Log-Normal Distribution of Tablet Pore Diameters

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Abstract □ The use of the log-normal distribution applied to the pore characteristics of tablets is discussed. An analytical method for the determination of the geometric mean pore diameter is presented and applied to several tablet samples. The method eliminates the necessity of plotting the pore volume data, eliminates subjective evaluation, and is amenable to computerized calculations.

Keyphrases □ Pore diameters, tablets—analytical method using log-normal distribution, advantages discussed □ Log-normal distribution—applied to pore characteristics of tablets, analytical method developed □ Tablets—analytical method presented to determine pore characteristics using log-normal distribution

Interest in the porous nature of pharmaceutical tablets has been growing steadily in recent years. As early as 1952, Higuchi *et al.* (1) stated: "... it seems reasonable to assume that the volume of void space in a given tablet would greatly influence its disintegrating property."

Two major parameters are associated with the porous nature of a tablet: *(a)* the volume of the void space designated as the porosity or pore volume, and *(b)* the size of those pores characterized by their diameters. This report deals with the second parameter.

Mean pore diameter has been used to characterize tablet pore size; one method of measurement used (2, 3) is air permeametry and the Kozeny–Carman equation. Adsorption isotherms have also been used (4–6). Another reported method (7) involved the mercury intrusion porosimeter. These last two methods generate pore distributions from which a mean value can be derived, although, if desirable, one may discuss the entire distribution.

The mean pore diameter is of interest in pharmacy because it is a single number that can be used to compare one tablet with another. As the level of sophistication increases and correlations are found, the total distribution will certainly tell a more complete story.

DISCUSSION

One method used to characterize porosity and pore size of materials is the mercury intrusion porosimeter. To make a measurement by a porosimeter, mercury is forced into the pores of the sample (*e.g.*, a tablet) under hydraulic pressure. The size of the pore penetrated is a function of this applied pressure, P, and the two are related by Eq. 1 (8):

$$Pr = -2\gamma \cos\theta \qquad \text{(Eq. 1)}$$

where r is the pore radius, γ is the surface tension of mercury, and θ is the contact angle between the mercury and the pore surface. The value of γ for mercury at 25° is 474 dynes/cm and, assuming a contact angle of 130°, the pore diameter, d, and the applied pressure are related as shown in Eq. 2 (8, 9):

$$d = \frac{175}{P} \qquad \text{(Eq. 2)}$$

where the pore diameter is expressed in microns and the pressure in psi (absolute).

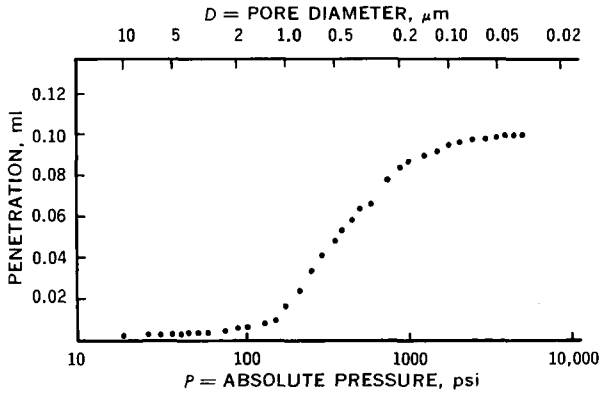

Figure 1—*Cumulative pore volume as a function of the logarithm of pressure or the logarithm of pore diameter.*

To illustrate the pore-size distribution, the cumulative pore volume is normally plotted *versus* the logarithm of the pore diameter. Alternatively, one may plot a frequency distribution. When the frequency distribution of a variable exhibits positive skewness, this distribution can be approximately described by a logarithmic normal distribution, which is shown in Eq. 3 for the variable X:

$$f(\ln X) = \frac{1}{\sigma_L\sqrt{2\pi}} \exp[-(\ln X - \ln \mu)^2/2\sigma_L{}^2] \qquad 0 < X < \infty \qquad \text{(Eq. 3)}$$

where μ is the mean value, and σ_L is the logarithm of the standard deviation. This equation is an extension of the equation for the normal distribution:

$$f(X) = \frac{1}{\sigma\sqrt{2\pi}} \exp[-(X-\mu)^2/2\sigma^2] \qquad \text{(Eq. 4)}$$

where the variable, X, is normally distributed, and μ and σ are the location and the scalar parameters of the normal curve, respectively (10). In Eq. 3, it is the logarithm of X, rather than X itself, that is normally distributed.

The log-normal or log-probability relationship has been used most frequently in pharmacy to describe the size distribution of particulate matter (11, 12), and it was suggested (13) that it be considered in connection with dissolution data. Recently for the first time, this distribution was applied to pore sizes in the hydrated cement paste system (14). That is, the parameter that is normally distributed is the logarithm of the diameter rather than the diameter itself.

