

Sampling and dispersion – the keys to accurate particle size analysis in pharmaceutical materials



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Of the pharmaceutical product forms available today, 70% of all actives are delivered as powders in the form of tablets and capsules. For other delivery methods, product intermediates or excipients will often be in the form of dry powders. In each case, the physical properties of the powdered materials are important in defining the drug release profile and eventual bioavailability of the product. In addition, particle size distribution can be useful in predicting the processability of the powder, for example the ease of tableting or conveyance of the powder within the process line.

Many methods are available for particle size analysis today, but probably more measurements are performed using laser diffraction than any other technique. Developed in the 1970's for the size analysis of sprays, laser diffraction is now widely accepted for the characterization of a broad range of products, including emulsions, suspensions and dry powders. Its speed of measurement, dynamic range and ability to measure porous and non-spherical particles confers many advantages over other techniques.

Particle size analysis using laser diffraction measurement may now be considered routine, but one aspect remains poorly understood - the need for good sample preparation. In this article, we examine the requirements for good powder sampling and dispersion, for both laboratory-based laser diffraction measurements and when measuring on-line, in real time,

within the process environment. We describe methods available for representative sample extraction from a process stream and techniques that ensure powder is dispersed effectively without affecting the measured primary particle size.

Is your sample representative?

One of the most important aspects of dry powder analysis is the need for representative sampling. Whatever the particle size analysis technique, only a small fraction of the powder being produced will be analyzed. Therefore the assumption is made that the results obtained are representative of the bulk material.

In-process measurements

Several methods exist for measuring powders on-line, directly in the process stream to provide real-time process feedback; or for withdrawing a grab sample for laboratory or at-line analysis.

With free-flowing material it is best to sample the powder while it is in motion, rather than from a storage vessel where segregation is more likely. It is also preferable to sample in vertical (i.e. extracted from a gravity-fed flow) rather than horizontal or angled pipes - and after a randomizing screen if possible. If the sample must be extracted from a pneumatic pipe it is essential to break up any roping created inside the pipe. Intrusive flow conditioners have been used for this, but are no longer

generally acceptable in pharmaceutical environments. Instead, a non-intrusive method has been adopted which successfully homogenizes the powder flow in the pipe without causing problems downstream.

The choice of measurement mode for laser diffraction within a process environment is highly dependent on the application. Direct measurement across the sample pipe can be advantageous, both in terms of sampling and simplicity of set-up. For certain lean phase applications (< 20 Kg/h), where the mean size is 20 microns or more, a direct in-line flow cell can be the most effective method for measuring the whole batch. However, it is necessary to assume that the degree of particle dispersion in the process stream is constant and that it is the primary particle size. Often this is not the case, with agglomerates being present in the powder stream. These will be dispersed only if the powder sample is passed through a suitable dispersion device. Where it is necessary to measure the agglomerated state of the powder as it naturally occurs in the process, in-line measurement becomes more important and may offer more relevance in understanding the processability of the powder.

Sampling for on-line measurement

Complex sampling devices have often been used to sample a powder stream prior to dispersion. Representative sampling has been



attempted by ensuring that sample is extracted across the entire cross-section of the powder flow. In practice, real powder flows do not always stay in the same place. It is therefore more valid to measure a homogenous flow than to attempt to chase powder flow instability around a pipe section. The other drawback of these sampling devices is that they are intrusive and potentially cause problems with powder flow downstream of the sampling region. Sample from the entire pipe is collected before measurement, a process which can take up to five minutes. Since jet mills have a response time measured in seconds, equipment that takes a long time to sample a powder is incapable of seeing unplanned events such as intermittent filter leaks, instabilities and timing errors in valve switching.

Simpler and more effective is the use of sampling probes strategically placed into the process stream. These allow extraction of samples in real-time, providing process engineers with the data required to directly control the process. An understanding of the nature of the process stream prior to the sampling point will provide the clues to help ensure representative sampling. When sampling is from a homogenous stream, it is acceptable to use a J tube probe with a single sample hole. This hole, which may vary in size from 5 to 12 mm, faces the sample flow and generally must sample from a vertical process pipe (figure 1). Homogeneity of the sample flow can be verified during installation of the probe by determining how the particle size varies with the position of the J tube across the pipe diameter. An example of this traverse, performed for a painkilling drug, is depicted in figure 2. Since measurements can be made every second, a line showing a consistent mean size on the particle size history log indicates homogeneity of the sample within the pipe. If there is a significant fall or rise in particle

size viewed on the screen as the J tube is traversed towards the centre of the pipe (figure 3), this indicates the lack of homogeneity and hence the need for an alternative strategy for that particular process.



