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THE DEVELOPMENT OF A MATHEMATICAL APPROXIMATION TECHNIQUE TO DETERMINE THE MASS MEDIAN AERODYNAMIC DIAMETER (MMAD) AND GEOMETRIC STANDARD DEVIATION (GSD) OF DRUG PARTICLES IN AN INHALATION AEROSOL SPRAY

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ABSTRACT

The aerodynamic diameter of an airborne particle is the key property in determining its respiratory deposition. Two particles may differ in their shape, size, and/or density and still be aerodynamically indistinguishable because they have similar behavior in a moving airstream. A cascade impactor has been used to measure the range of aerodynamic diameters for drug particles in an aerosol spray product. The two terms associated with aerodynamic particle sizing are Mass Median Aerodynamic Diameter (MMAD) and the Geometric Standard Deviation (GSD). Both terms are determined from the visual fit of a straight line to data manually plotted on log-probability paper. The plotting of this data is a time consuming activity and the fit of the line to the data can be very subjective.

Although this technique is an excellent candidate for computerization, it cannot be done directly since the probability

axis is an integral function not easily adaptable to the computer packages generally used in the laboratory. A mathematical approximation has been developed that in effect "linearizes" the probability axis. The mathematical relationship (a fifth degree polynomial expression) when incorporated into a general computer program allows for the direct computation of the two aerodynamic terms. Since the subjectiveness of manually plotting the data and fitting the line are removed, the results obtained are potentially more accurate. Also, the results are obtained more quickly with significantly less effort. This paper explores the development of the mathematical relationship and provides a comparison of values obtained by both the manual and computer methods.

INTRODUCTION

The human respiratory tract can be viewed as an aerodynamic classifying or particle sizing system for airborne particles.[1,2] Two particles may differ in shape, size, and/or density and yet be aerodynamically indistinguishable because they have similar behavior in an airstream. Aerodynamic diameter is the key property for respiratory deposition of airborne particles. In many cases, it is not necessary to know the true size, shape, or density of a particle if the aerodynamic diameter can be determined.[3] The cascade impactor has been proposed for the aerodynamic sizing of drug particles in an inhalation aerosol spray.[4]

A cascade impactor has been used to aerodynamically size drug particles in an inhalation aerosol product. The device consists of a series of separation plates (stages) with each representing an increasingly smaller aerodynamic diameter. The drug particles are introduced into the system via a moving airstream. The particles cascade through the increasingly smaller stages until they are impacted as a function of their aerodynamic diameters.

The amount of drug impacted on each stage is quantified as a relative percent of the total drug impacted on all of the stages. A cumulative percent value is then determined for each stage by adding the relative percent values for all stages aerodynamically smaller than stage of interest. The two terms associated with aerodynamic particle sizing, Mass Median Aerodynamic Diameter (MMAD) and the GSD (Geometric Standard Deviation), are calculated by manually plotting the cumulative percent data versus the aerodynamic diameter of each stage on log-probability paper and fitting a straight line. The plotting of this data is a time consuming activity and the fit of the line to the data is very subjective. Although this technique is an excellent candidate for computerization, it cannot be done directly since the probability axis is an integral function not easily adaptable to the computer packages generally used in the laboratory.

A fifth degree polynomial expression has been found that can be used to "linearize" the probability axis. This relationship when incorporated into a general computer program allows for the direct computation of the two aerodynamic terms. Results can now be obtained more quickly with much less effort. This paper will explore the development of the mathematical relationship and compare the values obtained to those obtained the manual plotting technique.

