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THE QUANTITATIVE EVALUATION OF A GRANULATION MILLING PROCESS II. EFFECT OF OUPUT SCREEN SIZE, MILL SPEED AND IMPELLER SHAPE

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ABSTRACT

The processing variables associated with the comminution of pharmaceutical granulations were investigated. The three variables chosen were mill speed, output screen size and impeller shape. Experiments were performed on an aspirin granulation using proper techniques of experimental design. Analysis showed that the three mill variables cannot be considered independently but rather at the level of combinations. A complete characterization of the mill output according to particle size distribution is then possible based upon these combinations of mill variables.

INTRODUCTION

The comminution of granulations is an essential unit operation in the manufacture of pharmaceutical tablets.[1] However,

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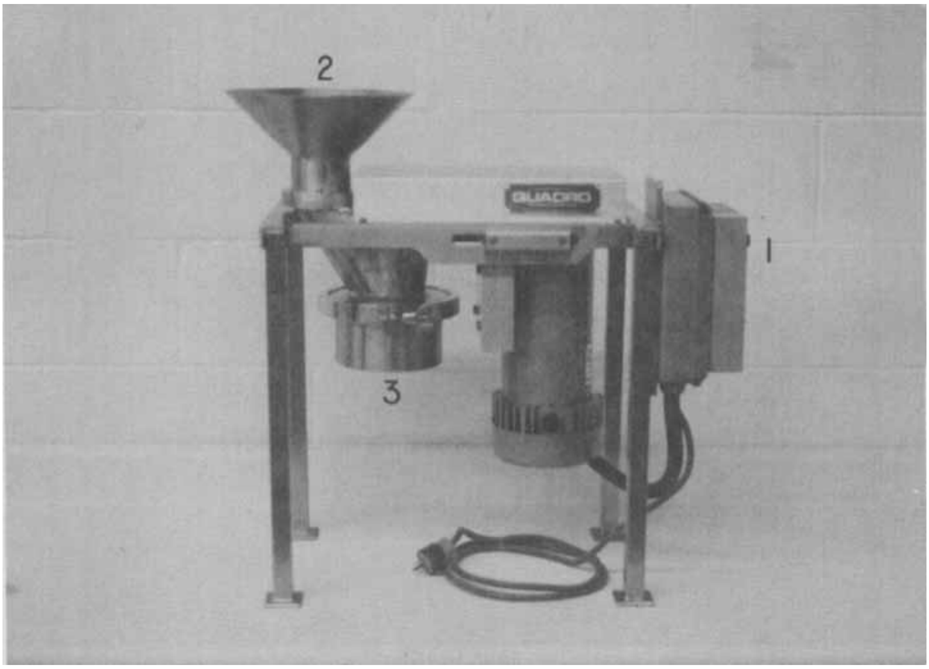

Figure 1. The Quadro Comil®: (1) variable speed control, (2) feed chute, (3) milling chamber.

in the pharmaceutical literature, little information is available which deals with the mechanisms or factors associated with the comminution operation.[2] The present study is an investigation into the processing variables associated with the comminution of pharmaceutical granulations. Three variables, mill speed, output screen size and impeller shape are investigated using the Quadro Comil®.[1]

MATERIALS AND METHODS

The comminution equipment used in this study was a laboratory model Comil® (Fig. 1). The mill, equipped with a variable speed

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1. Comil, Model 197-1-525, Quadro Engineering, Waterloo, Ontario, Canada.

