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OPTIMIZATION OF TABLET FRIABILITY, MAXIMUM ATTAINABLE CRUSHING STRENGTH, WEIGHT VARIATION AND *IN VITRO* DISSOLUTION BY ESTABLISHING IN-PROCESS VARIABLE CONTROLS

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ABSTRACT

The level of intragranular microcrystalline cellulose, volume of granulating water, granulation moisture content and tablet crushing strength were used as in-process variables for optimizing tablet friability, maximum attainable crushing strength, weight variation and *in vitro* dissolution. A computer optimized experimental design (COED) allowed optimal characterization of the variables by designing 22 experiments. The results were analyzed by means of a general quadratic response surface model. Response surfaces were generated for tablet friability, maximum attainable crushing strength, weight variation and *in vitro* dissolution as a function of the in-process variables. The study provided a useful method in setting optimum ranges for the in-process variables in order to optimize the important tablet parameters.

INTRODUCTION

In designing a solid dosage form, especially compressed tablets, the formulation, the process and the in-process variables should be optimized. The first step in optimization is to identify the independent (in-process) variables and dependent (response) variables. When dealing with the manufacture of tablets by means of a high shear mixing and granulating technique,

it is known that many in-process variables may affect the physical properties of the final tablet. These include the amount and rate of addition of granulating solution, mixing and granulating time, drying temperature, granulation moisture content at the time of compression and tablet crushing strength. The response variables would include tablet friability, in vitro dissolution, weight variation and tablet compressibility.

Previous investigations[1,2] from these laboratories reported the effect of granulation moisture content and tablet crushing strength on tablet friability and in vitro dissolution. A general quadratic response surface model was used to analyze the data. The response surface contour plots for tablet friability and in vitro dissolution were generated. The contour overlays of the friability and dissolution contour plots indicated a region where both friability and dissolution requirements could be satisfied by controlling the in-process variables.

As the number of in-process variables increases, the number of experiments required to fully evaluate the effect of several levels of each in-process variable increases substantially. An experimental design which uses a computer program called COED (Computer Optimized Experimental Design, Compuserve, P.O. Box 20212, Columbus, OH 43220) would give maximum information with a minimum number of experiments. This program is designed to pick an optimal subset of experiments to be run for the total number of possible experiments. This selection process is based on the determinant optimality theory, i.e., it determines the experiments which minimize the error of prediction.

In this study four in-process variables at three different levels were evaluated with respect to four response variables. The in-process variables were percent intragranular microcrystalline cellulose, granulating water volume, granulation moisture content and tablet crushing strength. The response variables were tablet friability, in vitro dissolution, maximum attainable crushing strength and tablet weight variation. The

results generated by the 22 experiments designed by COED were analyzed by means of a general quadratic response surface model. Response surfaces were generated for the four response variables as a function of the in-process variables. These response surfaces were used to optimize the values of the in-process variables in order to obtain the best possible values of the response variables.

MATERIALS AND METHODS

Materials

The drug used in this study was water soluble, non-hygroscopic and at least 99% pure. The excipients were microcrystalline cellulose NF (Avicel PH 102, FMC Corp., Philadelphia, PA 19103), corn starch NF (Hubinger, Keokuk, IA 52632), povidone USP (BASF Wyandotte Corp., Wyandotte, MN 48192), citric acid USP (Pfizer Chemicals, New York, NY 10027), purified stearic acid powder NF (Hystrene 9718, Humko Sheffield Chemical, Memphis, TN 38101) and magnesium stearate NF (Mallinckrodt Inc., St. Louis, MO 63147).

Granulation

The formulation used in this study contained 64.1% drug, 23.4% microcrystalline cellulose, 10% starch, 1% citric acid, 1% povidone, 0.25% stearic acid and 0.25% magnesium stearate. Twenty-two tablet batches were prepared from nine separate granulations. The granulations differed in percent intragranular microcrystalline cellulose (25, 50 or 75%) and the amount of granulating water (35, 36.5 or 38% by weight of the powder mixture). The drug, starch and the appropriate amount of microcrystalline cellulose were mixed in a high shear mixer (model FM-50 130D Littleford Lodige Mixer, Littleford Bros., Florence, KY 41042) for 5 minutes. Citric acid and povidone were dissolved in the appropriate amount of water and the powder blend was granulated with the binder solution using an addition time of

5 minutes. After an additional one minute of mixing, the granulations were passed through a 7 mm aperture screen and dried at 50°C in a fluid bed drier (Flo-coater, Vector Corp., Marion, IA 52303) to a granulation moisture content of approximately 4%. The dried granulations were passed through a mill (Tornado Mill, Penwalt-Stokes, Warminster, PA 18974) equipped with a perforated plate containing 1.59 mm aperture openings at slow speed. Stearic acid was passed through a 0.4 mm aperture screen and mixed with magnesium stearate and the remaining microcrystalline cellulose in a planetary mixer (Hobart Model C-100) for 3 minutes. For each batch, the lubricant premix and the dried granules were mixed for 3 minutes in a blender (16 quart PK mixer, Patterson-Kelly Co., East Stroudsburg, PA 18301), subdivided into smaller batches and dried to 2.5, 3.0 or 3.5% granulation moisture content.

Compression

The tablets were compressed on a high speed rotary tablet machine (Manesty Betapress 16, Thomas Engineering, Hoffman Estates, IL 60195) to targeted crushing strengths of 5, 7 and 9 kiloponds (Kp) and maximum attainable tablet crushing strength. The punches and dies were 10.32 mm in diameter and the punches were deep concave in punch tip geometry. The tablets were compressed to a total weight of 390 mg per tablet.

Moisture Determination

The granulation moisture content was determined with a moisture analyzer (Compu-Trac Model MA-5A, Compu-Trac Inc., Tempe, AZ 85281) by exposure to a 700 watt nichrome wire. The percent weight loss was read off an LED display.

Tablet Crushing Strength

The tablet crushing strength was determined immediately after compression (Pharma Model HT 300 Hardness Tester, Key International Inc., Englishtown, NJ 07726). A minimum of 10

tablets were tested for each determination and the mean crushing strength was calculated.

Tablet Friability

For each determination 25 tablets were dedusted with a soft brush to remove all adhering particles and accurately weighed. The tablets were placed in a friabilator (Roche Type A), rotated for 4 minutes or 100 revolutions, dedusted to remove adhering particles and weighed. The difference in tablet weight was adjusted for any moisture loss during the test. Two determinations were completed for each batch and the mean percent friability was calculated.

In Vitro Dissolution

USP Method II was used and at least 6 tablets were tested for each batch. The apparatus consisted of USP paddles driven by a multiple spindle drive with a variable speed control (Model 72R, Hanson Research Corp., Northridge, CA 91324), 1 liter round bottom plastic kettles (Elanco, Indianapolis, IN 46285) and a water bath. The dissolution medium was 900 mL of deaerated 0.01 M hydrochloric acid equilibrated at 37°C and stirred at 50 rpm. The absorbance of the dissolved drug was determined at 236 nm using an automated monitoring system consisting of a peristaltic pump (Model 502 Watson-Marlow, Falmouth, England), 1 mm spectrophotometer flow cells and an automatic sample changer/spectrophotometer (Model 25, Beckman Instruments, Fullerton, CA 92634). The absorbances were plotted on a recorder until complete dissolution was achieved. The mean percent dissolved was calculated at the 15 minute sampling point.

Weight Variation

Tablets were sampled periodically from each batch during the compression run. Twenty tablets were weighed individually on an analytical balance and the mean, standard deviation and coefficient of variation (CV) was determined for each batch.

RESULTS AND DISCUSSION

Previous experience with the formulation was the basis for selecting three levels of each of the four in-process variables which may affect the granulations prepared in a high shear mixer. Table 1 gives the experimental design generated by COED. The data from the 22 experiments were plotted in Figs. 1-8.

The effect of the percent intragranular microcrystalline cellulose on maximum attainable tablet crushing strength at different granulating water levels is given in Fig. 1. In Fig. 2, plots of maximum tablet crushing strength versus percent granulating water for formulations containing 25, 50 and 75% intragranular microcrystalline cellulose are given. These data demonstrate a clear relationship between intragranular microcrystalline cellulose and maximum attainable tablet crushing strength. Higher amounts of intragranular microcrystalline cellulose reduced the tablet compressibility compared to the lower amounts. The compressibility of microcrystalline cellulose is at least partly attributed to the microporous structure. During the wet granulation process, the porosity of microcrystalline cellulose is reduced by the crystallization of drug solution inside the pores.

The effect of the granulation moisture content on maximum attainable tablet crushing strength was clearly demonstrated when a higher percent (38%) of granulating water was used in the granulation process. With these granulations, a higher maximum tablet crushing strength was obtained with 3.5% granulation moisture. The granulating water level alone between 35% and 38% did not appear to have a consistent effect on compressibility.