BACKGROUND

In a flowing stream of air, small spherical particles will have a lower inertia than larger spherical particles of the same density. If an obstacle is placed directly in the path of this flowing stream of air, the direction of the airstreams will be abruptly changed. Particles of high inertia will not be able to adapt to this change in direction and will impact upon the obstacle. The Stokes equation[5] is used to calculate the aerodynamic diameter (also called Effective Cutoff Diameter or ECD) associated with the obstacle. This obstacle serves as a separator of airborne particles into two sizes; particles impacted are larger than the aerodynamic diameter of the separator whereas particles that are not impacted are smaller than the aerodynamic diameter parameter associated with the separator. It is not the intent of this paper to provide a detailed discussion of impactor theory. A more detailed discussion of this topic can be found elsewhere in the references cited.

A cascade impactor consists of a series of up to eight stages with a collection disc positioned directly below each stage.[6] The collection disc serves as the obstacle to change the direction of the airstreams. Each stage represents an increasingly smaller aerodynamic diameter. Drug particles cascade down through the unit and are sized according to their aerodynamic diameter. The amount of drug found on each collection disc is determined and the mass of drug distributed over a range of aerodynamic diameters is then calculated. From this data, the MMAD and GSD are obtained.

MMAD AND GSD USING LOG PROBABILITY PAPER

The amount of drug impacted on each collection disc is quantified and a cumulative percent distribution of the drug is determined. The data obtained is plotted manually on log-probability graph paper.[7] The aerodynamic diameter or ECD (in microns) for each stage of the cascade impactor is plotted on the logarithmic scale axis versus the cumulative percent on the probability scale axis. The cumulative percent term represents the amount of drug (as a percent of the total amount of drug found on collection discs) for all of the stages with aerodynamic diameters less than the stage of interest. Table 1 shows typical data obtained for an eight stage cascade impactor.

TABLE 1

Typical Cascade Impactor Data

STAGE #	Cumulative %	ECD(microns)
Preseparator	98.0	9.00
1	95.0	6.20
2	92.0	4.37
3	75.0	2.99
4	50.0	2.02
5	20.0	1.09
6	12.0	0.70
7	5.0	0.52

Figure 1 is a plot of this data on log-probability paper. To calculate the aerodynamic terms a straight line is visually fit to the data points. The MMAD is obtained by determining the aerodynamic diameter (ECD) that corresponds to 50%. Next, the aerodynamic diameter (ECD) corresponding to 15.9% ($D^{15.9\%}$) and 84.1% ($D^{84.1\%}$) are determined. For a normal distribution, one standard deviation is equal to the difference between either the aerodynamic diameter at 50% and the aerodynamic diameter at 84.1% (or the difference between 15.9% and 50.0%). For a log-normal distribution which is normal with respect to aerodynamic diameter[8], the geometric standard deviation becomes:

$$GSD = \sqrt{\frac{D^{84.1\%}}{D^{15.9\%}}}$$

The GSD is a unitless term which can never be less than 1.0 and is only attainable when all particles have exactly the same aerodynamic diameter. The value obtained from the graph for MMAD is 1.8 microns. The values for $D^{84.1\%}$ and $D^{15.9\%}$ are 0.85 and 3.8 microns, respectively. The GSD calculated is 2.11.