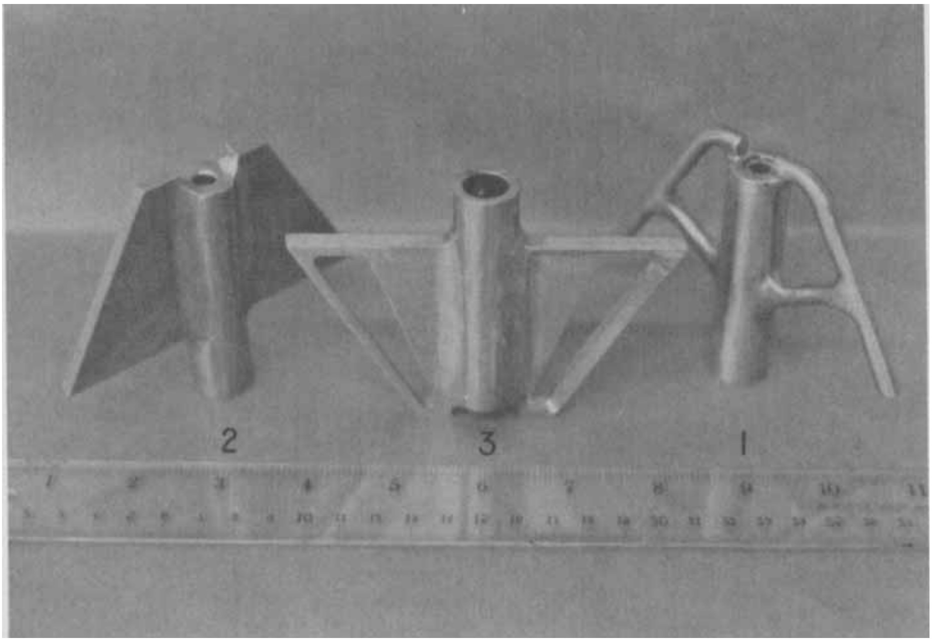

Figure 2. The three Comil® impellers used in the milling of the aspirin granulation.

control, could be operated at speeds from 900 to 2400 rpm. The mill was supplied with interchangeable output screens and impellers. The three impellers used in this study are shown in Fig. 2. The three output screens chosen for this study had circular openings of 1900 μm, 3175 μm and 3960 μm in diameter (Fig. 3). The three mill speeds used in this study were 900 rpm, 1500 rpm and 2,400 rpm. The three speeds were initially calibrated using a strobe.

The material used was a 1680-1180 μm (12-16 mesh) portion of a commercial aspirin-10% starch granulation.[2] For each combination of mill speed, screen size and impeller shape, the

2. Aspirin Granulation, Monsanto Chemical Co., St. Louis, MO.

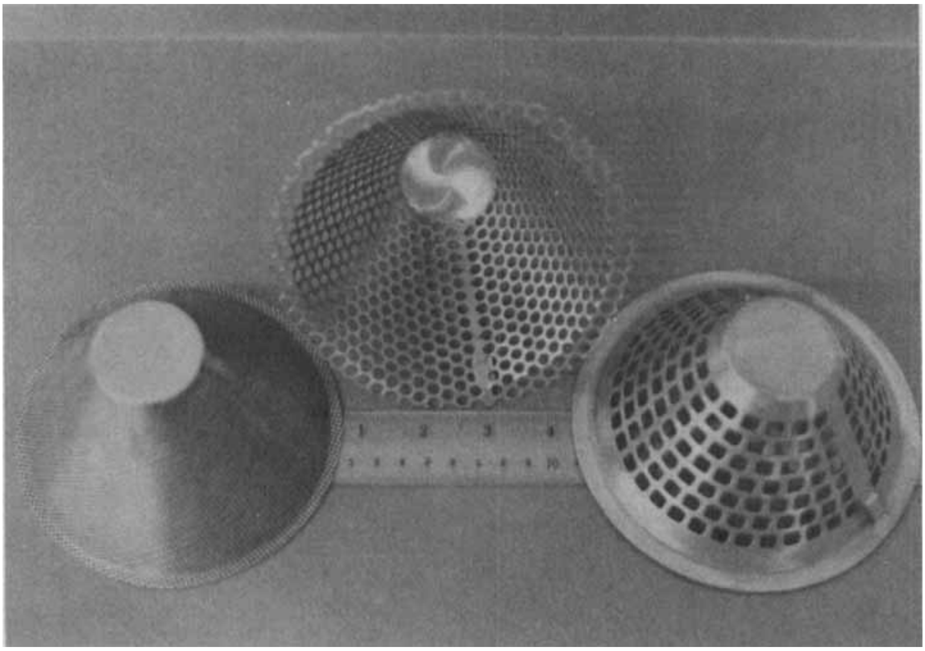

Figure 3. Sample Comil® ouput screens. The center screen represents the type of screen used in the milling of the aspirin granulation.

