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Research paper

Particle sizing measurements in pharmaceutical applications: Comparison of in-process methods versus off-line methods

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ABSTRACT

It has been previously described that when a sample's particle size is determined using different sizing techniques, the results can differ considerably. The purpose of this study was to review several in-process techniques for particle size determination (Spatial Filtering Velocimetry, Focused Beam Reflectance Measurements, Photometric Stereo Imaging, and the Eyecon® technology) and compare them to well-known and widespread off-line reference methods (laser diffraction and sieve analysis). To start with, a theoretical explanation of the working mechanism behind each sizing technique is presented, and a comparison between them is established. Secondly, six batches of granules and pellets (i.e., spherical particles) having different sizes were measured using these techniques. The obtained size distributions and related D_{10}, D_{50}, and D_{90} values were compared using the laser diffraction wet dispersion method as reference technique. As expected, each technique provided different size distributions with different D values. These dissimilarities were examined and explained considering the measurement principles behind each sizing technique. The particle property measured by each particle size analyzer (particle size or chord length) and how it is measured as well as the way in which size information is derived and calculated from this measured property and how results are presented (e.g., volume or mass distributions) are essential for the interpretation of the particle size data.

1. Introduction

Building quality into pharmaceutical products is the leading purpose of the Process Analytical Technology (PAT) initiative [1]. Particle size is a critical quality parameter in a number of pharmaceutical unit operations such as pre-mixing/mixing, granulation, drying, milling, roller compaction, spray-drying, coating, and compression. An adequate particle size distribution (PSD) is essential to ensure optimal manufacturability which will have an important impact on the end product's safety, efficacy, and quality. Therefore, monitoring and controlling particle size via in-process particle size measurements is essential to the pharmaceutical industry.

The application of in-process particle sizing tools for the assessment of the influence of process and formulation parameters upon critical product quality attributes has been studied for several pharmaceutical processes such as fluid bed granulation [2–4], hot melt granulation [5], spheronization [6], and crystallization [7–9]. However, differences between the measurement mechanisms and principles of the particle size analyzers (both offline and in-process) make the direct comparison between them a challenging task [7,10]. The aim of this paper is to review different in-process particle sizing techniques and compare them to acknowledged off-line techniques (laser diffraction (LD) and sieve analysis). To establish this comparison, six batches of granules and pellets (i.e., spherical particles) having different sizes were measured with the different equipments. The evaluated in-process techniques include Focused Beam Reflectance Measurements (FBRM), Spatial Filtering Velocimetry (SFV), Photometric Stereo Imaging, and the Eyecon® technology. Table 1 provides a comparison between the assayed equipments. It discloses the

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underlying theoretical assumptions behind each instrument's measurement mechanism, unveils the way in which size is acquired and presented by each instrument, describes their applicability, known capabilities and drawbacks. The choice of an appropriate analyzer for measuring particle size in a specific case has to take into consideration these listed characteristics. In an industrial environment, when a new particle size analyzer is implemented in a process environment, an often executed procedure is to attempt to correlate the data from the traditionally used off-line analyzer with the data from the new in-process analyzer. However, due to the different measurement principles behind each sizing technique, it is obvious that this is not an accurate and reliable procedure as mostly very different particle properties are measured by each sizing technique, hence providing uncorrelated results. A particle size distribution is usually depicted by a histogram where the size-related property measured by the analyzer (total particle volume, number of particles or counts, total particle length, total particle area, etc.) is plotted as a function of demarcated size classes. *D* values are parameters often used in the characterization of a PSD, a *Di* value of *x* indicating that particles with a size smaller or equal to *x* account for *i*% of the measured size-related property.

