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What is the "typical" particle shape of active pharmaceutical ingredients?

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ABSTRACT

The literature contains many articles describing the criticality of particle shape to the performance of pharmaceutical powders, however very little data has been published on this important particle property. To address this gap, particle shape data for over a thousand active pharmaceutical ingredients (API) were analyzed to provide an initial answer to the simple question of "What is the typical particle shape of APIs?" All of the data were collected using a contemporary dynamic imaging system with the particles dispersed in a moving air stream. The suitability of the selected instrument platform was verified by comparing calculated and experimental aspect ratio distributions for several particle shape reference materials and good agreement was obtained in all cases. The principal finding of this "big data" analysis is that particles of typical low molecular weight (<500 Da) API may be expected to have a median aspect ratio between 0.6 and 0.8. The analysis also reveals that the API particles typically have low surface roughness. When compared to commonly used excipients, the API particles are slightly less equant. Whilst the results of this analysis are limited to a single data source and single measurement technique, they provide a benchmark that can be used to help design improved manufacturing processes and online analytical methods for active pharmaceutical ingredients.

1. Introduction

It is well known that the shape and size of the active pharmaceutical ingredient (API) particles are important parameters to consider when designing and developing pharmaceutical dosage forms. These properties can affect the formulation [1–3], manufacturability [4–8], dissolution [9,10], and/or the bio-performance [11,12] of the dosage forms. As a result, most pharmaceutical manufacturers try to regulate these physical attributes during API manufacturing to ensure that a quality drug product is consistently produced.

The size and shape of API particles are typically controlled by the choice of final API isolation conditions. For APIs that are milled, spray dried or lyophilized then the particle size and shape will be controlled by the operating parameters used for those unit operations. For APIs that are crystalized directly, the particle size and shape will be controlled by the choice of crystallization solvent(s), rate of cooling, presence/absence of seeds, drying conditions, and the like. The shape (or habit) of the crystals will also be dictated to some extent by the dimensions and the space group of the unit cell [13],[1] the presence of impurities in the crystallization solvent, and the inherent tendency of the crystals to aggregate and/or agglomerate. Given the diversity in API chemical structures and isolation conditions it is obviously very difficult to predict a priori what the size or shape of any given API particle will be.

In the industrial setting, specifications for API particle size are very common with targets not just for the average particle size but also for the particle size distribution. Specifications for particle shape are much less common, in part because the analytical instrumentation and data analysis approaches for quantifying particle shape descriptors are less well developed. Conventional static image analysis using microscopy suffers from the drawback of limited sample size and low speed of analysis. It can also be biased by preferred particle orientation when particles are mounted and viewed on a standard microscope slide. As a result of these limitations, routinely conducting static image analysis to obtain quantitative particle shape data for API samples is quite uncommon.

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[1] Recently, a statistical analysis was conducted at Cambridge University using the crystal morphology information for single-component organic crystals extracted from the Cambridge Structure Database. The results showed that out of >300.000 crystal structures surveyed, 29% are prisms, 27% are blocks, 18% are plates, 14% are needles and 12% are of other shape. While this preliminary study was intriguing, the analysis was limited to materials that have single crystal structures, thus the trends may not be generally applicable.

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The lack of robust analytical methodologies for particle shape analysis also appears to have resulted in a limited quantitative particle shape data being available in the scientific literature. We were able to find fewer than twenty-five papers devoted to the study of particle shape effects in *Powder Technology* during the last ten years. A selected list of these publications are included in the reference [3,7,8,14–16]. The lack of quantitative particle shape data in the literature is a major hurdle to increasing the understanding of how particle shape may impact drug product performance and how to develop appropriate control strategies during API and drug product development.

Recently, advances in high-speed digital camera and computer technologies have enabled the development of dynamic imaging instruments that are capable of rapidly capturing two-dimensional images of particles that are dispersed in a fluid stream [17,18]. One of such instrument is the QicPic dynamic image analyzer from Sympatec Inc. (Clausthal-Zellerfeld, Germany). These dynamic imaging instruments are capable of capturing images of tens of thousands of particles within a matter of few minutes and thus they may be used for routine quality control measurements in an industrial setting [19–21].