aspirin was milled in 250 g units fed rapidly into the mill after the full set speed had been achieved. The screen and impeller were then removed, replaced with the next screen and impeller to be used and the speed reset. Particle sizes were determined for the entire milled sample using U.S. standard sieves measuring 105 µm, 125 µm, 250 µm, 420 µm, 840 µm and 1180 µm plus pan placed on a Ro-tap[3] sieve shaker for 5 minutes. The resulting particle size distribution was determined using the algebraic method for particle size analysis presented previously.[3]

In order to achieve statistically meaningful results it was necessary to use a properly designed experiment.[4,5] The design

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3. Ro-tap, W. S. Tyler Co., Cleveland, OH.

chosen for this study was a randomized complete block design (RCBD).[6] The 27 possible combinations of the three mill speeds, three screen sizes and three impeller shapes were evaluated in random order. Upon completion of all 27 combinations the entire experiment was then replicated using a different random order. Finally a third replication was performed using a third random order. Using the concept of restriction error,[4,5,6] this design allowed testing of the effects on particle size of mill speed, screen size and impeller shape, either alone or in combination.

RESULTS AND DISCUSSION

The results of the particle size analysis for the 3 replicates of the 27 combinations of mill speed, screen size and impeller shape is shown in Table 1. A typical plot of the data for a single run is shown in Figure 4. From Table 1, the standard deviations of the mean particle size (μ_d) were less than 6 percent in all but 3 cases. Likewise the standard deviations of the slope ($1/\sigma_d$) were less than 6 percent in all but 5 cases. The average values of the mean particle sizes and the slopes are shown in relationship to the mill variables in Figures 5 and 6, respectively. In this study experimental errors were reduced by analyzing the entire milled sample and by using a completely mathematical method of analysis. The small ranges and standard deviations shown in Table 1 are a good indication that data gathered with the Comil® is quite reproducible.

In order to investigate the effects of each of the mill variables an analysis of variance (ANOVA) was performed. Separate

Table 1. Particle size analysis for milling of aspirin using the Comil®.

Impeller	Speed (RPM)	Screen (μm)	Code	Mean[a] μ_d	S.D.[b]	Range	Slope[a] $1/\sigma_d$	S.D.[b]	Range
1	900	1900	111	566.43	3.10	34.40	0.7922	10.25	0.1607
1	900	3175	112	1180.23	1.07	23.80	0.6174	2.09	0.0255
1	900	3960	113	1313.91	2.30	56.70	0.6378	5.60	0.0704
1	1500	1900	121	375.32	4.30	30.80	1.0151	5.19	0.0999
1	1500	3175	122	667.46	4.30	51.50	0.6689	6.47	0.0797
1	1500	3960	123	953.49	1.20	22.00	0.6187	2.87	0.0347
1	2400	1900	131	276.77	2.40	13.00	1.2676	4.59	0.1095
1	2400	3175	132	382.99	1.30	9.70	0.8392	5.09	0.0853
1	2400	3960	133	563.73	14.50	144.90	0.8204	12.58	0.1832
2	900	1900	211	402.27	3.00	22.20	1.0080	4.52	0.0885
2	900	3175	212	745.91	6.60	86.00	0.6542	5.34	0.0652
2	900	3960	213	987.66	3.10	56.60	0.6258	5.39	0.0662
2	1500	1900	221	298.22	1.50	8.70	1.2225	3.04	0.0697
2	1500	3175	222	425.46	3.50	29.50	0.8694	3.56	0.0579
2	1500	3960	223	568.00	1.40	14.60	0.7483	5.83	0.0809
2	2400	1900	231	265.41	3.50	17.80	1.1926	10.48	0.2455
2	2400	3175	232	322.14	6.10	37.70	1.0264	3.66	0.0680
2	2400	3960	233	359.70	1.10	7.40	0.9052	3.30	0.0586
3	900	1900	311	366.12	1.70	12.50	0.9720	7.89	0.1529
3	900	3175	312	650.52	7.40	88.80	0.6967	3.21	0.0446
3	900	3960	313	912.32	5.90	101.20	0.6083	4.12	0.0486
3	1500	1900	321	323.06	1.10	7.10	1.0366	3.05	0.0604
3	1500	3175	322	432.37	5.70	47.50	0.7231	5.39	0.0702
3	1500	3960	323	566.05	0.70	7.70	0.6999	2.04	0.0259
3	2400	1900	331	292.53	1.50	7.80	1.0797	4.09	0.0801
3	2400	3175	332	358.45	4.80	34.10	0.8697	3.19	0.0538
3	2400	3960	333	411.48	3.40	26.10	0.7908	4.55	0.0679

[a] Average of 3 measurements.