The results of tablet friability versus tablet crushing strength for granulations made with 25%, 50% or 75% intragranular microcrystalline cellulose, granulated with 35% or 38% water and dried to 2.5% to 3.5% granulation moisture contents are given in Figs. 3-4. The results suggest that the tablet friability decreased as the intragranular microcrystalline cellulose level increased and the tablet crushing strength increased. The tablets

TABLE I

Computer Optimized Experimental Design
Level for Each In-Process Variable

Experiment #	Granulating Water Volume (% of Powder Mixture w/w)	Intragranular Microcrystalline Cellulose Level (%)	Granulation Moisture Content (%)	Tablet Crushing Strength (Kp)
1	36.5	50	2.5	5
2	38	25	2.5	9
3	35	25	3.5	9
4	35	75	3.5	5
5	38	75	2.5	5
6	35	25	2.5	9
7	35	25	2.5	5
8	38	25	2.5	5
9	38	25	3.5	5
10	38	75	3.5	9
11	35	25	3.5	5
12	38	75	3.5	5
13	35	75	2.5	5
14	38	75	2.5	9
15	35	50	2.5	7
16	35	75	2.5	9
17	38	50	3.0	9
18	36.5	75	3.0	7
19	38	25	3.5	9
20	35	75	3.5	9
21	36.5	25	3.5	7
22	35	25	3.0	7

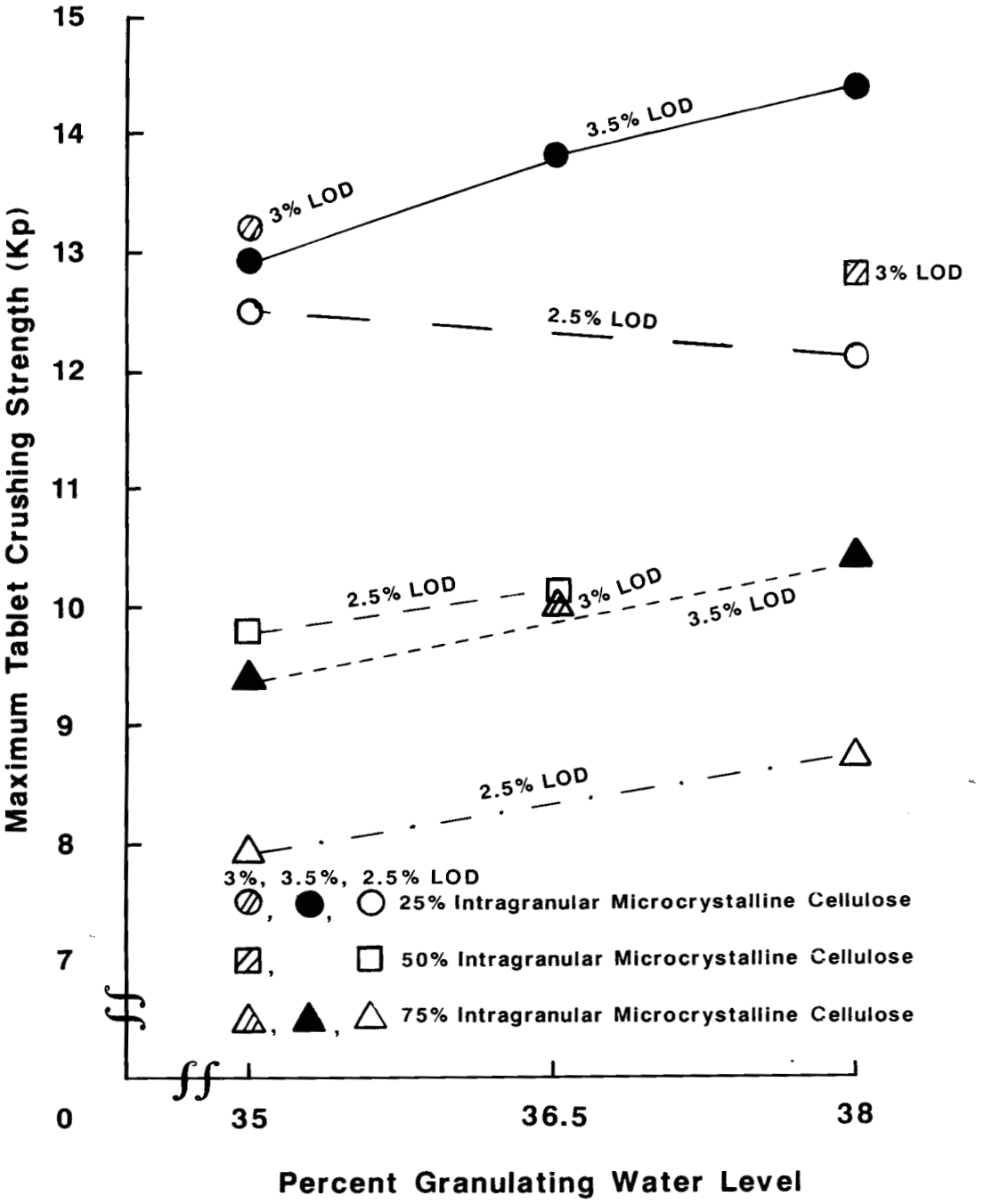

FIGURE 1

Plots of maximum tablet crushing strength versus percent granulating water.

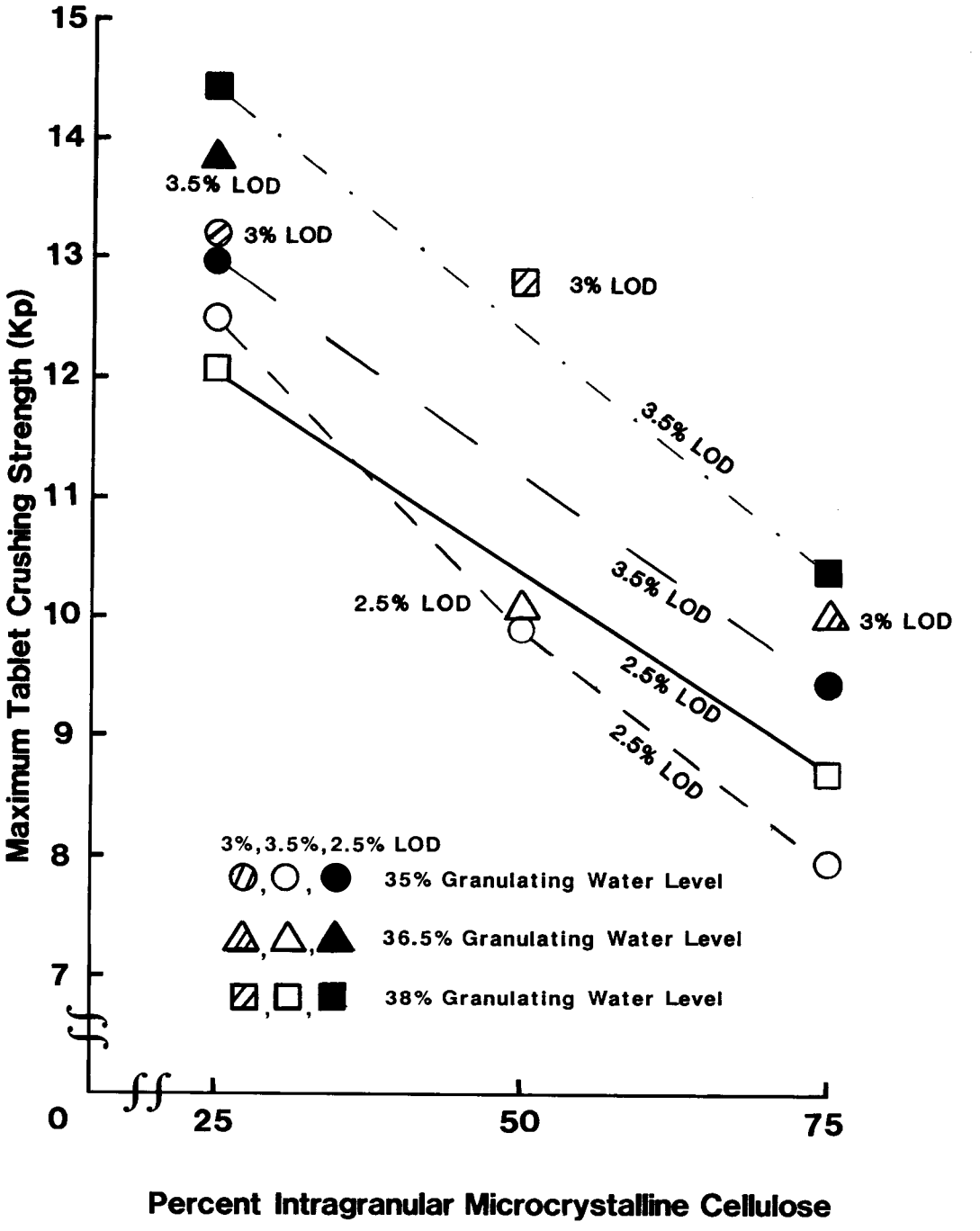

FIGURE 2

Plots of maximum tablet crushing strength versus percent intragranular microcrystalline cellulose.

