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THE QUANTITATIVE EVALUATION OF A GRANULATION MILLING PROCESS III. PREDICTION OF OUTPUT PARTICLE SIZE

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ABSTRACT

Regression analysis was performed using comminution data from the previously presented Comil®/aspirin granulation characterization study. Polynomial models were constructed using mill speed, output screen size and impeller shape as independent variables. The models were used to predict the mean particle size (μ_d) and geometric standard deviation (σ_d) of particle size distributions resulting from the comminution of aspirin using the Comil®. The predictions were found to compare well with observed values.

INTRODUCTION

The validation of a pharmaceutical manufacturing process requires that each unit operation in the process be controllable within predefined operational limits. Appropriate control of a unit operation can only be established when that unit operation

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and its input material are fully characterized. The output of a fully characterized and controlled unit operation should be predictable. Comminution is an important part of the successful development of granulations which are to yield tablets that are uniform, reproducible and physically and chemically stable. Since the comminution of granulations is an essential unit operation, a given mill/material system needs to be characterized for the purpose of establishing control specifications. These specifications will result in predictable comminution results.

Attempts by researchers to express comminution in terms of a general mathematical model have not been successful. There is no generally accepted theory of comminution or even a practical mathematical expression to represent the characteristics of a body of particles. Further, the individuality of each milling case requires a separate analysis for each operation[1]. However, when studying a specific milling system one needs only to describe comminution over a relatively narrow range of conditions. In the first report of this series an algebraic method of describing particle size distributions was presented[2]. The second report described the characterization of a specific mill/raw material system[3]. This report describes a method by which particle size distributions can be predicted for the output of the previously characterized comminution operation.

THEORY

In order to make predictions concerning mill output it is necessary to have a mathematical or statistical system which relates the mill variables to the resultant output particle size distribution. A previous study showed that the mill speed, output screen size and impeller shape must not be considered as independent factors but rather in combination[3]. Therefore one prediction model which could be used to describe mill output is a second order polynomial with three independent variables (Eq. 1).

$$y(I,S,P) = \sum_{i=0}^{2} \sum_{j=0}^{2} \sum_{k=0}^{2} b_{ijk} I^i S^j P^k \qquad \text{Eq. 1}$$

where

$y(I,S,P)$ = Predicted mill output

b = Regression coefficients

I = Impeller shape

S = Mill speed

P = Output screen size

The use of Equation 1 to predict output particle size requires that some measurement of mill output be designated as the independent variable $y(I,S,P)$. Computer simulations or equations of state which relate the mean particle size (μ_d) and the geometric standard deviation (σ_d) of the distribution to the processing parameters will allow the design of a process which yields a predetermined particle size distribution[2]. Therefore the two measurements which will be used as indicators of mill output are the mean particle size (μ_d) and the slope ($1/\sigma_d$) of the resultant particle size distribution.

A second consideration in the use of Equation 1 is that it consists of 27 terms. A procedure is required to estimate the coefficients in the equation and their relative importance in predicting the output variables. The statistical procedure used for this is regression analysis. Only those terms which are shown to make statistically significant contributions to the regression should be included in the model. Those terms which do not make statistically significant contributions should then be excluded from the model. This process can be repeated in a stepwise manner until no further additions to or deletions from the model can be made[4].

METHODS

Polynomial regressions were constructed for both the mean particle size (μ_d) and the slope ($1/\sigma_d$) using a commercially available statistical computer program[1]. A stepwise regression was used such that those terms which made statistically significant contributions to the model were included while those that did not were excluded. The significance levels were $\alpha < 0.10$ for inclusion into the model and $\alpha > 0.25$ for exclusion from the model. The data used for the regressions was from the three replications of the previously presented Comil/aspirin granulation characterization study[3].

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1. SPSS Regression, Statistical Package for the Social Sciences, Version 8.3.5, Vogelback Computing Center, Northwestern University, Evanston, IL.