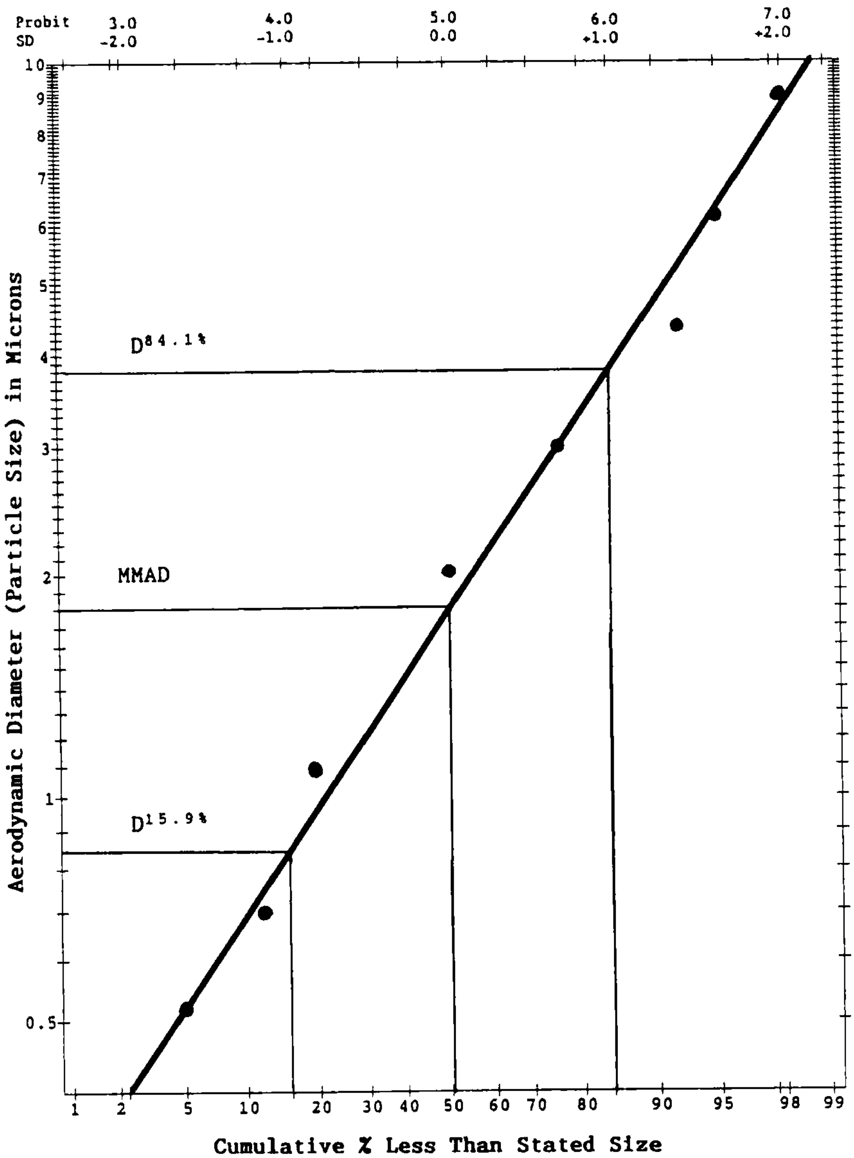

FIGURE 1

Manual Plot of Data On Log-Probability Paper

TABLE 2

Same Data in Tabular Probit and Log_{10} ECD Terms

STAGE #	Tabular Probit	Log ECD
Preseparator	7.06	0.954
1	6.65	0.792
2	6.41	0.640
3	5.67	0.476
4	5.00	0.305
5	4.16	0.037
6	3.83	-0.155
7	3.35	-0.284

MMAD AND GSD USING TABLE OF PROBIT VALUES

The 50% point on the cumulative percent (probability) axis represents the mid-point of a normal distribution. The point at 84.1% on the same axis is one standard deviation (+1.0) from this mid-point. The point at 15.9% is one standard deviation (-1.0) in the opposite direction from the mid-point. A probit term can be used to represent the linear displacement from the mid-point along this axis. The value assigned to a probit is the standard deviation term plus 5. In probit terms, the point at 15.9% is 4.0, the point at 50% is 5.0, and the point at 84.1% is 6.0. By using a Table of Probits[9], it is possible to assign any cumulative percent value a tabular probit value.

Most computer graphic packages require that both axes to be linear if the fit of a straight line to the data is desired. The use of probit values in effect "linearizes" the cumulative percent axis. The aerodynamic diameter axis can be linearized by simply taking the the logarithm of the ECD term. Table 2 contains the same data as Table 1 with the cumulative percent values assigned the tabular probit equivalents and the logarithm of the ECD values substituted for the ECD values.

Figure 2 is the graph created from the tabular probit and $\log_{10}$ ECD data contained in Table 2.