This article shows that the properties of the log-normal distribution are adequate to describe the pore structure for tablets of pharmaceutical interest and presents an analytical technique for the computations.

EXPERIMENTAL

Pore-size distribution was determined on several tablet samples (four sets of data) containing 22% hydrochlorothiazide USP. Qualitatively, the formulas for the samples discussed are the same. The manufacturing process involves a starch-gelatin granulation of the active ingredient with dicalcium phosphate and lactose. Starch (corn), talc, and magnesium stearate are added before compression. The tablets are compressed on a rotary press at the same weight; since the level of active ingredient remained constant, the changes noted were due to the level of inert ingredients or to compression pressures (Table I).

The pore-size distributions were determined by a mercury in-

Table I—Formulation Differences

Data Set	Calcium Phosphate, mg	Lactose, mg	Gelatin, mg	Starch, mg	Magnesium Stearate, mg	Pressure, tons
I	50.0	30.0	0.2	6.6	0.2	1.1
II	30.0	50.0	0.5	4.6	0.5	1.5
III	55.5	24.5	1.0	5.6	1.0	1.0
IV	40.0	40.0	0.5	6.0	0.3	1.0

trusion porosimeter[1]. Vacuum was drawn by a vacuum pump[2] attached to the porosimeter, and hydraulic pressures up to 351.5 kg/cm² (5000 psi) were used in the measurements.

RESULTS

The usual graphical representation of porosimeter data (Fig. 1) shows the volume of mercury penetration into the sample *versus* the logarithm of the pressure applied. The mean pore diameter corresponding to a given pressure may also be read directly from the graph supplied with the instrument by calculating 50% of the maximum penetration and selecting the corresponding diameter (0.48 μm in this case).

When cumulative data plot out as a sigmoid curve, it suggests that the distribution is normal, in this case log-normal since the abscissa is a logarithmic scale.

Instead of the cumulative frequency plot in Fig. 1, one may generate the cumulative normal curve by simply normalizing the data. This was done for the data in Fig. 1 by using Eq. 5:

$$P = \frac{\text{cumulative frequency}}{\text{total pore volume}} \times 100 \qquad \text{(Eq. 5)}$$

where P is the percent probability, and the cumulative frequency is the cumulative volume of pores up to any diameter. As shown in Fig. 2, the sigmoid shape is retained, but probabilities have been introduced by normalizing; the total probability, or area under the normal curve, is unity.

To convert the sigmoid curve to a straight line, one makes use of probability paper. When the data shown in Figs. 1 and 2 are plotted in this manner, Fig. 3 results. If the frequency distribution is approximately normal, the plotted points lie very nearly on a straight line.

The advantage of the probability plot is that the characteristic parameter, μ, can be read directly from the graph, and the other characteristic, σ, can be easily calculated from the appropriate points.

In practice, probability plots are not really linear. The points near the extremities of the distribution are not considered very significant (15). These data points at the extremities, especially the large sizes, tend to weight the data and thus prohibit the use of an arithmetic mean.

In Fig. 3, the ends of the distribution will certainly not be on any straight line which may be drawn but the decision must be made as to which points can be considered to be on the ends. This question is considered in the following analytical method.

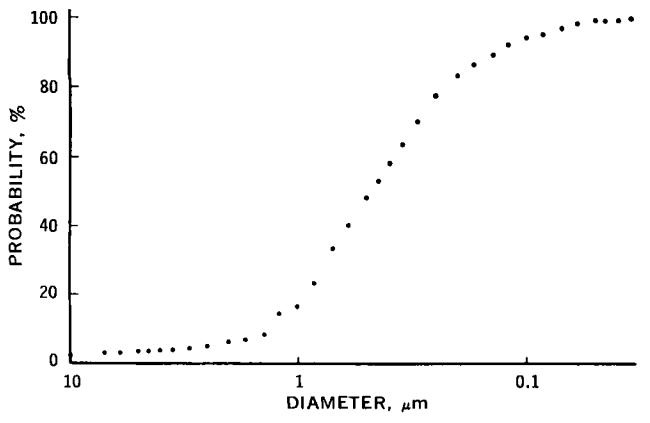

Figure 2—*Cumulative log-normal plot: percentage cumulative frequencies* versus *log pore diameter.*

Table II—Variation in Mean Pore Diameter as a Function of Proportion of Data Included

Probabilities[a], %	n^b	R^2, %[c]	D_m, μm	D_m, μm, Graphical Method
30–70	6	99.98	0.4821	0.48
25–75	7	99.97	0.4815	
20–80	9	99.90	0.4785	
15–85	11	99.60	0.4731	
10–90	14	99.60	0.4618	

[a] Points falling between these probabilities were used in the calculation. [b] Number of data points. [c] Index of determination.

