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THE USE OF FRACTAL GEOMETRY IN PHARMACEUTICAL SYSTEMS

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ABSTRACT

The nature of surface irregularity affects many phenomena including adsorption/desorption, catalysis, crystal growth, drug dissolution and chromatography. Many excellent models have been developed with the oversimplified assumption that all particles are smooth spheres; fractal geometry allows these models to be expanded to irregular surfaces by providing a quantitative means of assessing surface roughness.

An overview of fractal analysis is presented in the following , and the state of the art, as far as pharmaceutical systems are concerned are outlined. Erroneous approaches, as well as the directions pharmaceutical research and technology might take in the area of fractal analysis are suggested.

From a historical perspective, micromeritics (the science of particle size, shape and surface area) were first developed with the assumptions that all particles were smooth spheres.

Much excellent work has been developed with such an oversimplified model. For example, numerous workers have shown that particle flow through an orifice is a function of "particle

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Table I. Particle size distribution of griseofulvin.

Diameter (μm), d	Percent Above by Number	ln[d]
2	99	0.693
6	90	1.792
10	70	2.303
18	50	2.890
25	30	3.219
35	20	3.555
55	10	4.007

diameter", and experiments have most often been carried out on particles as close to spherical as possible, and as monodisperse as possible.

The science of micromeritics, the science of small particles, is the making of DallaValle (1943) who coined the term in a book of the same name which describes methods of particle size measurement, mostly used by soil scientists.[1]

Shape Factors From Particle Size and Area

In this article, we shall mostly focus on monodisperse populations for the purpose of concentrating on the surface characteristics.

The shape of a particle is a parameter which is completely ignored in such a view. Dalla Valle first attempted to introduce a type of *shape factor* by stating that for a given particle there were two "shape factors", one, α_s relating particle surface area, a, to surface mean particle "diameter", d_s:

$$a = \alpha_s d_s^2 \qquad (1)$$

one, α_v, relating particle volume, v, to the volume mean diameter, d_v:

$$v = \alpha_v d_v^3 \qquad (2)$$

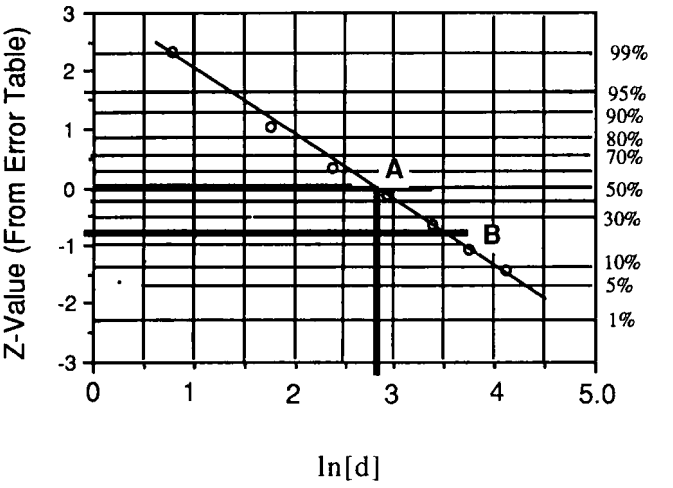

Fig. 1. Data from Table 1 plotted on probability paper using logarithmic scale. The right column indicates percent oversize.

The specific surface area, A_w, is then given by:

$$A_w = \alpha_s d_s^2/(\rho \alpha_v d_v^3) \qquad (3)$$

The question, of course, arises, how to obtain the values for α_s and α_v. A method of obtaining them is as follows: Most powders are log normally distributed. Table I shows an example of a sample of a powder which is log-normally distributed.

It is seen in Fig. 1 that these data are normally distributed, i.e. by plotting the second column (on a probit scale) versus the thrid column, a straight line ensues.

In particle counting work a certain number of particles in a certain particle size interval are counted. The diameters in the first column represent some midpoint of the size interval, and the number is converted to number percent or number fraction, f_i, by dividing the total number, N, of particles in the sample tested. This is not necessarily known, and often is taken as the value (obtained by iteration) which gives the data a log-linear distribution.

