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THE QUANTITATIVE EVALUATION OF A GRANULATION MILLING PROCESS I. ALGEBRAIC METHOD FOR PARTICLE SIZE ANALYSIS

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ABSTRACT

A method is presented which may be used to mathematically express particle size distributions of pharmaceutical granulations.

The method utilizes expresses of particle size and probability evaluated using a weighted linear regression technique. This method is suggested whenver particle size determinations are used in conjunction with statistical analysis, optimization techniques or any time a purely quantitative approach is needed.

INTRODUCTION

In depth studies of pharmaceutical manufacturing processes or unit operations often make use of mathematical methods of analysis such as statistics, simulation and optimization. The use of such methods of analysis assumes that the variables being tested and measured can be accurately described mathematically and will yield meaningful results. In order to analyze the comminution of pharmaceutical granulations it is therefore necessary to have a means of accurately describing granule size and size distribution mathematically. The analysis of particle size distributions of pharmaceuti-

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cal granulations has largely been a semi-quantitative process. Much attention is given to the sampling of granulations and to the collection of data, but the analysis of the collected data is usually performed graphically using log-probability plots. The use of the log-normal distribution function is well known in the study of pharmaceutical granulations[1-5]. The common practice of data analysis is to plot the percent of particles greater than (or less than) a given particle size versus the particle size. If the log-normal distribution describes the data then a plot constructed on log-probability paper will yield a straight line. A typical plot of this type is shown in Fig. 1. From this line the parameters of the distribution can be estimated. These parameters, the mean (μ_d) and the standard deviation (σ_d), completely describe the distribution[2]. However, in the pharmaceutical literature no methods are presented for the algebraic fitting of particle size data to log-probability plots. The exclusive method presented for producing such lines is visual curve fitting. When a measurable degree of accuracy in fitting curves to data is desired, algebraic and analytical methods are required. The objective of this presentation is to demonstrate a method by which log-probability plots can be described algebraically.

THEORY

The normal distribution may be expressed as[6]

$$P = \int_{-\infty}^{t} Z \, dt \qquad \text{(Eq. 1)}$$

with

$$Z = \frac{\exp(-t^2/2)}{\sqrt{2\pi}} \qquad \text{(Eq. 2)}$$

and

$$t = \frac{d-\mu_d}{\sigma_d} \qquad \text{(Eq. 3)}$$

where

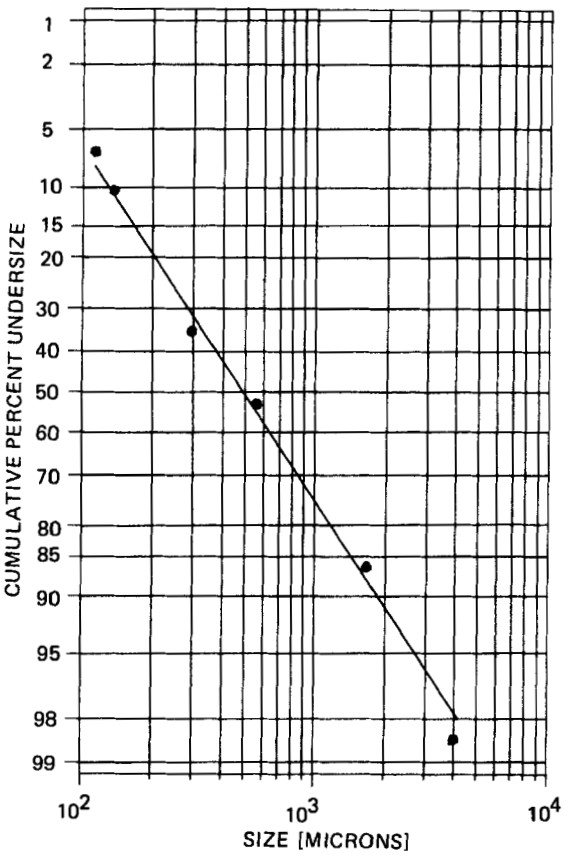

Figure 1.

An example of particle size data plotted on log probability paper.