[b] Standard deviation expressed as a percent of the average.

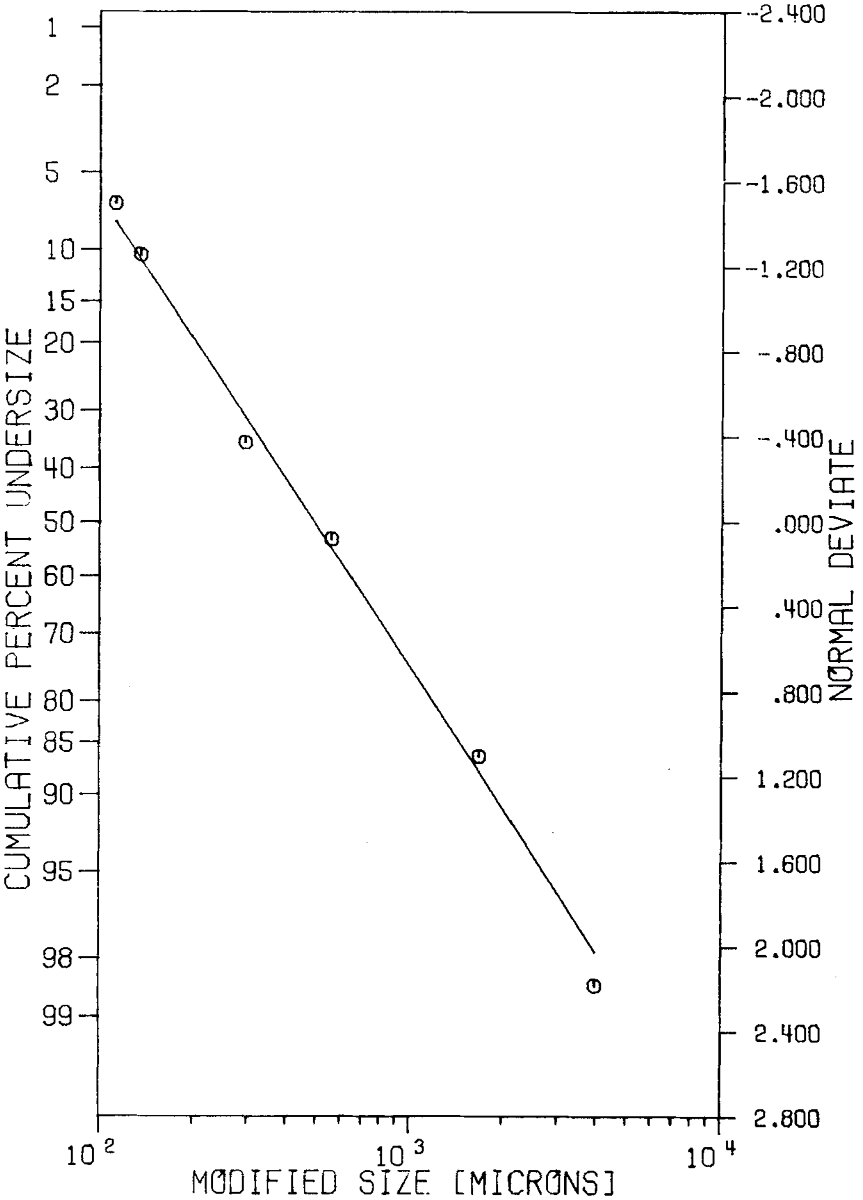

Figure 4. Typical plot of data from a single milling run (speed = 1500 rpm, screen = 1900 µm, impeller = 1).