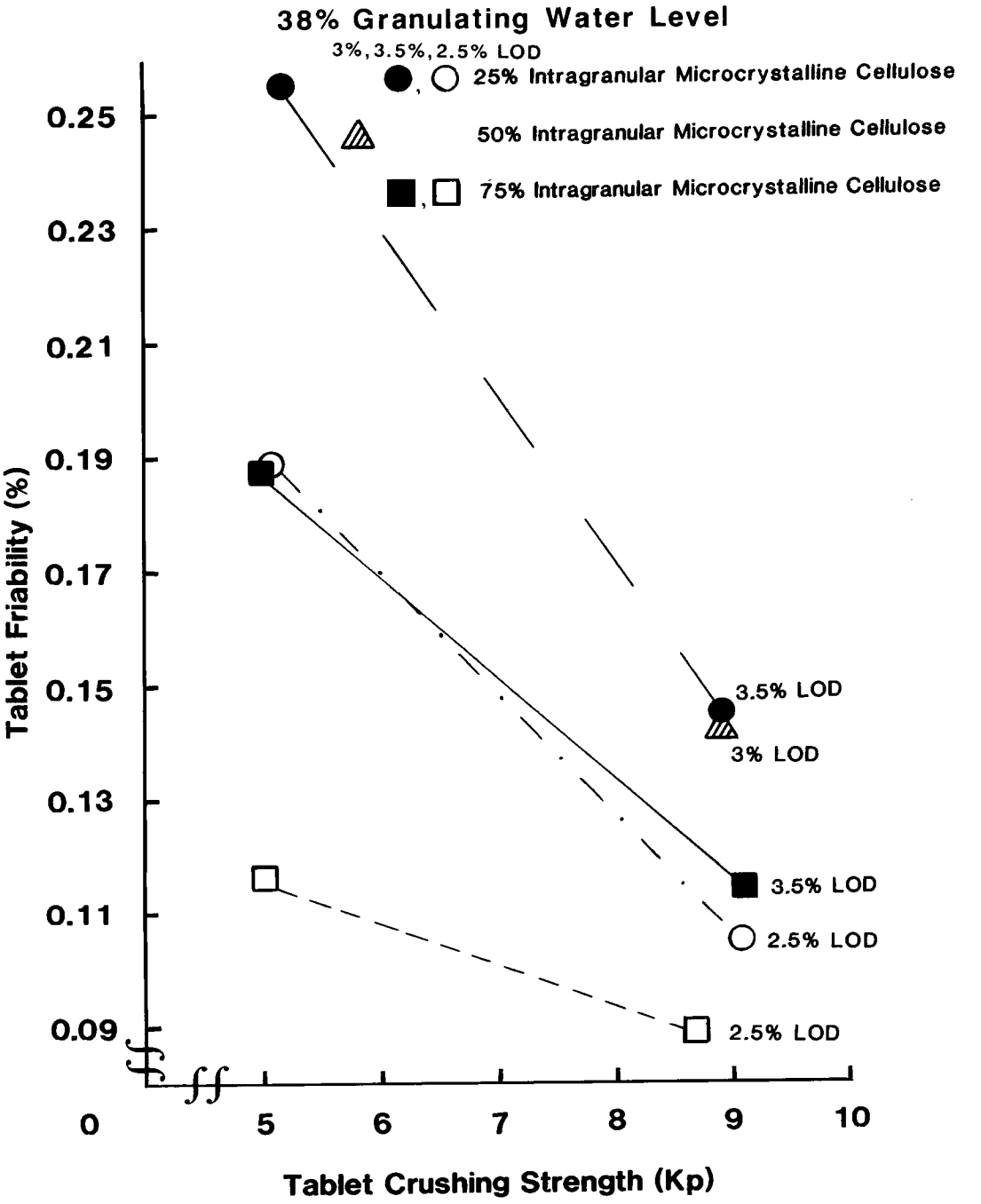

FIGURE 3

Plots of % tablet friability versus tablet crushing strength. The wet granulation process used 38% water.

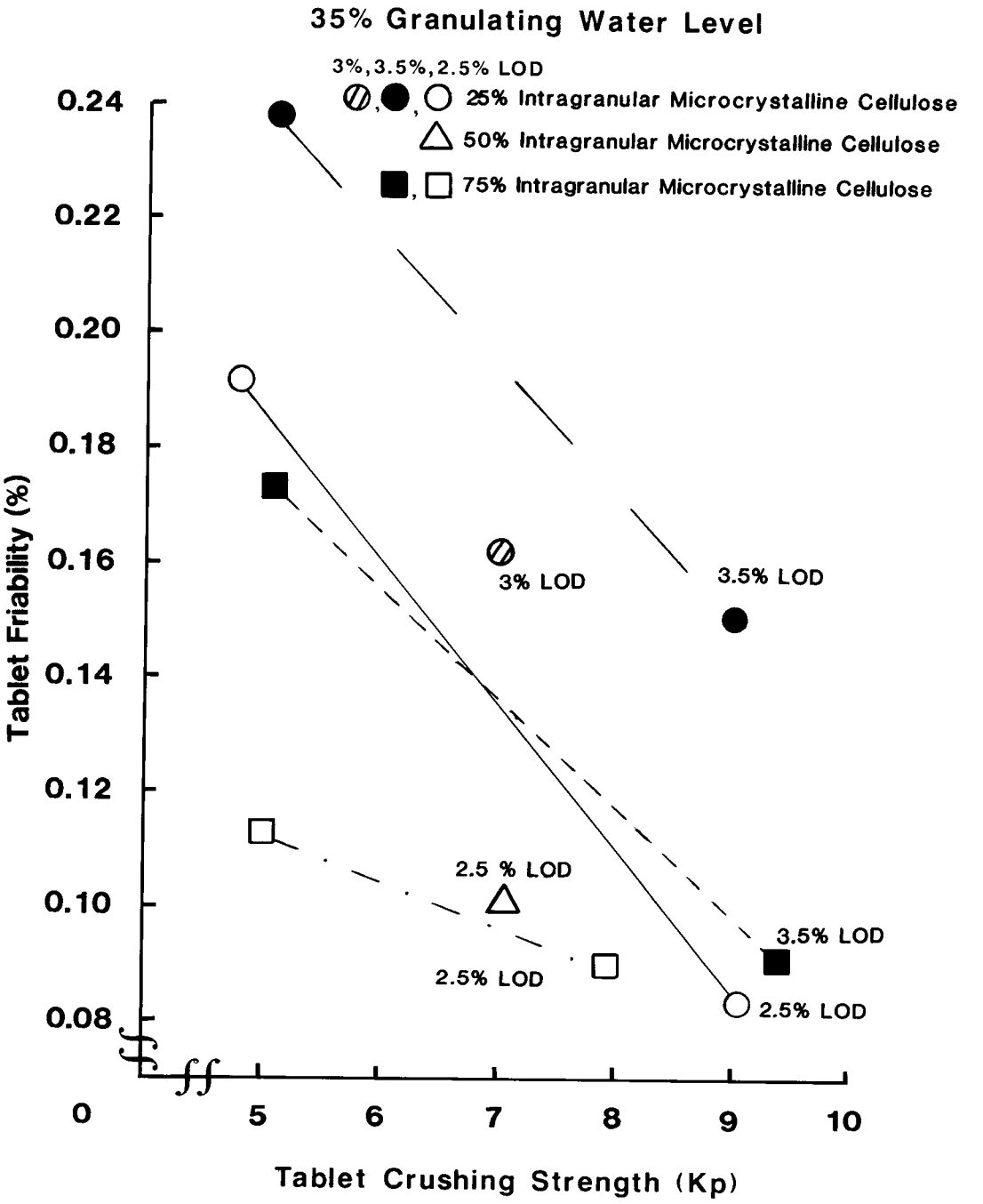

FIGURE 4

Plots of % tablet friability versus tablet crushing strength. The wet granulation process used 35% water.