P = Probability ($0 \leq P \leq 1$)

Z = Standardized frequency ($0 \leq Z \leq \infty$)

t = Normal deviate ($-\infty \leq t \leq \infty$)

d = Size of particle ($0 \leq d \leq \infty$)

μ_d = Mean particle size

σ_d = Standard deviation of d

Equation 3 relates the normal distribution to the analysis of a measurable particle size d. For a log-normal distribution:

$$d = \text{Ln } x \qquad \text{(Eq. 4)}$$

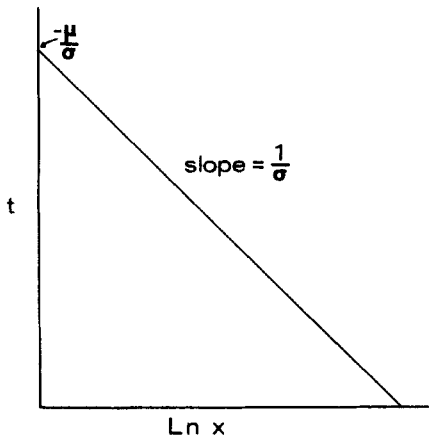

Figure 2.

The relationship of Equation 5.

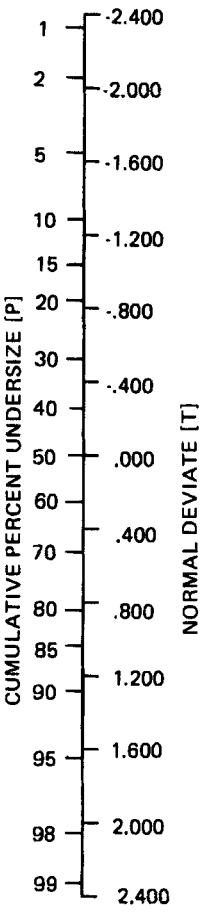

Figure 3. The relationship between the probability (P) scale and the normal deviate (t) scale.

The variable x is the actual measured value of particle size from microscope counting methods, sieving or other particle size measurement techniques. Equations 3 and 4 may be combined to yield the following equation of a straight line:

$$t = -\frac{\mu_d}{\sigma_d} + \frac{1}{\sigma_d} \text{ Ln } x \qquad \text{(Eq. 5)}$$

This relationship is illustrated in Fig. 2. The probability scale from the familiar log-probability charts is actually a linear t-scale with probability values inscribed[7]. Therefore the linearization of our particle size data occurs as a consequence of Eq. 5. The relationship between the values of t and the probability scale

is illustrated in Fig. 3. Values of t may be converted to probability values (and vice versa) using Eqs. 1 and 2.

Upon examination of Fig. 3 it should be clear that the magnitude of deviations, in units of t, about a point on the probability scale depends upon the level of probability at which they occur. For example, the interval from 1 to 2 percent probability is approximately 0.4 units of t while the interval from 49 to 50 percent probability is approximately 0.03 units of t. Since our particle size data is collected as probability units but in effect converted to units of t when plotted, then assessment of the deviation occurring about such a line (Fig. 1) becomes complicated. It is for this reason that methods which obtain lines by visual curve fitting are inadequate. The correct analysis of such deviation requires the use of weights. These weights are also necessary to correct for the errors inherent in the collection of probability data. The weight (W) given by Kottler[7] is:

$$W = \frac{Z^2 N}{P(1-P)} \qquad \text{(Eq. 6)}$$

where N is the number of particles counted and Z, P are as previously defined.

METHOD

A computer program was written which applies the above mathematical concepts to the analysis of data collected from pharmaceutical granulations. The program first converts observed values of probability to t values using Eqs. 1 and 2. The computational form used is

$$t = \sqrt{2}\, \mathrm{erf}^{-1}(1-2P) \qquad \text{(Eq. 7)}$$

which is an equivalent form of Eqs. 1 and 2. The inverse error function (erf^{-1}) used in Equation 7 is available on most mathematical

and statistical packages for computers such as IMSL[8]. An alternate method has been devised for calculating these values using a programmable hand calculator[9]. The program then uses the calculated values of t and Ln x to perform a weighted regression analysis[10] utilizing the weights given by Eq. 6. The program finally constructs a plot of the data points and the calculated regression line.