Figure 1 - J-Tube and Flute sample probes used with the Malvern Insittec on-line laser diffraction system

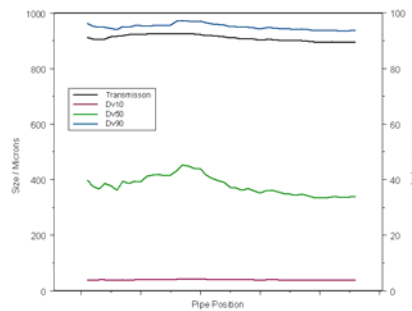


Figure 2 - Size parameters as a function of probe position within the process pipe. A flat Dv10, Dv50 and Dv90 indicates that the powder flow is homogeneous

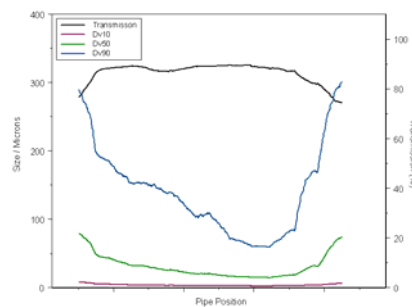


Figure 3 - Size parameters as a function of probe position within the process pipe. Large changes in the Dv50 and Dv90 are observed, showing that the powder flow is not homogeneous

Where there is non-homogeneity of the sample stream, sampling holes drilled at selected points along a sampling tube called a flute (figure 1) may be an appropriate choice. The optimum amount of sample required to achieve the optimum transmission can be determined. The area of hole needed to collect that amount of sample is then calculated. Holes are drilled at different points along the flute, to give a total area equivalent to that calculated. A balance must be struck between the number and size of the holes, and the need for the extracted sample to be representative of the bulk powder.

For each of these conditions, especially where non-homogeneity can occur, it is always recommended that a representative sample is collected and that the complete sample is measured off-line in order to verify the choice of sampling solution. Another route to take is that of static flow conditioning. This allows a representative sample to be produced and extracted even when upstream distribution of powder is uneven. CFD modelling for different sized particles of a particular API and pipe profiles assists in determining the most appropriate static conditioner spool piece dimensions to be installed (figure 4). Once the flow conditioning spool piece has been installed, a simple J-probe sampler may be installed typically five pipe diameters downstream of the conditioner.

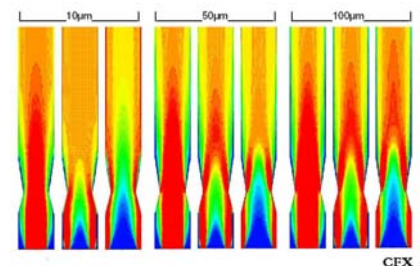
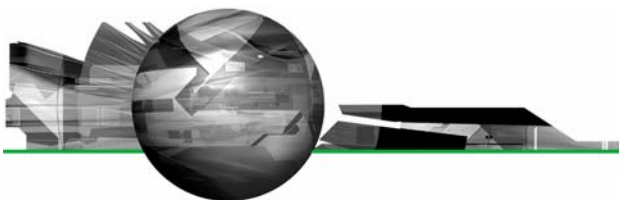


Figure 4 - CFD modelling for different sized particles and pipe profiles



Sampling for laboratory measurements

When collecting samples from the process line for analysis in the laboratory, the same requirements for good sampling apply. An additional concern is that powders taken to the QC laboratory for analysis may have been transported a significant distance, during which time segregation will probably have occurred. If not reversed, segregation will lead to biased results. Re-dispersion of the powder is therefore essential. Care must be taken in handling the powder, particularly if large particles (> 70 microns in size) are present, or the distribution covers a broad and/or bimodal size range. Laser diffraction is a volume-based measurement technique and is therefore sensitive to small changes in the amount of large material in the sample. This is because coarse particles occupy a large volume compared with smaller particles (one 100 micron particle has the same volume as one million 1 micron particles and will therefore give the same scattering response). It is therefore important that the fine and coarse particle fractions are mixed completely before sampling.

