >46% and to maintain friability <0.3%, Figs. 5 and 6 could be superimposed. The contour overlays are shown in Fig. 7. The shaded area shows the region where both the friability and dissolution requirements are met. From the deeply shaded rectangle, specifications on granulation moisture and tablet crushing strength could be set. If these specifications were unsatisfactory from a bioavailability or production viewpoint, other factors affecting friability and dissolution such as formulation and processing factors would have to be explored. It also may be possible to reduce tablet friability by considering the punch shape factor.

In conclusion, this study shows that a general multiple linear regression analysis is helpful in understanding the role of the granulation moisture and tablet crushing strength on tablet friability and *in vitro* dissolution. By superimposing the contour plots of tablet friability and drug dissolution, it is possible to set in process specifications for the granulation moisture content and tablet crushing strength.

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Relationship of Dissolution Rate to Viscosity of Polymeric Solutions

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Abstract □ The influence of viscosity on the dissolution rate of benzoic acid in aqueous solutions of methylcellulose, hydroxypropyl cellulose, and guar gum was investigated. The viscosities were measured by capillary and rotational viscometers and were calculated from experimental diffusion coefficients by means of the Stokes-Einstein equation. The relationship of the dissolution rate to viscosity may be represented by a single curve. An equation is presented relating the dissolution rate of benzoic acid to solubility, diffusion coefficient, and viscosity for these nonionic viscosity-enhancing agents. To demonstrate that additional factors affect the dissolution rate, similar data were determined using solutions of xanthan gum, which is anionic. The electrical effect modified mass transport so the quantitative relationship of dissolution rate and viscosity was not the same as in the nonionic carbohydrate solution.

Keyphrases □ Dissolution, rate—relationship to viscosity of polymeric solutions, benzoic acid □ Viscosity—relationship of dissolution rate of polymeric solutions, benzoic acid □ Benzoic acid—relationship of dissolution rate to viscosity of polymeric solutions

Although viscosity-enhancing polymers are present in many pharmaceuticals, little research has been reported on the influence of viscosity on the dissolution rate. Diffusion-controlled dissolution would be expected to decrease in rate with an increase in viscosity (1–4). Numerous empirical equations, which show the dissolution rate to be a function of the viscosity raised to a power ranging from −0.25 to −0.8, have been proposed (5–7).

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