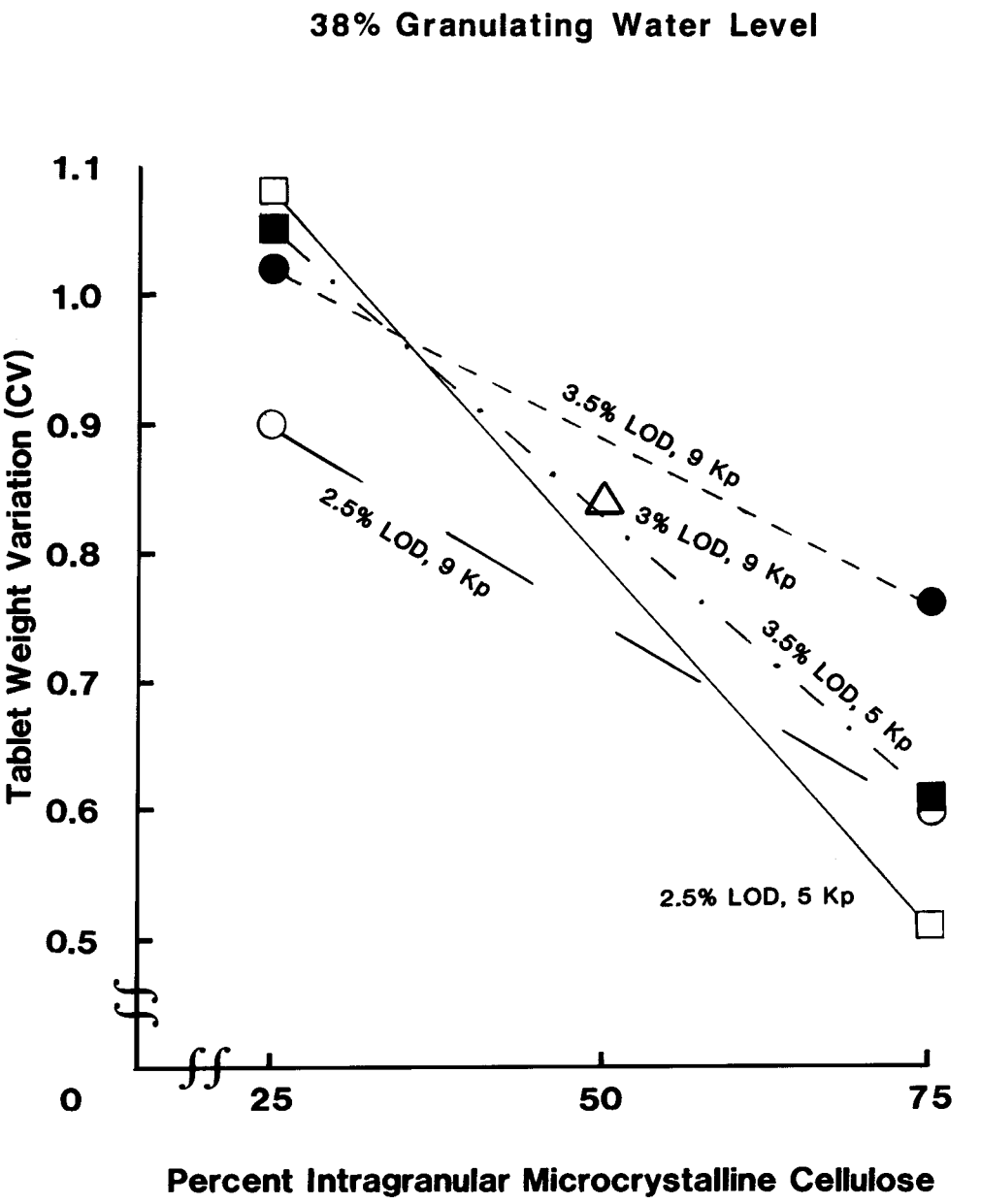

FIGURE 5

Plots of tablet weight variation versus percent intragranular microcrystalline cellulose granulated with 38% water.

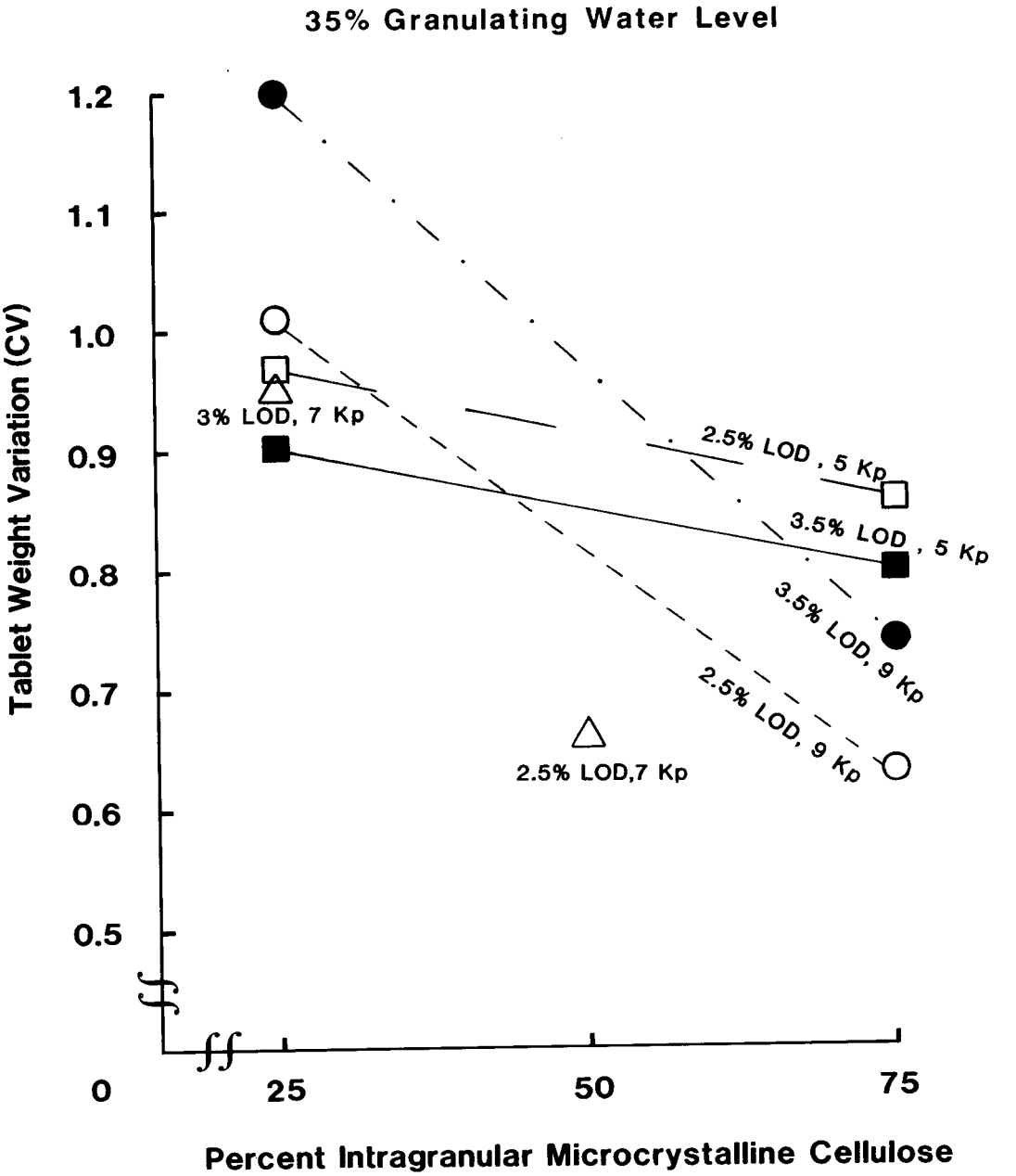

FIGURE 6

Plots of tablet weight variation versus percent intragranular microcrystalline cellulose granulated with 35% water.

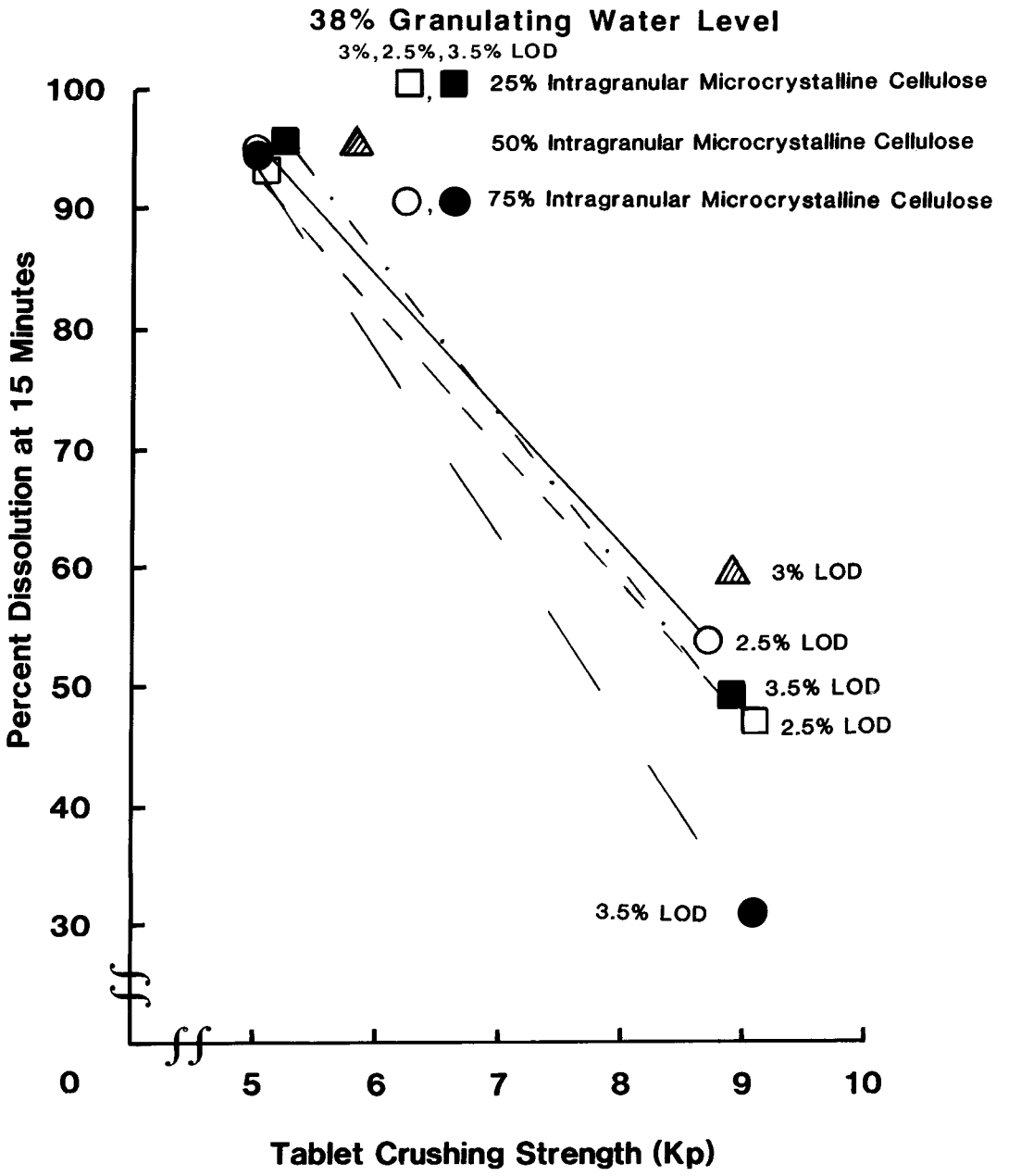

FIGURE 7

Plots of in vitro dissolution versus tablet crushing strength. The granulation process used 38% water.