ANALYTICAL

Although the graphical technique discussed will yield these values for the geometric mean pore diameter[3] and the geometric standard deviation, the method of plotting such data is time consuming. To provide a method allowing computerization of the calculation, an analytical method was developed.

The log-probability plot (Fig. 3) should linearize those data from a cumulative log-normal plot (Fig. 2), but in practice it does not do so completely. The cumulative log-normal plot is sigmoidal, but the center portion does approximate a straight line.

The parameters of interest can be read off the graph (Fig. 2); but since this set of data, or at least the straight-line portion, is amenable to regression analysis by calculator or computer, the parameters can also be calculated. The question then becomes how much of the data to include in the approximation.

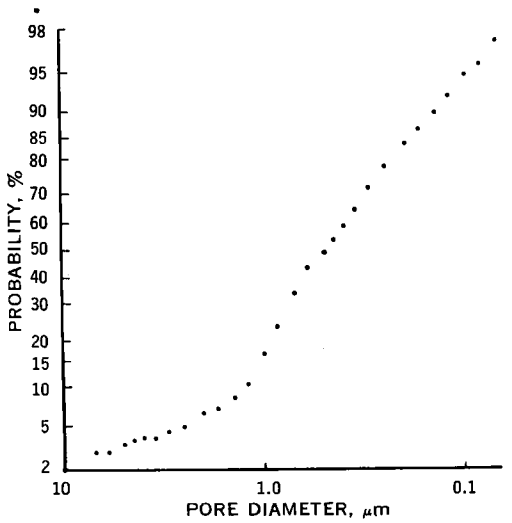

Figure 3—*Log–probability plot.*

[1] Aminco, American Instrument Co., Bethesda, Md.
[2] Cenco, Central Scientific Co., Chicago, Ill.

[3] The geometric mean diameter is equivalent, if the distribution is normalized in terms of the logarithmic variate, to the median.

Table III—Variation of Mean Pore Diameter as a Function of Proportion of Data Included

Probabilities[a], %	n^b	R^2, %[c]	D_m, μm	D_m, μm, Graphical Method
Data set 2:				0.18
30–70	6	99.40	0.1764	
25–75	8	99.64	0.1779	
20–80	10	99.72	0.1792	
15–85	12	99.83	0.1795	
10–90	15	99.72	0.1813	
Data set 3:				0.16
30–70	5	99.63	0.1610	
25–75	6	99.77	0.1613	
20–80	9	99.43	0.1637	
15–85	10	99.26	0.1649	
10–90	13	99.44	0.1651	
Data set 4:				0.16
20–80	4	99.70	0.1618	
15–85	5	96.21	0.1626	
10–90	6	85.90	0.1535	

[a] Points falling between these probabilities were used in the calculation. [b] Number of data points. [c] Index of determination.

Regression analysis was performed on these data, and Table II shows the effect of including various sections of the data in the calculations. The parameter of interest, mean pore diameter, D_m, does not change significantly as data are added or subtracted. Moreover, the index of determination for the regression[4] shows that the straight line does approximate the data satisfactorily. The same results are shown in Table III for additional sets of data yielding different mean diameters, and the diameters calculated by this method are in excellent agreement with those obtained by graphical methods in all cases.

For the calculation of the geometric standard deviation, the points at 15.87 and 84.13% probability are important[5]. It is recommended that probabilities between 15 and 85% be routinely included in the calculations. The geometric standard deviation, σ, can then be calculated by the following equations (11, 14, 16):

$$\sigma = \frac{\text{diameter at 84.13\% probability}}{\text{diameter at 50.0\% probability}} \quad \text{(Eq. 6)}$$

or:

$$\sigma = \frac{\text{diameter at 50.0\% probability}}{\text{diameter at 15.87\% probability}} \quad \text{(Eq. 7)}$$

[4] The index of determination is the square of the correlation coefficient.
[5] σ = 34.13% when probability is used.

The index of determination that determines the fit to the straight lines remains the criterion by which one can judge whether further analysis is necessary.

CONCLUSIONS

By using this method, a geometric value can be obtained for the mean pore diameter of tablets from pore distribution data generated by the porosimeter. It is not necessary to plot the data, which eliminates subjective evaluation; an additional parameter, the geometric standard deviation of the distribution, is also easily available. These parameters can be utilized as another method of comparing one tablet with another and of correlating other tablet properties or formulation parameters. The interpretation of differences in pore characteristics will be the subject of subsequent reports.

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