The true density, ρ (g/cm^3), is usually obtained independently, and it follows that for one gram:

$$\sum N f_i \alpha_v d_v^3 \rho = 1 \qquad (4)$$

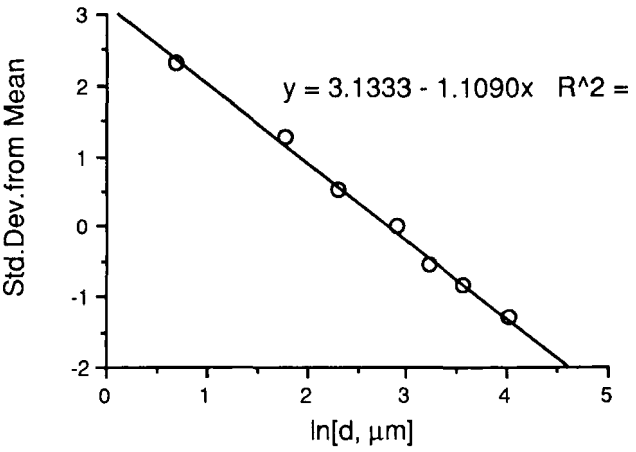

Fig. 2. Log-normal distribution.

where f_i is the fraction of particles of size d_i., i.e. n_i/N, where n_i is the number of particles of that size (or in an interval spanning that size). For fairly monodisperse powders Eq. 4 simplifies to:

$$N\alpha_v d^3 \rho = 1 \qquad (5)$$

or:

$$\ln[N] = -\ln[\alpha_v \rho] - 3\ln[d_v] \qquad (6)$$

The geometric mean diameter, d_g, is the median of the log-probability distribution and is represented (50%) as the point A in Fig. 1. Since 34% of the numbers, by normality, should fall between the mean and the mean minus one standard deviation, the standard deviation of the distribution, $\ln[\sigma]$ (a logarithmic number), can be obtained from graphs of the type of Fig. 1 by the abscissa difference between points A and B, where B corresponds to (50-34=) 16%.

d_g is of course not synonomous with d_s or d_v, but a series of equations, the so-called Hatch-Choate relations, give the connection between the two:

$$\ln[d_s] = \ln[d_g] + \ln^2[\sigma] \qquad (7)$$

$$\ln[d_v] = \ln[d_g] + 1.5\ \ln^2[\sigma] \qquad (8)$$

It is noted, in Fig. 1, that a different scale is shown on the left ordinate axis. This is the linearized probability axis. When data are plotted in this fashion, as shown in Fig. 2, then the mean ($\ln[d_g]$) is

the x-value for y = 0, and ln[σ] is obtained as the negative of the slope[2].

The number of particles per gram, N, can be obtained for a relatively monodisperse powder by counting of particles in a given small powder sample.[c] It is seen from Eq. 6 that if N and ρ are known, and if d_v is known from Eq. 8, then α_v is the only unknown, and is hence determinable. For the determination of α_s the following procedure is used:

It can be shown that[3]:

$$\ln[A_w] = -\ln[\rho\alpha_v] + \ln[\alpha_s] - \ln[d_g] - 2.5\ \ln^2[\sigma] \qquad (9)$$

When A_w is determined independently, the only remaining unknown in Eq. 9, is α_s, and the two α-values now constitute the "shape factor".

The method is based on a series of assumptions and is complex. It never gained popularity, and to the authors' knowledge has never been utilized in a pharmaceutical publication. It was recognized early that the need for knowledge of shapes and surfaces was important[4-6], but aside from microscopic methods (which are at best semiquantitative) only one attempt, that of Ridgway and Rupp[7] has been reported in the pharmaceutical literature, where a systematic study of shape factors was undertaken.

These authors[7] used a diamond sorter to separate mesh cuts of granulations into different shapes, and obtained bulk properties (flow rate, apparent density, repose angles for instance). They found that, in general, the more spherical the particle, the more optimal was it for pharmaceutical manufacturing.

The problem is that many pharmaceutical properties are functions not only of particle shape, but also of particle size and surface characteristics. The effect of particle size on flow has been reported often, e.g. the data by Carr[8], are shown in Fig. 3.

Shape Factors

It is noted that the shape factors in the preceding section are global in the sense that they encompass the over-all shape of the particle as well as surface roughness.

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[c] This is fairly simple for larger particle sizes. For small particles, a micro-weighed sample is distributed on the tacky end of tape, and counting done by area, and e.g. three counts prorated to the fully covered surface.