Particle size data for a pharmaceutical aspirin granulation is presented (Table 1) in order to illustrate the use of the above program. The data was generated by passing a 12-16 mesh sieve cut of aspirin granulation[1] through a Comil[2] at 1500 rpm using a screen size of 1900 µm. The particle size analysis was performed using standard U.S. sieves. The resulting computer generated plot is shown in Fig. 4. An examination of Fig. 4 shows that the data points appear to assymptotically approach a value on the x-axis. This phenomena occurs because the log-normal distribution function attempts to describe particle sizes ranging from zero to infinity.

Table 1. Particle Size Data for Aspirin Granulations

Screen Size µm	Screen Size Mesh	Percent Retained On Screen	Cummulative Percent Less Than Stated Size
1180	16	1.5	98.5
840	20	12.1	86.4
420	40	33.3	53.1
250	60	17.7	35.4
125	120	25.0	10.4
105	140	3.8	6.7
<105	pan	6.6	0.0

1. Aspirin Granulation, Monsanto Chemical Co., St. Louis, MO.
2. Comil, Model 197-1-525, Quadro Engineering, Waterloo, Ontario, Canada.

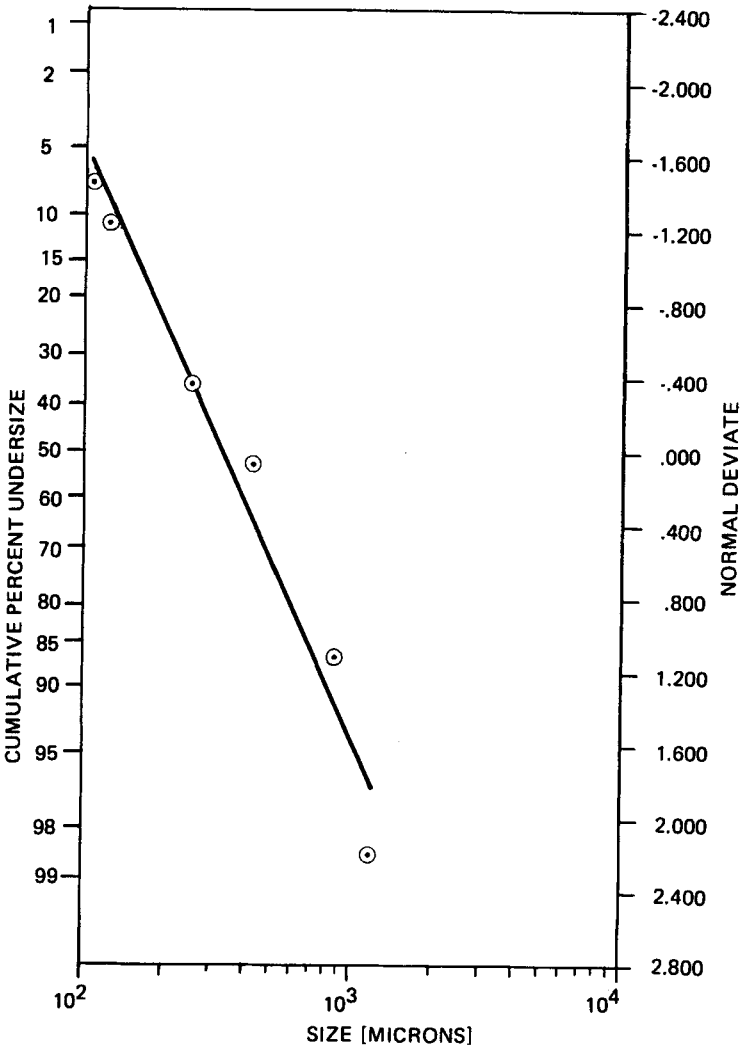

Figure 4. A plot of the aspirin granulation data from Table 1 using the weighted regression technique.