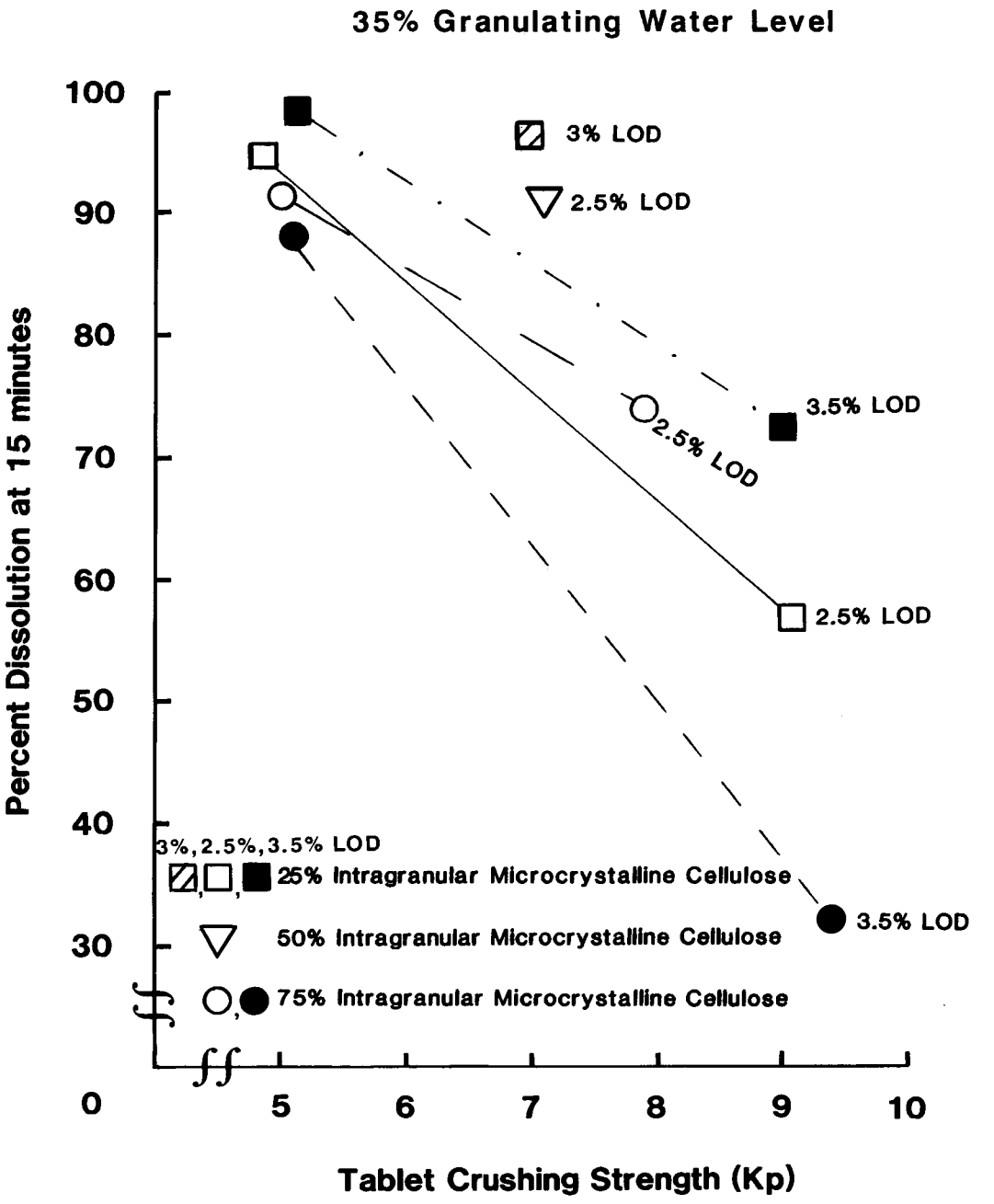

FIGURE 8

Plots of in vitro dissolution versus tablet crushing strength. The granulation process used 35% water.

also appear to be less friable when the granulations were dried to 2.5% compared to 3.5% moisture content.

The effect of the percent intragranular microcrystalline cellulose on tablet weight variation is shown in Figs. 5-6. It appears that a 25% intragranular microcrystalline cellulose level resulted in higher tablet weight variation compared to 75% intragranular microcrystalline cellulose. Other effects were not clearly demonstrated.

Figs. 7-8 give the results of *in vitro* dissolution as a function of changes in the in-process variables. The results suggest a decrease in the *in vitro* dissolution resulting from an increase in the tablet crushing strength. The effect of other in-process variables was not clear from these data.

Four in-process variables at three different levels for four response variables were investigated by experiments designed by COED. The results (Figs. 1-8) indicated that the effect of only a few in-process variables on some response variables could be clearly demonstrated from the experimental data. The effect of all 4 in-process variables on each response variable could not be clearly seen. This may be due to the limited number of experimental data points obtained from COED.

Several methods have been used for analyzing a multi-variable system[1-10]. In this study a general multiple linear regression analysis was used to analyze the data obtained from the 22 COED experiments. A computer program package, GLM (SAS Institute Inc., Cary, NC 27511), was used. The 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 model is written:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_5X_1X_2 + b_6X_1X_3 + b_7X_1X_4 + b_8X_2X_3 + b_9X_2X_4 + b_{10}X_3X_4 + b_{11}X_1^2 + b_{12}X_2^2 + b_{13}X_3^2 + b_{14}X_4^2 + \text{Error}$$

Where Y is the response surface such as tablet friability, in vitro dissolution, maximum attainable tablet crushing strength or tablet weight variation, and X_1, X_2, X_3 and X_4 are in-process variables, such as percent intragranular microcrystalline cellulose, percent granulation moisture content, percent granulating water and tablet crushing strength, and the coefficients b_0, b_1 . . . b_{14} are the least square regression coefficients.

The results of the regression analysis are given in Table 2. The multiple regression coefficients for friability, dissolution and maximum tablet crushing strength were excellent (0.979-0.992). The multiple correlation coefficient for weight variation was 0.857, which is related to the large differences in the flow properties of the granulations during the compression process.

Contour plots for each of the response variables were generated using all 14 terms of the general quadratic response surface model. The terms indicate the effects of the in-process variables on the response surface. Although several terms do not contribute significantly at the 95% confidence level to the model, these terms, as a group, do affect the shape of the contour plots. Comparisons of experimental data points with contour plots generated with only significant terms or with all terms in the equation indicated improved correlation of the data using the full 14 term models. Thus, the full-term-model contour plots are a more reliable predictive tool for setting in-process controls. Furthermore, model consistency is achieved by using the same 14 term equation for each response variable and which allows for overlay of contour plots if desired.

Various contour plots of the response variables are shown in Figs. 9-14. Fig. 9 gives the contour plots of maximum tablet crushing strength. The plots indicate that 25% intragranular microcrystalline cellulose compared to 50% or 75% and a granulation moisture content around 3.2% give higher maximum tablet crushing strengths.