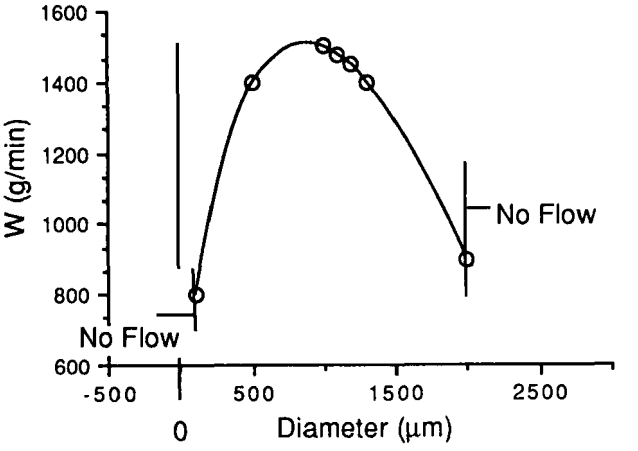

Fig. 3. Flow rate as a function of "diameter", in this case the average between neighboring mesh openings.

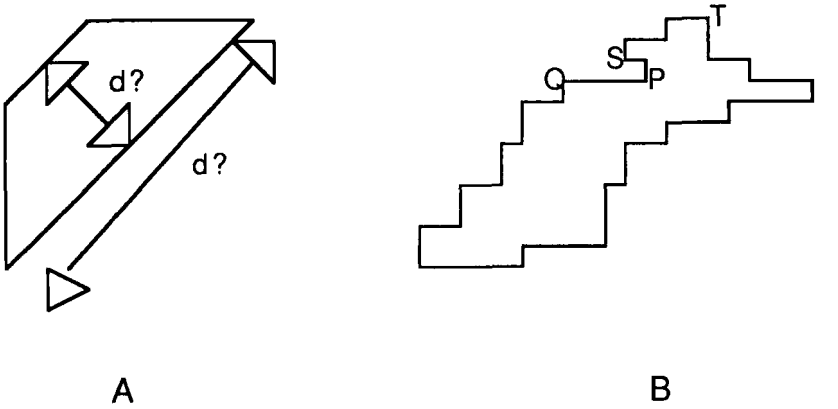

Fig. 4. Distinction between "shape" and "surface roughness"

The question is then, as shown in Fig. 4, where does a shape factor end and a surface roughness index begin? There are two criteria that could be used. One is to say that the shape is something that is common to all the particles. The other is to say that shape can be mathematically described by a *limited* number of parameters, e.g. 20 whereas roughness requires many more. This could be for instance 10 lengths and 10 angles.

Ridgway and Rupp[7], Short, Sharkey and Rhodes[9] and Patel and Carstensen[10], Pothisiri and Carstensen[11] and Lai and Carstensen[12],

have promoted the concept of a shape factor as opposed to a surface characteristic. This aids in the solving of many problems, such as dissolution. The shape factor, Γ, is defined as:

$$a = \Gamma v^{2/3} \tag{10}$$

The following are the shape factor values for some shapes:

Sphere	$\Gamma = 4.836$	(11)
Cube:	$\Gamma = 6$	(12)
Isometric cylinder[d]	$\Gamma = 5.536$	(13)

If a shape is such that the shape factor is independent of dimensional lengths, then it is called isometric. The three particle shapes mentioned are isometric.

The particle in Fig. 4(A) is not isometric. The base angle is $\pi/4$, and if it is a box with depth a, and if the sides are b and c, then its volume is:

$$v = (a/4)(c^2-b^2) \tag{14}$$

Its area is

$$a = h\{[(c^2-b^2)/2] + 2(2)^2(b-c) + b + c\} \tag{15}$$

so that even a fairly simply shaped particle has a complex shape factor, and one which is not independent of its size (a, b and c).

Conventional surface and volume mean diameters would be difficult to assign, since there is the uncertainty of what the "diameter" is (Fig. 4A).

Problems Solved with the Γ-Shape Factor

Short, Sharkey and Rhodes[9] modified the Hixson Crowell cube root law to shapes other than spheres by introducing the Γ-shape factor. Lai and Carstensen[12] adopted a method of approximating shapes by cylinders (needles and plates for instance), and showed that the change in the shape factor was only important after 80% of

[d] A circle-based, right cylinder, the height of which equals the diameter of the base.

the drug had dissolved in most cases. They documented their work with dissolution of oxalic acid cylinders of different dimensions. Veng Pedersen[13,14] essentially described dissolution by taking into account all the faces of the dissolving crystal, and thus avoiding shape factors, but the dissolution equations become rather complex.