However, the actual particle sizes of the granulation used range in size from some value less than 140 mesh (105μm) up to a possible maximum size of 12 mesh (1680μm). Irani[11] indicates that the nonlinearity resulting from this discrepancy can be corrected by replacing Eq. 4 with a new expression:

$$d = \text{Ln}\frac{(X-X_0)(X_\infty-X_0)}{(X_\infty-X)} \qquad \text{(Eq. 8)}$$

d = modified particle size

X_0 = smallest particle size

X_∞ = largest particle size

Using Eq. 8 we see that when X approaches X_0 then d approaches Ln(0) and when X approaches X_∞ then d approaches Ln(∞). This expression therefore transforms our particle size data into a form more compatible with the log-normal distribution. In pharmaceutical granulations X_0 may be as small as 5μm[3]. Therefore in such cases the assumption that X_0 is zero is not a bad approximation of the minimum particle size. However, the value of X_∞ in granulations is certainly always smaller than ∞ and is usually quite readily estimated from screen sizes and other restrictions imposed by the processing equipment. When the data in Table 1 is analyzed using X_0 = 0 and X_∞ = 1680 μm a much improved plot results (Fig. 5).

DISCUSSION

We now have a strictly algebraic method of analysis which can be used to describe particle size distributions. The method consists of (a) the transformation of particle size using Eq. 8; (b) the calculation of t-values from the cumulative percent data using Eq. 7; and (c) the application of a weighted regression analysis of the above transformed data using the weights indicated in Eq. 6. Numerical values such as the correlation coefficient (r) may be

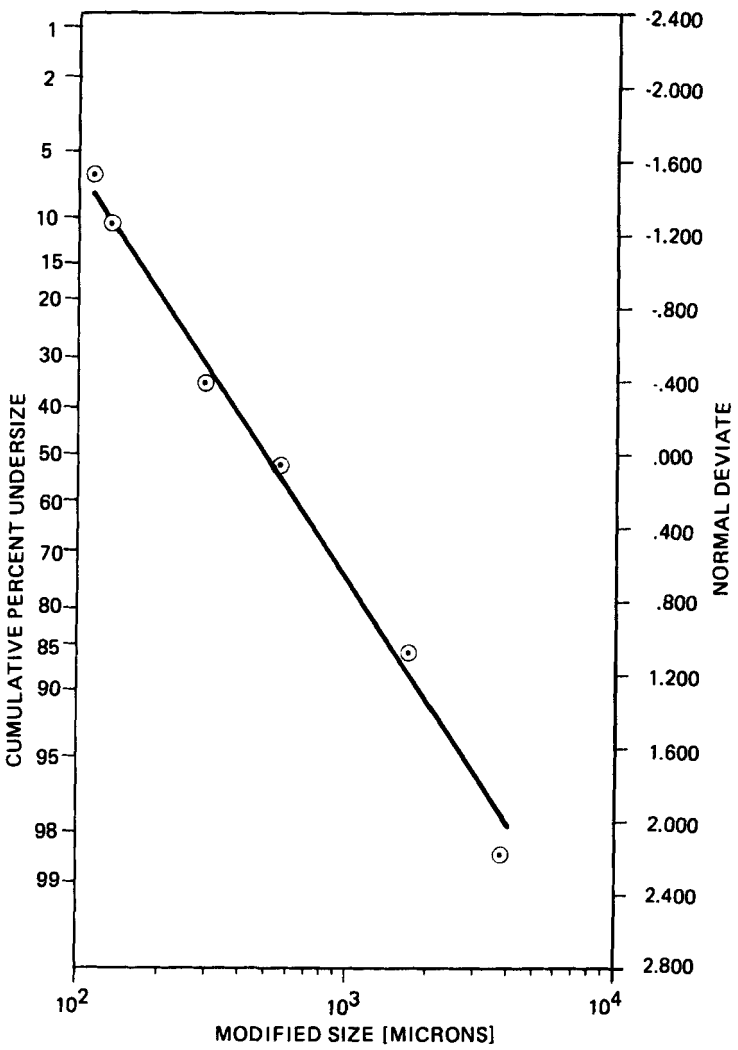

Figure 5.

A plot of the data from Table 1 using the weighted regression technique and the transformation of Equation 8.

Table 2. Summary of Analysis for Aspirin Data in Table 1.