The usefulness of the polynomial models to predict resultant particle size using parameter values outside the characterization study was investigated using two new mill speeds. Using the previously reported materials, methods and analysis[3], the nine original combinations of three impeller shapes and three output screen sizes were combined with the two new mill speeds, 1200 RPM and 2100 RPM. The resulting values of μ_d and $1/\sigma_d$ calculated from the polynomial regressions were then compared to the values observed using the two new mill speeds.

RESULTS AND DISCUSSION

The use of the stepwise regression procedure for the polynomial models resulted in eleven statistically significant terms describing μ_d and nine statistically significant terms describing $1/\sigma_d$. The coefficients for the polynomial models and their corresponding terms are shown in Table 1. In both cases the models consisted of substantially fewer terms than would have been the case if the full polynomial equation (Eq. 1) had been used. The observed

values of μ_d and $1/\sigma_d$ from the characterization study are compared with the values calculated by the regression equations in Table 2. The relationships between the calculated and observed values of μ_d and $1/\sigma_d$ are further illustrated in Figures 1 and 2, respectively. The results of the observed and predicted particle size analysis for the comminution of aspirin at the two new mill speeds are shown in Table 3. Graphs of the data in Table 3 for μ_d and $1/\sigma_d$

Table 1. Coefficients for Polynomial Regression Models for μ_d and $1/\sigma_d$

Term	Regression Coefficient	
	μ_d	$1/\sigma_d$
Constant	-2.4821×10^{2}	1.9558
I	0	0
I^2	0	0
S	0	0
S^2	0	0
IS	1.1820×10^{-1}	0
IS^2	0	0
I^2S	0	0
I^2S^2	0	0
P	7.8066×10^{-1}	-1.0172×10^{-3}
P^2	0	1.6324×10^{-7}
IP	-1.2199×10^{-1}	0
IP^2	0	0
I^2P	0	0
I^2P^2	2.2517×10^{-6}	0
SP	-2.0431×10^{-4}	0
SP^2	0	0
S^2P	0	0
S^2P^2	0	0
ISP	-2.1564×10^{-4}	3.7741×10^{-7}
ISP^2	0	-8.4998×10^{-11}
IS^2P	1.9840×10^{-6}	-4.4267×10^{-11}
IS^2P^2	0	1.1275×10^{-14}
I^2SP	5.2997×10^{-5}	-7.2692×10^{-8}
I^2SP^2	0	1.5824×10^{-11}
I^2S^2P	-5.4273×10^{-7}	0
$I^2S^2P^2$	5.5774×10^{-13}	0

Table 2. Observed and Calculated Particle Size Analysis for Milling of Aspirin Using the Comil®.

Impeller	Speed (RPM)	Screen (μm)	Observed[a] Mean μ_d	Calculated[b] Mean μ_d	Observed[a] Slope $1/\sigma_d$	Calculated[b] Slope $1/\sigma_d$
1	900	1900	566.43	581.17	0.7922	0.8737
1	900	3175	1180.23	1074.07	0.6174	0.5932
1	900	3960	1313.91	1384.05	0.6378	0.5986
1	1500	1900	375.32	391.24	1.0151	1.0087
1	1500	3175	667.46	713.48	0.6689	0.7166
1	1500	3960	953.49	918.95	0.6187	0.6739
1	2400	1900	276.77	255.00	1.2676	1.1527
1	2400	3175	382.99	423.39	0.8392	0.8653
1	2400	3960	563.73	536.65	0.8204	0.7890
2	900	1900	402.27	409.10	1.0080	0.9890
2	900	3175	745.91	749.07	0.6542	0.6863
2	900	3960	987.66	977.37	0.6258	0.6380
2	1500	1900	298.22	272.51	1.2225	1.1619
2	1500	3175	425.46	439.82	0.8694	0.8475
2	1500	3960	568.00	566.28	0.7483	0.7411
2	2400	1900	265.41	260.52	1.1926	1.3041
2	2400	3175	322.14	309.57	1.0264	1.0167
2	2400	3960	359.70	375.38	0.9052	0.8997
3	900	1900	366.12	372.43	0.9720	0.9586
3	900	3175	650.52	671.55	0.6967	0.6511
3	900	3960	912.32	896.42	0.6083	0.6060
3	1500	1900	323.06	298.95	1.0366	1.0722
3	1500	3175	432.37	436.38	0.7231	0.7646
3	1500	3960	566.05	572.72	0.6999	0.6890
3	2400	1900	292.53	321.38	1.0797	1.0669
3	2400	3175	358.45	332.06	0.8697	0.8258
3	2400	3960	411.48	418.35	0.7908	0.8197