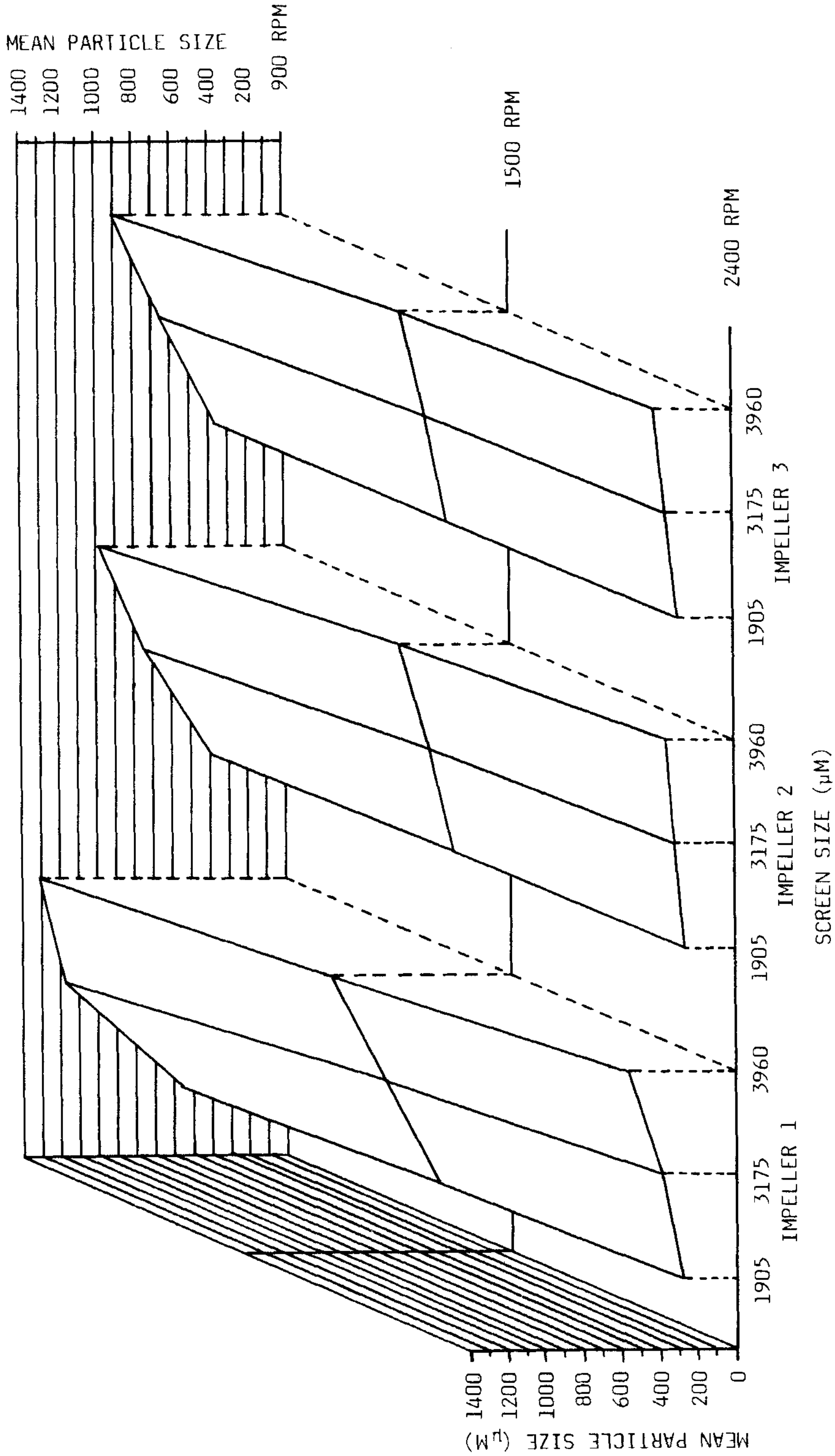

Figure 5. Mean particle size from the milling of the aspirin granulation. Each point on the surfaces is an average of three measurements.