A variety of techniques are available in the laboratory environment to ensure selection of a sample that is representative of the bulk powder (figure 5). If simple scoop sampling is used - where the powder is directly sampled from the top of the powder container - large errors can result, as this technique fails to overcome the issue of powder segregation. Use of a spinning riffler, where samples of the correct mass are obtained by continuously sampling a moving particle stream, provides the most efficient method of minimizing any sample bias.

Method	Estimated max error (%)	Efficiency (%)
Cone & Quartering	22.7	0.013
Scoop Sampling	17.1	0.022
Table Sampling	7.00	0.130
Chute Riffing	3.40	0.560
Spinning Riffing	0.42	36.30
Random Variation	0.25	

Figure 5 - Sampling methods for dry powders and their associated errors

Dispersion techniques

Accurate control of powder dispersion has also been most poorly understood in the past even though it has a major impact on dry powder measurement using laser diffraction. Malvern Instruments experience gained over 23 years in the design and optimal use of dispersion devices is key to providing deliverable solutions even for the most difficult of applications.

Agglomerates are dispersed when the adhesion forces that exist between the particles in the sample are overcome. At large particle sizes (>10 microns) these forces are quite small (figure 6) and dispersion can be achieved simply by tumbling the sample. However, below 10 microns the forces of attraction between particles can be very great, ranging from 101 g at 10 microns to 103 g at 1 micron. Significant energy is required to achieve dispersion when measuring particles within this range. This generally comes from passing the powder through a compressed air-driven venturi in which particles can be subjected to high shear where it is warranted. This, coupled with particle-particle and particle-wall collisions, helps to disperse agglomerates. The key to a good dry measurement is to apply sufficiently high pressure to cause particle dispersion. However care must be taken when measuring

friable materials such as crystalline Active Pharmaceutical Ingredients (APIs) because the use of high dispersion pressures may result in fracture of the material and milling of the product.

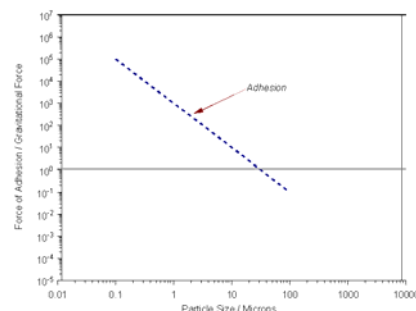


Figure 6 - Force of adhesion as a function of particle size - Ref: Aerosol Science, Ed. C N Davies, Academic Press, London and New York, 1966

The only way to assess whether dispersion or milling is taking place is to perform a “pressure or flow rate titration” [REF – ISO13320-1]. This simply involves measuring the particle size as a function of the compressed air pressure or flow rate used to drive the venturi, in order to determine which setting is most suitable. By comparing the dry results against a well-dispersed result obtained using wet dispersion, the correct pressure can be selected. In all cases a dry measurement result can never be finer than one obtained using the correct wet dispersion method. This is



because the energy and time available for dispersion in a slurry, are much greater than can be achieved when particles are placed under shear in an air stream.

Case study

An example of how dispersion of a typical crystalline pharmaceutical powder can be achieved using a dry powder dispersion system is shown in figure 7. Here the dispersion pressure has been increased from 0 to 4 bar, during which a large decrease in particle size is observed. This is most obvious for the reported Dv_{90} value, where there is a shift from almost 50 to below 20 microns. What is unknown is whether this is the result of agglomerate dispersion or the break up of primary particles.

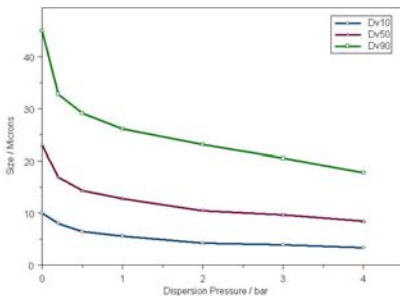


Figure 7 - Pressure titration for a pharmaceutical powder

Comparison with a well-dispersed wet result allows understanding of the dry dispersion process to be understood. In this case, a good wet-dry correlation is observed at 0.2 bar (figure 8), suggesting that particle milling would occur for measurements performed above this pressure and produce a bias in the reported fine particle fraction.