[a] Average of 3 measurements.

[b] Calculated using regression equation from Table 1.

Table 3. Predicted and Observed Particle Size Analysis for Two New Mill Speeds Using the Comil®.

Impeller	Speed (RPM)	Screen (μm)	Predicted[a] Mean μ_d	Observed Mean μ_d	Predicted[b] Slope $1/\sigma_d$	Observed Slope $1/\sigma_d$
1	1200	1900	469.63	448.25	0.9259	0.9478
1	1200	3175	873.37	937.57	0.6519	0.6566
1	1200	3960	1118.27	1151.35	0.6349	0.6416
1	2100	1900	285.26	326.63	1.1552	1.2917
1	2100	3175	466.70	434.35	0.8265	0.8481
1	2100	3960	620.42	611.19	0.7500	0.7238
2	1200	1900	336.80	350.06	1.0662	1.0965
2	1200	3175	587.57	542.24	0.7422	0.8350
2	1200	3960	740.69	709.97	0.7062	0.7005
2	2100	1900	258.95	283.01	1.3081	1.3693
2	2100	3175	310.11	327.18	0.9620	1.0360
2	2100	3960	385.68	424.22	0.8590	0.9151
3	1200	1900	319.13	339.50	1.0597	1.0336
3	1200	3175	550.31	510.54	0.7005	0.7458
3	1200	3960	691.68	625.68	0.6536	0.6783
3	2100	1900	284.10	296.27	1.0970	1.0683
3	2100	3175	338.39	373.56	0.8347	0.8434
3	2100	3960	415.82	461.20	0.7665	0.7913

[a] Calculated using regression equation from Table 1.