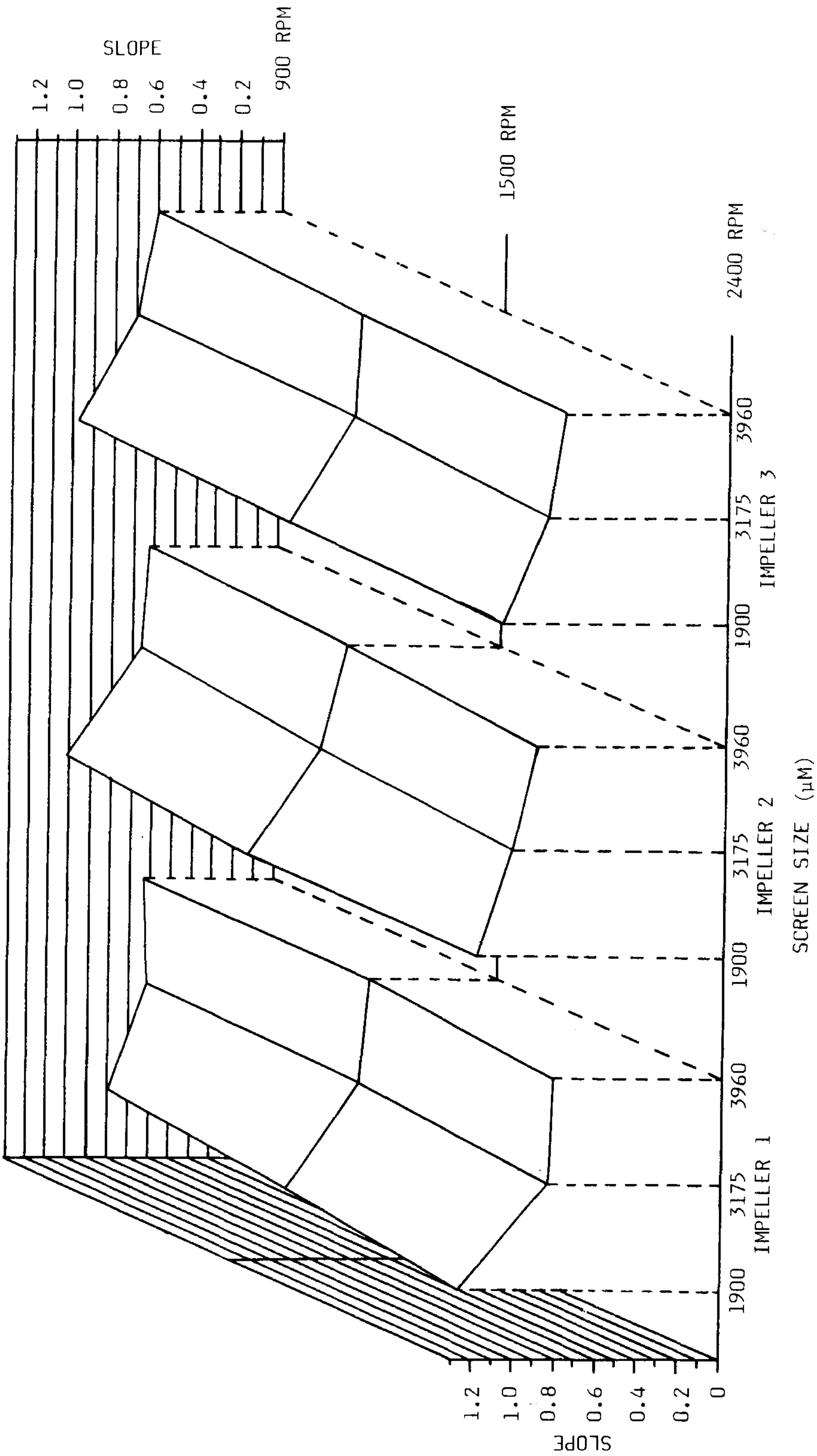

Figure 6. Slopes of particle size distribution from the milling of the aspirin granulation. Each point on the surfaces is an average of three measurements.