The fit of a straight line to the data is then made by the computer.

The resulting equation for the line fit is: $y = mx + b$

where: $y = \log_{10}$ of aerodynamic diameter for the stage

x = probit value corresponding to the cumulative %

b = y-intercept

m = slope of line

From the slope and intercept of the line the $D^{15.9\%}$, MMAD and $D^{84.1\%}$ can be calculated. The MMAD occurs where the cumulative percent is 50% or when x equals 5. When $x = 5$, $y = 5m+b$ and represents the $\log_{10}$ of the aerodynamic diameter at 50%, the MMAD becomes 10^{5m+b}. At 15.9% cumulative percent, $x = 4$ thus $y = 4m+b$. The aerodynamic diameter at 15.9% is 10^{4m+b}. At 84.1% cumulative percent, $x = 6$ so $y = 6m+b$. The aerodynamic diameter at $D^{84.1\%}$ is 10^{6m+b}. For this example, $D^{15.9\%}$ = 0.87 microns, MMAD = 1.82 microns, and $D^{84.1\%}$ = 3.82 microns. The GSD is calculated as 2.10.

This approach is a major improvement over the manual plotting technique but it still requires looking up probit values in a table.

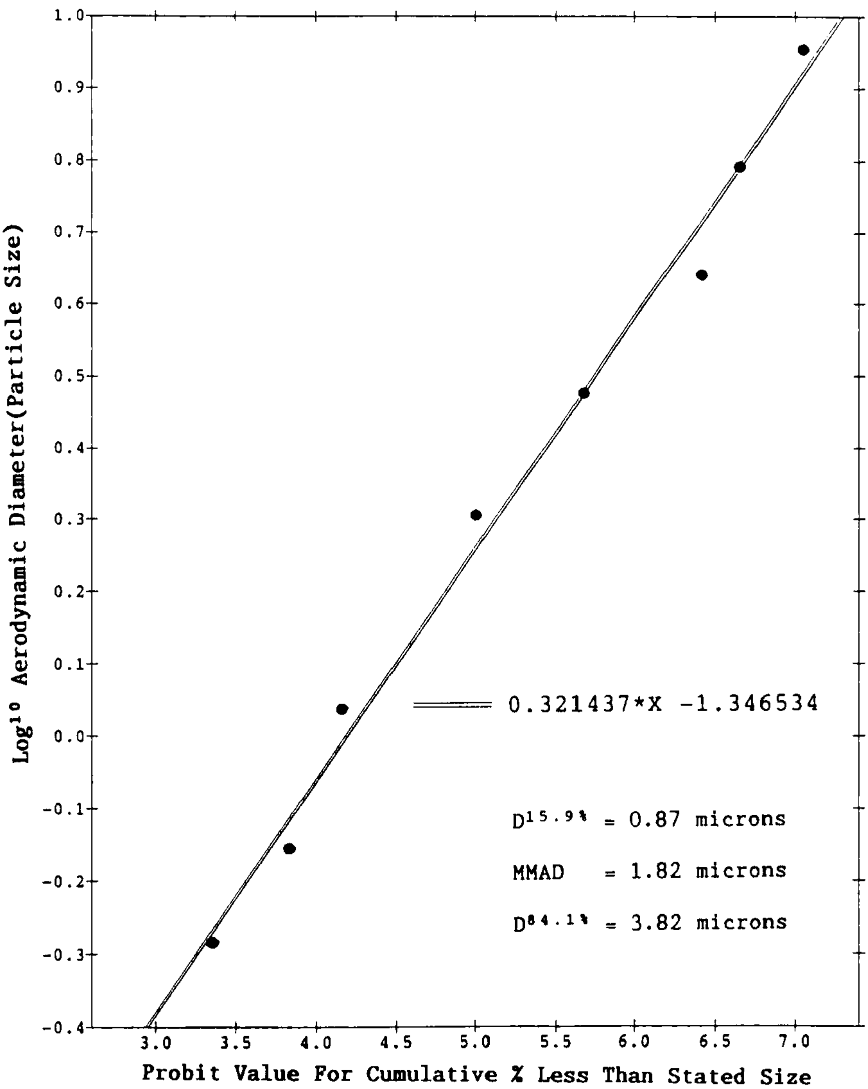

FIGURE 2

Computer Plot of Data Using Tabular Probits

MMAD AND GSD USING CALCULATED PROBIT VALUES

The probability (cumulative percent) axis is a normal distribution represented by the following integral expression:

$$P = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{Y-5} e^{-\frac{1}{2}t^2} \, dt$$

where (represented by the probit):

$$Y = \frac{x - \mu}{\sigma} + 5$$

Attempted use of this integral function in a computer program was viewed as undesirable. A plot of tabular probit values versus the corresponding cumulative percent was made in an attempt to determine if a more quantifiable relationship could be established. Through the empirical fit of a function to the data it was found that a fifth degree polynomial expression could be used to transform cumulative percent to probit values which can plotted on a linear axis. The expression obtained through this technique is:

$$CPV = 4.347524e^{-09}x^5 - 1.086881e^{-06}x^4 + 1.046449e^{-04}x^3 - 4.827924e^{-03}x^2 + 0.133068x + 2.770212$$

where: CPV = the calculated probit value
x = the cumulative percent value

Figure 3 shows a fit of the function to the tabular probit values that correspond to the cumulative percent. Comparing the tabular probit values with the calculated probit values over range of 2 % to 98 % (see Table 3) shows very good agreement.