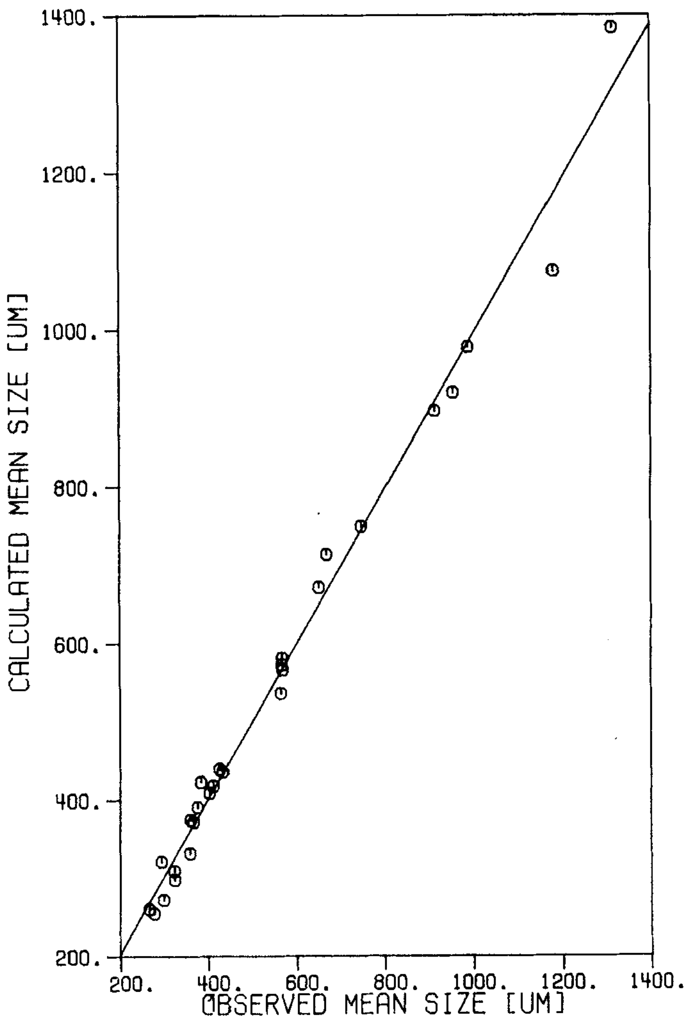

Figure 1

The relationship between the mean particle sizes (μd) calculated from the polynomial regression model (Table 1) and the observed values of μd. (Slope = .9873, R^2 = .9874).

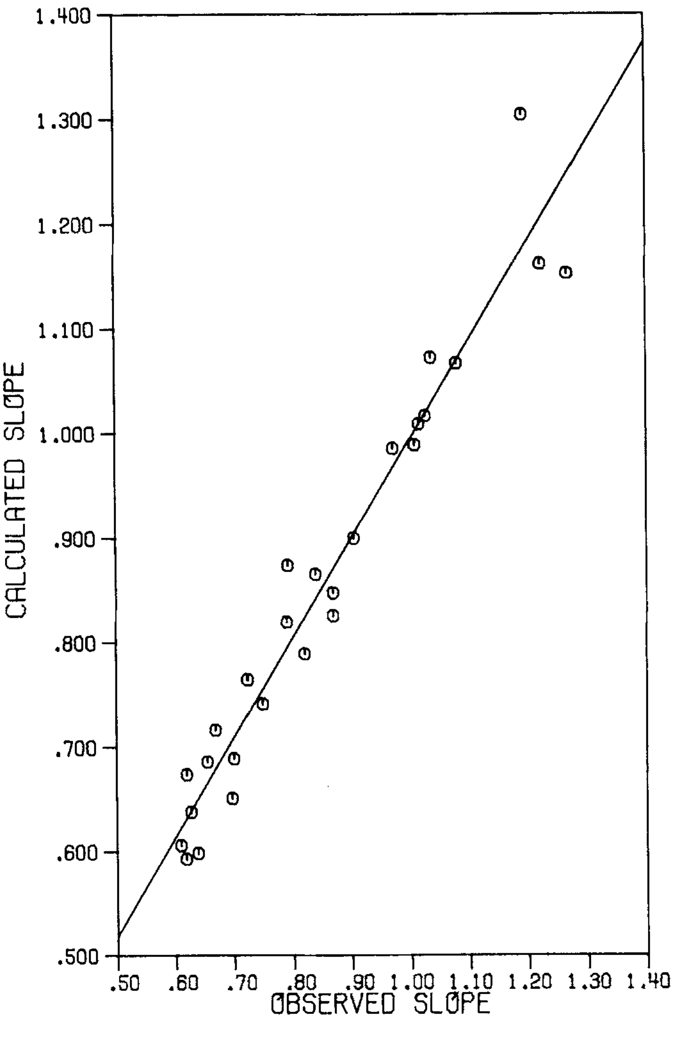

Figure 2

The relationship between the slopes ($1/\sigma_d$) calculated from the polynomial regression model (Table 1) and the observed values of $1/\sigma_d$. (Slope = .9496, R^2 = .9462).