ANOVA's were constructed to test effects of the mill variables on the mean particle size (μ_d) and the slope ($1/\sigma_d$) of the resultant particle size distributions. A complete description of the model and resultant tests appears in Appendix 1. The ANOVA indicates that there is a statistically significant effect on both the slope and the mean particle size due to a three-way interaction of the mill variables. From this interaction, two conclusions must now be made. First, the effects of mill speed, screen size and impeller shape on the particle size distribution cannot be evaluated individually but must be evaluated at the level of each combination of the three. Second, a statistically significant difference exists among the average values of μ_d and $1/\sigma_d$ produced by the 27 combinations of mill variables used. The differences between the 27 combinations of mill variables cannot be directly evaluated. However, the presence of the three-way interaction allows the model to be analyzed as a one-way classification with 27 levels of the combinations of mill speed, screen size and impeller shape (see Appendix 1). The Newman-Keuls test[7] may now be used to discern the differences between these combinations.

A Newman-Keuls test was performed at a significance level of $\alpha = 0.05$ and yielded 10 statistically different groups of slopes ($1/\sigma_d$) and 12 statistically different groups of mean particle sizes (μ_d). These results are shown in Table 2. Each row in the table represents a range of μ_d which is statistically different from other ranges (rows) of μ_d. Within a row the differences between μ_d's are not statistically distinguishable. Likewise a

Table 2. Results of the Newman-Keuls test for the mill data collected. Three digit codes are from Table 1.

RANGES OF MEAN PARTICLE SIZE \ RANGES OF SLOPES	0.60 –0.72	0.61 –0.76	0.66 –0.80	0.69 –0.82	0.72 –0.84	0.74 –0.87	0.79 –0.91	0.87 –0.97	0.97 –1.10	1.20 –1.30
265–323									232 321 331	131 221 231
298–360						332	233 332	233 332	232 321	221
322–383					132	132 332	132 233 332	233 311 332	121 232 311 321	
358–425			333	333	132 333	132 222 332 333	132 222 233 332 333	222 233 311 332	211 311 121	
366–432	322	322	322 333	322 333	132 322 333	132 222 333	132 222 333	222 311	121 211 311	
556–568	323	223 323	111 223 323	111 133 223 323	111 133 223	111 133 223	111 133			
650–668	122 312	122 312	122 312	312						
746	212	212								
912–954	123 313	123								
953–987	123 213	123 213								
1180	112	112								
1314	113	113								

column in the table represents a range of slopes which is statiscally different from other ranges (columns) of slopes. Therefore, the intersection of a row and a column yields a cell containing the mill parameters which yield a particle size distribution which is statistically different in both mean and slope from other distributions (cells). In this way, Table 2 shows that there are 48 statistically different particle size distributions available for the mill parameters and material used in this study. The actual number of pharmaceutically useful particle size distributions is less than 48 since two adjacent cells may contain the same mill conditions. For example, column 3 row 4 and column 4 row 4 may be statistically different but are probably not pharmaceutically different.

The most useful feature of Table 2 is that it provides a complete characterization of the mill for the conditions and material tested in this study. It is now possible to check if a certain particle size distribution is obtainable as well as how to obtain a possible distribution just by examining Table 2. A future paper will report the applicability of this method for predicting mill output as well as other methods which make predictions about combinations of mill variables not yet tested.

Appendix 1

Experimental Design

The model for the measurement of mean particle size is given below:

$$Y_{ijkl} = \mu + R_i + \delta_{(i)} + I_j + S_k + IS_{jk} + P_l + IP_{jl} + SP_{kl} + ISP_{jkl} + \text{error}(a) + \varepsilon_{(ijkl)} \quad \text{(Eq. 1)}$$

where: $i = 1,2,3$ $j = 1,2,3$ $k = 1,2,3$ $l = 1,2,3$

Y_{ijkl} = mean particle size measurement using the l^{th} output screen of the k^{th} mill speed of the j^{th} impeller shape in the i^{th} replicate.

μ = overall mean.

R_i = effect of the i^{th} replicate (random).

$\delta_{(i)}$ = first restriction error (random).

I_j = effect of the j^{th} impeller shape (fixed).

S_k = effect of the k^{th} mill speed (fixed).

IS_{jk} = effect of the interaction of the k^{th} mill speed and the j^{th} impeller shape.