Over the last ten years, research groups at our company have been using dynamic imaging instrumentation to gather quantitative particle shape information on API and excipient samples. In this work, we have collated the particle shape data for a large number (>1000) of randomly selected API samples and have conducted a statistical analysis of this broad (and hopefully representative) population of APIs. In addition to analyzing measurements of particle shape and size for a large number of pharmaceutical materials, we have developed a theoretical algorithm to predict the aspect ratio distribution for common geometric shapes (such as a rod, cube, cylinder, etc.). The theoretical aspect ratio distributions generated using this algorithm should be very similar to those that are generated experimentally. By comparing the theoretical aspect ratio distribution to experimentally measured aspect ratio distributions for model materials it should be possible to assess if the trends in the measured data are reasonable. In totality, our analysis is intended to provide an initial answer to the question "*What is the* '*typical*' *particle shape distribution for APIs*?". Without such an understanding of the "normal" range of API particle shape properties it is very difficult for the scientific community to move beyond academic studies of idealized systems and to develop meaningful test methods and control limits (e.g. specifications) for use in an industrial setting.

2. Background

To describe particle shape in a quantitative manner several particle shape descriptors are used throughout this paper, all of which are derived from two-dimensional (2D) projection of the particle outline using geometric constructions. The shape descriptors used include aspect ratio, convexity and sphericity and for mathematical reasons these shape descriptors all vary from 0 to 1.0. A perfect circle has a value of 1.0 for aspect ratio, convexity and sphericity. The aspect ratio is defined as the ratio between the minimum and maximum Feret diameter. The maximal and minimal Feret diameters are respectively the longest and shortest distance between two parallel tangents to the contour of the particle after consideration of all possible orientations. Detailed definitions for the other particle shape parameters are provided in Table 1.

Using the modern research instruments it is possible to capture two dimensional images of many thousands of randomly oriented particles in an automated fashion. These images can then be analyzed by computer software so that frequency distribution of each particle shape descriptor can be obtained. Frequency distribution of particle shape can be plotted on a number-weighted or volume-weighted basis and can be described by Eqs. (1) and (2), respectively.

$$N\% = \frac{n(i)}{\sum_1^I n(i)} \tag{1}$$

$$V\% = \frac{v(i)}{\sum_1^I v(i)} \tag{2}$$

Where N% and V% are the number and volume fractions of particles in a given particle shape bin, respectively; n(i) is the number of particles in particle shape bin i; v(i) is the volume of particles in particle shape bin i, and is calculated by assuming that particles are spherical with an equivalent circular diameter (ECD, diameter of a circle with the same projected area as the actual particle). I is the total number of particle shape bins in a distribution.

From an experimental perspective, accurate particle shape measurement is much easier with coarse particles than with very fine particles. This is because particle shape measurement of very fine particles is less accurate and precise due to the small number of pixels in each image. The use of a volume-weighted distribution minimizes the impact of very fine particles on the overall particle shape distribution. Hence, in this work, we have used volume-weighted distributions to ensure that the results are not biased by the influence of very fine particles whose shape is hard to define accurately.

3. Methods & materials

3.1. Predicted shape distributions of common particle shapes

It is an implicit assumption of dynamic imaging techniques that the particles are randomly oriented in the particle dispersion process. This assumption is tested in this work as described below.

A custom computer algorithm was developed to mimic the measurement of particle shape in the dynamic particle imaging instrument. To begin, five model 3D shapes were defined (length, width, breadth, number of faces, angles between faces, etc.) as shown in Fig. 1. In turn, a particle of each shape was randomly assigned to an X-Y-Z orientation using a random number generator. A 2D projection of the randomly oriented 3D-shape on a single plane (X-Y) was then generated mathematically. To assess the aspect ratio, each 2D projection was incrementally rotated in the projection plane and the X and Y dimensions of the projected shape were calculated at each orientation as they were rotated. After 180° of rotation both the minimum and maximum dimensions of the 2D projected shape could be assigned. The aspect ratio (AR) for each 2D-projection was then calculated as the minimum dimension divided by the maximum dimension. These steps were repeated to obtain aspect ratio data for ten thousand random orientations of each 3D-shape. The accumulated data for each of the five particle shapes were then used to create a theoretical aspect ratio frequency distribution plots for randomly oriented particles of each geometric shape.

3.2. Particle shape reference materials

Several materials with uniform particle shapes and sizes were used for comparison to the predicted particle shape distributions. These materials are herein referred to as 'particle shape reference materials' and are listed in Table 2.

Scanning electron micrographs were collected for the particle shape reference materials using the FEI Quanta 200 scanning electron microscope (SEM) (FEI Company, Hillsboro, Oregon). Samples were gently sprinkled and mounted on stubs with double-sided conductive carbon tape and sputter-coated with gold/palladium before being imaged with the SEM. The dimensions of twenty particles of each material were measured using the SEM and the average values are provided in Table 2. The measured dimensions were used to predict the aspect