Weights (Eq.6)	Transform (Eq. 8)	Mean Particle Size (μ_d)	Slope ($1/\sigma_d$)	Correlation Coefficient (r)	($\hat{\chi}^2$) Chi-Squared
NO	NO	324.7 µm	1.40	0.9860	13.13
YES	NO	347.8 µm	1.28	0.9871	7.34
NO	YES	378.3 µm	0.99	0.9978	4.02
YES	YES	380.8 µm	0.96	0.9961	3.55

Table 3. Particle Size Data for Acetaminophen Granulation (Li Lot W-30-4)

Screen Size µm	Screen Size Mesh	Percent Retained on Screen	Cumulative Percent Less Than Stated Size
1410	14	1.7	98.3
1000	18	6.4	91.9
707	25	15.7	76.2
500	35	21.3	54.9
354	45	16.9	38.0
250	60	14.5	23.5
149	100	13.5	10.0
74	200	6.5	3.5
<74	pan	3.5	0.0

calculated which express the accuracy of fit of the data to the calculated regression line. A further indication is given by the chi-squared goodness of fit test[12,13]. The chi-squared test is generally used to test the hypothesis that the cumulative distribution of a sample is the same as that for a specified population. In the case of particle size analysis we will use the chi-squared test to compare the cumulative percent of particles less than a given particle size to the expected value for that size. The expected value is the value given by the regression line. Since the regression line constructed is based upon a modified log normal distribution (Eq. 1,2,3,8) then the chi-squared test will indicate how well the data fits the modified log-normal distribution function represented by the regression line. Small values of the chi-squared statistic indicate goodness of fit. A summary of the analysis performed on the data in Table 1 is presented in Table 2. The results show that the weighted regression analysis technique using the size transformation of Eq. 8 is superior to methods which do not utilize the weights of Eq. 6 or the transformation of Eq. 8.

In order to further illustrate the applicability of this method of particle size analysis the particle size data of Li[14] was analyzed. This data was generated by the milling of an acetaminophen granulation using a screen size of 2000 µm. Li prepared sixteen such granulations. When simple linear regression analysis or graphical procedures are used, not all granulations appear to follow a log-normal distribution. When the method of analysis outlined above is applied to the data all sixteen lots are described by modified log-normal distributions as indicated by the chi-squared statistic. A typical sample from this study (Table 3)