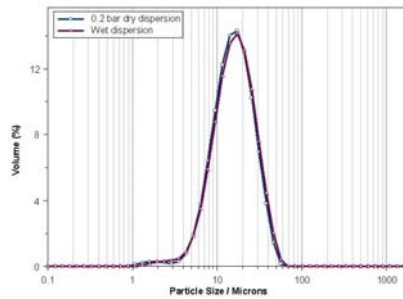


Figure 8 - Comparison of the particle size distribution reported at 0.2 bar with that obtained using wet dispersion

Dispersion for on-line analysis

Dispersion of dry powders during on-line analysis is achieved using a principle similar to that used in the laboratory. A gas-driven eductor draws sample from the process stream into the laser diffraction measuring zone. Eductor operation is based on the venturi principle with gas flow rate within the eductor being used to control the rate of sample extraction and dispersion. The eductor geometry can also be changed to provide the different shear rates required to disperse diverse sample types. Which gas is used depends on local safety requirements with air being the most common, and nitrogen more usual for IS applications.

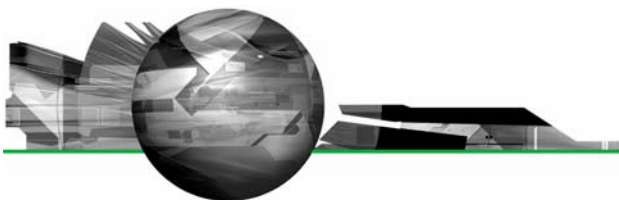
As with laboratory measurements, care must be taken when selecting the operating conditions used to achieve dispersion within the eductor. Dispersion must be achieved without causing the break-up of fragile particles, so it is important to determine how the measured particle size varies according to the gas flow rate. Typically the correct measurement conditions are chosen by comparing the on-line results with those verified previously in the laboratory

Two types of eductor can be used with the Malvern Insitac system to achieve powder dispersion before sample enters the laser diffraction measurement zone. The standard eductor (figure 9) is the most common and is ideal for dispersing coarse and fine powders. Here the shear applied to the powder during sampling is high because the gas flow is introduced at right angles to the particle stream. This allows dispersion of robust agglomerates, but is obviously less well suited to fragile powders. To ensure that powder is not milled a flow rate titration is performed. If repeatable results are achieved at different flow rates above a certain threshold, then the powder has been fully dispersed.



Figure 9 - Standard eductor – air/nitrogen is introduced at 90 degrees to the particle stream through pneumatic fitting in top right hand side of photo

For fragile particles, the eductor geometry can be changed to a coaxial arrangement, where the gas flow is introduced and aligns in the same direction as the powder flow. Here efficient powder transportation is achieved with only a gentle dispersing action. Coaxial eductors are therefore appropriate for the measurement of coarser fragile granules, or where the sample is already well dispersed but is of a sticky/cohesive nature and minimal particle/wall and particle/particle interactions are desired. Again the simple task of performing a flow rate titration will indicate when the agglomerates have been dispersed, but without creating a secondary fines population.



Confirmation of the applicability of the coaxial eductor for fragile particles is seen in figure 10. Here a coaxial eductor is used to gently disperse/transport coarse lactose to the measuring zone without abrading the particles. Confirmation of the measured size (< 2% difference in the Dv(50)) was effected with a Mastersizer 2000 using a very low air pressure (0.5 Bar).

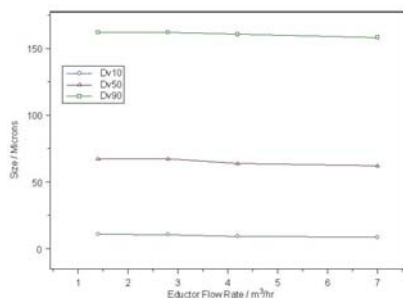


Figure 10 - Coaxial eductor flow rate titration

For finer lactoses, such as pharmaceutical grades, there is a need for greater dispersive capabilities. This can be seen in figure 11 where a flow of 8.4 m³/hr of nitrogen applied to the standard eductor is required to disperse the lactose to its base constituent particles. On the Mastersizer 2000 lab instrument the same results were achieved when 2-3 bar air pressure was used to disperse the fine lactose.

