An approach to particle size stability

Understanding particle size stability and monitoring particle size changes may be vital to product success

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The particle size of active pharmaceutical ingredients is widely recognized as a critical attribute in determining the overall performance of some drug product formulations. The role of particle size has become increasingly important with the emergence of so many poorly soluble drugs and low-dose formulations in the last several decades. Understanding the mechanisms by which changes to particle size occur and monitoring such changes through ongoing stability testing may be vital to the commercial success of a product. Failure to consider particle size stability in the early stages of drug development can lead to costly setbacks, batch rejection and delays in clinical trials. It is also important to consider the method used to determine particle size and to ensure that it is stability indicating.

Obtaining the optimum particle size for a particular drug product often requires the addition of a manufacturing step, such as micronization, following initial crystallization of the active pharmaceutical ingredient (API). It is tempting to assume that the particle size of the API will remain constant following this step. However, manufacturing steps designed to reduce particle size typically require the input of large amounts of energy. The drug particles produced in the process can have significantly greater surface area and surface energy relative to the starting material. Changes in particle morphology and surface topography are also likely to occur. These changes can have a significant effect on the way in which discreet particles interact with one another in bulk. Whether the particle size reduction process adversely affects physical stability should be determined, as should the mechanisms by which this occurs. In many cases, the particle size may remain stable for years. In other instances, significant increases in particle size (real or apparent) can occur within hours or days.

Methods of particle size analysis

Changes in particle size can be categorized as "real" (resulting from the growth of discreet particles or the fusion of two or more particles to form a single entity) or "apparent" (resulting from the formation of particle agglomerates that reduce the effective surface area of the API). In order to understand and/or assess potential changes to particle size over time, it may be necessary to develop two distinct methods of analysis. For the purposes of this article, particle size methods will be discussed in terms of the commonly used laser diffraction technique. To determine whether micronization produces particles having the desired size specification, for example, a method capable of dispersing and measuring discreet (i.e. individual) particles may be required. Such a method might involve the use of a surfactant coupled with ultrasonication or high speed mixing to separate fine particles that have a tendency to adhere to one another. This approach assumes that a wet dispersion

method laser diffraction method is being used. A dry dispersion method designed to measure discreet particles may use a relatively high disperser pressure (e.g. 3 or 4 bar). The same wet dispersion method might not be particularly effective in measuring particle agglomerates, however, as the energy of sonication may overcome the energy holding the particle agglomerate together.

Modified methods employing less energy to disperse particles would be desirable for the measurement of agglomerates. Table 1 shows the results obtained for a micronized powder analyzed using wet dispersion laser diffraction methods with and without sonication. To measure discreet particle size, the sample is prepared in a dispersant containing surfactant and is sonicated for 60 seconds prior to analysis. Agglomerate size is measured using the same dispersant, but ultrasonication is replaced with mild stirring using a magnetic stir plate.

Table 1

Results for a micronized powder analyzed using wet dispersion laser diffraction methods with and without sonication

Method	D(v,0.1)	D(v,0.5)	D(v,0.9)
With sonication	0.7 µm	1.9 µm	5.4 µm
Without sonication	1.2 µm	6.5 µm	170 µm

In addition to the direct measurement of particle size by a method such as laser diffraction, ancillary methods that indirectly measure characteristics related to particle size should also be considered. Dispersing drug substance in a liquid medium, for example, may not be an accurate indicator of the way in which the same particles would react in a dry state. In such cases, a method that measures particles in a dry environment with minimal handling may be quite useful. A technique such as surface area analysis, for example, may indicate whether particle agglomeration occurs in the dry powder. As particles form agglomerates, previously exposed surfaces may be masked by adjacent particles. In a tightly bound structure the adsorbate gas (typically nitrogen) may not be able to penetrate the interior of the agglomerate. In either case, a significant reduction in the measured surface area of a powder is likely to occur. The preparation of samples for surface area analysis requires nothing more than a nitrogen purge or vacuum degassing step to ensure a "clean" particle surface. Thus, minimal manipulation of the sample is needed. Perhaps even more useful is an imaging technique such as scanning electron microscopy (SEM). High speed camera or laser imaging systems are also available and can measure larger sample quantities very quickly.