These methods do not take surface roughness into account at all. One experimental assessment of this has been suggested by Carstensen[15] as the ratio between the geometric surface area obtained by sieving and actual BET surface areas. Here, however, a spherical shape is assumed, and the method is approximate only.

A fractal approach to dissolution of particles (such as suggested by Farin and Avnir[22]) is probably not sound because self-similarity may not be maintained as the particles dissolve, since the particles become smoother as the dissolution process goes on.

Fractal Geometry

The introduction of fractal geometry as a mathematical tool is attributable to Mandelbrot[16]. There are many applications of the concept, and the intent here is, first to describe what it is, and then to show how it can be applied to pharmaceutical problems.

Without delving into the intricacies of this approach, the general philosophy of it is as follows: If, for instance, the length of a contour such as depicted in Fig. 4B were to be measured, then the length obtained would depend on the "length of the measuring stick", the scaling length, ℓ; if, for instance, this were of the length PQ in Fig. 4B then the fine structure in segment ST would not be included, and the periphery measured would be less than had a smaller scaling length been used. This is the origin of the practical application of fractal dimensions, because interest in it started with the work of Richardson[17], who had the task of measuring the length of the coastline of Great Britain.

In general it can be shown that the length, L, of a perimeter depends on the scaling length, ℓ, by the relation:

$$\log[L] = -D\log[\ell] + Q \qquad (16)$$

where Q is a constant, and where D is referred to as the fractal dimension (and as demonstrated in Eq. 16 emerges as the negative of the slope of a logarithmic L versus ℓ-plot). Such plots are knows as Richardson plots, coast line plots or walking yardstick plots because of their origin in geographical/topological science.

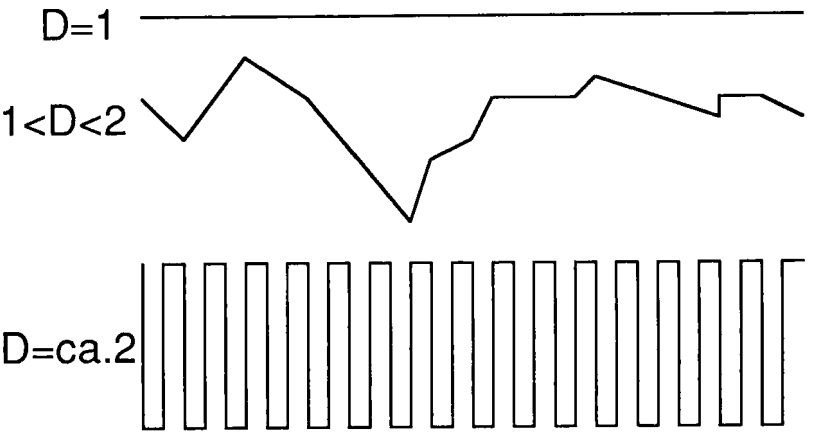

Fig. 5. Fractal Dimensions of a contour. The curves and concepts are approximate and are shown for definition purposes only. The point where a curve becomes a plane filling curve (e.g. a Peano curve) is complex and beyond this writing.