TABLE 2

Multiple Linear Regression Analysis

Coefficients		Dissolution Y1	Friability Y2	Maximum Tablet Crushing Strength Y3	Weight Variation Y4
b_0		364.205300	1.560310	-83.413244	-37.711580
b_1	X_1	-0.563979	-0.000144	-0.112075	0.006894
b_2	X_2	-38.166546	-0.096814	4.635674	2.117909
b_3	X_3	153.031902	0.357667	9.264923	0.505985
b_4	X_4	81.769594	-0.061228	-1.341825	-0.195957
b_5	X_1X_2	0.057182	-0.000020	-0.000734	0.001012
b_6	X_1X_3	-0.188386	-0.000303	-0.001805	0.000160
b_7	X_1X_4	-0.050756	0.000236	0.000755	-0.000261
b_8	X_2X_3	0.756554	0.002074	0.508452	0.023000
b_9	X_2X_4	-1.059577	0.000376	-0.000399	0.000646
b_{10}	X_3X_4	-0.675335	-0.007512	-0.073716	0.031420
b_{11}	X_1^2	0.007596	-0.000008	0.000067	0.000248
b_{12}	X_2^2	0.592717	0.001260	-0.081886	-0.029600
b_{13}	X_3^2	-18.706614	-0.052619	-4.284553	-0.248953
b_{14}	X_4^2	-3.524467	0.002800	0.111172	0.006997
Multiple Correlation Coefficient	R^2	0.986581	0.978672	0.991820	0.857291

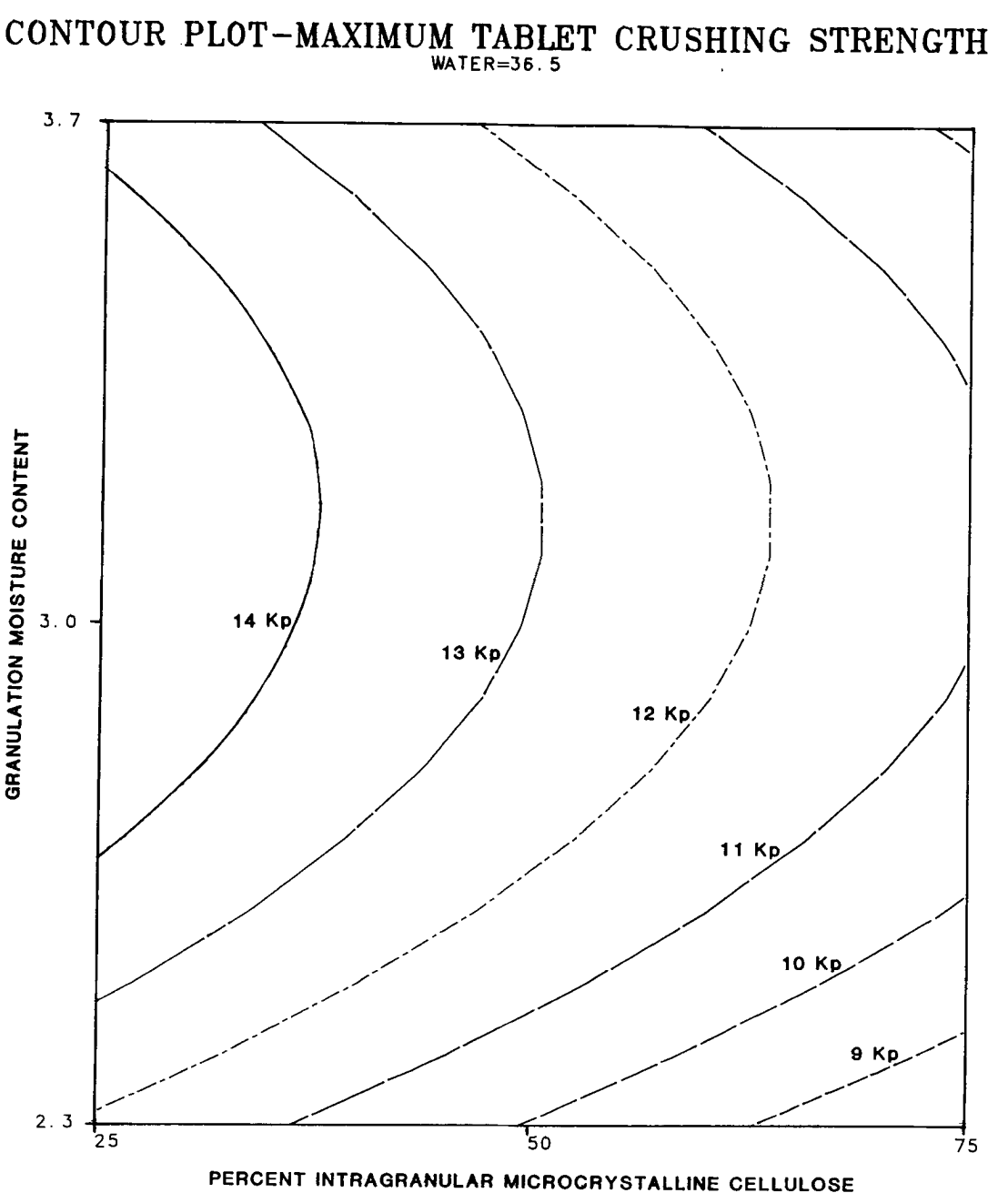

FIGURE 9

Contour plots of maximum tablet crushing strength. The granulation process used 36.5% water.

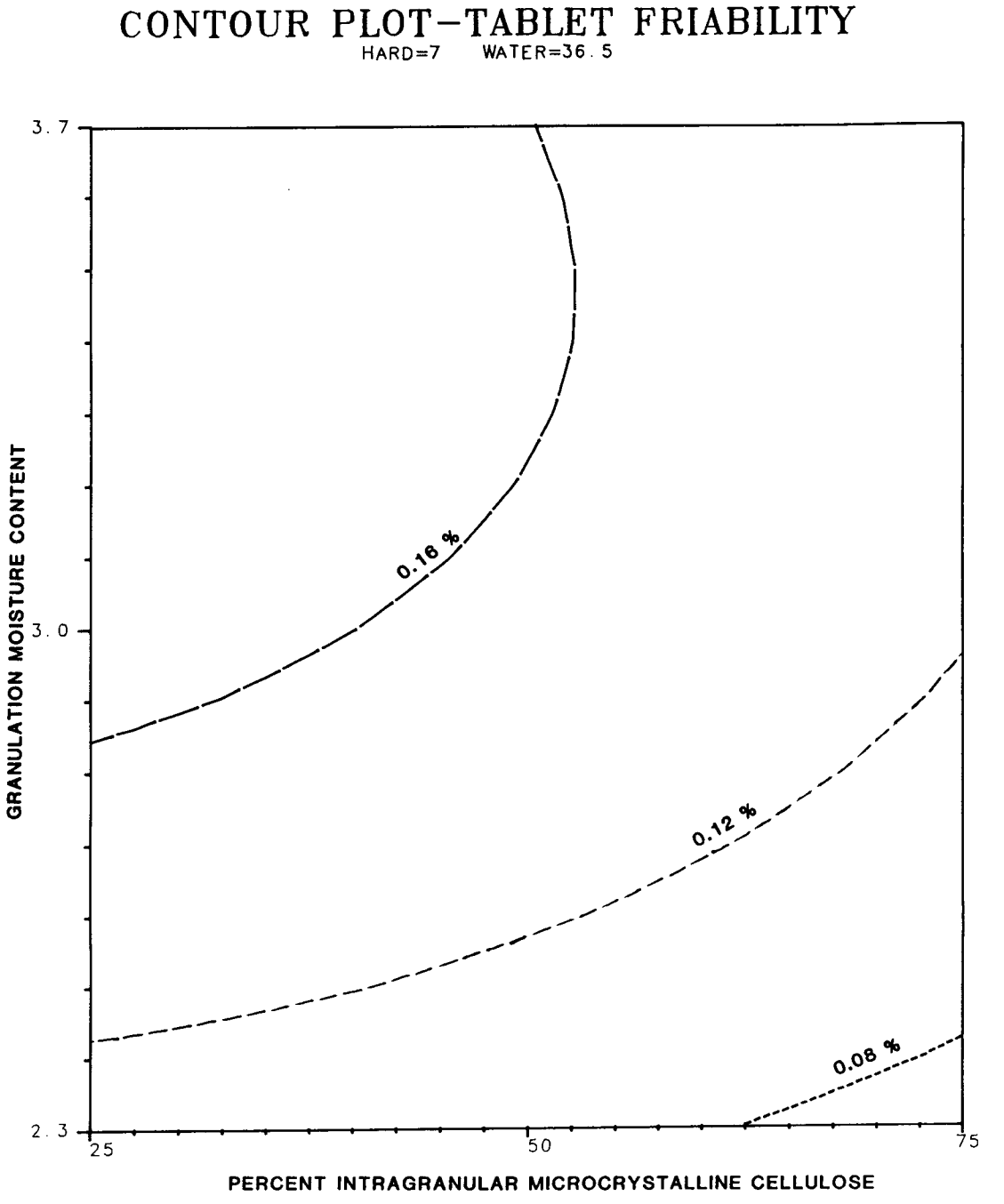

FIGURE 10

Contour plots of tablet friability for a tablet crushing strength of 7 Kp. The granulation process used 36.5% water.