Although laser diffraction particle size analyzers are extremely reliable and accurate, particle size measurements are largely dependent on good sample preparation. A sample preparation that fractures particles, for example, can mistakenly convince the analyst that particles are smaller than they are in reality. Conversely, a method that does not adequately wet the sample powder will not be effective in dispersing particles and may produce particle size values that are larger than actual. Imaging methods are more "objective" in this respect. When using laser diffraction methods for product release or stability, one should consider using an imaging technique as a "reality check" to ensure that the method of analysis is providing accurate results.

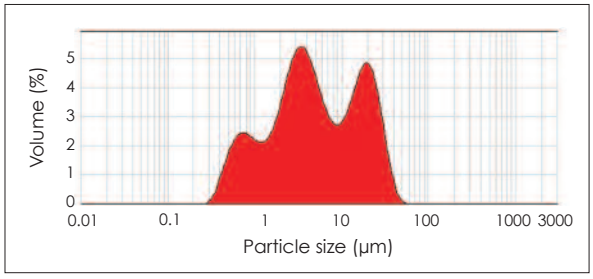
Case study

In the following case study, the effect of particle size stability on the uniformity of a low dose drug product formulation and the methods used to characterize particle size will be discussed.

"MTI 10891" was micronized in a fluid energy jet mill to a particle size of approximately 4-6 microns (90th percentile). The micronized drug substance was then shipped to a contract research organization (CRO) for blending and subsequent formulation. The drug content of the final formulation is approximately 0.1%. The predominant excipient was starch, which was used as a filler and binder. A feasibility batch was manufactured and successfully formulated, followed by three successful validation batches. Two additional batches (batch #5 and #6) were later micronized for clinical trials, but were not blended/formulated for several months from the date of micronization. The batches failed blend and content uniformity testing and could not be used for scheduled clinical trials. A subsequent investigation was begun to determine the cause of the batch failures. As part of the investigation, a 9-month-old retain sample from batch #5 of the micronized drug substance was submitted for particle size testing using the current laser diffraction method (wet dispersion with 30 seconds of sonication). The retain sample produced a D90 value of approximately 25 microns (Figure 1) versus a D90 of 4 microns at the time of micronization (Figure 2).

Figure 1

Particle size distribution of micronized sample after 9 months of storage



The histogram shown in Figure 1 clearly shows a significant change in the particle size distribution of the retain sample. Despite this obvious change, a D90 of 24 microns does not fully explain why the batch failed blend and content uniformity testing. Work done by Rohrs et. al.[1] suggests that an *average* particle size as high as 32 microns should be sufficiently small to achieve good content uniformity for the blend in question. The retain sample of batch #5 clearly met this requirement.

To verify the particle size results, scanning electron micrographs were obtained for the sample. The image shown in Figure 3 shows that the vast majority of drug substance particles had become significantly agglomerated. These agglomerates ranged in size from approximately 50 microns in diameter to approximately 120 microns. Particle agglomerates in this size range would certainly present a challenge to content uniformity for this 0.1% blend. In this instance, the laser diffraction data was effective in showing that a change to the particle size of the API has occurred, but it does not adequately demonstrate the true extent of this change. A D(v,0.9) of 24 microns simply does not correlate to the SEM image. The discrepancy can be attributed to the sample preparation steps required by the test method, particularly the use of ulrasonication. The method used to analyze the retain sample was originally developed to measure the size of discreet particles following micronization. The method was not designed to measure particle agglomerates that can be disrupted by ultrasonication. While ultrasonication did not completely de-agglomerate the sample it did significantly reduce most particle agglomerates to sizes of approximately 25 microns or less. The failure in blend uniformity, however, suggests that agglomerates larger than 25 microns remain intact during the formulation process. Thus, SEM in conjunction with laser diffraction was needed to explain the content uniformity failure.