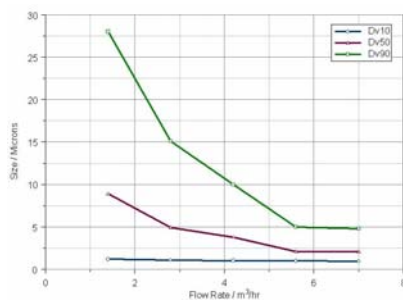


Figure 11 - Standard flow rate titration

An example of the data obtained using two eductor types on the same sample is shown in figure 12, where

particle size has been measured as a function of flow rate for a pharmaceutical excipient. The standard eductor shows a constant decrease in size as the flow rate is increased, whereas the particle size measured using the coaxial eductor is stable. Comparison with laboratory measurements allows an assessment of whether particle dispersion or break-up is achieved using the standard eductor (figure 13). In this case the standard eductor system, operated at a flow rate of 8.4m³/hr, provided the best dispersion without particle break-up, whereas with the coaxial system incomplete dispersion was observed on all except Grade 1.

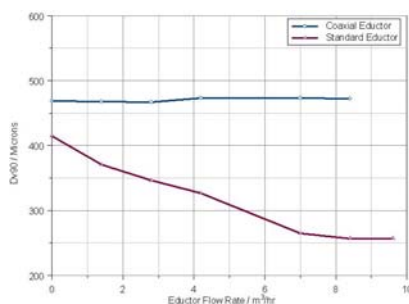


Figure 12 - Change in size with gas flow rate for each eductor type

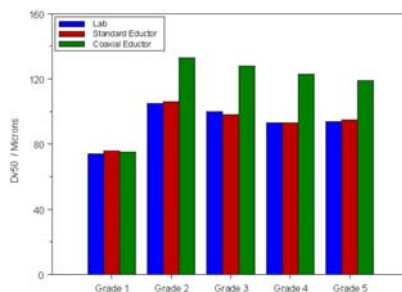


Figure 13 - Measurements made on different excipient grades using the Insitec with two different on-line eductors (8.4 m³/hr) compared to the Mastersizer 2000 (1.5bar dispersion pressure). Complete dispersion is seen using the standard eductor for each grade.

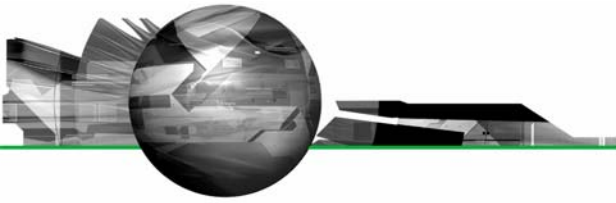
Conclusions

The particle size of powdered APIs and excipients is an important parameter to be monitored and controlled both in their manufacture and end use. The amount of thought needed to perform particle size measurements correctly and reliably should not be underestimated. Correct measurement requires an understanding of the way in which statistically representative sampling and dispersion of the API/excipients can best be achieved. Once an appropriate sampler, eductor, conditioner and gas flow rate have been selected, it is useful to compare results from on-line analysis with laboratory-based measurements using the appropriate standard operating procedure. This ensures confidence in the results. These consistent measurements can then be used to provide process control of the product in the full knowledge that correlation with QC measurements has already been demonstrated.

An additional benefit of on-line and in-line techniques is safety. There is minimal exposure of the API to the operators or the environment outside of the containment vessel. Material is returned directly to the process line, or for smaller processes the whole batch can be measured in-line and returned to a filter in an isolator.

It is most important to note that no one single solution will provide the answer for all pharmaceutical applications. Care and attention must be paid to a number of factors before adopting a final solution for an application.

Malvern Instruments has the depth of knowledge, range of hardware and proprietary software available to provide you with the tools to solve both your on-line and laboratory particle sizing requirements whether they be coarse/fine, cohesive or free flowing.



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