Fractal Analysis of Pharmaceutical Particles by Atomic Force Microscopy

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Purpose. Reliable methods are needed to characterize the surface roughness of pharmaceutical solid particles for quality control and for finding the correlation with other properties. In this study, we used fractal analysis to describe the surface roughness.

Methods. Atomic force microscopy (AFM) was used to obtain three-dimensional surface profiles. The variation method was used to calculate fractal dimensions. We have measured fractal dimensions of four granule samples, four powders, and two freeze-dried powders.

Results. A computer program was written to implement the variation method. The implementation was verified using the model surfaces generated by fractional Brownian motion. The fractal dimensions of most particles and granules were between 2.1 and 2.2, and were independent of the scan size we measured. The freeze-dried samples, however, showed wide variation in the values of fractal dimension, which were dependent on the scan size. As scan size increased, the fractal dimension also increased up to 2.5.

Conclusions. Fractal analysis can be used to describe surface roughness of pharmaceutical particles. The variation method allows calculation of reliable fractal dimensions of surface profiles obtained by AFM. Careful analysis is required for the estimation of fractal dimension, since the estimates are dependent on the algorithm and the digitized model size (i.e., number of data points on the measured surface profile) used. The fractal dimension of pharmaceutical materials is also a function of the observation scale (i.e., the scan size) used in the profile measurement. The multi-fractal features and the scale-dependency of fractal dimension result from the artificial processes controlling the surface morphology.

KEY WORDS: fractal analysis; fractal dimension; atomic force microscope; surface roughness; surface morphology; surface topography.

INTRODUCTION

Solid dosage forms have been used as the major means to deliver therapeutic compounds (1). The manufacturing of solid dosage forms requires processing of pharmaceutical solid particles including powders and granules. Characterization of the particle size, shape and surface morphology is critical for quality control and assurance of the physicochemical properties of final products. Although the methods for characterizing particle size (2) and particle shape (3) are available, additional efforts are needed to study surface roughness or irregularity. Surface roughness is known to play an important role in the manufacturing processes and to affect the physicochemical properties of the drug products (3–7). The surface roughness of particles is influenced by manufacturing processes, molecular reactions, and microscopic processes occurring during production. Thus, characterization of surface roughness of a pharmaceutical material not only helps predict its physicochemical properties but also provides a reference to reflect any mechanical or physicochemical process involved in the surface formation.

Characterization of surface roughness involves two steps: instrumental measurement and quantification of the surface roughness. In our study, an atomic force microscope (AFM) was used to measure the surface topography. AFM allows measurements of the surface profiles at the nanometer scale. Studying the surface roughness at nano- or micro-scale can add more information to finding relationships between the surface morphology and the surface properties. Quantifying the surface roughness includes two attributes: roughness heights and lateral dimensions (8). It has been a tradition to use roughness heights to represent surface roughness. These include arithmetic mean surface roughness, root mean square roughness, average peak to valley height between five highest peaks and five deepest valleys within the sampling length, and skewness (9,10). These parameters, however, were known to be poor representations of surface roughness (9,10). Another attribute of surface roughness, lateral dimension, describes how frequently the surface height changes. It is conceptually simple, but finding a good quantitative representation of the lateral dimension in practice is not easy. The power spectrum method describes a measured surface profile as a superposition of different waveforms by applying Fourier transform methods (11,12). This method is able to describe the lateral dimensions of surface texture as well as the roughness heights. However, it is not a simple or straightforward representation of surface roughness and is difficult to directly correlate the power spectrum to the properties of solid materials.

Fractal dimension is able to represent lateral dimension. In 1977, Mandelbrot established the basic theory of fractal analysis (13). Since then, this concept has been studied in depth. For a three-dimensional surface, the fractal dimension is a decimal number between 2 and 3. It describes the space-filling ability. The higher the value, the rougher the surface. The surface/interface topographies of all materials are fractals at the molecular level (14). It has been demonstrated that the fractal analysis, a methodology to compute the fractal dimension of an object with various algorithms, is an ideal tool to evaluate surface irregularity (8,15,16). In our study, we have chosen the variation method to calculate fractal dimension. We report a study on the surface roughness characterization based on AFM measurements and fractal analysis.

FRACTAL ANALYSIS

Fractal analysis is a resolution analysis that tracks the recurrence of topographical surface at different length scales (17). Traditional Euclidean geometry depicts a perfect straight line, an ideal plane, and an ideal cube as 1-D, 2-D, and 3-D features, respectively. All these dimensions are topological and straightforward. For a much rugged line such as a coastline, however, its length critically depends on the size of a measuring ruler. As the resolution to look at the coastline is increased, i.e., the ruler size to measure the length is decreased, the length of the coastline is increased without an upper limit. Quite often

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one can observe the self-similarity of a coastline. The self-similarity is a property that part of the curve (or surface) is indistinguishable from the whole. The shape of the whole curve repeats even on a tiny part and the repeatability can be observed at all resolution levels. If a straight line is cut into M segments of the same size, the linear size of each segment is reduced by M fold. On the other hand, if a curve can be cut into M pieces of the same linear size, the linear size of each piece is reduced by M^{1/D} fold. This curve is called a fractal, and the D value is called a fractal dimension which can be calculated to characterize its self-similarity.