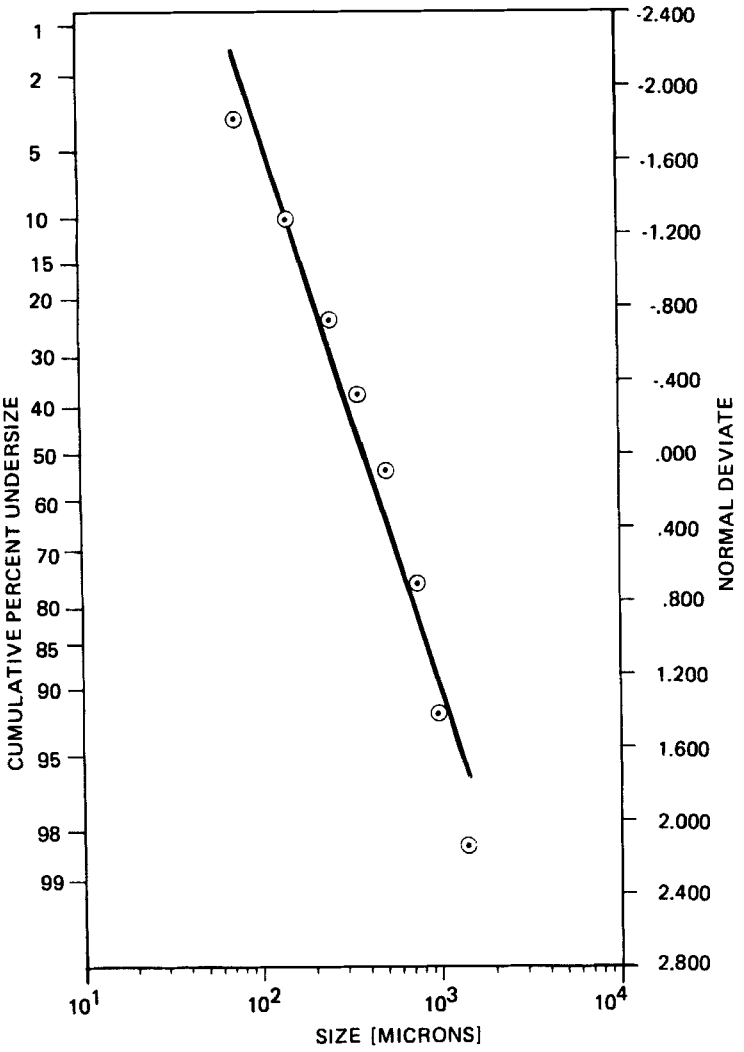

Figure 6.

A plot of acetaminophen particle size data using standard regression techniques.

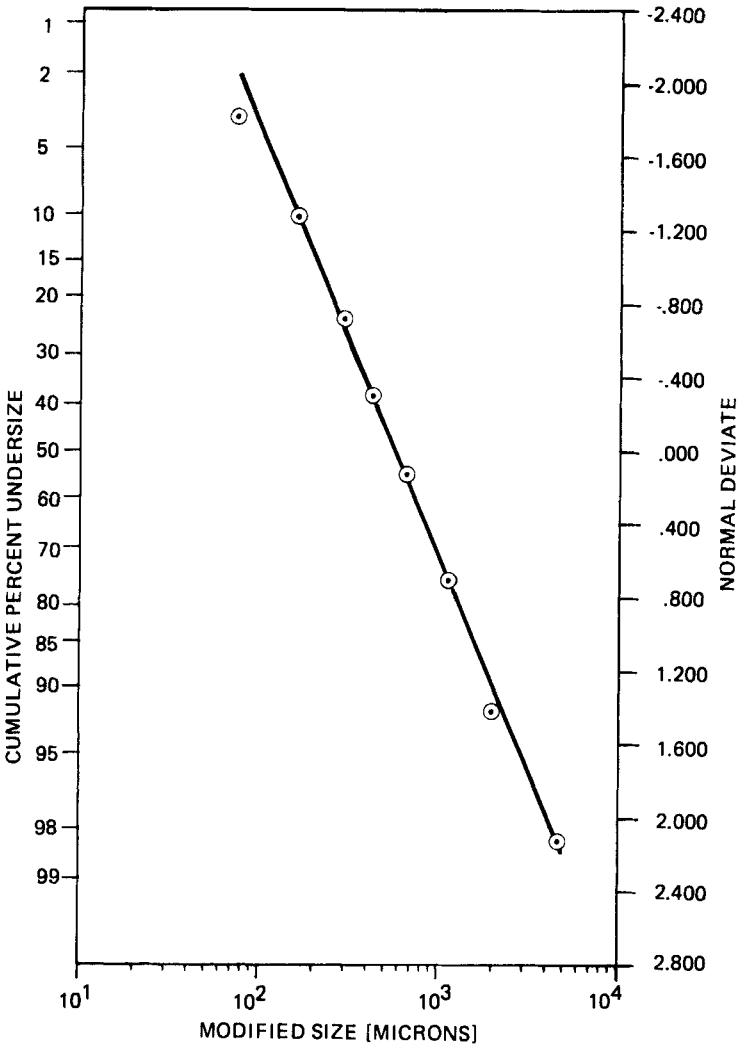

Figure 7.

A plot of acetaminophen particle size data using the weighted regression technique and the transformation of Equation 8.

is shown before and after application of the weighted regression technique (Figs. 6 and 7).

Another advantage to using these algebraic methods of analysis is that the particle size distribution is completely described by the regression parameters μ_d and σ_d (Fig. 2). Therefore equations of state or computer simulations which relate μ_d and σ_d to processing parameters will allow the design of a process which yields a predetermined particle size distribution. This may be accomplished via the explicit choice of μ_d and σ_d or by specifying the percent of particles desired between two particle sizes. The later method implicitly denotes μ_d and σ_d and will be utilized in a future study of the milling of pharmaceutical granulations.

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