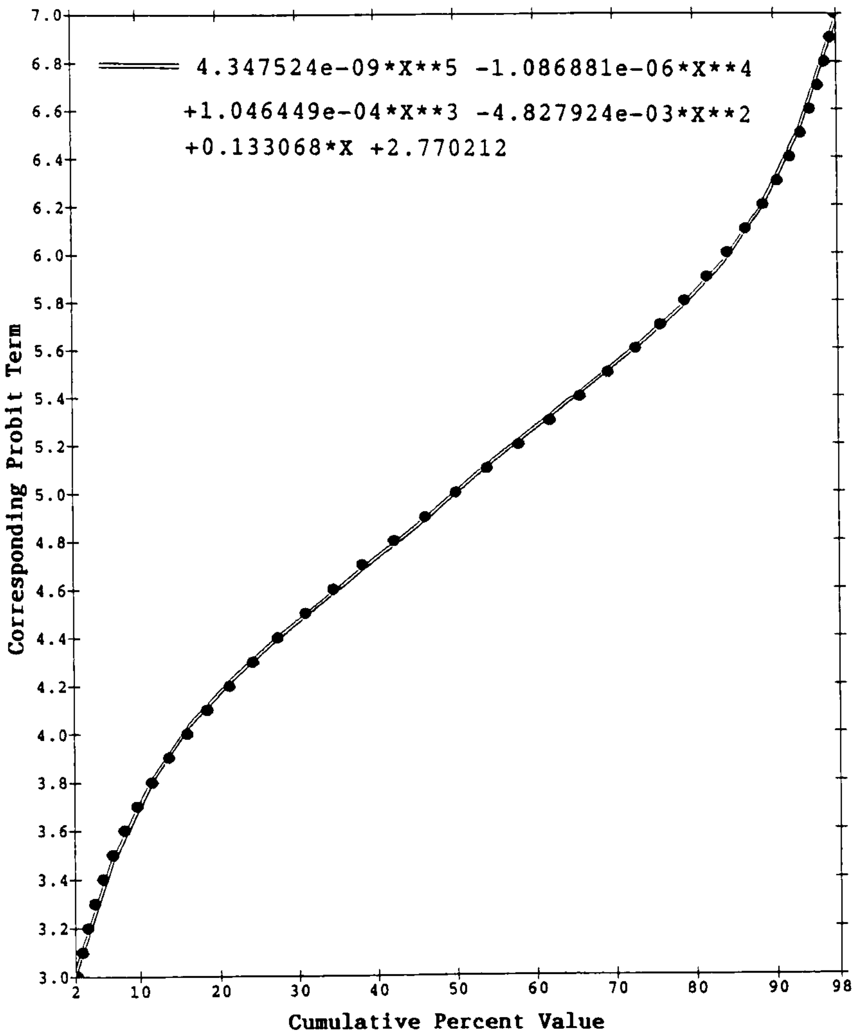

FIGURE 3

Plot of Cumulative Percent Versus Tabular Probits

As in the previous example, a graph can be constructed by plotting the logarithm of the aerodynamic diameter(ECD) for each stage versus the probit term. However, instead of assigning a probit term to each cumulative percent value from a probit table, it can now be directly calculated using the mathematical relationship. Table 4 contains the same data as Table 2 except

TABLE 3

Comparison of Calculated and Tabular Probits

Percent	Tabular	Calculated	Difference
98.00	7.06	6.98	0.08
97.72	7.00	6.95	0.05
96.41	6.80	6.81	-0.01
94.52	6.60	6.63	-0.03
91.90	6.40	6.42	-0.02
88.50	6.20	6.20	0.00
84.10	6.00	5.98	0.02
78.80	5.80	5.78	0.02
72.60	5.60	5.60	0.00
65.50	5.40	5.42	-0.02
57.90	5.20	5.22	-0.02
50.00	5.00	5.00	0.00
42.10	4.80	4.78	0.02
34.50	4.60	4.58	0.02
27.40	4.40	4.40	0.00
21.20	4.20	4.22	-0.02
15.90	4.00	4.00	0.00
11.50	3.80	3.80	0.00
8.10	3.60	3.58	0.02
5.48	3.40	3.37	0.03
3.59	3.20	3.19	0.01
2.28	3.00	3.05	-0.05
2.00	2.95	3.02	-0.07

that the probit values have been calculated using the polynomial expression.