For a rugged surface, which can be regarded between a smooth plane and a fully filled cube, fractal analysis can be used to evaluate the roughness. Fractal dimension is a universal number that can be used for numerical evaluation of the degree of surface irregularity or the space-filling ability. Because fractal dimension is an intrinsic feature of a fractal object, the fractal analysis is a perfect tool to characterize the lateral dimension and thus it is becoming a widely accepted approach to evaluate surface roughness (14, 18, 19). There are many methods to calculate fractal dimension of a rough surface. One method is based on the number of balls or boxes needed to cover the surface as the size of the ball or box is decreased (17). This method, called “box-counting method”, computes fractal dimension from the relation between the number and the size of boxes. Fractal dimension can be defined based on the Minkowski-Bouligand denotation (20-22): 

\[ \Delta(E) = \lim_{e \to 0} \left(3 - \frac{\log(V(E(e)))}{\log e}\right) \]  

(1)

where \( E \) is a bounded set in Euclidean space, and \( E(e) \) is set of all points within \( e \) distance from \( E \). \( E(e) \) is called the Minkowski sausage. Since \( V(E(e)) \) is hard to evaluate and the Minkowski sausage is equivalent to the union of all the balls with radii \( e \) centered on \( E \), an approximation can be achieved using union of cubes (side length of \( e \)) to cover \( E \). Thus, fractal dimension can be calculated by the following definition:

\[ \Delta(E) \approx \lim_{e \to 0} \left(\frac{\log \Omega_e}{\log(1/e)}\right) \]  

(2)

where \( \Omega_e \) is the number of cubes. This box-counting method, however, has been shown to be unsuitable for calculation of fractal dimensions from the digitized data (21). Calculation of fractal dimension by the power spectrum method (23, 24) has also been shown to be unsuitable, since it generates relatively low-precision fractal dimensions (21). Recently, a much more robust method, known as the variation method, has been developed (20-22, 25). The variation method uses a different approach to represent the Minkowski sausage. If the supremum, \( v(x, y, e) = \sup |f(x_1, y_1) - f(x_2, y_2)| \), is taken over all the points such as \( \max(x - x_1, |x - x_2|, |y - y_1|, |y - y_2|) \leq e \), then the fractal dimension can be computed from integration of the supremums over all the points on the surface:

\[ \Delta(E) = \lim_{e \to 0} \left(3 - \frac{\int \int v(x, y, e) \, dx \, dy}{\log e}\right) \]  

(3)

One of its useful features is that this method is not affected by an affine transformation of the amplitude. Let \( Z = f(x, y) \) be a continuous function. For a constant \( C, f \) and \( Cf \) (affine transformation) should have exactly the same fractal dimension values. It has been demonstrated that the box-counting method is affected by an affine transformation but the variation method is not, even with the discrete digitized data (20, 21).

**EXPERIMENTAL.**

**Materials.**

Caffeine (anhydrous powder, USP, Knoll AR, Ludwigshafen, Germany), chlorpheniramine maleate (USP, Schering-Plough, Kenilworth, NJ), lactose (hydrous, capsulating grade, Sheffield Products, Norwich, NY), hydroxypropyl methylcellulose (HPMC) (Methocel, K100M, The Dow Chemical, Midland, MI), ethylcellulose (EC) (Ethocel, 7FP, The Dow Chemical, Midland, MI), and, cellulose acetate phthalate (CAP) (Eastman Chemical Products, Kingsport, TN) were used for wet granulation. Dibasic calcium phosphate dihydrate (Di-Tab, USP, Rhône-Poulenc, Cranbury, NJ), croscarmellose sodium (Ac-Di-Sol, NF, FMC, Newark, DE), microcrystalline cellulose (Avicel, PH101, NF, FMC, Newark, DE) and mannitol (AR, Mallinkrodt Baker, Paris, KY) were used as received.

**Samples for Fractal Measurements.**

Four wet granule samples were obtained from Dr. Garnet Peck at School of Pharmacy, Purdue University. The four samples were prepared using the following compositions: [1] caffeine (171.43 g), lactose (257.14 g), HPMC (114.29 g), CAP (28.57 g), EC (28.57 g), and wetting solvent (300 ml); [2] caffeine (171.43 g), lactose (257.14 g), HPMC (51.14 g), CAP (51.14 g), EC (51.14 g), and wetting solvent (155 ml); [3] chlorpheniramine maleate (171.43 g), lactose (257.14 g), HPMC (114.29 g), CAP (28.57 g), EC (28.57 g), and wetting solvent (300 ml); and [4] chlorpheniramine maleate (171.43 g), lactose (257.14 g), HPMC (51.14 g), CAP (51.14 g), EC (51.14 g), and wetting solvent (155 ml). The wetting solvent was prepared with acetone, ethanol, and water in the volume ratio of 20:20:1. Each sample was prepared by screening all ingredients with a 40-mesh sieve and then weighed. Drugs, polymers, and lactose were mixed with a V-shape blender for 10 min. Powders were transferred to a planetary mixer and sprayed with the wetting solution to make wet granules. The wet mass was screened with a 10-mesh sieve, and wet granules were dried in a hot air oven at 60°C overnight. Dried granules were screened with a 20-mesh sieve.

Di-Tab, Ac-Di-Sol, and Avicel were used as received to measure surface profiles. The fractal dimension values of mannitol powders were analyzed before and after freeze-drying. Freeze-dried mannitol powders were provided by Dr. Steven Nair at School of Pharmacy, Purdue University. The first set of mannitol samples (10% w/w) were prepared by freezing (at shelf temperature of -45°C for 6 hours), followed by primary drying (at -25°C for 48 hours under chamber pressure of 100 mTorr) and then secondary drying (at 25°C for 12 hours under 100 mTorr) in an FTS Dura-Stop freeze-drier (FTS System, Stone Ridge, NY). The second set of mannitol samples (10% w/w) were prepared by mixing with a red dye (0.5% w/w), Amaranth Red (Fisher Scientific, Pittsburgh, PA), followed by freeze-drying. The only difference in freeze-drying was that the primary drying took 60 hours. After freeze-drying, powders