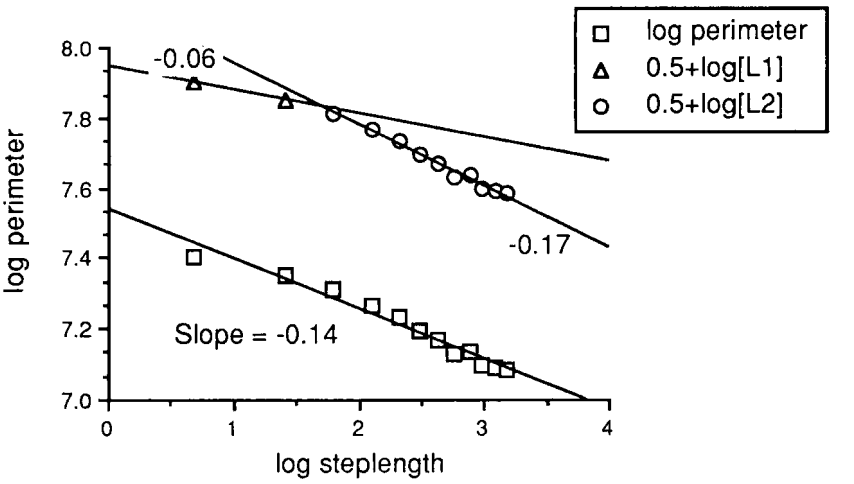

Fig. 6. L as a function ℓ (steplength) for natural microspheres. The lower curve shows all the data plotted in simple linear regression. The points in the upper graph are those in the lower graph + 0.5. This is done for graphical clarity. In the upper graph, the points are shown as bimodal, indicating that there are two self-similarity populations.

An intuitive understanding of D is demonstrated in Fig. 5. For the straight line on top of the figure, the dimension is one. For the wiggly line on the bottom of the figure, the space is to a great extent filled[e] up by the line, and one could visualize this as having a dimension of two. The topological dimension is still one, but the Euclidian dimension is two. For the line in the middle the fractal dimension could be visualized as being between one and two.

It is now possible to define the surface irregularity of a particle by the fractal dimension, D (defined in Eq. 16). To do so it would be necessary, by image analysis, to obtain a cross-sectional representation of the particle and from this obtain the fractal dimension. This indeed has been done, in the pharmaceutical literature, and Fig. 6 below is taken from the work by Ramadan and Tawashi[18].

The slope is[f]

$$H = 1\text{-}D \qquad (17)$$

the fractal *increment*, which is a measure of the surface roughness. It is noted that the curve is not linear (although the authors have treated it as such). Both the photomicrographs (smooth spheres with "pimples") published by the authors and the upper curves in Fig. 6 imply that there are two surface populations (perimeter lengths L_a and L_b) and the same group of investigators (Thibert et al.[19]) indeed, later, reported such a behavior in the fractal analysis of lactose granules; their plot is reproduced in Fig. 7.

Again it is noted that there are two distinct line segments, indicating two types of surface morphology. In the case of lactose, assumedly, fine structure of surface pores has a fractal dimension different than that of the non-porous part of the surface.

Projection of cross-sectional images can be misleading in that the observation can be a function of the orientation of the solid particle. This method is the better, the more spherical the particle is. It is time-consuming, and sampling (as in any other type of microscopy) represents a problem.

It is possible to probe surfaces in a more convenient manner, viz. by gas adsorption. Here the property values are averages over the entire surface, and sampling, hence, is less of a problem

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[e] It is not possible to entirely fill up space with a line.

[f] In reference 18 the authors quote H as being D^{-1} but that would seem to be a typographical error.

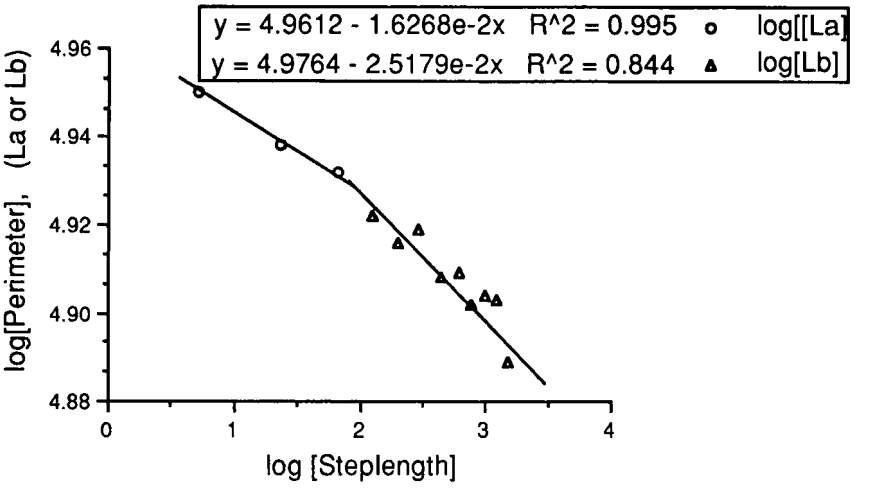

Fig. 7 Figure constructed from data published by Thibert et al.[19] on the fractal character of lactose granulations[g].

(although sample sizes are still small in such work, they are not simply one particle).