Figure 2

Particle size distribution of micronized sample immediately after micronization (time zero)

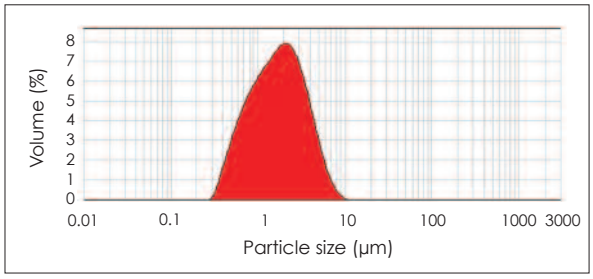
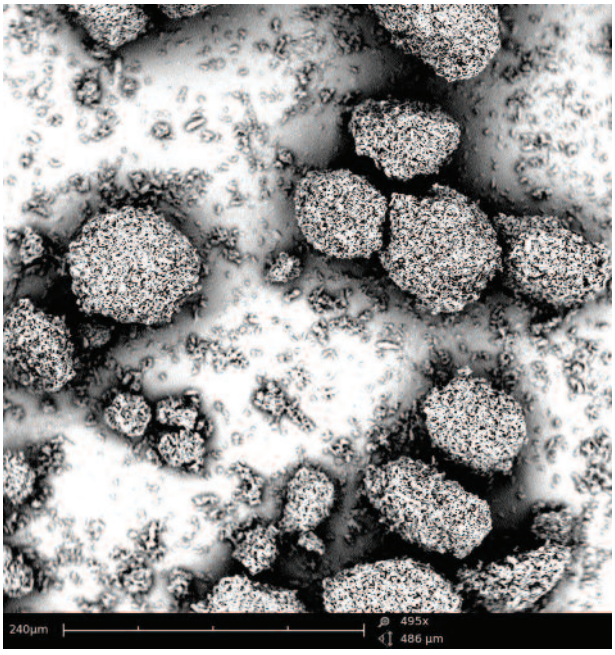


Figure 3

Scanning electron micrograph of micronized sample after 9 months of storage (495X magnification)



Although the laser diffraction particle size method was reasonably successful in showing changes to the 9-month-old retain sample, the same method was less successful when applied to younger samples stored under controlled conditions. As part of the ongoing investigation to determine the root cause of the blend and content uniformity failures, a fresh batch of drug substance was micronized. Samples of the micronized drug were then stored at 25°C/60%RH and 40°C/75%RH and tested over a 3-month period. Particle size analysis and SEM tests were conducted. (Additional tests were conducted to determine the mechanism responsible for the agglomeration but are not relevant to the assessment of particle size and not discussed here.) Within a few days of storage at 40°C/75%RH, the samples showed clear evidence of particle agglomeration when examined by SEM. These agglomerates again ranged in size from approximately 50 microns to 120 microns. Laser diffraction results, however, showed only a modest increase in particle size from approximately 5 microns at the initial time point to approximately 10 microns after 3 months.

Results from analysis of the initial retain sample suggest that the samples stored under controlled conditions should also have produced D90 values in the 20-25 micron size range. The fact that D90 values increased only a few microns indicates that the method was more effective in dispersing agglomerates in the younger samples. This leads to the conclusion that the agglomerates observed by SEM were not as robust in these samples (i.e. they could not withstand the dispersive force of ultrasonication). This is not to say, however, that given

sufficient time to "mature" (i.e. 9 months) these same agglomerates would not present problems when blending and formulating. If the intent of stability testing in this study was to determine the extent of agglomeration, the laser diffraction method alone would not have provided the most convincing data. Of the two methods used to assess particle size of the stability samples, only SEM proved useful in assessing the extent of agglomeration.

The case study presented above clearly demonstrates the importance of monitoring particle size stability. Even if a formal stability program had been in place from the earliest stages, however, an eventual problem with blend/content uniformity might not have been averted. A typical study design might only have included the same laser diffraction method used to test the freshly micronized drug substance. This method would not have accurately measured the extent of particle agglomeration. The addition of a simple (and cost effective) SEM test would have provided indisputable evidence that extensive and potentially troublesome particle agglomeration was occurring very quickly. Not every lab, however, is equipped with a scanning electron microscope. It is therefore important to consider developing more than one laser diffraction technique so that both discreet particle size as well as particle agglomeration can be measured. Other methods such as surface area analysis could also be used to detect and quantify the extent of particle growth or agglomeration and should be considered as a supplement to particle size analysis.

Reference

1. Rohrs BR, Amidon GE, Meury RH, Seacrest PJ, King HM, Skoug CJ. 2006. Particle size limits to meet USP content uniformity criteria for tablets and capsules. J. Pharm. Sci. 95(5): 1049-1059.

Recommended Reading

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