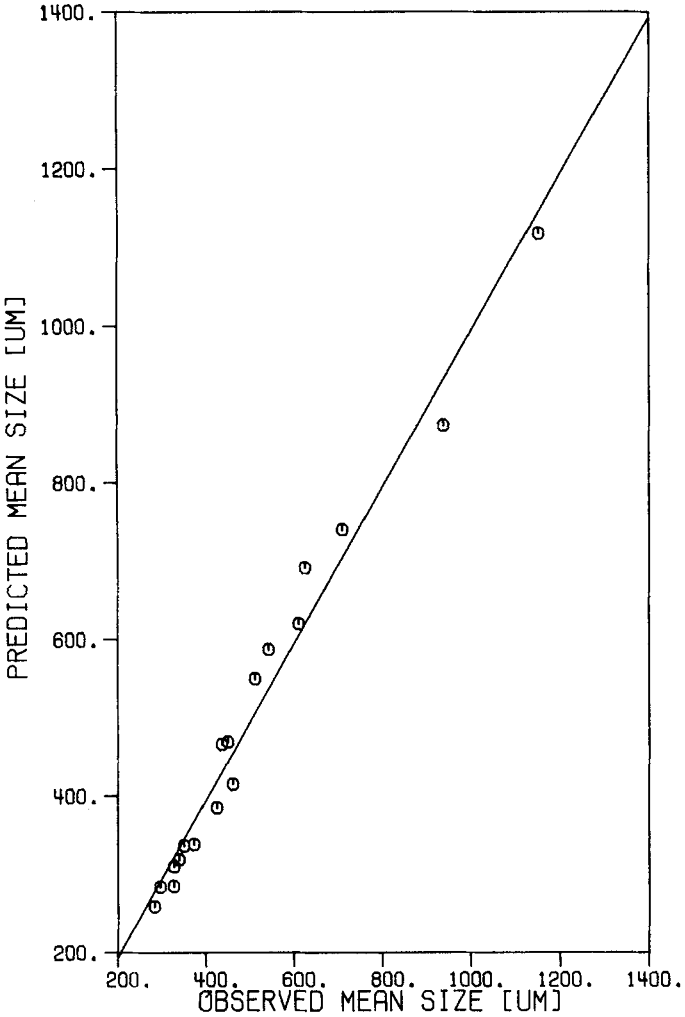

Figure 3

The relationship between the predicted mean particle size (μd) calculated from the polynomial regression model (Table 1) and the observed values using the two new mill speeds (Slope = .9981, R^2 = .9751).