Fractal approaches to surface sampling by gas analysis are based on the principle outlined in Fig. 8. If a small adsorbent molecule is employed (Fig. 8A), then more of the roughness will manifest itself than if a larger molecule (Fig. 8B) is used. Here, again, the measured surface should be the larger the smaller the sorbed probe is.

In the case of adsorption the cross-sectional area of the molecule is a function its diameter, ℓ, squared. If the molecule has a circular cross-section of area α and is packed by square arrangement, then the sorbed area is simply ℓ^2 per molecule. Hence:

$$\alpha = \ell^2 \qquad (18)$$

or

$$\ell = (\alpha)^{1/2} \qquad (19)$$

[g] The text in Reference 19 is not quite clear as to which of the materials form the base for its Fig. 1, but presumably it is lactose granulations.

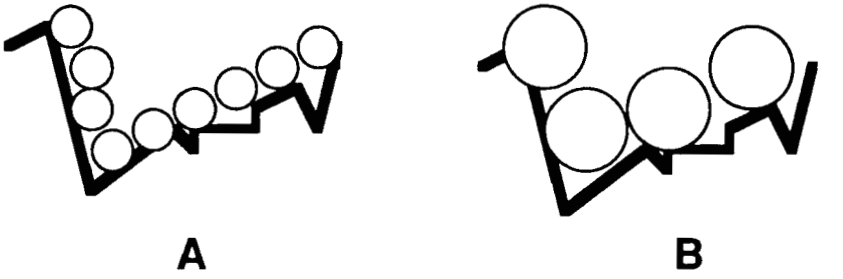

Fig. 8. Coverage of an irregular surface by different size adsorbant molecules

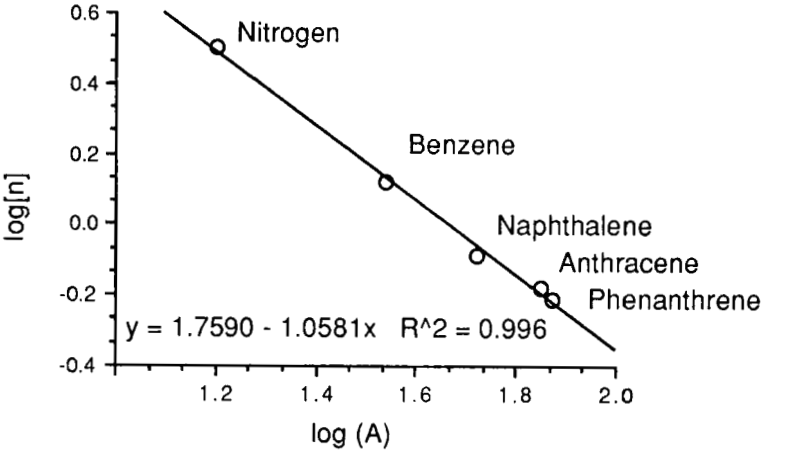

Fig. 9. Fractal plot of carbon black. Amount of adsorbate , n (mmol/g) in monolayer as a function of cross-sectional area ($Å^2$) of adsorbing molecule.

Inserting this into Eq. 16 gives

$$\ln[n_m] = -D\ln[(\alpha)^{1/2}] + Q = -(D/2)\ln(\alpha) + Q \qquad (20)$$

where n_m is the number of molecules in a monolayer. The more general case where the molecular packing is other than square packing can be treated similarly, where now

$$\alpha = q\ell^2 \qquad (21)$$

Fig. 9 is constructed from data published by Avnir et al.[20]

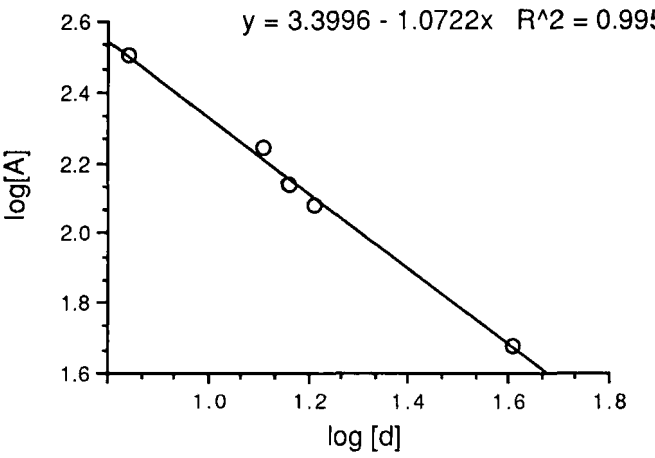

Fig. 10. BET surface area, A (m^2/g) as a function of particle diameter, d (nm) of various Aerosils. Graph constructed from data published by Avnir et al.[20]