1.1. Off-line particle sizing methods

1.1.1. Laser diffraction

LD is the most applied technique for the particle size measurement of pharmaceutical powders and granules. It can be used as an in-process method [11] or as an off-line method. A dispersed sample passes through a beam of monochromatic light causing light scattering, which is measured as a function of scattering angle by a multi-element detector. As the scattering pattern, i.e., scattered intensity as a function of scattering angle, is largely particle size dependent, it follows that particle size information can be extracted from the experimentally determined pattern. Older instruments mainly rely on the Fraunhofer approximation to derive particle size information from the scattering pattern, while recent LD particle size analyzers are based on Mie's theory [10]. The Fraunhofer approximation is based on a number of assumptions: it assumes that particles are opaque disks, that light is scattered at only narrow angles, and that all particle sizes scatter with the same efficiency. Furthermore, it does not take into consideration the optical properties of the measured material, and therefore, its use is recommended when measuring mixtures of different materials. Differently, Mie's theory predicts the scattering intensity induced by particles, irrespective of the fact whether they are transparent or opaque. It is based on the assumptions that the measured particles are spherical, that the dispersion is dilute, so that light is scattered by one particle and detected before it interacts with other particles, that the optical properties of the particles and the medium surrounding them are known and that particles are homogeneous i.e., uniform in composition. Nowadays, the ISO13320 standard for LD particle size analysis acknowledges the superiority of Mie's theory [12,13]. LD particle size analyzers that use Mie's theory (e.g., Mastersizer® S) base their particle size calculation on the assumption that particles are spherical, which is rarely true. This is a solution to deal with the fact that the only shape that can be described by a single dimension is the sphere. LD results are generally presented as a volume-weighted particle size distribution. Thus, LD results reporting that the median value (D_{50}) of a volume-based PSD is 100 μm means that particles with a size up to 100 μm account for 50% of the measured sample volume. Alternatively, a number-weighted distribution can be extracted, depending on the analyzer's software.

1.1.2. Sieve analysis

Before the introduction of LD, sieving used to be the most commonly applied sizing method, and it is still widely used for the determination of particle size because of its inexpensiveness. It is described in the European Pharmacopoeia [14] that sieve size is the "size of the aperture measured perpendicular to the wire through the center of the opening." The mass of material that is retained on a specific sieve is weighted and presented as a percentage of the total assayed material. Therefore, a mass-based PSD is generated. The results are generally presented as a cumulative mass distribution. In this case, a median (D_{50}) of 100 μm indicates that 50% of the total weight of the measured material is constituted by particles that would pass through a sieve with 100 μm apertures. It is acknowledged that for a particle to pass through a sieve, it must have two dimensions smaller than the sieve size. This is why it can be assumed that sieve analysis separates particles according to their second largest dimension. Some of the described disadvantages of sieve analysis are as follows: test sieves require regular care in order to maintain their performance, their cleaning must be careful as vigorous brushing may distort sieve openings, it is not possible to perform sieve analysis on sprays or emulsions, measurement of dry powders with sizes under 38 μm is very difficult as electrostatic charges may cause loss of material (wet sieving may be a solution but this technique provides very poor reproducibility and is difficult to carry out), and cohesive or agglomerated materials are problematic to measure as they form aggregates that will not pass through the sieve's aperture [10,15]. Sieve analysis also requires a relatively large amount of sample and, as a consequence, is not appropriate for costly materials or materials of which only small quantities are available. Samples can be eroded due to attrition during the analysis making sieving unsuitable for these materials. Measurement times and operating methods (e.g., shaking) need to be standardized as the longer the measurement is performed, the smaller the obtained particle size is as particles have time to orient themselves to fall through the sieve. This is particularly important when dealing with odd-shaped particles which are difficult to sieve and may generate peculiar results. For instance, measuring the particle size of needle-like or rod-like particles by means of sieve analysis might not be the best choice. Additionally, there is an increase in the risk of particle erosion as sieving time increases. These and further disadvantages of this method are described in Table 1.

1.2. In-process particle sizing methods

1.2.1. Methods based on chord length measurements

There are in-process particle size analyzers that measure chord length instead of actual particle size such as SFV and FBRM. A particle's chord length can be defined as a geometric line segment whose endpoints both lie on the surface of the particle. These analyzers utilize a laser beam that crosses the particle randomly acquiring a chord length. The number of times a given chord length is measured takes the form of a probability density function. In case of spherical particles, the diameter is the largest chord possible, and the probability of the measured chord length is independent of the particle orientation toward the laser beam (Fig. 1-1), while for irregular and odd-shaped particles, shape and orientation will influence the measured chord lengths (Fig. 1-2a and 1-2b). Hence, the chord length distribution (CLD) depends on both the PSD and the particle shape. Presenting the results as particle size is easier to interpret than chord length as particle size is often directly related to product quality, and it allows the comparison to particle size measured by other instruments [16]. Both SFV and FBRM utilize a laser beam for their measurements: SFV calculates the chord length from the shadows cast by the particles that cross the laser beam, and FBRM calculates it from the laser light that is