The fit of a straight line to the data by the computer is again used to calculate the slope and intercept. Figure 4 is a plot of the data from Table 4 using calculated probit values. For this example, $D^{15.9\%}$ = 0.87 microns, MMAD = 1.83 microns, and $D^{84.1\%}$ = 3.84 microns. The GSD is calculated as 2.10.

TABLE 4

Same Data in Calculated Probit and Log_{10} ECD Terms

STAGE #	Calculated Probit	Log ECD
Preseparator	6.98	0.954
1	6.67	0.792
2	6.42	0.640
3	5.67	0.476
4	5.00	0.305
5	4.18	0.037
6	3.83	-0.155
7	3.32	-0.284

EVALUATION OF THE FIT OF THE FUNCTION

It has already been shown that the calculated probit values are in excellent agreement with the table probit values. However, there is some divergence at the tails below 2% and above 98%. This divergence occurs because probit values calculated from the fifth degree polynomial expression never exceed 2.77 (0%) and 7.33 (100%). Upper and lower limits are not attainable using a probit table because the distribution is infinite. This divergence is a minor issue since it would not be wise to place a significant weighting on these extreme values when generating the graph used to calculate MMAD and GSD. In fitting the line to the data the heaviest weighting should be given to cumulative percent values of between 20% and 80%.[10]

SUMMARY

The same data set was examined by the three calculation approaches discussed. The aerodynamic terms calculated are