It is seen that the slope is

$$-D/2 = -1.0581, \text{ so that } D = 2.16 \quad (22)$$

In the above case the molecules are fairly spherical, and it should be noted that if an adsorbents lies flat on a surface, then the fractal equation becomes:

$$\log n = (-D+1)\log[v] \quad (23)$$

where v is the molar volume of the sorbed molecule.

Experiments such as described are still rather cumbersome, and it is more convenient (although still not practical from a quality control point of view), to do nitrogen adsorption on various mesh fractions of the solid.

Fig. 10 is constructed from data published by Avnir et al.[20], and shows the BET (nitrogen) surface area of different size fractions of Aerosil (colloidal silica).

when this approach is used, the applicable equation is:

$$\log[A] = (D-3)\log[d] + \text{constant} \quad (24)$$

where A is the surface area obtained by gas (nitrogen) adsorption and d is the particle diameter.

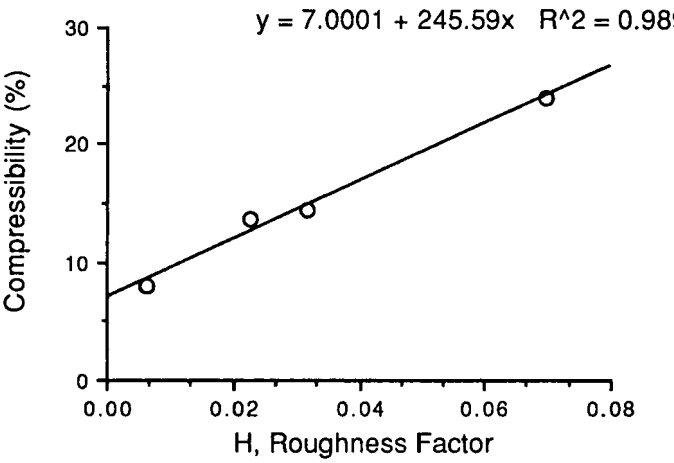

Fig. 11. Compressibility ratios as a function of roughness factor. Plot constructed from tabular data published by Thibert et al.[19].

Fractal Analysis Based on Pharmaceutical Parameters

In general, shape is recognized as a contributor to macroscopic pharmaceutical properties. Recently, for instance, Brittain et al.[21] showed the effect of surface morphology of stearic acid on the lubricative effectiveness of a series of samples, noting that only rounded flakes (e.g. not angular flakes) were good lubricants.

It is obvious that it is desirable both from a formulation point of view as well as from the point of view of quality assurance-control of rawmaterials and intermediate pharmaceuticals alike to be able to characterize the nature of surfaces.

Thibert et al[19] measured the fractal dimensions of a series of materials and tabularly listed a series of properties (amongst which the compressibility ratio) as a function of the corresponding roughness factor, H (=1-D). It should be noted that the degree to which a bed of powder can consolidate (the compression ratio) is not a function of its actual, true density, but rather of its particle shape and size. Hence, although the materials differ, it is possible to plot them on a single plot, and this is done for the compression ratio in Fig. 11.

Summary

There has always been a need for a rational means of describing surfaces, e.g. their roughness. Such methods are not

routinely used, primarily because the means of obtaining such parameter values are difficult and time consuming.

Fractal dimensional work is by far the most meaningful descriptive measure, and in situations where investigational procedures are called for (formulation, scale-up, trouble-shooting of batches that are abnormal). A material, for instance, might fill a capsule well, compress well, flow well, if it had a particular surface fractal, whereas deviation from this value might cause operational difficulties. All of the methods described for fractal analysis above are time-consuming methods. The most practical procedure would probably be the determination of BET surface areas of different mesh cuts of the raw material or intermediate pharmaceutical in question. But gas adsorption is still so time-consuming that it cannot be employed for in-process testing.

Present day research in the area attempts to arrive at simpler methods for obtaining fractal dimensions, so that such methods could be used for raw material and intermediate material control.

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