P_l = effect of the l^{th} output screen size (fixed).

IP_{jl} = effect of the interaction of the l^{th} output screen size and the j^{th} impeller shape.

SP_{kl} = effect of the interaction of the l^{th} output screen size and the k^{th} mill speed.

ISP_{jkl} = effect of the interaction of the l^{th} output screen size and the k^{th} mill speed and the j^{th} impeller shape.

error(a) = pooled (RI_{ij}, RS_{ik}, RP_{il}, RIS_{ijk}, RIP_{ijl}, RSP_{ikl} and $RISP_{ijkl}$).

$\varepsilon_{(ijkl)}$ = random error within the l^{th} output screen size of the k^{th} mill speed of the j^{th} impeller shape in the i^{th} replicate.

There is one restriction on randomization inherent in the randomized complete block design (RCBD) which is accounted for in the above model. This restriction (δ) occurs since the three replications of the experiment are performed stepwise.[4,5] The pharmaceutical scientist would not expect to see any significant interaction between the replications and any of the other factors. Therefore those factors are pooled into error(a) which is given above. The corresponding Analysis of Variance (ANOVA) is shown in Table 3. The tests for I_j, S_k, P_l and their interactions are performed using error(a). An identical model is used for testing the effects of the variables on the slope of the particle size distribution.

Interpretation of the ANOVA begins with the three-way interaction ISP. If this interaction is not found to be significant then one may proceed to test the three two-way interactions. Main effects are tested only when all interactions which contain those effects are shown to be not significant. Since the three-way interaction ISP is shown to be significant then the levels of the combinations need to be investigated. The new model[8] is given below:

$$Y_{im} = \mu + R_i + \delta_{(i)} + C_m + \text{error(a)} + \varepsilon_{(im)}$$

where $i = 1,2,3 \quad m = 1,2,\ldots,27$

$Y_{im} \quad = Y_{ijkl}$ of Equation (1)

$\mu \quad = \mu$ of Equation (1)

$\varepsilon_{(im)} \quad = \varepsilon_{(ijkl)}$ of Equation (1)

Error(a) = error(a) of Equation (1)

Table 3. ANOVA using the RCBD model (Eq. 1) with the data from Table 1.

Source	df	Estimated mean squares	$F_{(\mu_d)}$	$F_{(1/\sigma_d)}$
Replications (R)	2	$\sigma_\varepsilon^2 + \sigma_a^2 + 27\sigma_\delta^2 + 27\sigma_R^2$	None	None
Restriction error(δ)	0	$\sigma_\varepsilon^2 + \sigma_a^2 + 27\sigma_\delta^2$		
Impeller shape (I)	2	$\sigma_\varepsilon^2 + \sigma_a^2 + 27\phi(I)$	574.51*	37.86*
Mill speed (S)	2	$\sigma_\varepsilon^2 + \sigma_a^2 + 27\phi(S)$	1797.97*	169.50*
IS	4	$\sigma_\varepsilon^2 + \sigma_a^2 + 9\phi(IS)$	1416.38*	401.50*
Screen size (P)	2	$\sigma_\varepsilon^2 + \sigma_a^2 + 27\phi(P)$	84.66*	9.24*
IP	4	$\sigma_\varepsilon^2 + \sigma_a^2 + 9\phi(IP)$	61.38*	1.84
SP	4	$\sigma_\varepsilon^2 + \sigma_a^2 + 9\phi(SP)$	185.59*	3.00*
ISP	8	$\sigma_\varepsilon^2 + \sigma_a^2 + 3\phi(ISP)$	11.18*	6.06*
Error (a)	52	$\sigma_\varepsilon^2 + \sigma_a^2$		
Within (ε)	0	σ_ε^2		

* Significant at the 0.05 level.

C_m = effect of the m^{th} combination of the l^{th} output screen size with the k^{th} mill speed and the j^{th} impeller shape in the i^{th} replicate.

The model is now a one-way classification with 27 levels of the combinations of mill speed, screen size and impeller shape.

The cell means may now be ranked according to the Newman-Keuls test in order to aid in the interpretation of the data and formulation of conclusions.

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