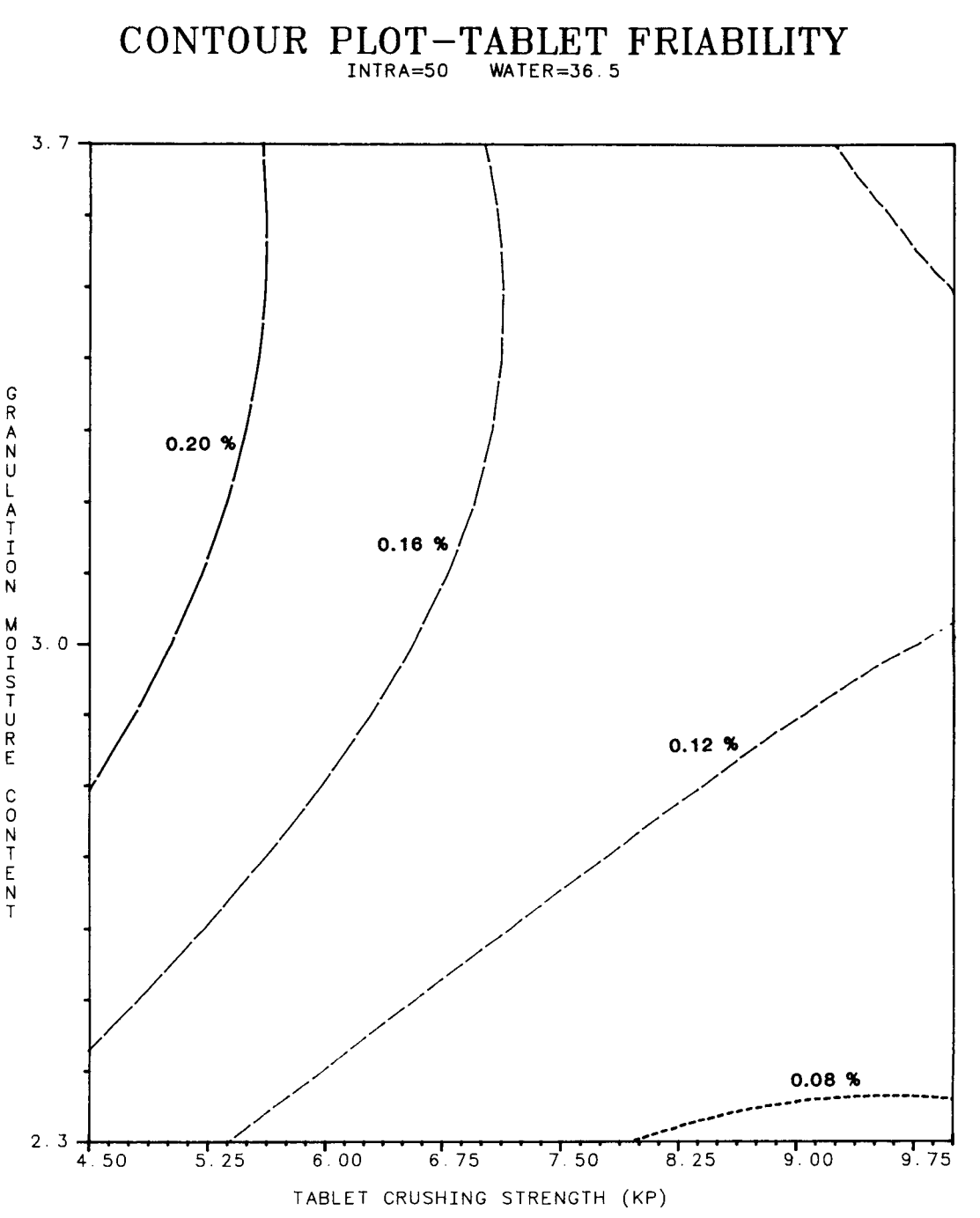

FIGURE 11

Contour plots of tablet friability. The intragranular microcrystalline cellulose level was 50% and 36.5% water was used in the granulation process.

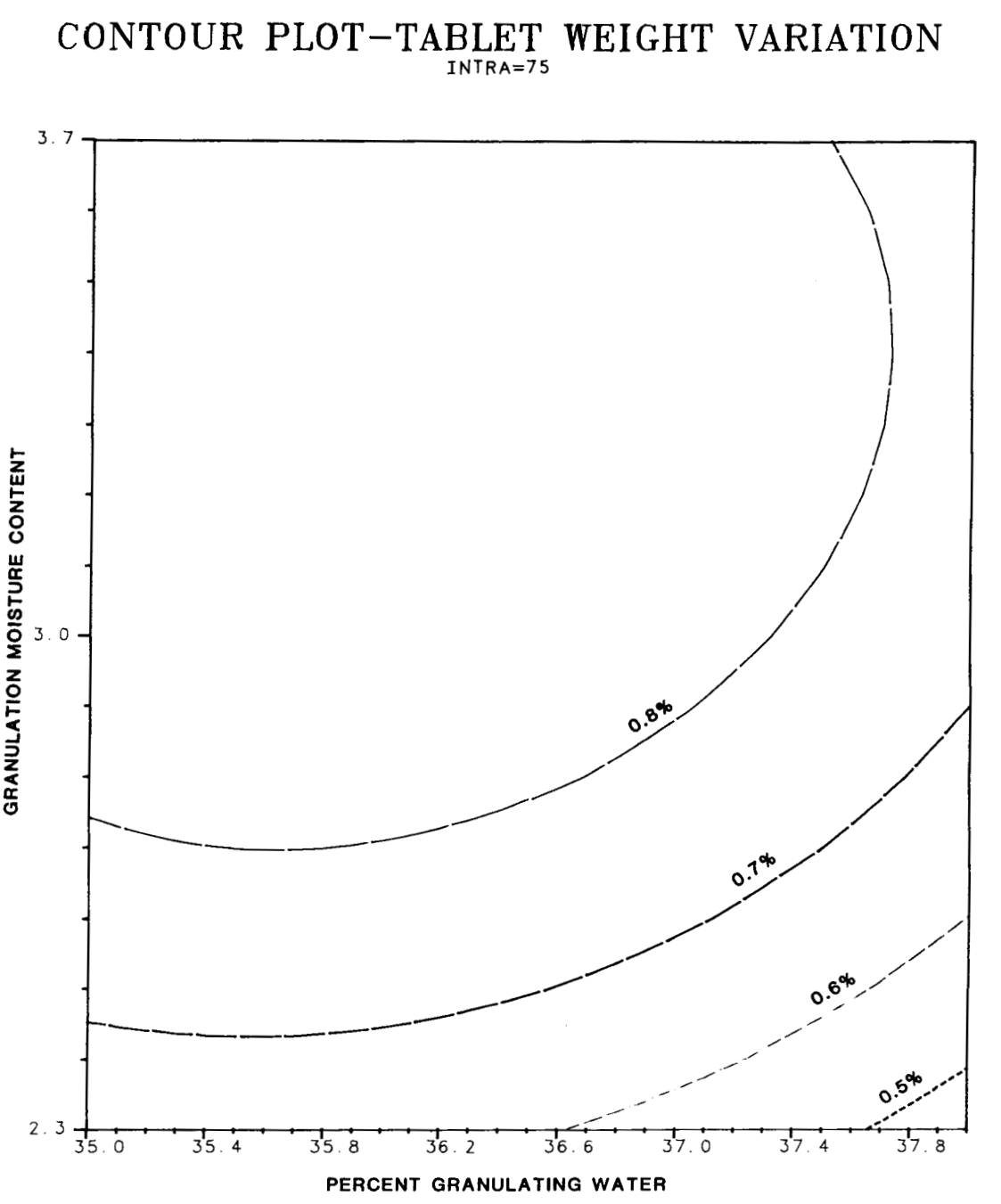

FIGURE 12

Contour plots of tablet weight variation. The granulation process used 75% intragranular microcrystalline cellulose.