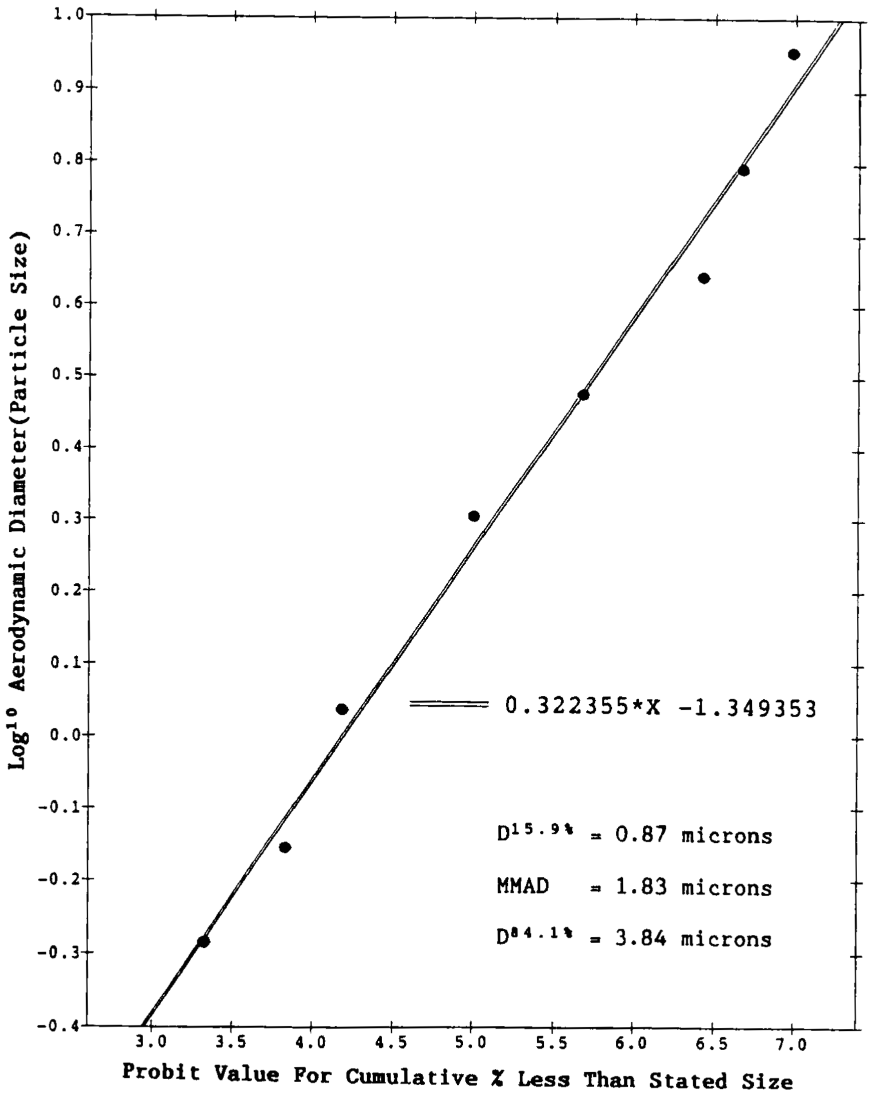

FIGURE 4

Computer Plot of Data Using Calculated Probits

TABLE 5

Comparison of Aerodynamic Terms Obtained

	Manual Plot	Tabular Probit	Calculated Probit
MMAD	1.80	1.82	1.83
GSD	2.11	2.10	2.10

summarized in Table 5. The results obtained by all three approaches are in very good agreement.

The major benefit derived in using calculated probit values is that the mathematical expression used to calculate them can be incorporated a general computer program. The fit of a line to the data by the computer allows for the direct computation of the two aerodynamic terms from the slope and intercept values. The tedious and time consuming activity of manually plotting the data is eliminated. The manpower effort required to obtain the results is significantly reduced.

In the example studied, the fit of a line to the data was not very challenging. Most of the time this is not the case and the visual fit of a straight line to the data becomes very subjective. The use of a computer to fit a line to the data eliminates this subjectiveness. Since both aerodynamic terms are dependent upon the fit of the line to the data, potentially more accurate results are now attainable using the approximation relationship.

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