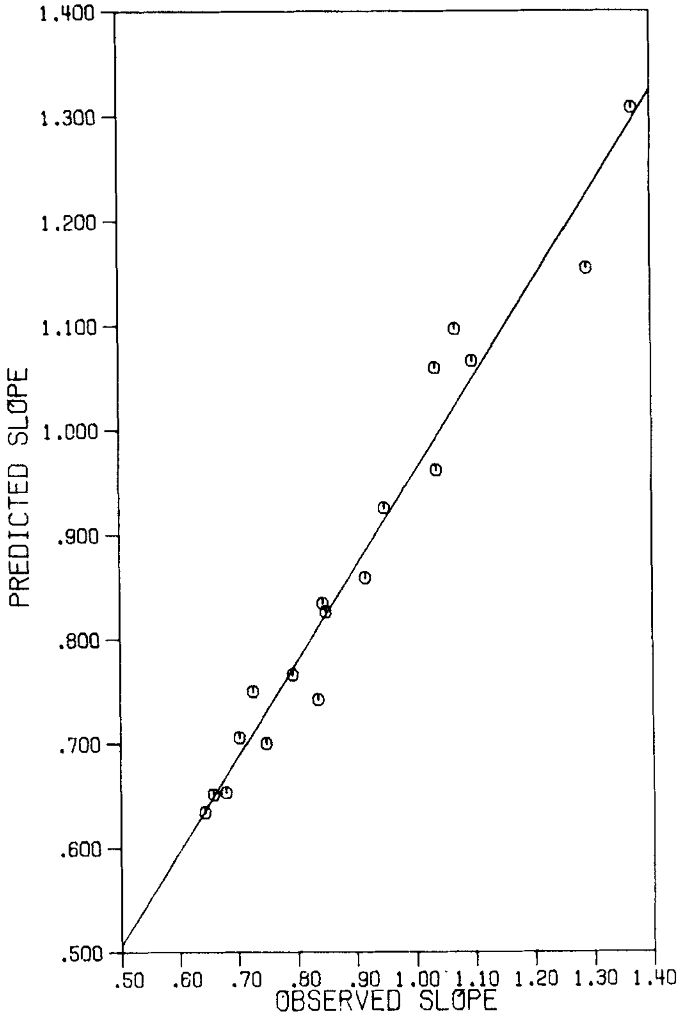

Figure 4

The relationship between the predicted slopes ($1/\mu_d$) calculated from the polynomial regression model (Table 1) and the observed values using the two new mill speeds (Slope = .9077, R^2 = .9616).

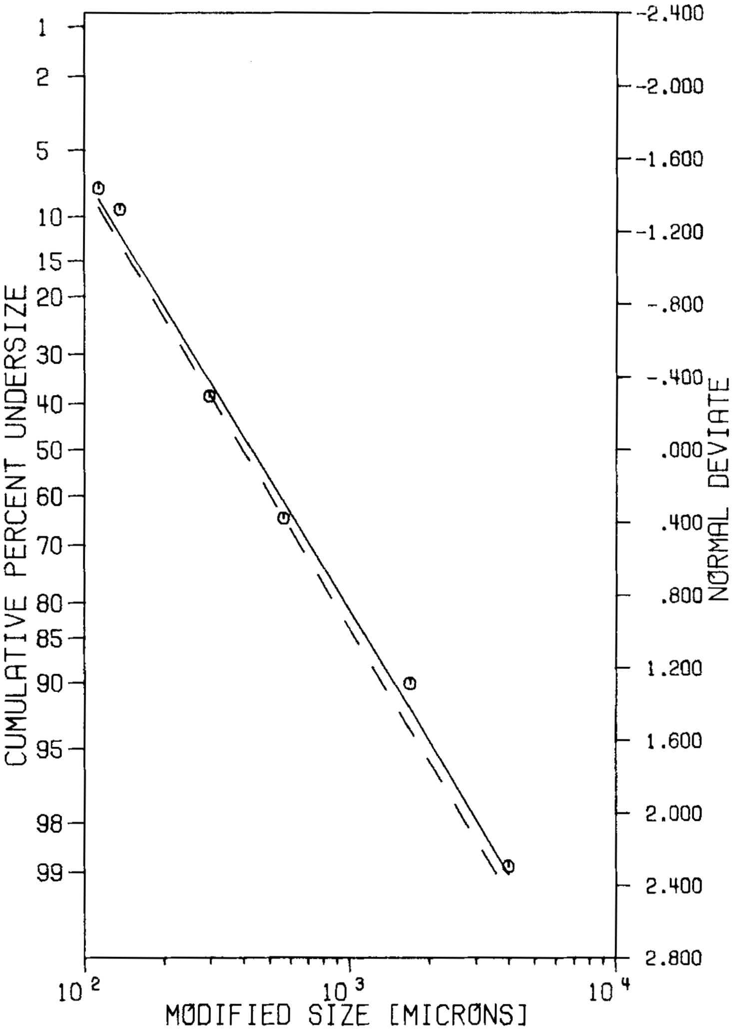

Figure 5
Log-probability plot of data from a single run using a new mill speed (I = 3, S = 1200 rpm, P = 1900 μm). Dashed line represents values calculated from the predicted mean and slope given in Table 3. The solid line represents the observed values.

are shown in Figures 3 and 4. A typical log-probability plot of a single run is shown in Figure 5. The agreement between the predicted and observed values when new mill speeds are tested shows that the model can be used to determine how changes in the mill speed will affect mill output.

This series has shown that it is possible to characterize a granulation milling operation and predict the results of deviations from a given combination of variables. Future work will concentrate on the more basic measurement of retention time of granules in the milling chamber, how it is affected by the mill variables and its effect on resultant particle size.

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