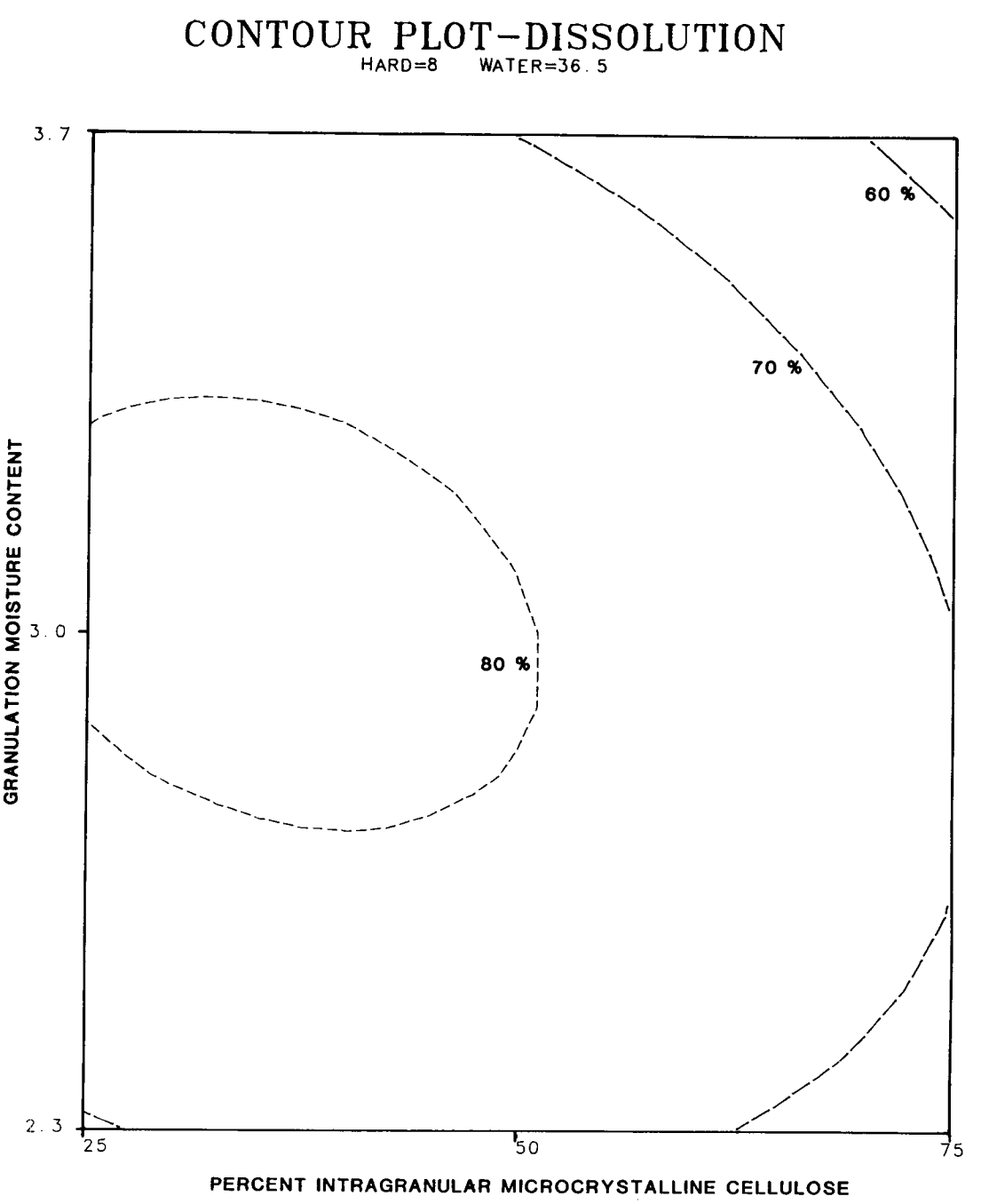

FIGURE 13

Contour plots of in vitro dissolution. The tablet crushing strength was 8 Kp and the wet granulation process used 36.5% water.

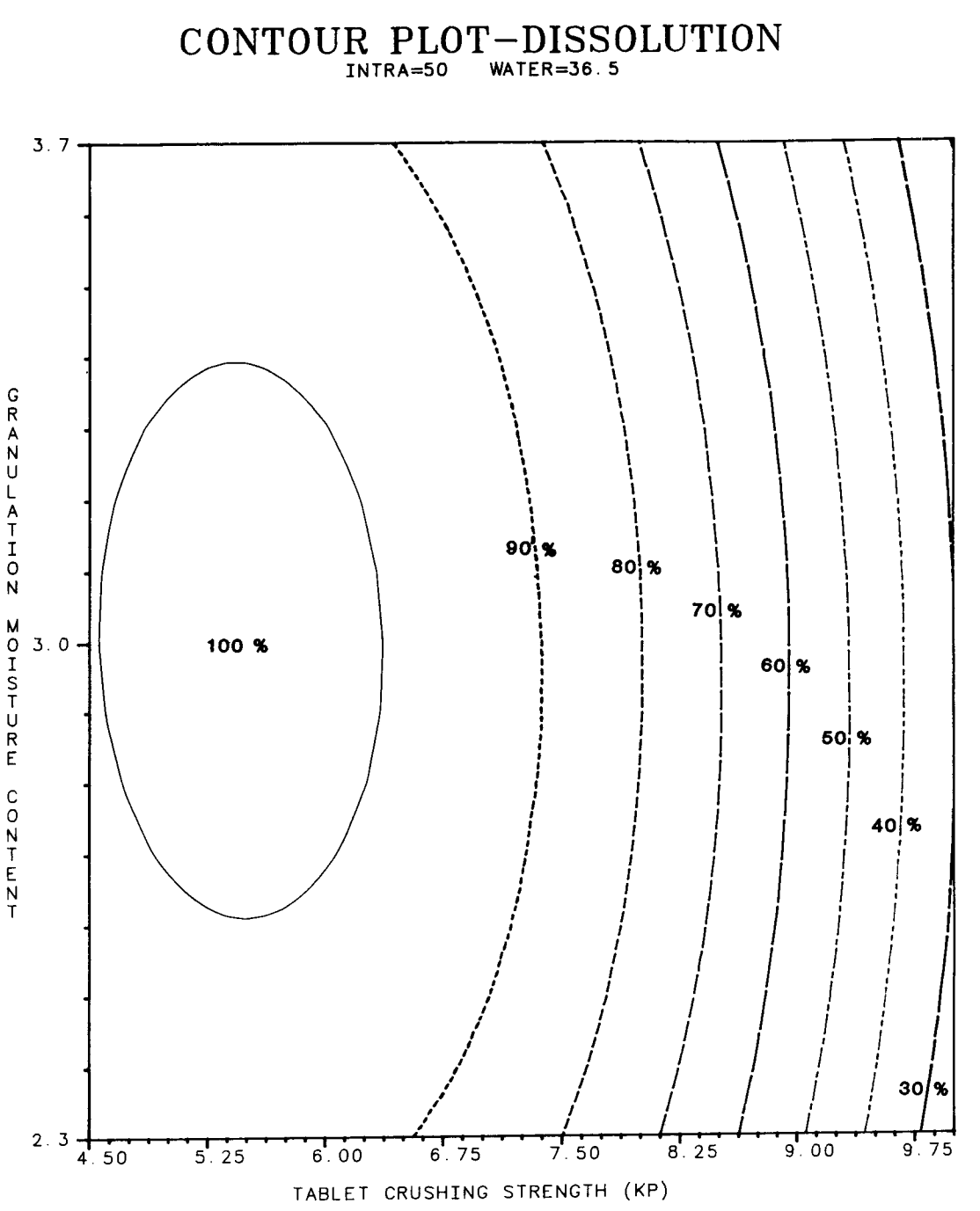

FIGURE 14

Contour plots of *in vitro* dissolution. The percentage of intragranular microcrystalline cellulose was 50% and the granulation process used 36.5% water.

Figs. 10-11 give the contour plots of tablet friability. These plots indicate that as the granulation moisture content increased, the tablet friability increased and the friability values were higher with formulations containing 25% intragranular microcrystalline cellulose. Fig. 10 indicates that the tablet friability decreased as the percent intragranular microcrystalline cellulose increased. The tablet friability decreased (Fig. 11) as the tablet crushing strength increased. Virtually no effect of the granulating water level on tablet friability was observed.

The weight variation data and resultant contour plots were affected by in-process adjustments during the compression process for some of the batches. Poor flow properties were obtained from granulations prepared with 25% intragranular microcrystalline cellulose. As a result of excessive fines generated during the milling process, additional vibration at the hopper was required during compression for those batches. However, the contour plots did show the effects of the in-process variables on weight variation. As shown in Fig. 12, lower weight variation was obtained at lower granulation moisture contents and higher granulating water levels.

Figs. 13-14 give the contour plots for *in vitro* dissolution. These plots indicate that 25% intragranular microcrystalline cellulose, a granulation moisture content of around 3% and tablet crushing strength of approximately 5 Kp resulted in the fastest *in vitro* dissolution.

The optimum values obtained from the contour plots for the in-process variables in order to obtain the best values for each of the four response variables are given in Table 3. The percent intragranular microcrystalline cellulose required to optimize tablet friability and weight variation was 75%. However, the optimal level of microcrystalline cellulose for *in vitro* dissolution and maximum tablet crushing strength was 25%. Since all four response variables are important, the best value for intragranular microcrystalline cellulose is between 25% and 75%.

The optimum values of granulation moisture content to optimize the different response variables are 3.2, 3.0, 2.5 or lower.

TABLE 3

Optimum Values of In-process Variables to Obtain The Best Possible Response Variables.

IN-PROCESS VARIABLES \ RESPONSE VARIABLES	FRIABILITY	IN VITRO DISSOLUTION	MAXIMUM CRUSHING STRENGTH	WEIGHT VARIATION
INTRAGRANULAR MICROCRYSTALLINE CELLULOSE, %	75	25	25	50 or 75
GRANULATION MOISTURE CONTENT, %	2.5 or LOWER	3.0	3.2	2.5 or LOWER
GRANULATING WATER, %	NO EFFECT	35	38	38
TABLET CRUSHING STRENGTH, Kp	9	5	NOT APPLICABLE	NO EFFECT

Since a range of the granulation moisture is generally desirable, the granulation moisture content should be controlled within 2.5-3.2%.

The percent granulating water had virtually no effect on friability. For in vitro dissolution, 35% granulation water resulted in faster dissolution than 38%. Tablet weight variation and maximum tablet crushing strength were improved with granulations made with 38% granulating water. These results suggest that for this size and type of granulating equipment, a granulating water level of 36.5% of the powder mixture (w/w) will be optimum.

The optimized tablet crushing strength for tablet friability was 9 Kp or above and for in vitro dissolution was around 5 Kp. Since a minimum tablet crushing strength is required to minimize abrasion during film coating, packaging and shipping, a range of 5-8 Kp may satisfy the required needs.

CONCLUSION

The results of twenty-two experiments designed by COED were analyzed by means of a quadratic response surface model. The multiple regression coefficients for all four response variables were excellent. Based on this analysis, it was possible to set in-process variable specifications which would consider all response variables simultaneously.

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